Impulsive-compulsive behaviours in Parkinson's disease: a behavioural, neuroimaging and neurophysiological investigation

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A thesis submitted for the degree of Doctor of Philosophy

June 2022

Keele University

Abstract

Background: Persons with Parkinson's (PwP) may develop Impulsive-compulsive behaviours (ICBs) as side-effect of dopamine replacement therapy (DRT). The unresolved question addressed by this thesis is why only some PwP develop ICBs. This is an important clinical question that impacts on other populations, and has implications for incentive-driven decision-making theories. The thesis objectives are to integrate and extend the body of knowledge using systematic reviews, meta-analyses and original studies. The guiding framework is the use of multiple levels of analyses that include behavioural correlates (cognition, mood and motivation), brain circuits and neurophysiology. The underlying premise is that for any feature to be a reliable marker, it should be evident across multiple levels of analyses.

Method: Study 1 is a behavioural small-scale study of ICBs correlates that informs Study 3; Study 2 is a meta-analysis of behavioural correlates of ICBs; Study 3 is a behavioural multicentre replication study; Study 4 is a pilot neurophysiological study; Study 5 is a systematic review of structural and functional neural correlates of ICBs; Study 6 is a meta-analysis of striatal dopaminergic neurotransmission in ICBs.

Results: First, ICBs showed reduced negative feedback processing in the behavioural small-scale study, but not in the multicentre and in the neurophysiological studies. Second, ICBs showed increased functional activity and dopaminergic neurotransmission in reward processing brain areas in the systematic review and in the meta-analysis. Third, ICBs showed poorer cognitive control in the behavioural meta-analysis and in the multicentre study. The systematic review evidenced reduced frontostriatal connectivity, important for cognitive control. Forth,

ICBs showed increased depression in all behavioural studies. Fifth, ICBs showed reduced dopamine transporter binding in the meta-analysis.

Conclusions: This thesis partially addressed the objective of understanding why only some PwP develop ICBs. A longitudinal study is required for understating whether correlates reflect pre-existing traits, DRT-related changes or both.

Publications associated with this thesis

1. Martini, A., Ellis, S. J., Grange, J. A., Tamburin, S., Dal Lago, D., Vianello, G., & Edelstyn, N. M. (2018). Risky decision-making and affective features of impulse control disorders in Parkinson's disease. *Journal of neural transmission*, *125*(2), 131-143.

2. Martini, A., Dal Lago, D., Edelstyn, N. M., Grange, J. A., & Tamburin, S. (2018). Impulse control disorder in Parkinson's disease: a meta-analysis of cognitive, affective, and motivational correlates. *Frontiers in neurology*, *9,* 654.

3. Martini, A., Dal Lago, D., Edelstyn, N. M., Salgarello, M., Lugoboni, F., & Tamburin, S. (2018). Dopaminergic neurotransmission in patients with Parkinson's Disease and impulse control disorders: a systematic review and meta-analysis of PET and SPECT studies. *Frontiers in neurology*, *9,* 1018.

4. Martini, A., Tamburin, S., Biundo, R., Weis, L., Antonini, A., R., Pizzolo, C., Leoni, G., Chimenton, S., Edelstyn, N. (2020). Incentive-driven decision-making networks in de novo and treated Parkinson's disease with impulsive-compulsive behaviours: a systematic review of neuroimaging studies. *Parkinsonism and Related Disorders*, *78,* 165-177.

Publication related to this thesis (collaborative work)

1. Martini, A., Weis, L., Fiorenzato, E., Schifano, R., Cianci, V., Antonini, A., & Biundo, R. (2019). Impact of Cognitive Profile on Impulse Control Disorders Presence and Severity in Parkinson's Disease. *Frontiers in Neurology*, *10*, 266.

2. Martini, A., Mantovani, E., & Tamburin, S. (2021). Comment on “The association between pain and impulse control behaviours in Parkinson's disease”. *Parkinsonism and Related Disorders*, *83,* 126-127.

Declaration of collaborative work

Chapter 3: Single-centre empirical investigation of cognitive, affective and motivational correlates of ICB in PD (Study 1)

Eligible PD participants identification was done by research nurse. The screening visit was performed by Simon Ellis (CI/PI, consultant neurologist), and the research nurse. Cognitive, affective and motivational assessments were performed by Alice Martini, and data analysed by Alice Martini.

Chapter 3: Systematic review and meta-analysis of cognitive, affective and motivational correlates of impulsive-compulsive behaviours in Parkinson's disease (Study 2)

Databases were searched by Alice Martini. Title and abstract screening was performed, independently, by Alice Martini and Denise Dal Lago (neuropsychologist). Full-text screening was performed, independently, by Alice Martini, Denise Dal Lago, and Stefano Tamburin (neurologist). Data were extracted, independently, by Alice Martini and Denise Dal Lago. Data were analysed by Alice Martini.

Chapter 3: A multicentre empirical investigation of cognitive, affective and motivational correlates of impulsive-compulsive behaviours in Parkinson's disease (Study 3)

In the first site, eligible participants identification was done by Stefano Tamburin (National PI, neurologist). Screening visit was performed by Stefano Tamburin and Alice Martini, and ICBs assessment was performed by Alice Martini. Cognitive, affective and motivational assessments were performed by Alice Martini

and data were analysed by Alice Martini. In the second site, eligible participants identification was done by Roberta Biundo (Second site PI, neuropsychologist). Screening visit was performed by Elisabetta Gasparoli (neurologist), and ICBs assessment was performed by Roberta Schifano (neuropsychologist). Cognitive, affective and motivational assessments were performed by Roberta Schifano, and data were analysed by Alice Martini.

Chapter 4: A pilot investigation of feedback-related negativity in Parkinson's disease and Impulsive-compulsive behaviours (Study 4)

EEG data collection was performed by Alice Martini and Roberta Schifano (neuropsychologist). EEG data were pre-processed and analysed by Alice Martini.

Chapter 5: Brain correlates of Impulsive-compulsive behaviours in Parkinson's disease: a systematic review of neuroimaging studies (Study 5)

Databases were searched by Alice Martini. Title, abstract and full-text screening was performed, independently, by Alice Martini and Silvia Chimenton (MD). Data were extracted, independently, by Alice Martini and Silvia Chimenton. Qualitative synthesis was undertaken by Alice Martini. The systematic review has been updated the 30 March 2020. For the update, databases search was performed by Alice Martini. Title, abstract and full-text screening was performed, independently, by Alice Martini and Clara Pizzolo (master's degree student). Data were extracted, independently, by Alice Martini and Clara Pizzolo. Qualitative synthesis was undertaken by Alice Martini.

Chapter 5: Dopaminergic neurotransmission in persons with Parkinson's disease and Impulsive-compulsive behaviours: a systematic review and meta-analysis of PET/SPECT studies (Study 6)

Databases were searched by Alice Martini. Title, abstract and full-text screening was performed, independently, by Alice Martini and Denise Dal Lago (neuropsychologist), and discrepancies were resolved with Stefano Tamburin (neurologist). Data were extracted, independently, by Alice Martini and Denise Dal Lago. Data were analysed by Alice Martini.

Abbreviations

ACC	Anterior cingulate cortex
BART	Balloon Analogue Risk Task
BIS-11	Barratt Impulsiveness questionnaire
BOLD	Blood Oxygen Level Dependent
CEN	Central executive network
CI	Chief Investigator
Cth	Cortical thickness
CAMCOG	Cambridge Cognitive Examination
COMT	Catechol-O-methyltransferase
DA	Dopamine
DAED	Dopamine agonist equivalent daily dose
DAT	Dopamine transporter
DAWS	Dopamine agonist withdrawal syndrome
DLPFC	Dorsolateral prefrontal cortex
DBS	Deep brain stimulation
DDS	Dopamine dysregulation syndrome
DMN	Default mode network
$D_{2/3}$	Dopamine $D_{2/3}$ receptors
DRT	Dopamine replacement therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders fifth edition
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders fourth edition text revised
DSS	Digit span sequencing task
DTI	Diffusion Tensor Imaging

DWI	Diffusion weighted imaging
EEG	Electroencephalography
ERP	Event-related potentials
ESS	Epworth sleepiness scale
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
FRN	Feedback-related negativity
G-SAS	Gambling Symptom Assessment Scale
HADS	Hospital Anxiety and Depression scale
HC	Healthy control
H&Y	Hoehn and Yahr scale
I-DAS	Italian Dimensional Apathy Scale
ICB	Impulsive-compulsive behaviour
ICB+	Parkinson's disease patient with Impulsive-compulsive behaviour
ICB-	Parkinson's disease patient without Impulsive-compulsive behaviour
ICD	Impulse control disorder
IGT	Iowa Gambling Test
LD	Levodopa
LEDD	Levodopa equivalent daily dose total
LD-LEDD	Levodopa equivalent daily dose Levodopa only
MAO-B	Monoamine oxidase type B inhibitors
MD	Mean diffusivity
MDS	Movement Disorders Society
MIDI	Minnesota Impulse Disorders Interview
MMSE	Mini-Mental State Examination

MRI	Magnetic Resonance Imaging
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NIHM	US National Institute of Mental Health
NMS	Non-motor symptoms
PET	Positron Emission Tomography
PD	Parkinson's disease
PI	Principal Investigator
PwP	Persons with Parkinson's disease
QUIP	Questionnaire for Impulsive-compulsive disorders in Parkinson's disease
QUIP-rs	QUIP rating scale
RadD	Radial diffusivity
RDoC	Research Domain Criteria framework
ROCF	Rey-Osterrieth complex figure test
Rs-fMRI	Resting-state functional magnetic imaging
SAS	Starkstein Apathy scale
SMD	Standardized mean difference
sMRI	Structural Magnetic Resonance Imaging
SN	Substantia nigra
SOGS	South Oaks gambling screen
SPECT	Single Photon Emission Tomography
SPSS	Statistical Package for the Social Sciences
STN	Subthalamic nucleus
TMT	Trail Making Test

UKPDSBB	UK Parkinson's Disease Society Brain Bank criteria
UPDRS	Unified Parkinson's disease rating scale
VBM	Voxel-based morphometry
WAIS-IV	Wechsler Adult Intelligence Scale fourth edition
WTAR	Wechsler Test of Adult Reading

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Acknowledgements

This thesis would not have been possible without the contribution of all the people who crossed my path during this journey.

The person I would like to thank the most is my supervisor, Professor Nicky Edelstyn, who inspired me, sustained me during the difficult moments, and celebrate with me the goals during all these years. It made a great difference having at my side a critical thinker person, always available, and with a focus on the relevance and the impact of the work. Nicky is a great role model, a representation of a researcher I aspire to be.

I would also like to thank Dr Stefano Tamburin for the clinical advice and expertise on Parkinson's disease. He has been constantly involved in the project and he has always been enthusiastic about research, the studies and future directions.

I would like to thank my second and third supervisors, Dr Jim Grange and Dr Joe Brooks. Jim provided me with expert advice on methodologies, and Joe provided me with expert advice on EEG and ERP.

A special thanks to a person who joined me during this journey, Dr Roberta Biundo. She believed in me and she agreed to be involved in the multicentre study of this thesis. She has been a source of inspiration, always passionate about research, kind and in good spirits. I am also very grateful to her collaborators, Dr Roberta Schifano and Dr Luca Weis. Without their help and involvement some studies would have not been possible.

A huge thanks to my collaborators, who helped with the studies of this thesis. I gratefully acknowledge Denise Del Lago, Greta Vianello, Chiara Pizzolo, Giuseppe Leoni, Omar Ferro and Giorgia Albanese from Keele University, Silvia Chimenton

from University of Verona, Roberta Schifano and Luca Weis from S. Camillo Hospital of Venice.

A special thanks to my friends Claudia, Denise, George, Greta, Laura, Shula, Alessandro, Marinela, and Marija whose support was valuable. I shared with them the happiest and the deepest moments of this journey, both in the lab and outside the lab. Thanks to their support, laughs, dinners together and the trips around England I felt at home. A special thanks also to my friends and colleagues (also squash colleagues!) Agi (there are no words for thanking her enough!), Nick and Sammyh for making me feel part of the School. The moments we spent together were ones of the most beautiful of my time in Keele. I own you a squash match and a drink in the KPA!

I would like to thank all the persons who took part in the studies of this thesis, without their time, patience and kindness all this work would have not been possible. Part of what I know about Impulsive-compulsive behaviours and Parkinson's disease is due to their willingness of sharing their experiences and concerns.

Finally, I would like to thank my family. My mum, dad and Filippo who supported me in any moment. At last but not least, I would like to thank Luca who has always believed in me even when I doubted myself. This thesis is dedicated to the baby we are expecting, with the hope that he will manage to do in his life what he would be really passionate about and he would pursue his dreams despite difficulties.

Chapter 1 Overarching Thesis Aim and Rationale

Thesis aim

Persons with Parkinson's (PwP) may develop one or more impulsive-compulsive behaviours (ICBs) during their condition. Prevalence of ICBs in medicated PwP ranges between 5.9% and 58%. Since ICBs are a side-effect of dopamine replacement therapy (DRT) and the majority of PwP are medicated with DRT, the unresolved question is why only a subset of PwP develop ICBs. The first step towards addressing this question is the identification of neural and psychological (cognitive, affective and motivational) correlates of ICBs in already diagnosed cases; the second step will be to track these correlates over time in a longitudinal study of newly diagnosed PwP as they start DRT. The purpose of this thesis is to address the first step of identifying psychological and neural correlates of ICBs.

Thesis rationale

The unmet need

ICBs are a range of behaviours characterized by the inability to resist an urge, drive, or temptation to perform an act that are the cause of significant distress to the individual concerned and/or their close family member (American Psychiatric Association, 2013). Terminology regarding ICBs in Parkinson's disease (PD) differs between studies and specialist centres (e.g., impulse control and related disorders, impulse control disorders and related behaviours, impulsive compulsive behaviours,

impulse control behaviours) (Erga, Alves, Tysnes, & Pedersen, 2020; Gatto & Aldinio, 2019; Hurt et al., 2014; Okai et al., 2013; Voon et al., 2017; Weintraub & Claassen, 2017; Weintraub, David, Evans, Grant, & Stacy, 2015). In general, ICBs comprise the four main impulse control disorders (ICDs) and other repetitive and compulsive behaviours (Voon et al., 2017; Weintraub & Claassen, 2017; Weintraub et al., 2015). ICDs include gambling disorder, when the impulse to gamble cannot be resisted with potentially devastating financial consequences; hypersexuality, when sexual urges become intense and may result in excessive requests for sex from a partner, promiscuity, or compulsive pornography use, and might be felt at inappropriate times leading toward social isolation; compulsive shopping, when the urge of shopping cannot be resisted and may result in buying what it cannot be afforded or needed; and binge eating, when loss of control over food craving causes consumption of large amount of food in a short period of time, and over-time may lead to malnutrition. Other repetitive and compulsive behaviours included in the ICBs category are punding and hobbyism, which are stereotyped behaviours characterized by an intense fascination with a simple (punding; e.g., assembling and disassembling objects) or complex (hobbyism; e.g., gardening, painting) non-goal oriented, repetitive and excessive activity. While performing the act, physiological needs such as hunger and sleep, as well as social responsibilities such as work and family are neglected. In some cases, PwP develop dopamine dysregulation syndrome (DDS), which is a pattern of compulsive dopaminergic medication use in excess of the dose required to adequately control motor symptoms. As a result, marked dyskinesia, motor fluctuation and hypomania can be developed and in the longer-term emergency psychiatric admission may be required. PwP may experience feelings of guilt or shame for these behaviours when perceived in conflict with a

person's belief and personality (i.e., ego-dystonic), whilst carers often show high levels of caregiver burden (Leroi, Harbishettar, et al., 2012). In the longer-term, ICBs may result in financial problems and debt, relationship discord and breakdown, social isolation, anxiety and depression, poorer health outcomes, and poorer quality of life. It has been proposed that when they impact significantly on social and occupational functioning, they warrant the term "disorder" (Okai et al., 2016).

ICBs exist across a spectrum of clinical severity. Clinically significant ICBs are defined as behaviours that impact on social and/or occupational functioning. Non-clinical ICBs (or subclinical ICBs) refers to a change in behaviour – either an exacerbation of previous behaviours or their novel occurrence – which is not per se sufficient for affecting social and/or occupational functioning. Prevalence of ICBs in medicated PwP ranges between 5.9% and 58%. Reasons for the wide range of prevalence reported include between-studies variability in ICBs diagnostic procedures with some studies only reporting clinically significant ICBs (confirmed by clinical interview), whereas in others the outcomes of the screening instrument used were not confirmed by the neurologist therefore overestimating the real prevalence by also including subclinical ICBs and/or false positives. In some studies lifetime prevalence has been reported (i.e., ICBs present at any time of individuals life), whereas in other studies only current prevalence has been considered (i.e., ICBs present only at the time of the assessment). Furthermore, in some studies not all ICBs types have been assessed therefore potentially underestimating the real overall prevalence. Other reasons include environmental (e.g., availability of performing the behaviour such as Casino availability) and cultural factors (e.g., stigma), and medication practices (type and dosage of DRT, with some medications

increasing further the risk of ICBs – see section "Impulsive-compulsive behaviours and Parkinson's disease medication", page 59).

ICBs are recognised as side-effects of $D_{2/3}$ dopamine agonist treatment and, to a lesser extent, levodopa and other PD-related medications such as amantadine and monoamine oxidase-B inhibitors (MAO-B). This is apparent from retrospective case reports and prospective studies showing that ICBs onset, reduction or resolution covary with DRT (Mamikonyan et al., 2008; Seedat, Kesler, Niehaus, & Stein, 2000). Furthermore, ICBs prevalence rates in PwP under DRT are higher than the ones reported in de novo PwP (i.e., drug naïve) (~17%) and in healthy older adults (~11%) (Antonini et al., 2011; Erga, Alves, Larsen, Tysnes, & Pedersen, 2017).

ICBs are thought to originate from underlying changes to dopamine activity in the brain areas that regulate incentive-driven decision-making thereby resulting in unbalanced reward-seeking behaviours. The suggested hypothesis about ICBs pathophysiology comprise overactivation or overdose of the mesolimbic dopaminergic system which modulates responses to rewards (Voon, Mehta, & Hallett, 2011), heightened sensitivity for endogenous and exogenous dopamine of postsynaptic receptors (Prieto et al., 2011; Vriend, 2018), differences in binding profiles across DRT types (Gerlach et al., 2003; Weintraub et al., 2010), or altered equilibrium of the phasic dopamine, resulting in impairments in negative feedback processing (Frank, Seeberger, & O'Reilly, 2004).

Reward-seeking behaviours can rapidly escalate to clinical ICBs within few months after commencing DRT, or in some cases the onset is more insidious taking up to 5 years to develop (Corvol et al., 2018).

The ICBs management mainly focus on changing DRT; however, in many cases this is not effective or may be not feasible due to the worsening of motor

symptoms (National Institute for Health and Care Excellence, 2017). Alternative strategies have been explored such as Cognitive Behavioural Therapy (CBT) (Okai et al., 2013) or subthalamic deep brain stimulation (DBS) (Lhommée et al., 2012). In a small-scale randomized controlled trial comparing 12 sessions of CBT vs. a waiting list control condition, the frequency and impact of the ICBs were significantly reduced over the 6-month period in the treatment group. Despite the promising results, the study needs to be replicated in a separate larger sample of PD and with longer (>6 months) follow-up (Okai et al., 2013). In a prospective investigation of 63 PwP who were assessed before and 1 year after subthalamic DBS, all cases (30 PwP) of preoperative ICBs were resolved at the 1-year follow-up after surgery, probably mainly as result of reductions in DRT. However, subthalamic DBS should be cautiously considered as 18/30 PwP with preoperative ICBs developed apathy during the postoperative year. Further studies with larger sample size are required in order to considered subthalamic DBS as a possible treatment for ICBs.

The size of the problem

According to Parkinson's UK (2018), the estimated prevalence of PwP in the UK is 145,519 individuals and up to 58,208 of those (40%) could be positive for ICBs now, or have been in the past (Erga, Alves, Tysnes, & Pedersen, 2019). Since the world's population is aging, these figures are predicted to rise in the next years. The number of PwP in the UK is expected to reach 168,582 individuals in 2025 and 256,609 in 2065, which will in turn result in increased number of PwP with ICBs (Parkinson's UK, 2018).

PD is the second most common neurodegenerative disorder and, considering the healthcare costs associated, the fourth most expensive neurological disease

(Andlin-Sobocki, Jönsson, Wittchen, & Olesen, 2005). A cost-of-illness study suggests that direct costs include consultations, diagnostics, call and ambulance, emergency and inpatient services and medication (estimated £1,285,354 to the National Health System (NHS) and £161,920 to PwP as out-of-pocket expenses), whereas indirect costs include employment earning loss, productivity loss and sick-leave, early retirement, anxiety, depression, pain, caregiver burden. On the top of the direct and indirect costs, ICBs resulted in heavy out-of-pocket expenditure with some respondents reporting over £10,000 expenses on reward-seeking activities such as gambling and shopping. To control for ICBs, PwP had purchased over the counter medications or supplements. ICBs contribute to the indirect costs through increased psychiatric comorbidity, functional impairment, and caregiver burden (Gumber et al., 2017).

Given the negative consequences of ICBs, the number of persons affected and the lack of treatment available, the best strategy should be preventing them. However, we do not know who are the PwP at risk of developing one or more ICBs, because, in the first place, we lack of a clear understanding of the mechanisms supporting ICBs.

Gaps in the literature

Previous studies of neural and psychological correlates of ICBs have been inconsistent in their findings. This because most of the studies are constrained by small sample size, and therefore low statistical power. Clinical characteristics of the studies' sample are heterogenous in terms of PD severity stage and progression, PD duration, age at evaluation, dopaminergic medication type and doses, all factors associated with ICBs. Other conditions such as dementia and substance abuse are not

always excluded, despite both conditions being independently associated with cognitive and neural changes. Finally, ICBs diagnostic criteria used are not uniform across studies, with some only using screening questionnaires without confirming ICBs presence by clinical interview thereby possibly inflating the number of ICBs false positives.

Implications

There are three related reasons why research on the neural and psychological correlates of ICBs is needed now: i) a better understanding of ICBs pathophysiology will inform psychological intervention and potentially drug treatments, ii) findings from i) may have a transdiagnostic application to ICBs arising in other conditions such as restless leg syndrome, fibromyalgia and addiction in non-PD population, and iii) if ICBs are related to deficiencies in incentive-driven decision-making, then this population will provide a means for testing the validity of cognitive and neural models of incentive-driven decision-making in the healthy population.
Each of these points are explored in greater depth in the following section.

A better understanding of ICBs correlates will inform psychological intervention and potentially drug treatments. ICBs provide many challenges for the PwP, their caregivers, and treating clinicians. When diagnosed with PD, PwP and caregivers have to face the immediate and longer-term psychological and physical impact of being told they have an incurable neurodegenerative condition, that will lead to increasing physical disability and cognitive decline. On the top of that, the mainstay medication used to improve motor symptoms is also responsible for triggering disruptive behaviours that affect occupational functioning, personal finances, interpersonal relationship, increase caregiver burden, and in extreme cases

can lead to severe financial and legal consequences. Clinicians have to face the reality that ICBs are triggered by the DRT prescribed, there is no way to know who is going to develop ICBs and, once developed, there are no treatment options available other than modifying DRT type.

In the UK, the current National Institute for Health and Care Excellence (NICE) guidelines advise clinicians to 1) increase health literacy about ICBs by giving people and their family members and carers (as appropriate) oral and written information about the increased risk of developing ICBs when taking DRT, and that these may be concealed by the person affected; 2) who to contact if ICBs develop; and, 3) discuss potential ICBs at review appointment, particularly when modifying therapy (National Institute for Health and Care Excellence, 2017).

However, in the clinical practice ICBs are generally under-recognised as people seldom report them spontaneously to their treating clinicians (Perez-Lloret, Rey, Fabre, Ory, Spampinato, Montastruc, et al., 2012); PwP may be motivated to conceal ICBs due to embarrassment or shame, or may be ambivalent regarding ceasing the behaviour (Weintraub, 2020), or may lack awareness of their ICBs as supported by discrepancy between PwP and the knowledgeable informant reports (Baumann-Vogel, Valko, Eisele, & Baumann, 2015). Assessment of ICBs can require more time than recognised in routine appointments, which are mainly focused on discussing the effectiveness of DRT in controlling motor or other co-occurring non-motor symptoms; this because the progressive course of the PD requires to adjust the DRT based on the worsening of the symptoms. For all these reasons, early detection of ICBs is complicated and they may come to the clinical attention only once are fully developed, attached and their negative consequences irremediable.

Once the treating clinician is aware of the ICBs, management consists in either reducing the dose or switching to another DRT type. A work of Samuel et al. (2015) reviews ICBs management approaches pointing out that DRT change may be complicated by motor symptoms worsening and — if PwP are under dopamine agonists — by the development of dopamine agonist withdrawal syndrome (DAWS). DWAS symptoms resemble those of other psychostimulant drugs withdrawal syndromes (i.e., panic attack, agoraphobia, anxiety, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension, and drug craving) and do not respond to substitution with levodopa or other DRT types.

In some cases, ICBs can persist or relapse in subclinical forms even if the DRT has been modified; when DRT changes are not effective, NICE guidelines advise clinicians to offer specialist cognitive behavioural therapy targeting at ICBs. However, since the first attempt to manage ICBs to the decision to start non-pharmacological therapies, months could have passed and the behaviour could have become attached and more difficult to treat. Even if successfully treated, some negative consequences are irreversible; compulsive buyers or gamblers could have already lost large amounts of money and PwP with hypersexuality could have broken social relationships and experienced social retirement.

As described so far, the reactive approach promoted by the NICE guidelines is inadequate and a shift toward a preventive approach is required. Patients at risk of ICBs should be early identified, carefully monitored and, if subclinical changes emerge, they may be offered psychological therapies.

With improved understanding of neural and psychological correlates of ICBs, novel agents and non-pharmacological treatments may be identified. To date, there is

no effective treatment for ICBs as add-on therapies and psychological interventions lack evidence on effectiveness (Samuel et al., 2015; Seppi et al., 2019, 2011).

Findings related to neural and psychological correlates of ICBs may have a transdiagnostic application to ICBs arising in other conditions such as restless leg syndrome, fibromyalgia and addiction in non-PD populations. For example, low doses of dopamine agonists and levodopa are effective in the treatment of restless legs syndrome, and dopamine agonists are also used off-label for treating fibromyalgia. In both conditions, some treated individuals develop ICBs (Cornelius, Tippmann-Peikert, Slocumb, Frerichs, & Silber, 2010; Holman, 2009; Voon, Schoerling, et al., 2011). These disorders, as well as behavioural addictions in general populations, may share some pathophysiological mechanisms, neural circuits and cognitive processes, and may respond to similar interventions that target these common underlying mechanisms (Yücel et al., 2018). This is in line with the Research Domain Criteria (RDoC) framework promoted by the US National Institute of Mental Health (NIMH) and by the American Psychiatric Associations (Insel et al., 2010). The RDoC framework assumes that behaviours such as reward-seeking exists on a continuum that spans the full range of normal human behaviour, with varying degree of dysfunction cutting across traditional diagnostic boundaries e.g., bipolar disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, addiction, and by implication also ICBs. The final aim is to provide novel insights into etiological and maintenance processes which may be shared across conditions. The RDoC framework does not substitute the Diagnostic and Statistical Manual for Mental Disorders 5th edition (DSM-5) (American Psychiatric Association, 2013) used for disease diagnosis, but represents a complementary framework; as findings emerge from research conducted under the RDoC framework, they will be fed into

future versions of the DSM which will improve care for individuals with mental disorders. Therefore, research on ICBs in PD may have a wider clinical impact and its transdiagnostic value grounds on an approach promoted by the clinical and scientific community.

If ICBs are related to deficiencies in incentive-driven decision-making, then this population will provide a means for testing the validity of cognitive and neural models of incentive-driven decision-making in the healthy population. Incentives are outcomes that are associated with a specific behaviour, and are assumed to motivate that behaviour. Incentives can be positive or negative, such as achieving a gratification or avoiding a punishment. In everyday life we constantly take decisions based on incentives and ICBs in PD provide the opportunity to look at the dynamic of the processes involved in the incentive-driven decision-making. In ICBs in PD decisions are mainly driven by rewards. For example, a PwP with compulsive shopping would fail to control his urge of buying unnecessary items being his decisions mainly driven by immediate gratifications, that over-time may result in huge loss of money. A PwP with binge eating would fail to control himself from eating tasty but rich in fat food, that over-time may result in obesity. Therefore, ICBs in PD can be used as clinical model for testing whether patterns of performance are predicted by the current understanding of the mechanism supporting incentive-driven decision-making.

In summary, research on ICBs in PD has both clinical and scientific relevance. ICBs are a problem for PwP, carers and clinicians, but are also an opportunity for shedding light into addictive behaviours in non-PD population and for understanding incentive-driven decision-making processes.

Theoretical model

In this thesis, mechanisms supporting ICBs in PD have been investigated using a conceptual framework of incentive-driven decision-making (Sinha, Manohar, & Husain, 2013) (detailed information is provided in chapter 3, Study 1). In this framework, incentive-driven decision-making has been split in several stages: option generation, option selection, action initiation or inhibition, and learning (Sinha et al., 2013). The value of this framework is that it includes, in a comprehensive way, several models of incentive-driven decision-making that alone only account for a specific process involved. For example, the 'option selection stage' includes incentive salience (Berridge & Robinson, 1998, 2016) and temporal discounting (Myerson, Baumann, & Green, 2014; Myerson & Green, 1995) theories, whereas the 'action initiation or inhibition stage' include the model of competition between action and inhibition processes in the direct and indirect pathways (Cilia & van Eimeren, 2011). Finally, the 'learning stage' involves reward prediction error used in reinforcement learning models (Frank et al., 2004; Holroyd & Coles, 2002; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006). Importantly, it has been proposed that processes in each of these stages may be modulated by dopamine, with higher levels leading toward reward-driven behaviour and lower levels leading toward apathy, based on the concept of an 'inverted U'-shaped relationship between the level of dopamine and a cognitive function (Cools, Altamirano, & D'Esposito, 2006). Furthermore, factors other than dopaminergic modulation such as depression and anxiety can influence processes within each stage.

Picture a young woman who wants to buy a new car. To achieve her goal, she might decide to saving money regularly. Every time she goes for shopping, she might wonder whether to buy new items or not and, if needed, whether to buy the

cheapest ones (option generation). She might hesitate, thinking she needs those things. However, she might also think that if she does not save money, she will not be able to buy the car or she will do it in a longer time than planned. Our daily life is rich in similar situations, such as following a particular diet and refrain from eating tasty but rich in fat foods, or studying for an exam instead of hanging out with friends. Each decision made to engage in a specific activity is the result of weighing up the predicted reward value of following that particular goal, traded-off against the effort involved in achieving the goal, the risk involved and the time to outcome delivery, versus the alternative option(s) that are not pursued (option selection stage) (Botvinick & Braver, 2015; Sinha et al., 2013). Once the behavioural option has been selected, the behaviour has to be implemented or inhibited if the wider context changes and the chosen behavioural option is no longer advantageous (action initiation or inhibition stage). Once the behaviour has been acted, the real outcomes are compared with the predicted ones; such comparison is important for decisions that will be taken in the future (learning stage). It has been suggested that each of these stages can be modulated in some extent by dopamine (Sinha et al., 2013).

In this thesis, ICBs in PD have been investigated using the incentive-driven decision-making framework proposed by Sinha et al. (2013) (see Chapter 3, Study 1). The final aim is to comprehend what mechanism (or mechanisms) are affected in PwP with ICBs.

Thesis Framework

The guiding framework of this thesis is the use of multiple levels of analyses, which include behavioural (cognition, affective and motivation), brain circuits and neurophysiology for investigating ICBs in PD; this means that the same

phenomenon has been investigated from different points of view with the final aim of looking at convergence across them. The underlying premise is that for any feature to be a reliable marker of ICBs, it should be evident across multiple levels of analyses. Changes in behaviours (e.g., reward-seeking attitude) should be accompanied by changes in the brain areas supporting these processes. When changes are evident only at one level, but not in the others, their reliability as indicators of ICBs should be questioned. This approach is consistent with other approaches such as the one used by the RDoC framework (Insel et al., 2010).

In this thesis, the existing body of knowledge has been integrated and extended using systematic review, meta-analysis and empirical studies.

The levels of analyses included in this thesis are behavioural (measured by cognitive tasks and self-report questionnaires – studies 1, 2 and 3 using two empirical studies and one systematic review and meta-analysis – reported in chapter 3), neurophysiological [measured by electroencephalography (EEG) and event-related potentials (ERPs) – study 4 using one empirical investigation - reported in chapter 4] and brain circuits [measured by Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT), Voxel-based morphometry (VBM), Diffusion Tensor Imaging (DTI), and resting-state functional magnetic imaging (rs-fMRI) – studies 5 and 6 using one systematic review and one systematic review and meta-analysis – reported in chapter 5]. In the final chapter of this thesis (chapter 6) the findings of this thesis are integrated.

A summary of the studies included in the thesis is provided in Figure 1.1. In the general discussion of the thesis (Chapter 6), the right-hand side of the diagram will be completed with the main findings.

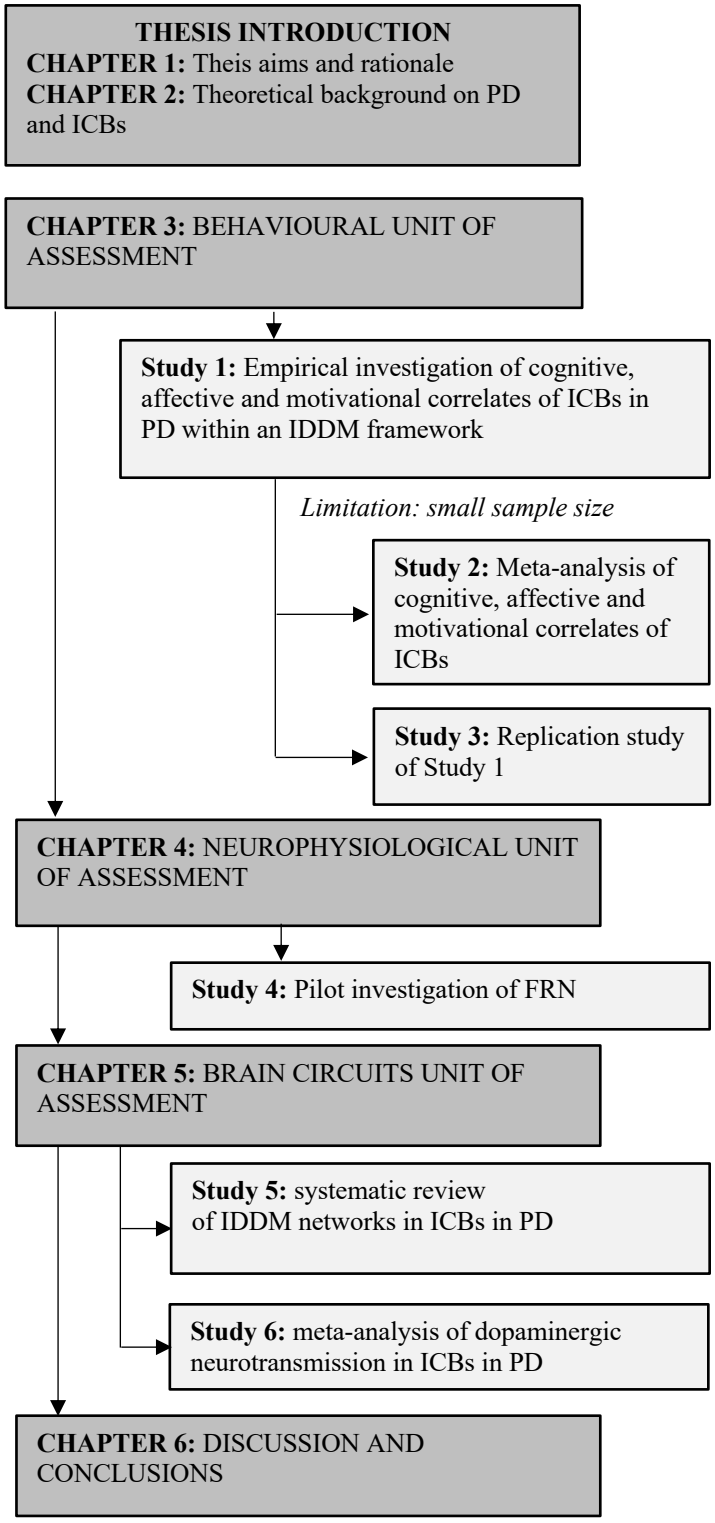


Figure 1. 1 Summary of the studies included in the thesis. PD: Parkinson's disease; ICBs: impulsive-compulsive behaviours; IDDM: incentive-driven decision-making; FRN: feedback-related negativity.

Chapter 2 Introduction

This chapter provides a literature review of the epidemiology, pathophysiology, risk factors, diagnosis and management of Parkinson's disease (PD) (part 1) and Impulsive-compulsive behaviours (ICBs) (part 2).

Part 1: Parkinson's disease

PD is an incurable, chronic, progressive neurological disorder that is characterized by the motor symptoms of bradykinesia, tremor at rest, rigidity, and postural instability (see section "Motor symptoms", page 26). The condition was first described as neurological syndrome by James Parkinson in 1817, and 50 years later was named "Parkinson's disease" by the French neurologist Jean-Martin Charcot [for a review on the history of PD see (Goetz, 2011)]. The first descriptions of the disease mainly focused on motor characteristics; however, it is now well known that non-motor symptoms frequently co-occur (see section "Non-motor symptoms", page 27).

Epidemiology

PD is the second most common neurodegenerative condition after Alzheimer's disease. In 2016, a systematic analysis of the literature estimated that there were 6.1 million people with Parkinson's (PwP) worldwide (2.9 millions of whom were females and 3.2 millions were males), compared with 2.1 million in 1990 (Ray Dorsey et al., 2018). The disease prevalence reflects both the incidence and the duration of a disease; the first is related to risk and protective factors (see section "Aetiology", page 20), the latter is related, at least in part, to longevity.

However, the age-standardised prevalence rates increased by about 22% (similarly in males and females), therefore suggesting that the number of PwP is not only related to the increased number of older people, but other factors may play a role (e.g., greater awareness of diagnosis, availability of higher quality studies) (Ray Dorsey et al., 2018). Age-standardised prevalence is higher in North-America and in western Europe (with similar prevalence in the UK and in Italy), and lower in eastern Europe, Asia, Australia and Africa (see Figure 2.1).

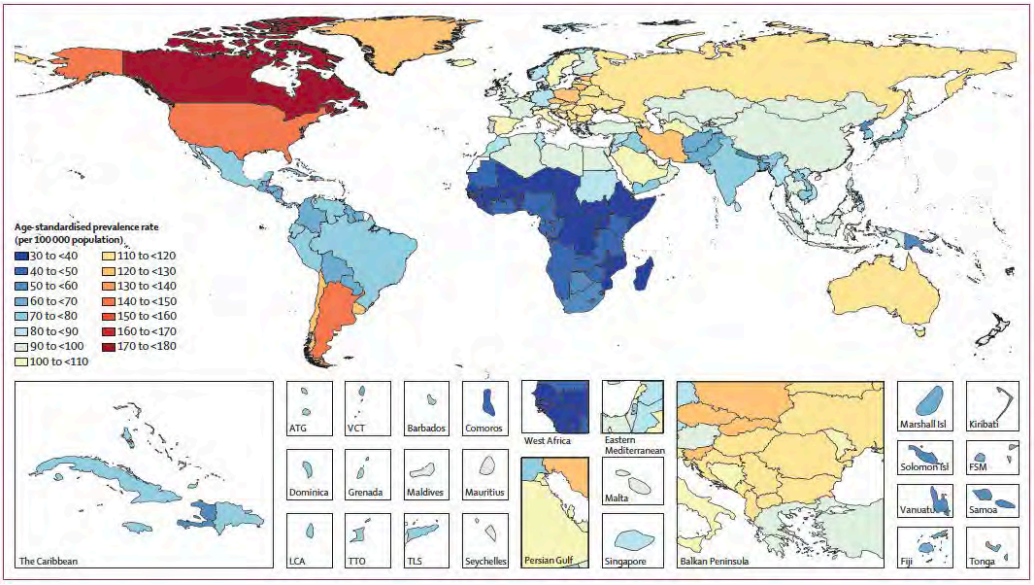


Figure 2. 1 Age-standardised prevalence of Parkinson's disease per 100,000 population by location for both sex, 2016. ATG: Antigua and Barbuda; FSM: Federated States of Micronesia; LCA: Saint Lucia; TLS: Timor-Leste; TTO: Trinidad and Tobago; VCT: Saint Vincent and the Grenadines. Reprinted under the terms of the Creative Commons CC-BY license from Ray Dorsey et al. (2018).

The mean age of PD onset is about 60 years; in 5-7% of cases onset is between age 20 and 40, and is classified as "young-onset PD" (Mehanna & Jankovic, 2019). Prevalence increases with age, roughly doubling with every decade after age

50 (global prevalence data is presented in Table 2.1) (Pringsheim, Jette, Frolkis, & Steeves, 2014). PD is more prevalent in men than women (Georgiev, Hamberg, Hariz, Forsgren, & Hariz, 2017; Hirsch, Jette, Frolkis, Steeves, & Pringsheim, 2016; Ray Dorsey et al., 2018), although no differences have also been reported (Pringsheim et al., 2014).

Table 2. 1 Prevalence of Parkinson's disease across age. Reprinted under permission from Pringsheim et al. (2014), John Wiley and Sons and Copyright Clearance Center.

Age group	**Prevalence (n per 100,000)**
40-49	41
50-59	107
55-64	173
60-69	428
65-74	425
70-79	1087
> 80	1903

Incidence increases with age; in females incidence peaks between the ages 70-79, whilst in male tends to rise after age 80 (global incidence data is reported in Table 2.2) (Hirsch et al., 2016). It should be noted that rates across studies vary consistently possibly due to differences in diagnostic criteria used and under-diagnosis of PD, especially in elderly population (Tysnes & Storstein, 2017).

Table 2. 2 Incidence of Parkinson's disease across ages and gender. Reprinted under permission from Hirsch et al. (2016), Karger Publisher and Sons and Copyright Clearance Center.

Age group	**Incidence in female (n per 100,000)**	**Incidence in male (n per 100,000)**
40-49	3.26	3.57
50-59	8.43	14.67
60-69	30.32	58.22
70-79	93.32	162.58
>80	103.48	258.47

Gender differences in prevalence and incidence rates — as well as in PD features i.e., women are more prone to develop tremor-dominant PD but are less rigid than men, and present more pain symptoms, and higher depression (Georgiev et al., 2017) — suggest differences in the brain pathways involved in the disease (De Micco et al., 2019). However, studies investigating gender differences are still scarce and longitudinal studies analysing gender differences in PD and comparing them to matched healthy controls are needed. Since then, it is important for studies to properly match the gender of their samples in order to avoid biases related to possible differences in their pathophysiological profiles.

Aetiology

In around 85% of cases, PD develops in individuals with no history of PD in their family (Tran, Anastacio, & Bardy, 2020); these cases are sporadic and are classified as "idiopathic PD". In around 15% of cases, PwP have a documented

history of PD in their family; these cases are classified as “familial PD” (Figure 2.2a) (Tran et al., 2020).

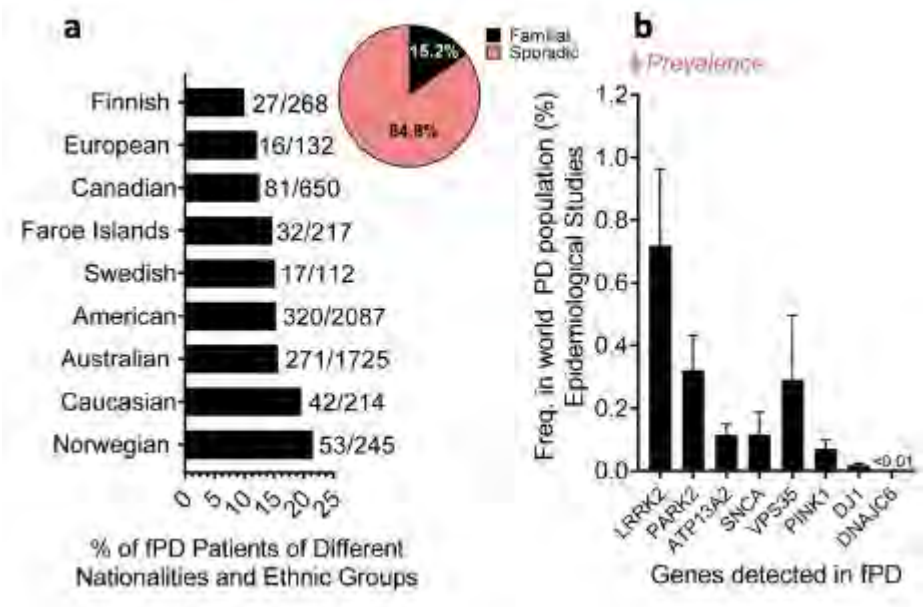


Figure 2. 2 The genomics of Parkinson’s disease. A) In the PD world-wide population, 85% of PD cases are idiopathic and 15% are familial (fPD). B) Mutations occur at low (< 0.8%) and varying frequencies (Freq.). Data represented as mean ± SEM. Reprinted under the terms of the Creative Commons CC-BY license from Tran et al. (2020).

Whether or not idiopathic and familial PD represent the same disease entity is debated [for a review see (Correia Guedes, Mestre, Outeiro, & Ferreira, 2020)]. From a clinical perspective, there is an overlap between the two conditions as both share higher incidence in males, similar distribution of the initial motor symptom (tremor) and its location (upper extremities), and asymmetric parkinsonism during disease course (Baba et al., 2006). Clinically, management of familial and idiopathic PD does not differ.

However, pathophysiologically they may share substantia nigra (SN) neurodegeneration and a-synuclein accumulation in Lewy bodies, although other neuropathological features may differ (Schiesling, Kieper, Seidel, & Krüger, 2008), with potentially brain systems differently affected.

The aetiology of idiopathic and familial PD probably differs; in the latter, genes appear to play a greater role. However, whether the same genes are also implicated in idiopathic PD, and the role of environmental factors in mediating epigenetic changes is uncertain.

Several mutant genes have been associated with familial PD, with the most common mutated genes i.e., LRRK2 and PARK2, reported in 0.7% and 0.3% of all the people showing PD symptoms, respectively (Tran et al., 2020) (world prevalence of genes detected in familial PD are provided Figure 2.2b); this means that mutations in some of these genes are also evident in idiopathic PD.

Environmental factors that may mediate epigenetic changes include air pollution (Hu et al., 2019), rural living, well-water consumption, farming and the use of pesticides, herbicides, insecticides, fungicides or paraquat (Breckenridge, Berry, Chang, Sielken, & Mandel, 2016), 25-hydroxyvitamin D insufficiency and deficiency (<30 and <20 ng/mL, respectively), and reduced exposure to sunlight (Zhou, Zhou, Zhang, & Li, 2019). Conversely, smoking cigarettes has been linked to a reduced risk of developing PD (Breckenridge et al., 2016); whether this association is causal is controversial (Ritz, Lee, Lassen, & Arah, 2014). Advancing age can also cause a cascade of stressors in brain pathways underpinning PD pathophysiology, thereby decreasing the ability of the neurons to respond to further insults (Tran et al., 2020).

The worldwide used diagnostic criteria for PD [i.e., UK Parkinson's Disease Society Brain Bank – UKPDSBB (Gibb & Lees, 1988)] considers family history of PD as an exclusion criterion, supporting the hypothesis that idiopathic and familial PD are not the same disease. However, according to other diagnostic criteria family history of PD is no longer an absolute exclusion for being diagnosed with PD, therefore accepting that there may be familial forms of PD that may be part of a broad PD spectrum (see "diagnosis" section, page 33).

More studies are needed to understand whether idiopathic and familial PD are or not the same entity; since then, studies investigating idiopathic PD should not include familial cases, in order to increase homogeneity of the sample and reliability of studies' findings.

Pathophysiology

The main pathological hallmark of PD is a pronounced and progressive loss of dopamine (DA) producing neurons in the SN of the midbrain (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004), and progressive and widespread α-synuclein aggregation and neuronal loss in specific areas of the central and peripheral nervous systems (Marinus, Zhu, Marras, Aarsland, & van Hilten, 2018), giving rise to the development of Lewy pathology.

Braak et al. (2004) proposed a six-stages model for PD progression based on a specific pattern of α-synuclein spreading, beginning in definite sites. The Lewy body pathology initiates in the medulla oblongata and olfactory bulb, causing autonomic and olfactory disturbances (Oppo, Melis, Melis, Tomassini Barbarossa, & Cossu, 2020) (stages 1-2), then expand to the brainstem, causing sleep and motor disturbances (stages 3-4), and finally spreading to the limbic and neocortical regions,

causing emotional and cognitive impairments (stages 5-6) (Halliday, Lees, & Stern, 2011). The description of the brain sites involved in Lewy pathology based on Braak et al., (2004) model, together with a visual illustration, is provided in Table 2.3.

Table 2. 3 Six-stages model of PD progression.

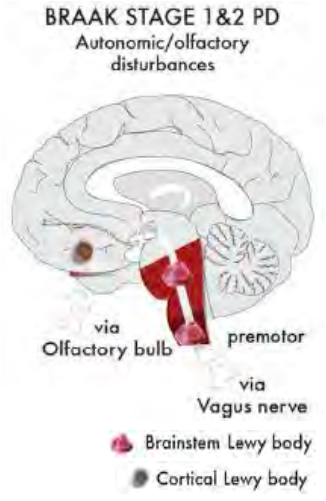
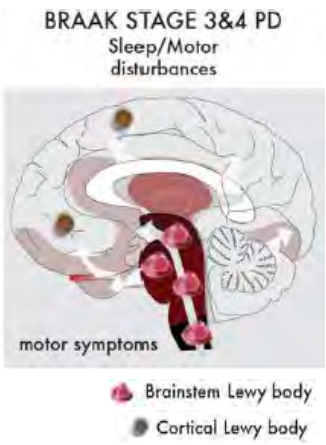
PD Stages	**Lewy pathology sites**	**Lewy pathology illustrated**
Stage 1	Dorsal motor nucleus of the vagus nerve, olfactory bulb and the anterior olfactory nucleus	
Stage 2	Lower raphe nuclei and magnocellular portions of the reticular formation, as well as the coeruleus–subcoeruleus complex.	
Stage 3	Basal portions of the midbrain and forebrain. The pathology begins in the posterolateral subnucleus of the pars compacta and goes on to affect the posterosuperior and posteromedial subnuclei. At the same time, the disease process encroaches on the central subnucleus of the amygdala and from there extends into the basolateral nuclei. Additional brain regions involved are: the cholinergic tegmental pedunculopontine nucleus, the oral raphe nuclei, the cholinergic magnocellular nuclei of the basal forebrain, and the hypothalamic tuberomammillary nucleus.	
Stage 4	Temporal mesocortex, whose anteromedial part projects to the limbic circuit areas such as the entorhinal region, hippocampal formation, and amygdala.	

Table 2. 3 (continued) Six-stages model of PD progression.

PD Stages	Lewy pathology sites	Lewy pathology illustrated
Stages 5 and 6	The inclusion body pathology gradually spreads over the entire neocortex.	

Legend. PD: Parkinson's disease. The dark shading represents the severity of pathology, the darker the more severe the pathology is. Reprinted under permission from Halliday et al. (2011), John Wiley and Sons and Copyright Clearance Center.

Motor symptoms

The cardinal motor features of PD are bradykinesia, resting tremor, rigidity, and postural instability. *Bradykinesia* indicates the slowness of initiation of voluntary movement associated with progressive reduction in the speed of repetitive actions (Marsili, Rizzo, & Colosimo, 2018; Schilder, Overmars, Marinus, van Hilten, & Koehler, 2017). *Resting tremor* can involve the upper or the lower limbs, or both. When it involves the upper limb, the tremor is most commonly a resting pill-rolling type of tremor of the hands; pill-rolling relates to the tendency of the index finger to get in contact with the thumb creating a circular movement. *Rigidity* is characterized by resistance to passive movements that occur due to increased muscle tone, and in some cases can be associated with pain and discomfort. *Postural instability* is characterized by impairment in the ability to recover and maintain

balance after perturbation, and may lead to falls and injuries. Some PwP may present freezing of gait, which is a brief and sudden episodic inability to initiate ambulation when intending to walk. Other motor symptoms include speech disturbances (e.g., very quiet and hurried speech) and hypomimia (e.g., loss or reduction of facial expressiveness) [for a review see (Hess & Hallett, 2017)]. Although PD is described as a motor disorder, nonmotor symptoms (NMS) are also prominent and are the source of great distress for PwP and their care-givers.

Non-motor symptoms

The recognised NMS of PD encompass a wide range of domains such as neuropsychiatric, autonomic, gastrointestinal and sensory symptoms, and sleep disorders (Chaudhuri, Odin, Antonini, & Martinez-Martin, 2011). The range of NMS in PD and possible aetiology are provided in Table 2.4.

Table 2. 4 The range of non-motor symptoms in Parkinson's disease, and their possible aetiology. Adapted from Chaudhuri et al. (2011). Reprinted under permission by Elsevier and Copyright Clearance Center.

Symptoms	**Possible aetiology**
Neuropsychiatric symptoms	
Sadness, depression	Possible pre-motor
Apathy, Anxiety, Anhedonia	
Hallucinations, delusions	May be drug-induced
Psychosis	May be drug-induced
Delirium	May be drug-induced
Cognitive impairment	
ICBs	May be drug-induced
Panic attacks	Could be "off" related
Autonomic symptoms	
Bladder disturbances	
Sexual dysfunction i.e., erectile impotence	May be drug-induced
Sweating abnormalities i.e., hyperhidrosis	
Orthostatic hypotension i.e., falls related to orthostatic hypotension	
Gastrointestinal	
Dribbling of saliva	
Dysphagia i.e., difficulty in swallowing	
Ageusia i.e., loss of sense of taste	
Constipation	Possible pre-motor
Nausea, Vomiting, Reflux	
Faecal incontinence	

Table 2. 4 (continued) The range of non-motor symptoms in Parkinson's disease, and their possible aetiology.

Symptoms	**Possible aetiology**
Sensory symptoms	
Pain	
Paraesthesia i.e., abnormal sensation of the skin	
Olfactory disturbances	Possible pre-motor
Sleep disorders	
RBD	Possible pre-motor
Excessive daytime somnolence	May be drug-induced
Restless legs syndrome, periodic leg movements	
Insomnia	
Sleep disorder breathing (obstructive sleep apnoea)	
Non-REM parasomnias (confusional wandering)	
Other symptoms	
Fatigue	
Visual disturbances (diplopia, blurred vision)	
Seborrhoea i.e., excessively oily skin	
Weight loss, weight gain	Weight gain may be related to ICBs (i.e., binge eating)

Legend. REM: rapid eye movement; ICBs: impulsive-compulsive behaviours; RBD: rapid eye movement sleep behaviour disorder.

The aetiology of NMS is complex; some of them correlate with advancing disease, whilst others such as constipation, hyposmia, rapid eye movement disorder, and depression may precede PD diagnosis by 10-15 years, and increase the risk of developing PD (Adams-Carr et al., 2016; Claassen et al., 2010; Galbiati, Verga, Giora, Zucconi, & Ferini-Strambi, 2019; Haehner et al., 2007; Ishihara & Brayne, 2006; Lieberman, 2006; Schapira, Chaudhuri, & Jenner, 2017) (see Table 2.4). The presence of NMS preceding PD diagnosis suggests three not mutually exclusive reasons: (1) they are manifestation of early PD; (2) they are risk factors for PD and have a causal association with subsequent disease; or (3) NMS preceding PD diagnosis and PD are both outcomes of a common exposure (Adams-Carr et al., 2016). Finally, it is possible that these symptoms are comorbid conditions, not strictly associated with PD.

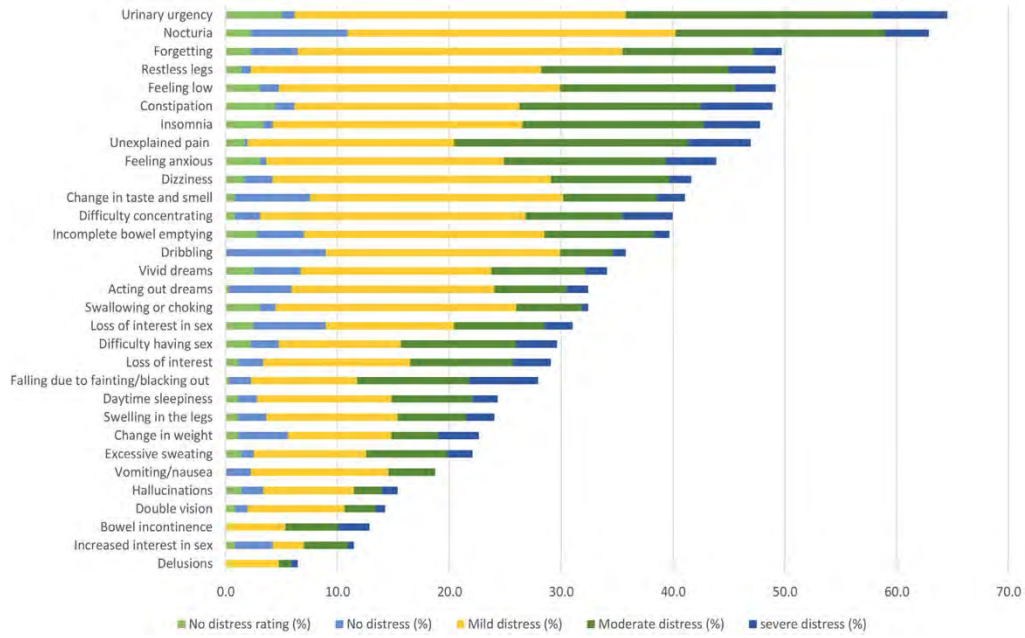
In some cases, NMS may be medication side-effects as their appearance and resolution covary with medication use and dosage (see Table 2.4). For example, psychosis may improve with DA agonists dose reduction or cessation, excessive daytime sleepiness may be cause or exacerbated by DA agonist use, and clinically significant ICBs can be developed months or years after dopamine replacement therapy (DRT) initiation and may improve with dose reduction or switched to another DRT type (Latt, Lewis, Zekry, & Fung, 2019).

The scenario is more complicated when NMS develop in later stages of PD, when PwP have been for years under the chronic use of DRT therefore making it difficult to understand whether NMS represent PD-related features or are the result of medication, or an interaction between both.

NMS are no less important than motor symptoms; they increase the cost of PD care and may affect quality of life at a greater extent than motor symptoms (Hinnell, Hurt, Landau, Brown, & Samuel, 2012; van Uem et al., 2016; Visser et al., 2008). This is possibly because DRT offers reasonably good control over the motor symptoms, but then leaves the NMS more exposed. With motor symptoms under control, PwP and carers' attention may be more focused on the NMS.

Despite their importance, NMS are seldom screened even in specialized centers (Chaudhuri et al., 2011) and, regardless being directly asked, PwP may under-report their presence. The unbalanced attention of clinicians toward motor vs. NMS, together with the lack of reporting by PwP results in a negative loop where distressing symptoms remain untreated.

A recent study of 358 PwP (PD duration: mean=5.96 years, range: 1-33 years) investigated prevalence of NMS and associated levels of distress, as well as



overall and symptoms specific barriers to seeking help (Hurt et al., 2019a). Overall, 1.1% of PwP had no NMS (4/358), 18.4% had 1–5 symptoms (mild burden), 27.7% had 6–9 symptoms (moderate burden), 26% had 10–13 symptoms (severe burden) and 26.8% had greater than 13 NMS representing very severe burden. The most common NMS were urinary urgency and nocturia (i.e., the need to awaken one or more times per night to void), whilst bowel incontinency, increased interest in sex, and delusions were the least common (see Figure 2.3).

Figure 2. 3 Frequency of NMS in a total sample of 358 PwP. Symptoms are ranked from most to least frequent. Coloured bars represent the level of distress, with no distress rating meaning symptom was endorsed but distress data was missing. Reprinted under the permission from Hurt et al. (2019a), Elsevier and Copyright Clearance Center.

Failure to disclose NMS to the healthcare provider was common for loss of interest in sex, increased interest in sex, and difficulties having sex (not reported to the healthcare provider by the 72.1%, 58.8%, and 58.5% of PwP, respectively),

whilst falling to fainting was the most reported NMS (not reported to the healthcare provider by the 15% of PwP) (Hurt et al., 2019a). The most common barriers to help-seeking (endorsed by 100 or more PwP, with no differences between males and females) were: acceptance of the symptom as part of life (n=292), uncertainty that effective treatment is available (n=222), uncertainty whether the symptom is part of PD (n=206), belief that the symptom is not serious (n=156), concern that treatment will require change of PD medication or taking extra medication (n=125), not a priority at the time (n=114), belief that raising the problem not socially acceptable (n=108), and lack of priority to NMS in the consultation (n=108) (Hurt et al., 2019a).

Being NMS common in PD and considering the potential distress they may cause, it is important that PwP and carers are properly informed about their presence at any time of the disease and during consultancy.

Diagnosis

Since its original description, the diagnosis of PD has been clinical and centred on a defined motor syndrome (Postuma et al., 2015). It should be noted that, regardless of the criteria used, diagnosis is confirmed only *post mortem* through histopathological evidence of neural degeneration with Lewy bodies in the SN.

A continuous re-evaluation process can improve diagnostic accuracy and reduce misdiagnosis which is common when only the initial diagnosis is considered (Hughes, Daniel, Ben-Shlomo, & Lees, 2002). In the early stages, response to dopaminergic treatment is less defined and symptoms related to atypical parkinsonisms (e.g., multiple syndrome atrophy and progressive supranuclear palsy) may not be present yet. Moreover, misdiagnosis problems increase when elderly individuals are evaluated, which may present mixed pathology (Jellinger & Attems,

2015). It is advisable that the diagnosis is performed by expert in movement disorders vs. non-experts (e.g., general neurologists, geriatricians, or general practitioners), since their diagnostic accuracy is higher (83.9% vs. 73.8%, respectively) (Rizzo et al., 2016).

Several diagnostic criteria have been proposed, which include: (i) the UKPDSBB criteria (Gibb & Lees, 1988), (ii) the Gelb criteria (Gelb, Oliver, & Gilman, 1999), (iii) the Movement Disorder Society (MDS)-PD criteria, and other sets of criteria which have gained little attention (Calne, Snow, & Lee, 1992; Larsen, Dupont, & Tandberg, 1994) [for a review on PD diagnostic criteria see (Marsili et al., 2018)].

The UKPDSBB criteria are the first formal diagnostic criteria developed for PD (Gibb & Lees, 1988), and are still the most commonly used criteria worldwide, both in clinical and research settings.

A recent systematic review and meta-analysis of clinic- and community-based studies reporting PD diagnostic parameters confirmed by pathological examination (as a gold standard) shows that the UKPDSBB criteria has a diagnostic accuracy of 82.7% (Rizzo et al., 2016). They have high specificity (i.e., proportion of patients with PD who had initial diagnosis of PD) and sensitivity (i.e., proportion of patients without PD who had no initial diagnosis of PD), which have been estimated to be 98.4% and 91.1%, respectively (Hughes et al., 2002). Their use has been recommended by the National Institute for Health and Care Excellence (NICE) guidelines that advise clinicians to diagnose PD based on the UKPDSBB criteria (National Institute for Health and Care Excellence, 2017; Rogers, Davies, Pink, & Cooper, 2017). The NICE guidelines recommendations are also followed in countries other than the UK, as, for example, Italy (Candiani & Villa, 2013). In the

research setting, the extensive use of the UKPDSBB criteria has the advantage of promoting homogeneity in the studies samples therefore increasing the comparability and reproducibility of studies' findings.

The main limitation of the UKPDSBB criteria is the exclusive focus on motor symptoms, while it has been acknowledged that NMS may precede PD diagnosis and are considered for the diagnosis of prodromal PD. Prodromal PD is used to refer to a clinical scenario where PD symptoms and signs are present but insufficient for a full clinical diagnosis (Berg et al., 2015). It has also been questioned that presence of genetic risk factors (more than one relative affected by PD) should not exclude the diagnosis of PD (Gasser, Hardy, & Mizuno, 2011; Marsili et al., 2018).

The UKPDSBB criteria are based on three benchmarks:

1) bradykinesia and at least one of the following: rigidity, 4–6 Hz rest tremor, postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction;
2) exclusion of other causes of parkinsonism including history of repeated strokes or head injury with stepwise progression of parkinsonian features, history of definite encephalitis, oculogyric crises, neuroleptic treatment at onset of symptoms, familial history, unilateral features after 3 years, supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement or dementia, unexplained Babinski sign, presence of a secondary cause on imaging, negative response to levodopa and exposure to toxic agents;
3) at least three of the following supportive (prospective) features: unilateral onset, rest tremor, progressive disorder, persistent asymmetry

primarily affecting side of onset, excellent response (70–100%) to levodopa, severe levodopa-induced chorea (dyskinesia), levodopa response for 5 years or more, clinical course of 10 years or more.

The Gelb criteria (Gelb et al., 1999) differentiates between possible and probable PD, based on temporal symptoms onset. The main criticism to the Gelb criteria is that they do not include bradykinesia as an essential feature of PD, which is now considered the most important motor symptom for the diagnosis (Marsili et al., 2018).

The MDS task force proposed new diagnostic criteria specifically designed for research, but also useful as guidance in clinical settings. The MDS clinical diagnostic criteria define PD based on two levels of diagnostic certainty: "clinically established PD" and "clinically probable PD" (Postuma et al., 2015). For the first time, the use of supportive laboratory testing such as those documenting olfactory loss, cardiac sympathetic denervation has been included. Also, when brain imaging is performed, normal presynaptic dopaminergic system functioning is considered as an absolute exclusion criterion (Postuma et al., 2015). However, the MDS-PD criteria are scarcely employed by clinicians (Marsili et al., 2018), and supportive laboratory testing may not be available in not specialized centres. Being very recent, the number of studies in the literature using the MDS criteria is scarce, which in turn limits the comparison of studies' findings.

Management

The management of PD is complex; this because, despite providing symptomatic relief, medication has to be constantly reviewed as disease progresses and motor symptoms worsen. When treated, PwP may develop side-effects such as

dyskinesia (i.e., uncontrolled, involuntary movements that can involve one body part or the entire body), ICBs, excessive daytime sleepiness, hallucinations, which are also problematic. DRT dose reduction for the management of side-effects may be complicated by the increasing of motor symptoms and, if PwP are treated by DA agonist, by the development of dopamine withdrawal syndrome (DAWS) in up to the 16.7% of cases (Patel et al., 2017). Symptoms of DAWS resemble those of other psychostimulant drug withdrawal syndromes and include panic attack, agoraphobia, anxiety, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension and drug craving, and do not respond to substitution with levodopa or other DRT types (Rabinak & Nirenberg, 2010; Samuel et al., 2015).

Non-pharmacological treatments such as deep brain stimulation (DBS) may improve motor symptoms in advanced PD and in those at early stage of PD with motor complications (Klingelhoefer, Samuel, Chaudhuri, & Ashkan, 2014). However, in some cases, other non-motor symptoms such as ICBs can appear or worsen although in other cases improve [for a review on the effect of DBS on ICBs see (Eisinger et al., 2019; Klingelhoefer et al., 2014)].

As motor symptoms are the main focus of PD management, presumably motor symptoms side-effects such as dyskinesia also get the main focus, whereas other NMS side-effects are less prominent in terms of being brought to the attention of the clinicians. The type of medication used for the management of PD, how they act, and examples of side-effects are provided in Table 2.5.

Table 2. 5 Dopaminergic replacement therapies used in Parkinson's disease.

DRT type	**Description**	**Side-effects**
Levodopa	It is the precursor of DA. It crosses the blood-brain barrier where it is metabolized to DA. It is administered in combination with a decarboxylase inhibitor such as carbidopa or benserazide to prevent peripheral metabolism in the gastrointestinal tract and the activation of DA receptors in the area postrema which are not protected by the blood-brain barrier causing nausea and vomiting.	Dyskinesia, nausea, orthostatic hypotension, confusion, hallucinations, somnolence, ICBs
DA agonists: -Pramipexole -Ropinirole -Rotigotine -Apomorphine	They are a class of DRT that pass the blood-brain barrier and mimic the action of DA on the postsynaptic DA receptors. DA agonists have affinity to the DA receptors D_1, D_2 and D_3 subtypes. The first introduced DA agonists were ergot derivates (e.g., bromocriptine, pergolide, cabergoline) and were associated with ergot-related side effects, including cardiac valvular damage. They have been replaced by a second generation of non-ergot DA agonists (e.g., pramipexole, ropinirole, rotigotine).	Nausea, orthostatic hypotension, hallucinations, somnolence, ICBs, DAWS, application site reactions (Rotigotine)
MAO-B inhibitors: -Rasagiline -Selegiline -Safinamide	They block central DA metabolism and increase synaptic concentrations of DA.	Dyskinesia (as they potentiate the effect of levodopa)
COMT inhibitors: -Entacapone -Opicapone -Tolcapone	They prevent levodopa metabolism reducing the off-time period.	Dyskinesia (as they potentiate the effect of levodopa), Hallucinations Drug-induced liver damage (tolcapone)

Legend. DA: dopamine; DRT: dopamine replacement therapy; ICBs: impulsive-compulsive behaviours; DAWS: dopamine agonist withdrawal syndrome.

According to the current NICE guidelines, in early PD, levodopa is the preferred first line medicine for people with troublesome motor symptoms, whilst levodopa, DA agonists, or irreversible and reversible inhibitors of monoamine oxidase type B (MAO-B) should be considered when motor symptoms do not affect quality of life. In advanced PD, continuous subcutaneous apomorphine infusion or intermittent apomorphine injection may be considered. When symptoms are not well controlled, DBS may be considered (National Institute for Health and Care Excellence, 2017; Rogers et al., 2017). A visual summary of the management strategies of motor and non-motor symptoms based on the current NICE guidelines is provided in Figure 2.4.

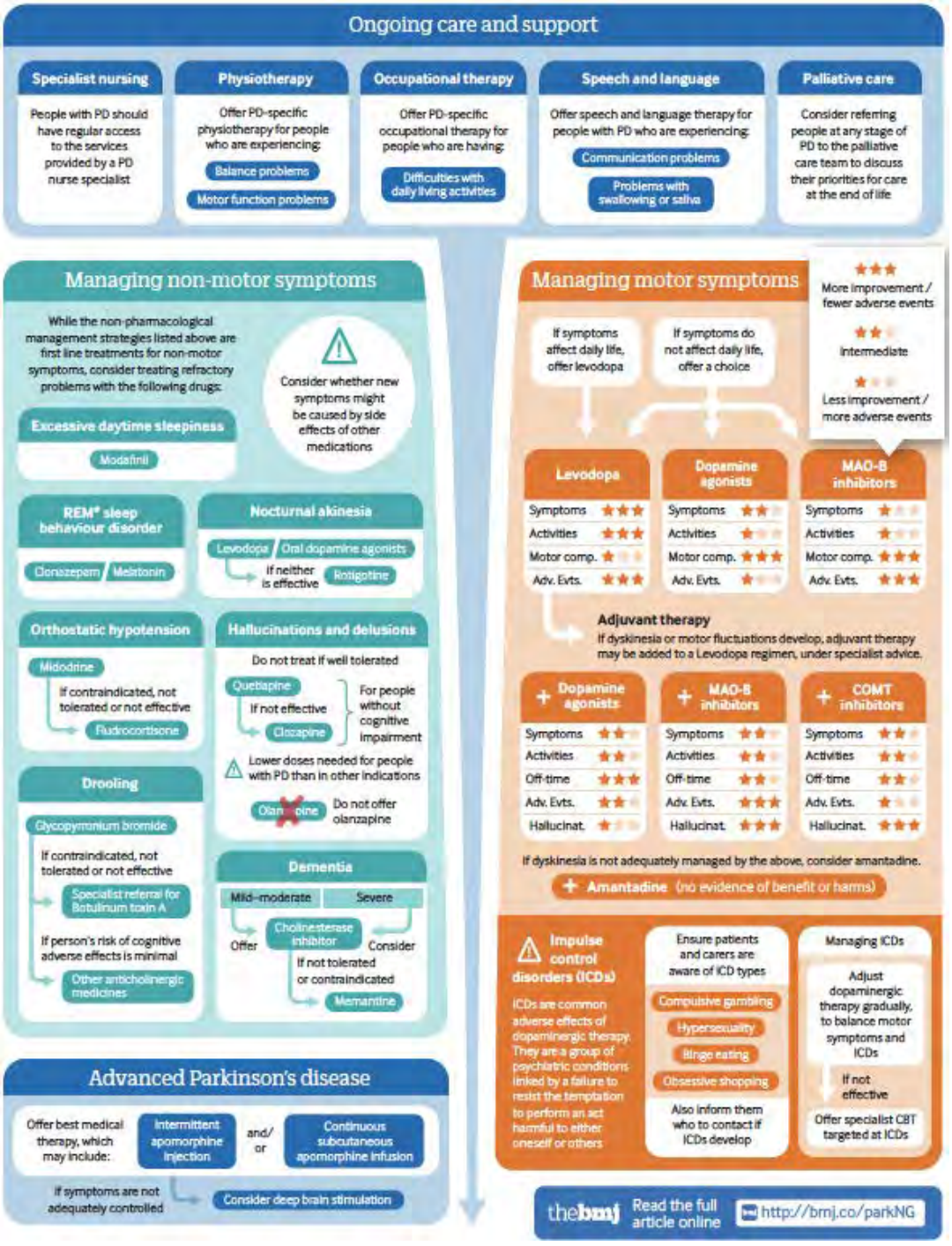


Figure 2. 4 Visual summary of the management of motor symptoms of Parkinson's disease, according to the National Institute for Health and Care Excellence guidelines (2017). Reprinted under the permission from Rogers et al. (2017), Copyright Licensing Agency.

Part 2: Impulsive-compulsive behaviours in Parkinson's disease

This section provides background information on ICBs in PD. Information about defining characteristics and diagnosis, epidemiology, association with DRT, correlates, assessment and management will be provided. This is important because it sets up the thesis in relation to the studies aims and methodologies presented in the following chapters.

Defining characteristics and Diagnosis

ICBs are a range of behaviours characterized by the inability to resist an urge, drive, or temptation to perform an act that are the cause of significant distress to the individual concerned and/or their close family member (American Psychiatric Association, 2013). ICBs are extremely time consuming and can negatively impact on social functioning, relationship and well-being, leading also to legal and financial consequences (Leroi, Harbishettar, et al., 2012; Phu et al., 2014). ICBs may differ in terms of severity, which range from subtle change from premorbid functioning to severe impairment in daily life; pathology is usually defined by its interference with personal, family, and/or professional life.

Diagnosis of ICBs is done clinically, based on the presence of behaviours reported by PwP and carers. It should be noted that uniform diagnostic criteria for ICBs in PD currently do not exist; this has been recently recognized by the MDS task force, which commissioned a systematic review of scales to assess ICBs in PD (Evans et al., 2019) (for detailed information see section "assessment", page 71). This is problematic as the lack of uniform diagnostic criteria for ICBs may account, at least in part, for variability of research findings and clinical management across centers.

In PD, ICBs include the four major impulse control disorders (ICDs) i.e., gambling disorder, binge eating disorder, hypersexuality and compulsive shopping, and related behaviours i.e., punding, hobbyism, and dopamine dysregulation syndrome (DDS). Gambling disorder and binge eating are commonly diagnosed according to established diagnostic criteria of the last edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), whilst compulsive shopping, hypersexuality, punding and hobbyism, and DDS are commonly diagnosed based on proposed provisional criteria (Giovannoni, O'Sullivan, Turner, Manson, & Lees, 2000; McElroy, Keck, Pope, Smith, & Strakowski, 1994; Voon & Fox, 2007; Voon et al., 2006). Defining characteristics of ICBs based on commonly used diagnostic criteria are provided in Table 2.6.

Gambling disorder is characterized by a lack of control over gambling. The behaviour gradually increases in terms of time (e.g., spending an increasing amount of time in the Casino), or in terms of amount of money to bet in order to achieve the same excitement as previously. In some cases, gambling may be a way to cope with negative feelings. PwP often hide their involvement with gambling from family and friends. Once the behaviour becomes an addiction, attempts to cut it are unsuccessful (American Psychiatric Association, 2013) (see Table 2.6). Preferred gambling activities in PD include slot machines, lottery, scratch cards, and gambling online (Gallagher, O'Sullivan, Evans, Lees, & Schrag, 2007).

Binge eating is characterized by a lack of control over eating. An amount of food that is larger than most people would eat during the same period of time and under similar circumstances may be consumed (American Psychiatric Association, 2013). PwP with binge eating may also show a general overeating behaviour, food addiction and/or night eating syndrome (i.e., a circadian delay in the pattern of daily

food intake: evening hyperphagia and/or nocturnal ingestions of food with full awareness) (de Chazeron et al., 2019) (see Table 2.6).

Compulsive shopping is characterized by an irresistible and intrusive preoccupation with buying or shopping, which may result in buying huge amounts of items that are not needed, or afforded (McElroy et al., 1994) (see Table 2.6).

Hypersexuality has been defined as sexual thoughts and behaviours that are excessive or show an atypical change from the previous pattern of behaviour (Voon et al., 2006) (see Table 2.6). In PD, reported hypersexual behaviours encompass excessive masturbation, compulsive pornography use, extramarital affairs, plain increased libido and excessive request for sex from the partner (Nakum & Cavanna, 2016).

Punding is a stereotyped behaviour characterized by an intense fascination with excessive, repetitive, non-goal-oriented activities such as shuffling papers, reordering bricks, or sorting handbags. Conversely, hobbyism includes more complex acts, such as gardening, painting, writing, or excessive computer use (Voon & Fox, 2007) (see Table 2.6).

DDS is a pattern of compulsive DRT use, characterized by the need for increasing doses of DRT in excess of those normally required to relieve Parkinsonian symptoms and signs (Giovannoni et al., 2000) (see Table 2.6). PwP with DDS seem to be seeking to avoid dysphoria rather than excitement and euphoria; Okai et al. (2011) proposed a cognitive model according to which cues not necessarily related to PD (being incidental or physiological, such as fatigue) are misinterpreted as an impending off-time and culminate in a state of anxiety. This may drive PwP to take further DRT to avoid off-time, even if unnecessary, in order to alleviate this anticipatory anxiety (Okai, Samuel, Askey-Jones, David, & Brown,

2011). As a result, dyskinesias are developed together with a misperception of the "on" medication state which is perceived as such only when markedly dyskinetic. Attempts to reduce the DRT doses are met with strong resistance. When DRT is reduced, PwP may develop a withdrawal state characterised by dysphoria, depression, irritability, and anxiety (Warren, Gorman, Lehn, & Siskind, 2017). In order to continue to abuse DRT, PwP may develop strategies such as lying or stockpile medications. In relation to high doses of DRT, hypomanic, manic, or cyclothymic affective syndrome can be developed.

Other behaviours reported in PD are walkabout, reckless generosity (O'Sullivan, Evans, Quinn, Lawrence, & Lees, 2010) and driving (Avanzi et al., 2008), and compulsive smoking (Bienfait, Menza, Mark, & Dobkin, 2010).

Table 2. 6 The most commonly used diagnostic criteria for Impulsive-compulsive behaviours in Parkinson's disease.

Gambling disorder (DSM-5, 2013)
A. Persistent and recurrent problematic gambling behaviour leading to clinically significant impairment or distress, as indicated by the individual exhibiting four (or more) of the following in the last 12 months: o Needs to gamble with increasing amounts of money in order to achieve the desired excitement o Is restless or irritable when attempting to cut down or stop gambling o Has made repeated unsuccessful efforts to control, cut back, or stop gambling o Is often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, planning the next venture, thinking of ways to get money for gambling) o Often gambles when feeling distressed (e.g., helpless, guilty, anxious, depressed) o After losing money gambling, often returns another day to get even (“chasing” one’s losses) o Lies to conceal the extent of involvement with gambling o Has jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling o Relies on others to provide money to relieve desperate financial situations caused by gambling B. The gambling behaviour is not better explained by a manic episode.

Table 2. 6 (continued) The most commonly used diagnostic criteria for Impulsive-compulsive behaviours in Parkinson's disease.

Binge eating (DSM-5, 2013)

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   - Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances.
   - A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).

B. The binge eating episodes are associated with three or more of the following:
   - eating much more rapidly than normal
   - eating until feeling uncomfortably full
   - eating large amounts of food when not feeling physically hungry
   - eating alone because of feeling embarrassed by how much one is eating
   - feeling disgusted with oneself, depressed or very guilty afterward

C. Marked distress regarding binge eating is present

D. Binge eating occurs, on average, at least 1 day a week for 3 months

E. Binge eating is not associated with the recurrent use of inappropriate compensatory behaviours as in Bulimia Nervosa and does not occur exclusively during the course of Bulimia Nervosa, or Anorexia Nervosa methods to compensate for overeating, such as self-induced vomiting.

Table 2. 6 (continued) The most commonly used diagnostic criteria for Impulsive-compulsive behaviours in Parkinson's disease.

Compulsive shopping (McElroy et al., 1994)
Inappropriate preoccupations with buying or shopping, or inappropriate buying or shopping impulses or behaviour, as indicated by at least one of the following: 1. Frequent preoccupations with buying or impulses to buy that are experienced as irresistible, intrusive, and/or senseless 2. Frequent buying of more than can be afforded, frequent buying of items that are not needed, or shopping for longer periods of time than intended o The buying preoccupations, impulses, or behaviours cause marked distress, are time-consuming, significantly interfere with social or occupational functioning, or result in financial problems (e.g., indebtedness or bankruptcy). o The excessive buying or shopping behaviour does not occur exclusively during periods of hypomania or mania.

Table 2. 6 (continued) The most commonly used diagnostic criteria for Impulsive-compulsive behaviours in Parkinson's disease.

Hypersexuality (Voon, Hassan et al., 2006)

A. The sexual thoughts or behaviours are excessive or an atypical change from baseline (before dopaminergic treatment initiation) marked by one or more of the following:
- Maladaptive preoccupation with sexual thoughts
- Inappropriately or excessively requesting sex from spouse or partner
- Habitual promiscuity
- Compulsive masturbation
- Telephone sex lines or pornography
- Paraphilias

B. The behaviour must have persisted for at least 1 month

C. The behaviour causes at least one of the following:
- Marked distress
- Attempts to control thoughts or behaviour unsuccessful or result in marked anxiety or distress
- Are time consuming
- Interfere significantly with social or occupational functioning

D. The behaviour does not occur exclusively during periods of hypomania or mania

E. If all criteria except C is fulfilled the disorder is subsyndromal.

Punding (Voon & Fox, 2007)

An intense fascination with excessive, repetitive, non–goal-oriented behaviours. Repetitive behaviours include less complex acts, such as shuffling papers, reordering bricks, or sorting handbags.

Table 2. 6 (continued) The most commonly used diagnostic criteria for Impulsive-compulsive behaviours in Parkinson's disease.

Hobbyism (Voon & Fox, 2007)
An intense fascination with complex, excessive, repetitive, non–goal-oriented behaviours. The behaviours include more complex acts, such as hobbyism (gardening, painting), writing, or excessive computer use.
Dopamine Dysregulation Syndrome (Giovannoni et al., 2000)
A. Need for increasing doses of DRT in excess of those normally required to relieve Parkinsonian symptoms and signs B. Pattern of pathological use: expressed need for increased DRT in the presence of excessive and significant dyskinesias despite being 'on', drug hoarding or drug seeking behaviour, unwillingness to reduce DRT, absence of painful dystonias (i.e., prolonged muscle contractions) C. Impairment in social or occupational functioning: fights, violent behaviour, loss of friends, absence from work, loss of job, legal difficulties, arguments or difficulties with family D. Development of hypomanic, manic, or cyclothymic affective syndrome in relation to DRT (only for supporting the diagnosis) E. Development of a withdrawal state characterised by dysphoria, depression, irritability, and anxiety on reducing the level of DRT F. Duration of disturbance of at least 6 months.

Legend. DRT: dopamine replacement therapy. DSM-5: diagnostic and statistical manual of mental disorders, fifth edition.

ICBs are diagnosed in taxonomies — which are categorical in nature — based on observed constellations of symptoms. This approach has clinical utility as it provides reliable clinical diagnosis (Insel et al., 2010). However, from a research perspective these categories, based upon presenting signs and symptoms, may not capture fundamental underlying mechanisms of dysfunction (Insel et al., 2010), which may transcend traditional diagnostic boundaries and form a shared pathophysiological mechanism (Yücel et al., 2018). For example, some symptoms

are not disease-specific but they can be shared across conditions (e.g., lack of control in the obsessive-compulsive and substance use disorders), and different disorders may respond to similar interventions that target common underlying mechanisms (e.g., naltrexone which is effective in treating both alcohol use disorder and gambling disorders in the general population) (Yücel et al., 2018).

These limitations are evident in the debate over ICBs nosology; ICBs share features both with obsessive-compulsive and substance use disorders (Vriend, Pattij, et al., 2014). Both conditions are characterized by a difficulty to control the behaviour despite the negative consequences, but the main difference is related to the purpose behind the act; in the obsessive-compulsive disorder the compulsion is acted in order to decrease the anxiety, in the substance use disorder the purpose is to achieve gratification (Okai et al., 2011). The difference in the intent of the behaviour makes ICBs more similar to the addictive disorders and their connection is even stronger according to similar risk factors, neurobiological, cognitive and clinical features (Brewer & Potenza, 2008; Dagher & Robbins, 2009; Ray & Strafella, 2013). Gambling disorder represents a clear example of the debated ICBs nosology; the last edition of the DSM i.e., DSM-5 (American Psychiatric Association, 2013) has seen moving gambling disorder from the "Impulse Control Disorder and Related Condition" section to the "Substance – Related and Addictive Disorders" section.

Considering the limitations of the traditional categorical approach to mental disorders, the National Institute of Mental Health (NIMH) has promoted the Research Domain Criteria (RDoC) project (Insel et al., 2010). The RDoC project encourages first research and then clinic to move beyond the simply rearrangement of symptoms constellation for disorders diagnosis, toward the use of 'neurocognitive endophenotypes' derived from measures of brain as well as behaviour, and using

them transdiagnostically across disorders to discern possible commonalities that may highlight new genetic or therapeutic avenues, or detect subgroups for treatment selection.

In this thesis, a transdiagnostic approach has been used within ICBs categories (i.e., grouping together different ICBs types); it assumes that irrespective of the phenotype (being either gambling, hypersexuality, eating, etc.) the underlying neurocognitive underpinnings will be shared. This is an important point as it implies that research should not separate each ICBs but investigate them overall, as this may limit the applicability of findings.

Epidemiology

Prevalence of ICBs in medicated PwP ranges between 5.9% and 58.3% (prevalence rates across countries are provided in Table 2.7).

Longitudinal studies show that prevalence increases from 20% to nearly 33% after 5 years of follow-up (Corvol et al., 2018), albeit other studies found prevalence is stable (Antonini et al., 2017) or decreases from around 30% at initial assessment to 22% after 4 years (Erga et al., 2019).

Prevalence rates vary between countries; in Europe, any type of ICBs in PwP are reported to be (in decreasing order) 58.3% in Spain, 8.1-36% in Italy, 19.7-32.8% in France, 35.9% in Denmark, 34.8% in Finland, 30.4% in Norway, and 17.8% in the UK. In Turkey ICBs have been reported in the 5.9% of PwP. In North and South America, any type of ICBs in PwP are reported to be (in decreasing order) 25.6% in Mexico, 13.6% in the US, and 6.1%-13.6% in Canada. In Asia, any type of ICBs in PwP are reported to be (in decreasing order) 31.6%-42.8% in India, 35% in

Malaysia, 31% in China, 12.9%-21.5% in Japan, and 10.1%-15.5% in Korea (see Table 2.7).

Variability in ICBs prevalence rates may be due to several reasons.

First, between-studies methodological differences should be taken in count such as ICBs diagnostic criteria and definitions used, sensitivity of screening instruments and procedures. For example, studies include a plethora of screening instruments such as the South Oaks Gambling Screen (SOGS) and the Massachusetts Gambling Screen for gambling disorder, the Lejoyeux's questionnaire for compulsive shopping, punding questionnaire for punding, the Minnesota Impulse Disorders Interview (MIDI) for hypersexuality, compulsive shopping and gambling disorder, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) and the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale-Rating Scale (QUIP-rs) for all ICBs types (see Table 2.7). In many studies screening instruments outcomes were not confirmed by a diagnostic clinical interview, which decreases the likelihood of false positives (see Table 2.7). For example, Vela et al. (2016) reported that ICBs are present in 58.3% of PwP, only based on the outcome of the QUIP; however, without a clinician confirming the diagnosis, it cannot be excluded that prevalence reported reflects false positives or milder behavioural changes that cannot be considered as true ICBs. In future studies, outcomes of these screening questionnaires should always be confirmed by clinical interview. Caution should apply also when interpreting the results of studies in which these surrogate markers have an imaging or neurophysiological correlate. Being the surrogate marker possibly a false positive, the correlate may be not reliable.

Furthermore, some studies were conducted by mail and telephone interview (Joutsa, Martikainen, Vahlberg, Voon, & Kaasinen, 2012; Voon et al., 2006) (see Table 2.7), which may not detect conditions such as depression, anxiety and diminished cognitive function that are likely to confound the results of self-reports. Some studies focused only on some ICBs types, therefore underestimating the real ICBs overall prevalence. For example, in the two prevalence studies based in the UK only gambling disorder, hypersexuality, compulsive shopping, and hobbyism (Hurt et al., 2014) or only punding (Evans et al., 2004) were assessed thereby possibly underestimating the real prevalence of all ICBs, which may be higher than 14-17.8% (see Table 2.7). Some studies report lifetime prevalence whilst others report the prevalence of current ICBs, with higher prevalence rates in the former. Lifetime prevalence is the proportion of individuals in a population that at some point in their life have experience an ICB, whilst prevalence of current ICBs refers to the proportion of individuals that have an ICB at the time of the assessment.

Second, medication practices, which involve both type and dosage of DRT prescribed, may impact on the rate of ICBs; it has been observed that, across a 3 years period, incident rates of ICBs increases in those PwP taking DRT whilst decreasing in those not on DRT (Smith, Xie, & Weintraub, 2016). Furthermore, albeit ICBs can be developed with any type of DRT, some medications further increase the risk (see section “Impulsive-compulsive behaviours and Parkinson’s disease medication”, page 59).

Third, environmental and cultural factors may impact on the likelihood of developing ICBs; for example, lower availability of casinos (and therefore reduced probability to engage in a specific risky behaviour) may account for lower rates of gambling disorder in Canada vs. North America (Weintraub et al., 2010). Low rates

of gambling disorder are reported in countries where it is illegal or severely restricted, such as Malaysia, South Korea, Turkey and India (Kenangil, Özekmekçi, Sohtaoglu, & Erginöz, 2010; Lee et al., 2010; Sharma et al., 2015), which may be the consequence of reduced availability of gambling-related activity, or may be related to the reluctance of disclosing behaviours that are illegal and therefore punishable. Cultural stigma associated with ICBs may increase the feelings of shame and embarrassment and prevent behaviour disclosure (Kim, Kim, Kwon, et al., 2013; Sarathchandran, Soman, Sarma, Krishnan, & Kishore, 2013).

In summary, the more reliable estimated prevalence of ICBs may be around the 30% of PwP (Antonini et al., 2017; Rodríguez-Violante, González-Latapi, Cervantes-Arriaga, Camacho-Ordoñez, & Weintraub, 2014; Tanaka, Wada-Isoe, Nakashita, Yamamoto, & Nakashima, 2013). These rates take into account studies (i) investigating all ICBs types and (ii) in which ICBs diagnosis was confirmed by a clinical interview. For a reliable ICBs estimate, studies (i) performed in countries were some ICBs are severely restricted (Kenangil et al., 2010; J. Kim et al., 2013; J.-Y. Lee et al., 2010; Sarathchandran et al., 2013; Sharma et al., 2015) or (ii) including PwP with dementia (Poletti et al., 2013) are not taken into account.

It should be noted that the reported prevalence rates probably represent an underestimation of the real figure. For example, PwP with hypersexuality may be reluctant to disclose sensitive symptoms of sexual nature (Hurt et al., 2019b; Nakum & Cavanna, 2016), which are often reported by the carer, after initial denial by the PwP (Hassan et al., 2011). Also, PwP may lack awareness of their ICBs (Baumann-Vogel et al., 2015), and prevalence rates increase when information from the knowledgeable informant is taken in count (Lim et al., 2011) (see Table 2.7).

Prevalence of ICBs is higher in PwP compared to healthy controls; this is supported by a recent systematic review and meta-analysis of case-control studies which shows higher ratio of individuals with gambling disorder, hypersexuality, binge eating, punding, and hobbyism in PwP vs. healthy controls (Molde et al., 2018). This may suggest that either PD itself or DRT may increase the risk for developing ICBs; however, in the study of Molde et al. (2018) both drug naïve (i.e., not medicated yet) and under DRT PwP were included therefore preventing any distinction between PD- or DRT-related factors.

Studies based on drug naïve PwP only show similar rates of ICBs in drug naïve and healthy controls, which indirectly suggest that ICBs develop in response to DRT instead of PD *per sè* (Antonini et al., 2011; Weintraub, Papay, Siderowf, & Parkinson's Progression Markers Initiative, 2013).

It should be noted that the reported ICBs prevalence in drug naïve PD may also include subclinical ICBs (i.e., change in behaviour that are not by per se sufficient for affecting daily functioning) and/or false positives. For example, in the study of Antonini et al. (2011) the scales used for assessing ICBs are screening instruments that may overestimate the rate of compulsive behaviours by also including subclinical ICBs or false positives. This also applies for the study of Weintraub et al. (2013) where ICBs were only assessed by screening assessment and the outcome was not confirmed by the neurologist for ascertain whether ICBs were clinically significant and therefore impacting on social and/or occupational functioning. The real estimated prevalence of clinically significant ICBs in drug naïve PD are unknown and future studies should address this question.

Table 2. 7 Prevalence of any type of Impulsive-compulsive behaviours in persons with Parkinson's disease under dopamine replacement therapy.

Ref	Population	PwP (N)	Screening instrument	Screening method	ICBs assessed	ICBs Prevalence (%)
Voon et al. 2006	Canadian	297	SOGS; Lejoyeux's questionnaire; HS questionnaire	Survey; phone interview	GD, HS, CS	6,1% (lifetime)
Weintraub et al. 2010	US, Canadian	3090	MAGS; MIDI for HS and CS; and DSM-IV TR research criteria for BE	Interview	GD, HS, CS, BE	13.6% (current)
Lee et al. 2010	South Korean	1167	MIDI	Interview	GD, HS, CS, BE, punding/hobbyism	10.1% (current)
Evans et al. 2004	UK	123	Punding questionnaire	Interview	Punding	14%
Kenangil et al. 2010	Turkish	554	Clinical interview	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	5.9%
Lim et al. 2011	Malaysian	200	QUIP	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	PwP + informant: 35.0%; PwP alone: 24.6%; Informant alone: 27.4%
Perez-Lloret et al. 2012	French	203	QUIP	Interview	GD, HS, CS, BE	25%
Joutsa et al. 2012	Finnish	575	SOGS; QUIP	Postal survey	GD, HS, CS, BE, punding/hobbyism	34.8% (current)
Kim et al. 2013	Korean	297	QUIP	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	15.5%
Tanaka et al. 2013	Japanese	118	QUIP; clinical interview	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	ICDs: 12.9% ICBs: 21.5%
Poletti et al. 2013	Italian	805	QUIP; clinical interview	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	8.1%
Sarathchandran et al. 2013	Indian	305	MIDI; clinical interview	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	31.6%
Callesen et al. 2014	Danish	490	QUIP	Postal survey		35.9% (lifetime) 14.9% (current)
Rodriguez-Violante et al. 2014	Mexican	300	MIDI; clinical interview QUIP-rs	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	25.6% (current)

Table 2.7 (continued) Prevalence of any type of Impulsive-compulsive behaviours in persons with Parkinson's disease under dopamine replacement therapy.

Ref	Population	PwP (N)	Screening instrument	Screening method	ICBs assessed	ICBs Prevalence (%)
Hurt et al. 2014	UK	500	MIDI	Interview	GD, HS, CS, punding/hobbyism	17.8%
Sharma et al. 2015	Indian	299	QUIP	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	42.8%
Vela et al. 2016	Spanish	87[a]	QUIP	Interview	GD, HS, CS, BE, punding/hobbyism	58.3%
Antonini et al. 2017	Italian	1069	mMIDI	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	BL: 28.6%: Y1: 29.3%; Y2: 26.5%
Biundo et al. 2017	Italian	251[b]	QUIP-rs	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	36%
Zhang et al. 2017	Chinese	142	QUIP	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	31%
Erga et al. 2017	Norwegian	125	QUIP	Interview	GD, HS, CS, BE, punding/hobbyism, DDS	30.4%
Corvol et al. 2018	French	411	clinical interview	Interview	GD, HS, CS, BE, hobbyism	BL: 19.7%; Y5: 32.8%

Legend. PwP: people with Parkinson's disease; Ref: reference study; N: number of PwP; SOGS: South Oaks Gambling Screen; MAGS: Massachusetts Gambling Screen; MIDI: Minnesota Impulse Disorders Interview; ICBs: impulsive-compulsive behaviours; ICDs: impulse control disorders; BL: baseline; Y1: year 1; Y2: year 2; Y5: year 5; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders fourth edition - text revised; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; QUIP-rs: Questionnaire for Impulsive-Compulsive

Disorders in Parkinson's Disease-Rating Scale-Rating Scale - Rating Scale; HS: hypersexuality; BE: binge eating; CS: compulsive shopping; GD: gambling disorder; DDS: dopamine dysregulation syndrome. [a]early onset PD; [b]advanced PD and dyskinesia.

Impulsive-compulsive behaviours and Parkinson's disease medication

Retrospective case reports and prospective studies suggest a link between ICBs and DRT since their onset and, in some cases, their reduction or resolution covary with dopaminergic treatment (Bastiaens, Dorfman, Christos, & Nirenberg, 2013; Corvol et al., 2018; Dodd et al., 2005; Mamikonyan et al., 2008; Munhoz, Fabiani, Becker, & Teive, 2009; Seedat et al., 2000; Smith et al., 2016). However, dose-response relationship is unclear (Biundo et al., 2017; Corvol et al., 2018; Erga et al., 2017; Hurt et al., 2014; Isaias et al., 2008; Perez-Lloret, Rey, Fabre, Ory, Spampinato, Brefel-Courbon, et al., 2012; Valença et al., 2013; Vela et al., 2016). The inconsistency in dose-response relationship findings may be due to individual differences in dose thresholds for ICBs appearance (Hurt et al., 2014).

ICBs have been mainly associated with DA agonists (i.e., pramipexole, ropinirole, rotigotine, cabergoline, bromocriptine, and apomorphine), although they can be developed with all forms of DRT such as levodopa, amantadine, and MAO-B inhibitors (Perez-Lloret, Rey, Fabre, Ory, Spampinato, Brefel-Courbon, et al., 2012; Vitale et al., 2019, 2013; Weintraub et al., 2010); in a cross-sectional study, ICBs were reported in the 17.7% of PwP taking both a dopamine agonist and levodopa, 14.0% taking a DA agonist without levodopa, and 7.2% taking levodopa without DA agonist (Weintraub et al., 2010). This means that, compared to other drugs, DA agonists increase almost three times the risk to develop ICBs, with the combination of DA agonists and levodopa increasing further the risk (Hurt et al., 2014; Weintraub et al., 2010). In a longitudinal study, cumulative frequency of ICBs after a median DA agonist treatment duration of 21 months were 39.1% (Bastiaens et al., 2013).

Prevalence of ICBs did not differ between pramipexole and ropinirole (17.7%-16.6% and 15.5%-12.5%, respectively), suggesting that DA agonists as a

class are associated with ICBs (Poletti et al., 2013; Weintraub et al., 2010); however, as disease progresses, PwP are often switched from one medication to another, making it difficult to establish a link between a specific type of medication and ICBs. Garcia-Ruiz et al. (2014) investigated ICBs presence in a cohort of PwP chronically treated with a single type of DA agonist. They found that 84/197 (42%) PwP treated with oral DA agonists such as pramipexole and ropinirole developed ICBs compared to 7/36 (19%) PwP treated with transdermal DA agonist rotigotine (Garcia-Ruiz et al., 2014). As the three drugs share a similar pharmacodynamic profile, the authors suggest that the route of administration may play a role.

The association between DA agonists and ICBs is further supported by reports of ICBs in restless legs syndrome and individuals with fibromyalgia treated with DA agonists (Cornelius et al., 2010; Holman, 2009; Voon, Schoerling, et al., 2011).

Although it is known that DRT can trigger or increase severity of pre-existing (subclinical) ICBs, exactly how this occurs is uncertain. The pathophysiological connections between DRT and ICBs, which are out of the topic of this thesis, have been published extensively elsewhere [for extensive reviews see (Voon et al., 2017; Vriend, 2018)]. Briefly, the theories suggested comprise overactivation or overdose of the mesolimbic dopaminergic system which modulates responses to rewards (Voon, Mehta, et al., 2011), heightened sensitivity for endogenous and exogenous DA of postsynaptic receptors (Prieto et al., 2011; Vriend, 2018), differences in binding profiles across DRT types (Gerlach et al., 2003; Weintraub et al., 2010), or altered equilibrium of the phasic dopamine, resulting in impairment in negative feedback processing important in the incentive-driven decision-making (Frank et al., 2004).

Correlates

It is unclear why not all DRT-exposed PwP develop ICBs, and why for some individuals ICBs become uncontrollable and problematic whilst for others are partially controlled and do not cause distress or interference with daily life (i.e., subclinical). It is likely that an interaction between DRT and unknown neurobiological vulnerability may increase resilience in some but may also increase vulnerability in others. The factors that may increase the risk of ICBs that are explored in this thesis are (i) affect and motivation, (ii) cognition, and (iii) neural substrate; however, there are other correlates that also have been identified such as socio-demographic, clinical, genetic and personality, which will also be briefly discussed.

Clinical and socio-demographic correlates. Several vulnerability risk factors have been identified, some of them are PD-related such as younger age at disease onset, higher doses of dopaminergic medication, longer disease duration, worse motor symptoms, dyskinesia, motor fluctuation and lower quality of life (Biundo et al., 2017; Erga, Alves, Tysnes, & Pedersen, 2020; Hurt et al., 2014; Kim, Kim, Kwon, et al., 2013; Valença et al., 2013; Weintraub et al., 2010). Young onset PD, possibly because of distinctive pathophysiology or the nature and the duration of the treatment, may contribute to higher DRT levels, which in turn are associated with motor fluctuations (Hurt et al., 2014). REM sleep behaviour disorders are associated with a more than twofold higher risk of developing ICBs, according to a recent systematic review and meta-analysis (Lu et al., 2020). Poor sleep efficiency and greater daytime sleepiness have been associated with ICBs (Scullin et al., 2013),

albeit they may not be related but simply co-occur as side-effects of DRT, especially DA agonists.

ICBs have also been associated with factors unrelated to PD such as smoking behaviour (Liu et al., 2019; Weintraub et al., 2010) suggesting that characteristics other than PD could increase the risk of developing ICBs in medicated PwP. Moreover, higher number of gambling problems in the relatives of PwP with ICBs (Weintraub et al., 2010) and personal or family history of alcoholism (Voon, Thomsen, et al., 2007; Weintraub et al., 2010) suggest genetic predisposition and/or environmental influence (i.e., living in a family context that facilitates behavioural addictions). The overall ICBs prevalence is higher in male than female (Antonini et al., 2017; Liu et al., 2019). Women are more likely to develop compulsive shopping and binge eating, whereas men are more likely to develop hypersexuality and gambling disorder (Nakum & Cavanna, 2016; Singh, Kandimala, Dewey, & O'Suilleabhain, 2007; Weintraub et al., 2010), similar to the gender differences noted in behavioural addiction in the general population (Holden, 2001).

Genetic correlates. The genetic of ICBs is currently unknown and this may be related to a methodological issue; the only genetic studies in PwP with ICBs adopted a candidate genes approach (Abidin et al., 2015; Cilia et al., 2016; Cormier-Dequaire et al., 2018; Erga et al., 2018; Kraemmer et al., 2016; Krishnamoorthy et al., 2016; Lee, Jeon, Kim, & Park, 2012; Lee et al., 2009). This approach is problematic because candidate genes studies are hypothesis driven, and when differences in gene variants or polymorphisms are evident, it is unknown how relevant or important they are because, pre-setting what will be investigated, millions of other polymorphisms that may play a prominent role are neglected.

A way to overcome this limitation is to use a Genome-Wide Association (GWAS) approach, which consists in exploring the entire human genome in a hypothesis-free manner with the purpose of discovering patterns in the entire human genome rather than investigating pre-specified relationships. Candidate genes studies are therefore useful only after GWAS studies, in order to confirm and extend findings. However, GWAS studies require big sample sizes, which may not be feasible for ICBs in PD.

Genetic studies are an area of future research as they can pave the way for developing screening tools for identifying PwP at risk of ICBs before DRT initiation and/or developing new therapeutic agents.

Personality. It has been suggested that personality traits may predispose PwP to develop ICBs under DRT. For example, PwP with ICBs show higher novelty seeking behaviours compared to PwP without ICBs (Djamshidian, O'Sullivan, Wittmann, Lees, & Averbeck, 2011; Evans, Lawrence, Potts, Appel, & Lees, 2005; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Voon, Sohr, et al., 2011). Novelty seeking refers to the way in which a person reacts to novel stimuli or situations, with lower levels leading to a conservative behaviour and higher levels leading to exploratory behaviour, curiosity, excitement, and easy bored attitude (Cloninger, 1987). High novelty seeking traits have been associated with drug abuse and reward-related behaviours, both in humans and animal studies (Beckmann, Marusich, Gipson, & Bardo, 2011; Churchwell, Carey, Ferrett, Stein, & Yurgelun-Todd, 2012). This association may be mediated by dopaminergic functioning as novel stimuli enhance dopaminergic response (Wittmann, Daw, Seymour, & Dolan, 2008). The strongest preference for novel options modulated by chronic increase of

dopaminergic levels could facilitate the engagement in reward-related behaviour, which may then become addictive (Djamshidian, O'Sullivan, Wittmann, et al., 2011). Drug naïve PwP, which are characterized by dopamine depletion, evidence low levels of novelty seeking behaviour, which are remediated following 12-weeks of DA agonists intake (Bodi et al., 2009). In PwP with ICBs, novelty seeking behaviour is significantly higher than in PwP without ICBs and healthy control regardless of being "on" or "off" medication (Djamshidian, O'Sullivan, Wittmann, et al., 2011). This suggests two hypotheses: (i) chronic, rather than acute dopaminergic load may trigger novelty seeking behaviour in PD or that (ii) novelty seeking behaviour in PwP with ICBs is a premorbid trait, which is evident before DRT initiation and it is not modulated by that. Whether (i), (ii) or both are true is unknown as no longitudinal study in drug naïve PwP who later developed ICBs has investigated novelty seeking yet.

Novelty seeking behaviour is related to the positive valence system construct of the RDoC framework, in particular reward responsiveness which includes reward anticipation, initial response to reward, and satiation subconstructs. Reward anticipation refers to processes associated with the ability to anticipate and/or represent a future incentive or reward, whilst response to reward reflects processes evoked by the initial presentation of a positive reinforcer. Finally, satiation includes processes associated with the change in incentive value of a reinforcer over time as that reinforcer is consumed or experienced (Insel et al., 2010). Novelty seekers may be individuals with higher reward anticipation, higher initial response to reward, and higher satiation. These individuals may be attracted by novel, possibly rewarded stimuli (e.g., engaging in gambling for the first time) and are easily bored therefore looking for new stimuli or higher levels of excitement (e.g., increasing bet size in

gambling tasks despite losses). Reward valuation, also part of the valence system, may also be involved in ICBs in PD. Reward valuation encompasses processes implicated in the assignment of incentive salience to stimuli based on probability of receiving the reward, the effort involved, and the delay to achieve the gratification. Dopamine has been proposed to play a key role in each of these functions [for a review see (Sinha et al., 2013)].

Affective and motivational correlates. Depression frequently co-occurs with ICBs in PD (Callesen, Weintraub, Damholdt, & Møller, 2014; Gallagher et al., 2007; Joutsa, Martikainen, Vahlberg, Voon, et al., 2012; Pontone, Williams, Bassett, & Marsh, 2006; Voon, Sohr, et al., 2011). The direction of the association is difficult to explain. In some cases, depression could be a psychological reaction to ICBs, as these behaviours are related to lower quality of life and caregiver burden (Erga et al., 2020; Leroi, Harbishettar, et al., 2012; Phu et al., 2014). Other PwP describe their ICBs as a way to cope with a condition as PD which can cause, among others, work retirement and social isolation; while engaged in the ICBs, PwP could avoid negative thoughts and emotions associated with having PD, thus using the behaviour as an emotion-focused coping strategy through emotional avoidance (Delaney, Simpson, & Leroi, 2012). Studies on association between depression and ICBs are further limited by DA agonists being potential confounds; DA agonists are one of the main risk factors for ICBs (Weintraub et al., 2010), but are also administered to improve depression in PwP (Seppi et al., 2019). Using the Parkinson's Progression Markers Initiative database, data from 354 PwP assessed across 4 years were analysed. The incidence rate of ICBs was 19.38 cases per 100 individuals for depressed PwP and 10.3 cases for non-depressed PwP, with depression at baseline associated with higher

ICBs risk. The risk remained significant after controlling for DA agonists use (Marín-lahoz, Sampedro, Martinez-horta, Pagonabarraga, & Kulisevsky, 2019), suggesting that depression increases the risk of ICBs independently from DA agonists.

ICBs in PD have also been associated with anhedonia (Pettorruso et al., 2014; Pontieri et al., 2015), anxiety (Hurt et al., 2014; Leroi et al., 2011; Voon, Sohr, et al., 2011), impulsivity and apathy (Pineau et al., 2016), although other studies reported no differences between PD groups (Merola et al., 2017; Pontieri et al., 2015). The lack of consensus about affective and motivational correlates warrants future investigation, possibly using systematic reviews and meta-analyses which increase sample size and therefore statistical power. A clear understanding of affective and motivational correlates may increase our understanding of ICBs pathophysiological underpinnings, as well as may pave the way for new therapeutic opportunities (e.g., targeting ICBs with non-dopaminergic agents used for treating affective and motivational symptoms).

Cognitive correlates. It is unclear what are the cognitive processes that become dysfunctional when PwP develop ICBs. Several individual studies have assessed cognitive performances across a wide range of cognitive domains in PwP with ICBs under DRT; however, their findings are inconsistent. For example, set-shifting, working memory, and risk-taking behaviour and decision-making have been found to be impaired in PwP with ICBs in some studies (Biundo et al., 2011, 2015; Djamshidian et al., 2010; Housden, O'Sullivan, Joyce, Lees, & Roiser, 2010; Rossi et al., 2010; Tessitore et al., 2016), but not in others (Bentivoglio, Baldonero, Ricciardi, De Nigris, & Daniele, 2013; Cera et al., 2014; Joutsa et al., 2015; Leroi et

al., 2011; Mack et al., 2013; Mosley et al., 2019; Paz-Alonso et al., 2020; Pineau et al., 2016; Piray et al., 2014). Discrepancy in the literature probably reflects small sample sizes and therefore reduced statistical power and reproducibility, variability in inclusion/exclusion criteria (e.g., conditions independently associated with cognitive decline, such as dementia, not always excluded), ICBs diagnostic procedure and therefore the number of false positives, variability in the tasks used for assessing cognitive processes, and variability in clinical and demographic characteristics of the studies' samples. Systematic reviews and meta-analyses can overcome these limitations. Systematic review with strict inclusion/exclusion criteria may exclude studies that may include presence of confounding factors that may bias findings (e.g., dementia), whilst in the meta-analysis low powered studies can be combined and differences in cognitive performance between PwP with and without ICBs estimated with a higher reliability.

Cognitive performance in specific domains/tasks may provide information about ICBs prognosis, as supported by a 2-years longitudinal study of 80 PwP that found that ICBs remission was associated with better performance at baseline in working memory/attention tasks (i.e., digit span and attentive matrices); moreover, PwP with ICBs showed a less pronounced worsening over time in their cognitive performance (Siri et al., 2015). However, a recent 4-years longitudinal study found that cognitive changes over time did not differ between PwP with and without ICBs (Erga et al., 2019). A better understanding of the cognitive profile of PwP with ICBs may shed light on their pathophysiological underpinnings, which in turn may inform the development of new therapeutic treatments such as cognitive training programmes targeting index cognitive skills in order to increase the chances of remission.

Whether cognitive impairments predate DRT initiation and ICBs development, thereby reflecting premorbid traits warrants further investigation. To date, only one 3-years longitudinal study investigated cognitive performances of drug naïve PwP who later developed ICBs, but no differences were found compared to PwP who did not develop any ICBs (Tessitore, De Micco, et al., 2017); however, this study is limited by small sample size and the use of an abbreviated neuropsychological tests battery that may fail to include cognitive tasks sensitive to cognitive changes related to ICBs (Yücel et al., 2018). Being longitudinal studies expensive in terms of time and resources, it is important to first identify reliable correlates of ICBs in already diagnosed cases, to then track these correlates over time in a longitudinal study of newly diagnosed PwP as they start DRT.

Neural correlates. Modern imaging studies are providing critical insight in the neural underpinnings of ICBs in PD, which involve both cortical and subcortical changes. In molecular imaging studies (i.e., Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT)), dysfunctions of ventral striatum have been found, in line with the overactivation of the mesolimbic dopaminergic system hypothesis (Voon, Mehta, et al., 2011). The ventral striatum is part of the mesolimbic system and it has been associated with incentive-driven decision-making and reward processing (Haber & Behrens, 2014). In response to DA agonists, PwP with ICBs, but no PwP without ICBs, show increase cerebral blood flow in the ventral striatum and frontal cortex (Claassen et al., 2017). During performance of gambling tasks or exposition to reward-cues PwP with ICBs show increased dopamine release in the ventral striatum (O'Sullivan, Wu, et al., 2011; Steeves et al., 2009; Wu et al., 2015). Moreover, in response to a single dose of levodopa, PwP

with DDS release more dopamine in the ventral striatum compared to PwP without ICBs (Evans et al., 2006). Other brain regions have been found to be differently activated in PwP with and without ICBs, which include inferior temporal gyri (Verger et al., 2018), orbitofrontal cortex, amygdala, insula, posterior cingulate cortex, hippocampus, parahippocampus and supramarginal gyri (Cilia et al., 2008; Marín-Lahoz et al., 2020). These areas are part of the brain networks supporting incentive-driven decision-making and reward processing (Botvinick & Braver, 2015).

Molecular imaging studies' findings are in keeping with those from functional Magnetic Resonance Imaging (fMRI) showing increased activation of the ventral striatum during the presentation of reward-related visual cues in PwP with hypersexuality (Politis et al., 2013) or gambling disorder (Frosini et al., 2010). However, during performance of risk-tasks, ventral striatum of PwP with ICBs show reduced activity (Rao et al., 2010; Voon, Gao, et al., 2011). Increased connectivity between the ventral striatum and limbic structures (e.g., habenula, amygdala, thalamus, insula) have been observed (Markovic et al., 2017; Petersen et al., 2018; Tessitore, Santangelo, et al., 2017). However, findings are not consistent as there are also reports of no changes in ventral striatum activity (Carriere, Lopes, Defebvre, Delmaire, & Dujardin, 2015) and decreased connectivity in limbic and prefrontal, parietal and temporal areas (Carriere et al., 2015; Markovic et al., 2017; Ruitenberg et al., 2018; Tessitore, Santangelo, et al., 2017).

Brain functional abnormalities should be accompanied by morphological changes. However, structural MRI studies did not find any volumetric differences in cortical areas between PwP with and without ICBs (Biundo et al., 2011; Ruitenberg et al., 2018; Tessitore et al., 2016). Furthermore, volume reductions of the ventral

striatum were reported in some (Biundo et al., 2015; Prasad et al., 2019), but not all studies (Marín-Lahoz et al., 2020; Pellicano et al., 2015). Cortical thickness studies present mixed results, with some studies showing both thinning (Biundo et al., 2015; Imperiale et al., 2018; Markovic et al., 2017; Prasad et al., 2019; Tessitore et al., 2016), increased thickness (Pellicano et al., 2015; Tessitore et al., 2016), or no difference (Carriere et al., 2015; Hammes et al., 2019; Hlavatá et al., 2020; Marín-Lahoz et al., 2020) between PwP with and without ICBs.

Discrepancy in studies' findings may be due to small sample sizes, differences in demographic and clinical characteristics of studies samples, variability in ICBs diagnostic procedures, and lack of consistency in MRI protocol of acquisition and data analysis. Using a meta-analytic approach, which overcomes some of these limitations, a recent study found increased activity in the ventral striatum and decreased activity in the anterior cingulate cortex of PwP with ICBs (Santangelo et al., 2019). However, findings should be considered with cautious as this meta-analysis was performed including only 14 studies, which limits its statistical power; according to the current recommendations (Eickhoff et al., 2016), 20 studies are needed in order to perform activation-likelihood estimation meta-analysis with enough statistical power, that is, reducing the risk that findings are driven by a single study. Once a satisfying number of imaging studies will be published, a new meta-analysis is warrant.

Whether the brain changes are present in the premorbid phase therefore representing a vulnerability factor, or are the consequence of repeated exposure to DRT, or to rewarding-related stimulus exposure and performance of the ICBs, or a combination of these factors is unknown. Only prospective studies can address this point. The few studies on drug naïve PwP who later develop ICBs show increased

connectivity in the salience network (usually activated by salient and rewarding stimuli) and decrease connectivity both in the central executive network (engaged when goal-directed behaviour requiring attention is being performed) and in the default mode network (active during internally-directed thoughts) (Tessitore, De Micco, et al., 2017), but no morphological changes (Ricciardi, Lambert, Micco, Morgante, & Edwards, 2018; Tessitore, De Micco, et al., 2017). These findings are promising as they show changes that predate ICBs, however more studies with higher sample size are needed to confirm and extend these results.

Assessment

This section provides information about ICBs assessment tools commonly used in clinical and research settings, and also reviews issues related to ICBs assessment.

ICBs are associated with impairments in social relationships and occupational functioning, financial problems, distress as well as caregiver burden; therefore, a prompt assessment of their presence or absence is important. If unrecognised, ICBs may potentially prologue their psychosocial consequences and become more difficult to treat.

Initially, ICBs have been investigated through instruments not specifically developed for PwP (e.g., the MIDI). In the last decade, tools for detecting, diagnosing, and rating ICBs in PD have been developed. Recently, the MDS commissioned a systematic review of clinimetric properties of the ICBs screening tools and scales (Evans et al., 2019). The diagnostic scales that (i) cover the range of ICBs recognised in PD and that (ii) met the criteria for being considered as "recommended" in PD are:

- Questionnaire for Impulsive-compulsive disorders in PD (QUIP);
- Questionnaire for Impulsive-compulsive disorders in PD rating scale (QUIP-rs).

The scales recommended for assessing ICBs severity are:

- QUIP-rs;
- Self-Assessment Scale For Dopamine Dependent Behaviors in Parkinson's Disease (Ardouin short screen).

The Scale for Outcomes in Parkinson's Disease–Psychiatric Complications (SCOPA-PC) is recommended for hypersexuality, gambling disorder, and compulsive shopping only, as those are the only ICBs included in the scale (Evans et al., 2019).

The QUIP is the first screening tool specifically developed for assessing ICBs in PD (Weintraub et al., 2009). A short and a full version of the QUIP exist. The short version of QUIP consists of 2 questions for each ICBs investigated i.e., gambling disorder, hypersexuality, binge eating, compulsive shopping, and DDS. Hobbyism, punding and walkabout are also investigated. DDS does not have a formal cutoff score as there were not enough PwP with DDS in the convenience sample. For all the other ICBs the optimal cutoff point is ≥ 1 affirmative answer. The QUIP ICD section (gambling disorder, hypersexuality, binge eating, compulsive shopping) has a sensitivity of 100% for identifying PwP with at least one ICD, and the total QUIP has a sensitivity of 94% for identifying PwP with at least one ICBs. The full version of the QUIP consists of 30 questions and it can be used when additional information is required (Weintraub et al., 2009). The QUIP is limited by the high number of false positives; according to Papay et al. (2011), the 40.3% PwP who are positive at the QUIP are not confirmed by diagnostic interview. This

suggests either overidentification by the QUIP or that many PwP present subclinical ICBs symptoms (Papay et al., 2011). As the QUIP cannot evaluate the severity of the behaviours, a rating scale was later developed.

The QUIP-rs is a brief 28-items patient-reported or clinician-rated scale. Each item is rated on a 5-points Likert scale assessing frequency of symptoms with a range of scores from 0 (never) to 4 (very often). The questions investigate gambling disorder, hypersexuality, binge eating, compulsive shopping, hobbyism, punding, and DDS during the preceding 4 weeks. The optimal cutoff point (based on the North American sample) for individual ICDs (possible score 0-16 for each ICD) are as follows: gambling disorder ≥6, compulsive shopping ≥8, hypersexuality ≥8, and binge eating ≥7. For combined ICDs (possible score 0-64), the optimal cutoff point is ≥10. Hobbyism-punding (possible score 0-32) has an optimal cutoff point of ≥7. As there were no cases of DDS in the convenience sample, the cutoff score for this behaviour has not been established (Weintraub et al., 2012). The QUIP-rs has been translated and validated in US, German, French, Spanish, Brazilian, Korean and Japanese populations and show satisfactory metric properties (Choi et al., 2020; Guerra et al., 2020; Marques et al., 2019; Martinez-Martin, Rodriguez-Blazquez, & Catalan, 2018; Probst et al., 2014; Tanaka et al., 2013; Weintraub et al., 2012). However, it has not been validated in other countries where it has been used for research purposes such as Italy (Biundo et al., 2017; Cera et al., 2014; Morgante et al., 2016; Pontieri et al., 2015; Tessitore, De Micco, et al., 2017). The extensive use of QUIP-rs indicates an unmet need of screening tools for ICBs in those countries where the QUIP-rs or analogous scales/questionnaires are missing.

Other tool frequently used for assessing ICBs presence in PD is the MIDI, which is a structured diagnostic interview based on Diagnostic and Statistical

Manual of Mental Disorders fourth edition text revised (DSM-IV TR) criteria originally developed for the diagnosis of gambling disorder, compulsive shopping, hypersexuality, kleptomania, trichotillomania, intermittent explosive disorder, and pyromania (Grant, 2008). The MIDI has been recently revised according to DSM-5 criteria, and binge eating and skin-picking disorders have also been included (Chamberlain & Grant, 2018). For each behaviour, a gateway question is provided and if positive, the clinical interview based on diagnostic criteria is completed. Positive response to all questions indicates presence of a given impulse disorder, except for gambling disorder where endorsement of 5 or more items is required. When used, the MIDI should be integrated with other tools for assessing the ICBs not included, as it does not take into account the full spectrum of ICBs. According to the MDS commissioned systematic review, the MIDI has been classified as "suggested" (not reaching the "recommended" level) since clinimetric data for its use in PD are missing (Evans et al., 2019).

There are several issues related to the assessment of ICBs in PD.

First, clinic appointments are often infrequent (usually one or two per year, both in the UK and Italy), short in duration (an estimated 10 minutes according to members of the UK patient-participant involvement panel) and therefore PwP are focused on discussing the effectiveness of DRT in controlling the motor symptoms of tremor, slowness, stiffness and poor balance.

Second, only a small proportion of PwP spontaneously report their ICBs. For example, Perez-Lloret et al. (2012) asked 203 PwP about any adverse events in connection with their current medications that had occurred during the previous week and only the 2% of them spontaneously reported ICBs; conversely, when a questionnaire listing the most common adverse events known to be related to DRT

was administered the figure rose to 27% (Perez-Lloret, Rey, Fabre, Ory, Spampinato, Montastruc, et al., 2012). PwP may be discouraged to spontaneously report their thoughts and behaviours by feelings of shame and guiltiness; however, there is also variability in the perception of the cause of the ICBs. Delaney, Simpson and Leroi (2012) interviewed 10 PwP with ICBs and observed that all of them made attribution about the cause of their behaviour ranging from perceiving them as egodystonic (i.e., not in line with their own personality) and caused solely by the medication, to being solely related to coping with PD and in keeping with their personality (i.e., egosyntonic) (Delaney, Simpson, et al., 2012). If the behaviour is egosyntonic, it may be not considered as problematic and therefore less likely to be reported. Conversely, if the behaviour is egodystonic, feelings of shame and guiltiness may prevent PwP to disclose ICBs.

Third, even if directly interviewed, some PwP may lack awareness of their ICBs as supported by low agreement about symptoms presence between PwP and the knowledge informant. For example, when comparing the self-assessments of 150 PwP and the ratings by their caregivers, significant differences with regard to the estimated prevalence of hypersexuality (PwP: 17% vs. caregivers: 55%), DDS (PwP: 3% vs. caregivers: 31%) and punding (PwP: 9% vs. caregivers: 22%) were found (Baumann-Vogel et al., 2015).

Considering all these factors, a thorough clinical interview is likely to be the best way to identify harmful behaviours (Evans et al., 2019). Clinicians should interview both PwP and carers separately, as PwP may be reluctant to disclose sensitive behaviours in presence of the carer. In case of discrepancy, the caregiver is usually considered the gold standard.

It should be noted that the onset or exacerbation of the behaviour is always a clinically significant event, even if the behaviour does not reach the diagnostic threshold or if it is considered as non-significant by the PwP. Detecting even subtle changes is important as they indicate increased risk of a more severe problem later (Okai et al., 2011).

Management

The NICE guidelines advise clinicians that, once ICBs are developed, they should be managed by modifying therapy by first gradually reducing any DA agonist or DRT. Together with DRT adjustments, clinicians are recommended to monitor whether ICBs improve and whether the person has any symptoms of DAWS (National Institute for Health and Care Excellence, 2017; Rogers et al., 2017), as PwP with ICBs have an increased risk to develop it (Limotai et al., 2012). Tapering of DA agonists should be done as soon as ICBs develop, because high cumulative DA agonists exposure increases the risk and the severity of DAWS and decreases the chance of successful DRT discontinuation and ICBs resolution (Rabinak & Nirenberg, 2010). Furthermore, no standard treatment protocols or ongoing clinical trials on DAWS are available (Vitale et al., 2019).

Despite the withdrawal of DA agonists or switching to another medication, some PwP may maintain their ICBs, presumably because the behaviour changes over time from reward-driven impulsive responding to habit-related compulsive responding (Fineberg et al., 2014).

If the approach of discontinuing or tampering DA agonists is not successful, cognitive behavioural therapy targeting ICBs may be offered (National Institute for Health and Care Excellence, 2017; Rogers et al., 2017). A psychosocial model posits

that some PwP may develop ICBs as a consequence of maladaptive coping mechanisms for the impact of the PD (Delaney, Leroi, Simpson, & Overton, 2012); in this sense, the ICBs may be a way to avoid thinking about the disease, that may be targeted by cognitive behavioural therapies. Recently, the MDS commissioned an evidence-based medicine review on NMS treatments. Studies included had a minimum of 20 PwP who were treated for a minimum of 4 weeks. According to the authors, cognitive behavioural therapy is "likely efficacious" and "possibly useful" for ICBs in PD (Seppi et al., 2019). PwP who gain more benefit are those under DA agonist, with lower dose of DRT, lower number of ICBs, higher work and social functioning, and lower psychiatric symptomatology (Okai, Askey-Jones, Samuel, David, & Brown, 2015). There are also case reports of ICBs improvements after attending gamblers (Kurlan, 2004) or sex addiction support groups (Mamikonyan et al., 2008).

Within non-pharmacological treatments, the role of DBS in alleviating ICBs symptoms is controversial; some studies show improvements of ICBs after surgery, probably linked to the reduction of DRT doses (Amami et al., 2015; Castrioto et al., 2015; Lhommée et al., 2018; Merola et al., 2017), whilst others show ICBs worsening or new onset after DBS (Hack et al., 2014; Kim, Kim, Kim, et al., 2013; Merola et al., 2017; Moum et al., 2012). Some new onset of ICBs after DBS are transient (Amami et al., 2015; Kim et al., 2018).

Add-on treatments such as antipsychotics (i.e., quetiapine, clozapine) and anticonvulsants (i.e., valproate, carbamazepine, topiramate, zonisamide) have been used for ICBs in PD, but reports are anecdotal and experimental evidence supporting their use in PD is lacking (Bach, Oertel, Dodel, & Jessen, 2009; Bermejo, 2008; Bermejo, Ruiz-Huete, & Anciones, 2010; Hicks, Pandya, Itin, & Fernandez, 2011;

Rotondo, Bosco, Plastino, Consoli, & Bosco, 2010; Sevincok, Akoglu, & Akyol, 2007). Furthermore, a pharmacoepidemiological study provides evidence that atypical antipsychotics and selective serotonin reuptake inhibitors and glutamatergic modulators do not decrease the risk of ICBs in PwP treated with DA agonists (Jeon & Bortolato, 2020).

Amantadine is a noncompetitive *N*-methyl-D-aspartate receptor antagonist which interacts with DA by enhancing release and inhibiting its reuptake and changing DA receptor affinity (Cera et al., 2014). Amantadine may improve ICBs symptoms (Thomas, Bonanni, Gambi, Di Iorio, & Onofrj, 2010), but it has also been associated with ICBs (Walsh & Lang, 2012; Weintraub et al., 2010).

Naltrexone is a competitive, nonselective opioid receptor antagonist which is efficacious in alcohol and opioid dependency treatment (Morris, Hopwood, Whelan, Gardiner, & Drummond, 2001; Tiihonen et al., 2012). In a randomized, double-blind, placebo-controlled study, 50 participants were either administered naltrexone or matching placebo for eight weeks (Papay et al., 2014). There were no differences in the clinician-based rating of global improvement, although naltrexone treatment led to a greater decrease in QUIP-rs score over time compared with placebo (Papay et al., 2014). Although these findings are promising, there is "insufficient evidence" to conclude on the efficacy of naltrexone for the treatment of ICBs (Seppi et al., 2019).

Finally, infusion therapies such as levodopa-carbidopa intestinal gel may improve ICBs symptoms (Catalan et al., 2018; Todorova, Samuel, Brown, & Chaudhuri, 2015). It is a carboxymethylcellulose aqueous gel that can be delivered continuously to the proximal jejunum via a percutaneous gastrojejunostomy tube connected to a portable infusion pump. A 3-years longitudinal study of 19 PwP

receiving levodopa-carbidopa intestinal gel found that 8 PwP with ICBs either remitted (n=6) or attenuated (n=2) their symptomatology, 2 continued to have ICBs (although one of them was also under dopamine agonist rotigotine patch) and none developed new ICBs (Todorova et al., 2015). However, in another report of 15 PwP, new occurrence of ICBs was described in 27% of cases treated with levodopa-carbidopa intestinal gel (Chang et al., 2016).

In summary, management of ICBs is complex and no treatment has enough evidence for being considered as efficacious and useful in clinical practice. NICE guidelines recommend that, once starting DRT, PwP and carers have to be provided with oral and written information about (i) the increased risk of developing ICBs which may be concealed by the person affected, (ii) the different types of ICBs, (iii) who to contact if ICBs are developed, and (iv) ICBs management strategy. Clinicians should ask about ICBs at review appointments at least once a year, and more frequently if changing DRTs (National Institute for Health and Care Excellence, 2017; Rogers et al., 2017). Until medication without side-effects linked to ICBs or add-on therapies will not be identified and/or developed, identifying PwP vulnerable to ICBs is crucial.

Summary

This chapter provided background information about PD and ICBs. PD is a chronic, neurodegenerative and incurable condition characterized by a wide range of motor and non-motor symptoms. In PD, the same medication used to improve motor symptoms and therefore quality of life, also cause the development of one or more ICBs in a subset of PwP. Despite the high prevalence rates of ICBs (25-40% of PwP), not all medicated PwP develop ICBs. Several clinical and demographical,

genetic, behavioural (cognitive, affective, motivational), personality and neurological correlates have been identified, but studies' findings are not consistent. Therefore, who are the PwP who will developed ICBs when administered with PD medication is still an unanswered question.

This thesis aims to address the question about why only a subset of PwP develop ICBs. Neural, cognitive, affective and motivational correlates of ICBs in already diagnosed cases will be identified. In future studies, correlates will be tracked over time in a longitudinal study of newly diagnosed PwP as they start medication. This is important because identifying individuals vulnerable of ICBs before they develop it is an unmet need as clinical management consists in reducing or modifying DRT type, which is often not feasible or effective.

Chapter 3 Behavioural correlates

This chapter presents the following three studies investigating behavioural correlates of impulsive-compulsive behaviours (ICBs) in Parkinson's disease (PD):

1) A small-scale single centre empirical investigation of cognitive, affective and motivational correlates of ICBs in persons with Parkinson's (PwP) with and without ICBs and health controls (HC);

2) A systematic review and meta-analysis of 25 behavioural studies;

3) A large scale multicentre empirical investigation of cognitive, affective and motivational correlates of ICBs in PwP.

The final section of this chapter will present an interim conclusion of the main results integrated across the three studies. Studies 1 and 2 have been published (Martini, Dal Lago, Edelstyn, Grange, & Tamburin, 2018; Martini, Ellis, et al., 2018) and manuscript of Study 3 is being prepared for publication.

Study 1: Single-centre empirical investigation of cognitive, affective and motivational correlates of Impulsive-compulsive behaviours in Parkinson's disease[1]

Abstract

Background: Around 25-40% of PwP develop ICBs as side-effects of dopamine replacement therapy (DRT). Cognitive, affective and motivational factors may increase the risk of ICBs in PD. The present study aims to investigate incentive-driven decision-making and associated cognitive processes in PwP with ICBs within a four-stages framework (Sinha et al., 2013). Relationship between ICBs and affective factors was explored.

Method: Thirteen PwP with ICBs (ICB+), 12 PwP without ICBs (ICB−), and 17 healthy controls were recruited. Overall incentive-driven decision-making and negative feedback effect were examined with the Balloon Analogue Risk Task (BART). A cognitive battery dissected decision-making processes according to the four-stage framework. Affective and motivational factors were measured.

Results: There was no effect of group on overall incentive-driven decision-making. However, there was a group × feedback interaction [F (2, 39) = 3.31, p = 0.047]. ICB+, unlike ICB- and healthy controls, failed to reduce risky behaviour following negative feedback. Risky behaviour reduction in the BART negatively correlated with the Go/No-Go false alarms [r_s (42) = − 0.336, p = 0.030]. A main

[1] Martini, A., Ellis, S.J., Grange, J.A., Tamburin, S., Dal Lago, D., Vianello, G., Edelstyn, N.M.J. (2018). Risky decision-making and affective features of impulse control disorders in Parkinson's disease. *Journal of Neural Transmission,* 125, 131-143.

effect of group was found for anxiety and depression [F (2, 38) = 8.31, p = 0.001, η_p^2 = 0.30], with higher symptoms in ICB+ vs. healthy controls. Groups did not differ in cognitive outcomes or affective and motivational metrics.

Conclusions: ICBs may show relatively preserved cognitive function, but reduced sensitivity to negative feedback during incentive-driven decision-making and higher symptoms of depression and anxiety. Failure to decrease the risky behaviour following negative feedback may increase vulnerability to psychopathology in PD, marked by, for example, gambling, over-eating, or unregulated shopping. In turn, the negative consequences of these activities – such as financial loss, morbidity associated with weight gain – may fail to modify the individual's behaviour.

Introduction

An estimated 25-40% of PwP are reported to develop clinically relevant ICBs (Antonini et al., 2017; Callesen et al., 2014; Erga et al., 2017; Joutsa, Martikainen, Vahlberg, Voon, et al., 2012; Perez-Lloret, Rey, Fabre, Ory, Spampinato, Montastruc, et al., 2012).

A widely held view suggests that ICBs are side effects of dopaminergic replacement therapy (DRT) prescribed to ameliorate the cardinal motor symptoms of PD (Voon, Mehta, et al., 2011; Voon, Potenza, & Thomsen, 2007). According to the "overdose hypothesis", the requisite dopaminergic state necessary to control motor symptoms has the potential to move the same patients away from their optimum for certain cognitive functions (Cools, 2006; Cools, Barker, Sahakian, & Robbins, 2001; Cools & Robbins, 2004; Rowe et al., 2008), including incentive-driven decision-making. According to this hypothesis, the relationship between the efficiency of neuronal activity and the state of dopaminergic modulation is represented by a Yerkes–Dodson inverted U-shaped curve with incentive-driven decision-making and cognitive function declining with deviation away from optimum dosage for motor symptoms, indicated by the centre of the curve. This model implies that DRT may both improve and impair risk-taking behaviour depending on baseline dopamine levels in the underlying mesocorticolimbic circuitry.

ICBs are more common in patients medicated with both dopamine (DA) agonist and levodopa compared to those taking only DA agonist or levodopa (Weintraub et al., 2010). A number of other factors, including younger age, being unmarried, current smoking, and a family history of gambling problems independently increased the risk of ICBs (Liu et al., 2019; Weintraub et al., 2010). This suggests a more complex relationship that includes both DRT and non-DRT

factors. Converging evidence suggests that psychological factors, including depression, anxiety, and apathy, may contribute to ICBs in PD (Callesen et al., 2014; Joutsa, Martikainen, Vahlberg, Voon, et al., 2012; Leroi, Andrews, et al., 2012; Marín-lahoz et al., 2019; O'Sullivan, Loane, et al., 2011; Pineau et al., 2016; Pontieri et al., 2015; Santos Garcia et al., 2021; Wu et al., 2015).

Sinha et al. (2013) provide a framework of incentive-driven decision-making which may account for specific forms of DA-dependent impulsivity in PD, which may result in ICBs. According to this framework, incentive-driven decision-making can be framed in four dissociable stages: option generation, option selection, action initiation or inhibition, and learning (see Figure 3.1). Abnormal functioning of each of these stages may result in a specific form of impulsivity. According to this framework, several behavioural options should be generated instead of producing a single option and acting without considering other alternatives (option generation); the generation of behavioural options relies, at least in part, on perceptual and attentional mechanisms. These options are then valued and compared based on features including predicted reward, punishment, effort required, time involved to outcome delivery, and probability of outcome (option selection). The chosen option is then associated with the appropriate action, but there is a fail-safe mechanism whereby such action can be inhibited if the wider context changes, which might mean that a behaviour is no longer advantageous (action initiation or inhibition). The real outcomes of behaviours are compared with predictions made prior to making these actions (learning). Such comparisons play a key role in learning and feeding back on option selection mechanisms. Cognitive processes underlying each of these stages may be modulated, to some extent, by DA, with either lower or higher DA levels leading toward apathy or impulsivity, according to the previously described

inverted U-shaped curve. Moreover, factors other than dopaminergic modulation such as depression or anxiety can also influence processes within each stage.

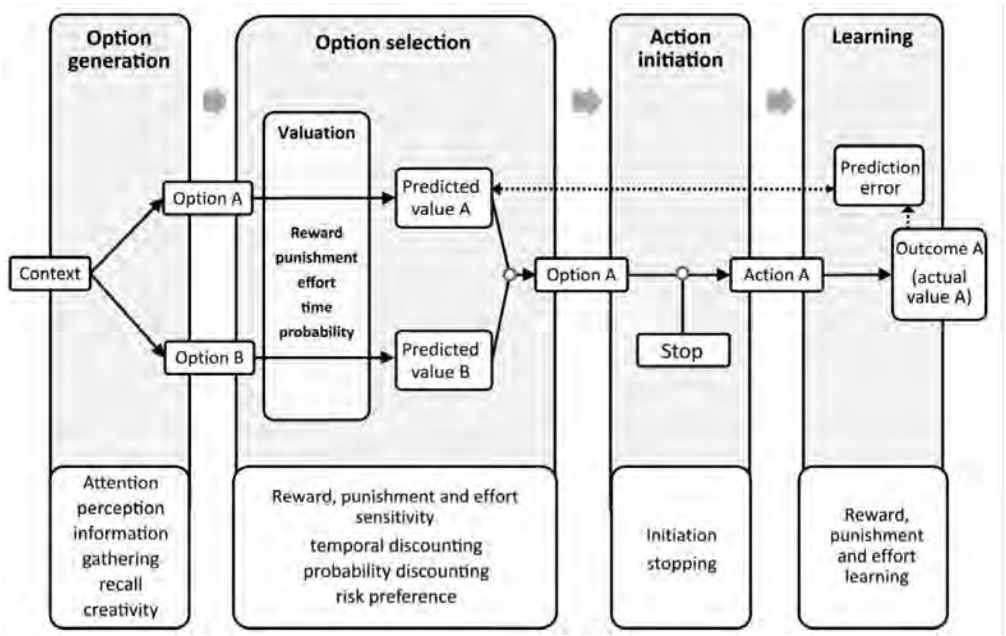


Figure 3. 1 Incentive-driven decision-making framework. Reprinted under permission from Sinha, Manohar, & Husain, 2013, John Wiley and Sons and Copyright Clearance Center.

Preliminary evidence provides partial support for this framework. PwP with ICBs gather less information before making a decision (Djamshidian et al., 2014, 2012), and show preference for immediate smaller rewards than delayed bigger ones (i.e., temporal discounting) (Housden et al., 2010; Leroi et al., 2013; Voon, Reynolds, et al., 2010), reflecting abnormal processes in the option generation and option selection stages, respectively. Action initiation and inhibitory control appear relatively spared in PwP with ICBs, based on performances on the Stroop task, the Stop Signal task and the Continuous Performance Task (Claassen et al., 2015;

Djamshidian, O'Sullivan, Lees, & Averbeck, 2011; Marín-Lahoz et al., 2018; Ricciardi et al., 2017). Learning from rewards was reported to be spared in PwP with ICBs (Housden et al., 2010; Piray et al., 2014; Voon, Pessiglione, et al., 2010), whereas the effect of negative feedback on learning appears equivocal, with studies reporting either impairment (Leplow et al., 2017; Piray et al., 2014), sparing (Djamshidian et al., 2010), or no differences (Claassen et al., 2011).

ICBs in PD might be associated with disruptive modulation of dopaminergic medication in some but not all stages of the incentive-driven decision-making process; no studies to date have specifically investigated all these stages within a single cohort of PwP with and without ICBs. Moreover, cognitive impairments might interact with other factors (e.g., low mood) facilitating the engagement on risk-taking behaviours; thereby, studies should also include measures of affective and motivational factors previously associated with ICBs in PD.

In this study, incentive-driven decision-making has been investigated with the Balloon Analogue Risk Task (BART) (Lejuez et al., 2002) and the stages of the underlying framework (Sinha et al., 2013) dissected through a battery of cognitive tasks. Over the variety of tasks, the BART has the advantages of being an ecological measure of incentive-driven decision-making as it mimics many real-world risks, where probability of loss is initially small but grows persisting in the behaviour (e.g., substance abuse) (Lejuez et al., 2002; Schonberg, Fox, & Poldrack, 2011). The BART has been extensively used with healthy as well as clinical populations, and performances in the task correlate with risky behaviours in real life such as drug abuse, smoking behaviour, sexual promiscuity and risky traffic behaviour (Hopko et al., 2006; Lejuez, Aklin, Jones, et al., 2003; Lejuez, Aklin, Zvolensky, & Pedulla,

2003; Lejuez et al., 2002; Raymond et al., 2020; Sehrig, Weiss, Miller, & Rockstroh, 2019; Vaca et al., 2013).

During the BART, participants are provided with several virtual balloons to pump up, one at time. With each pump money is earned; however, each balloon has a maximum unknown capacity over which additional pumps would result in balloon burst and money loss. Participants have to decide how much to inflate the balloon, trying to stop before it bursts in order to save the money.

Modified version of the BART has been used in PwP with ICBs (Claassen et al., 2011; Rao et al., 2010), which showed the task to be sensitive to ICBs. Diminished blood oxygen level dependent (BOLD) activity in the right ventral striatum during BART performances compared to PwP without ICBs has been observed, although there were no differences in the behavioural performances (Rao et al., 2010). Furthermore, DA agonists increase risk-taking behaviour of PwP with ICBs, whilst it did not affect risky behaviour in PwP without ICBs (Claassen et al., 2011). However, both those studies used a modified version of the original task in which the number of possible pumps is reduced [e.g., 1-12 or 1-14 and 1-7, instead of 1-128 as the original version (Claassen et al., 2011; Rao et al., 2010)], which may be less sensitive to individual variability in behavioural performances (Lejuez et al., 2002).

Aims and predictions

This study aims to investigate incentive-driven decision-making and affective and motivational features of ICBs in PD. To this aim, incentive-driven decision-making was investigated in PwP with (ICB+) and without ICBs (ICB-) and healthy controls (HC) using the BART. Also, the stages of the decision-making framework

proposed by Sinha et al. (2013) were dissected and explored through a battery of cognitive tasks. As affective factors may influence the processes in those stages promoting or reducing impulsivity, the relationship between ICBs and previously identified affective and motivational factors were investigated. In this study, a single cohort of demographically and clinically matched PwP were used, thereby controlling for differences in PD population. Demographically matched healthy adults have been included to provide baseline control data.

The predictions were that, ICB+, compared to ICB- and HC would show:

1. Increased risk-taking behaviour related incentive-driven decision-making in the BART;
2. Poorer performances on cognitive tasks assessing processes related to the option generation, option selection, and learning stages, consistent with the wider PD literature. Whether inhibitory control (action initiation and inhibition stage) is involved in ICBs in PD was uncertain, as performances of PwP with ICBs were reported to be relatively spared.
3. Increased levels of depression, anxiety and impulsivity, but not apathy as the latter seems to be associated with a hypodopaminergic instead of hyperdopaminergic state as ICBs.

Method

Peer Review and Ethic Approval

The study was approved in September 2014 by *NRES Committee West Midlands – Edgbaston* (Appendix A) following the submission of a complete protocol, participants' consent forms and information sheets, validated and non-

validated questionnaires and neuropsychological assessments. The study was also approved by Keele University Ethical Review Panel in August 2014 (Appendix B).

Participants

Persons with Parkinson's disease

Identification (Pre-screening). Three hundred forty seven eligible PwP with a diagnosis of idiopathic mild to moderate PD diagnosed according to the UK Parkinson's disease Society Brain Bank (UKPDSBB) diagnostic criteria (Gibb & Lees, 1988) were identified by a research nurse. Contact details were gathered from: (1) the PD database and clinic lists of the University Hospital of North Midlands, Department of Neurology; (2) Keele research team list of PwP who have taken part in previous studies, and have provided their consent to be contacted about participation in future research studies; and (3) volunteers who provided contact details following talks.

Recruitment. Sixty eligible PwP were sent a study pack consisting of a letter of invitation, information sheet, opt-in response slip and stamped addressed envelope (Appendix C). The stamped address envelope was addressed to the research nurse. After two weeks, a reminder letter was sent to PwP who did not return the response slip. PwP who did not reply to the reminder letter were not contacted again. PwP opting into the study were invited for a screening session with the chief investigator/principal investigator (CI/PI), consultant neurologist, and the research nurse.

Screening visit. Twenty-seven PwP attended the screening visit with the CI/PI and the research nurse. The screening visit took place in the morning during dedicated research clinics at the Guy Hilton Research Centre, University Hospital of North Midlands, and lasted about 60 minutes. Mental capacity to consent was assessed by CI/PI before PwP signed consent forms (Appendix D). Capacity to provide informed consent was based on a combination of Mini-Mental State Examination (MMSE) (Folstein et al., 1975) minimum score of 25 plus functional assessment of mental capacity with the Four Stage Assessment of Functional Capacity Questionnaire. No study procedure was initiated until PwP provided written informed consent.

During the screening visit the CI/PI was also responsible for: (1) reviewing inclusion/exclusion criteria; (2) clinical assessment of PD symptoms [modified Hoehn & Yahr (H&Y) Scale (Hoehn & Yahr, 1967), Unified Parkinson's disease rating scale (UPDRS) motor examination subsection and motor complications subsection (Fahn & Elton, 1987)]; (3) medical history record; and (4) PwP' allocation to the ICB+ or ICB- group according to a semi-structured interview (i.e., ICBs Screening Interview, Appendix E) which includes adapted diagnostic criteria for gambling disorder, binge eating (American Psychiatric Association, 2013); compulsive shopping (McElroy et al., 1994); hypersexuality (Voon et al., 2006); punding (Voon & Fox, 2007), and dopamine dysregulation syndrome (DDS) (Giovannoni et al., 2000). PwP allocated to the ICB+ group had clinically significant ICBs in the previous three months (active ICBs), thereby no ICBs remitters were included in the sample; this assures a more homogeneous sample and therefore more robust results and interpretations as some variables may be ICBs-related and not present once ICBs are resolved. PwP allocated to the ICB- group did not have ICBs

either in the present or in the past. It should be noted that PwP in this study had ICBs of such severity that they were deemed by the neurologist to be clinically significant.

Inclusion/exclusion criteria. PwP included in the study were both male and female, between 35 and 85 years of age, and with a diagnosis of idiopathic PD according to the UKPDSBB diagnostic criteria (Gibb & Lees, 1988). Since cognitive impairment and severe motor disease are common in later stage of PD, all participants were in the mild (i.e., 1, 2, 2.5) or moderate (i.e., 3) stages of the disease according to the modified H&Y scale and fully able to provide informed signed consent. PwP were currently medicated with either: immediate or prolonged release versions of pramipexole dihydrochloride monohydrate, 520 micrograms to 3.15 mg, or immediate or prolonged release versions of ropinirole hydrochloride, range 2 mg to 24 mg or rotigotine transdermal patch, dose range 2-16 mg per 24 hours and/or immediate or prolonged release preparation of levodopa and/or a MAO-B inhibitor (generic or branded versions as appropriate) and/or COMT inhibitor, apomorphine, amantadine.

PwP were excluded if younger than 35 and older than 85 years of age. Since the neuropsychological assessment battery is validated in a British population, participants who were not fluent in English were excluded. PwP were also excluded if had: (i) cognitive impairment as assessed with the assessment of functional capacity and the MMSE scoring lower than 25; (ii) moderate and severe PD, indicated by a score of 4, 5 on the modified H&Y scale; (iii) co-morbid for another neurological illness (other than PD); (iv) history of learning difficulty including dyslexia; (v) physical inability to attend or comply with treatment scheduling, such as upper limb amputations, crippling degenerative arthritis; (vi) active malignancy;

(vii) major psychotic phenomenology including hallucinations or lack of awareness of dyskinesias; and (viii) incapacitating dyskinesias on a stable dose of levodopa. PwP were also excluded if they were taking centrally acting anticholinergic drugs and/or atypical antipsychotics.

Persons with Parkinson's disease Participants. Twenty-seven PwP with idiopathic non-dementing PwP were enrolled in the study, but two of them were excluded. Reasons for exclusions were (1) wrong medication regimen, and (2) increased anxiety around the research visits. Therefore, 25 PwP (21 males, 4 females; mean age = 64.04, SD = 9.18) completed the study. All PwP were in the mild to moderate stages of PD (modified H&Y mean score = 2.46, SD = 0.54). Summary of PwP recruitment is listed in table 3.1.

Table 3. 1 Summary of eligible persons with Parkinson's disease identified and recruited.

Stage of recruitment	Number of PwP
Identified as eligible (pre-screening)	347
Invited (via invitation pack)	60
Declined to participate	33
Opted in the study	27
Excluded during the screening	1
Excluded during the research visit (withdrawn)	1
Participated in the study	25

Legend. PwP: persons with Parkinson's disease.

PwP were divided in two subgroups: thirteen PwP (11 males, 2 females) with ICBs were allocated to the ICB+ group, and 12 PwP (10 males, 2 females) with no ICBs history were allocated to the ICB- group. The ICB+ and ICB- subgroups had comparable age [$t(23) < 1$, $p = 0.75$, $d = -0.13$, 95% CI [-0.91, 0.66]], current levels of functioning [MMSE: $t(23) < 1$, $p = 0.29$, $d = -0.43$, 95% CI [-1.22, 0.36]], age at PD onset [$t(23) < 1$, $p = 0.88$, $d = 0.06$, 95% CI [-0.72, 0.85]], disease duration [$U(23) = 58.5$, $p = 0.29$, $r_{rb} = -0.25$, 95% [-0.61, 0.20]], motor functioning [UPDRS-III: $t(23) = 1.19$, $p = 0.25$, $d = 0.48$, 95% CI [-0.33, 1.27]] and complications of therapy [UPDRS-IV: $t(23) < 1$, $p = 0.68$, $d = -0.16$, 95% CI [-0.95, 0.62]], disease severity stage [modified H&Y: $t(23) < 1$, $p = 0.72$, $d = -0.15$, 95% CI [-0.94, 0.64]], DA agonist use (two-tailed Fisher exact test, $p = 0.41$) and total Levodopa equivalent daily dosage [total LEDD, mg: $U(23) = 61.00$, $p = 0.35$, $r_{rb} = -0.22$, 95% CI [-0.59, 0.24]] (Tomlinson et al., 2010).

Healthy controls

Recruitment. HC contact details were gathered from (1) a list of participants who have taken part in previous studies and agreed to be contacted again about participation in future research or (2) word of mouth. Also, (3) volunteers who provided contact details following talks were recruited.

Twenty-three eligible HC were contacted via e-mail or sent a study pack consisting of a letter of invitation, information sheet, opt-in response slip and stamped addressed envelope to return to the Keele research team (Appendix F). Two weeks later, a reminder letter was sent to participants who did not return the response slip. Participants who did not reply to the reminder letter were not contacted again. Participants opting into the study were invited for the first research visit at Keele University, School of Psychology. No study procedure was initiated until PwP provided written informed consent (Appendix G).

Inclusion/exclusion criteria. Participants included in the study were both male and female, aged between 35 and 85 years of age, English as first language. HC were excluded if: (i) diagnosed with PD; (ii) diagnosed with a neurological illness; (iii) attending a memory clinic; (iv) unable to provide informed consent due to cognitive decline; (v) history of learning difficulty including dyslexia; (vi) physical inability to take part in research, such as upper limb amputations, crippling degenerative arthritis; (vii) active malignancy; (viii) family history of PD (more than one relative affected by PD); (ix) psychiatric history including schizophrenia, depressive illness; (x) family history of schizophrenia, depressive illness; (xi) major psychotic phenomenology including hallucinations; (xii) hypotension; (xiii) history of ICBs; (xiv) history of alcohol and/or drug abuse. Normal controls were also

excluded if taking anticholinergics, antipsychotics (typical or atypical) and/or antidepressants drugs.

Healthy controls Participants. Seventeen HC (10 males, 7 females; age: M = 68.65, SD = 6.76) were enrolled in the study.

Matching Parkinson's disease subgroups and healthy controls. ICB+ and ICB- were matched to the HC for age [$F(2,39) = 1.59$, $p = 0.22$, $\eta_p^2 = 0.07$], sex [Fisher-Freeman-Halton test, $p = 0.27$], years of education [$F(2,39) = 1.27$, $p = 0.29$, $\eta_p^2 = 0.06$] and current level of functioning as assessed both with the MMSE [$F(2,39) <1$, $p = 0.46$, $\eta_p^2 = 0.04$] and the more comprehensive Cambridge Cognitive Examination (CAMCOG) (Roth, Tym, & Mountjoy, 1986) [$F(2,39) = 3.09$, $p = 0.06$, $\eta_p^2 = 0.14$]. Premorbid crystallized IQ, measured with the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2009a), was comparable between PD groups [ICB+: M = 108.23, SD = 9.83; ICB-: M = 101.92, SD = 6.39; $p = 0.16$, $d = -0.75$, 95% CI [-14.01, 1.38]] but significantly higher in HC [M = 116.12, SD = 7.15; HC vs. ICB+: p =0.03, $d = 0.94$, 95% CI [0.81, 14.97]; HC vs. ICB-: $p = 0.00007$, $d = 2.07$, 95% CI [6.95, 21.45]]. Daytime sleepiness, measured with the Epworth Sleepiness Scale (ESS) (Johns, 1991) was comparable between PD subgroups [ICB+: M = 13.42, SD = 3.65; ICB-: M = 9.58, SD = 4.38; $p = 0.10$, $d = -0.95$, 95% CI [-8.07, 0.40]] but significantly higher in the ICB+ vs. HC group [HC: M = 7.53, SD = 4.54; HC vs. ICB+: $p = 0.002$, $d = -1.40$, 95% CI [-9.80, -1.97]]. CAMCOG, WTAR and ESS data have been collected during the research visits (see section "testing session procedure", page 100). Table 3.2 shows baseline and clinical characteristics of the study sample.

Table 3. 2 Baseline data and clinical characteristics of the study sample.

Variables	**ICB+ (n=13)**	**ICB- (n=12)**	**HC (n=17)**	**F, t, χ^2 values**	***p***	***Post hoc***
Age (y)	64.62 ± 7.6, 65	63.42 ± 10.96, 66	68.65 ± 6.76, 68	$F(2,39)=1.59$	0.22	
Male, n (%)	11 (84.6%)	10 (83.3%)	10 (58.8%)		0.27[§|]	
Education (y)	13.77 ± 2.92, 13	13.58 ± 3.15, 12	15.23 ± 3.25, 15	$F(2,39)=1.27$	0.29	
ESS	13.42 ± 3.65	9.58 ± 4.38	7.53 ± 4.54	$F(2,38)=6.77$	***0.003***	HC < ICB+; HC = ICB-; ICB+ = ICB-
WTAR	108.23 ± 9.83	101.92 ± 6.39	116.12 ±7.15	$F(2,39)=11.69$	***0.00007***	HC > ICB+; HC > ICB-; ICB+ = ICB-
CAMCOG	96.77 ± 3.27, 97	94.75 ± 6.61, 95.5	99.29 ± 2.62, 99	$F(2,39)=3.09$[a]	0.06	
PD features						
Age at onset	56.38 ± 7.73	57.08 ± 13.42	NA	$t(23)<1$	0.88	
Duration	8 ± 4.06, 8	7.29 ± 7.51, 5.5	NA	$U(23)=58.5$	0.29	
UPDRS-III	17.31 ± 5.96	20.92 ± 9.03	NA	$t(23)= 1.19$	0.25	
UPDRS-IV	3.69 ± 3.97	3.17 ± 1.99	NA	$t(23)<1$	0.68	
H&Y	2.5 ± 0.35	2.41 ± 0.70	NA	$t(23)<1$	0.72	
Total LEDD (mg)	552.85 ± 353.42, 450	451.42 ± 293.77, 355	NA	$U(23)=61.00$	0.35	
DA agonist use, n (%)	10 (76.9%)	7 (58.3%)	NA		0.41[§§]	
ICB type						
Single ICB	3/ 1/ 1/ 3[b]	0	0			
Multiple ICBs	5[c]	0	0			

Legend. ICB: impulsive-compulsive behaviour; ICB+: PwP with ICBs; ICB-: PwP without ICBs history; HC: healthy controls; Education: years of formal education; ESS: Epworth sleepiness scale; WTAR: Wechsler Test of Adult Reading; CAMCOG: Cambridge Cognitive Examination (total score); UPDRS-III: Unified Parkinson's disease rating scale part III (motor score); UPDRS-IV: Unified Parkinson's disease rating scale part IV (motor complications); H&Y: modified Hoehn-Yahr disease severity rating scale; Total LEDD: total Levodopa Equivalent Daily Dosage; DA: dopamine; NA: not available. Continuous variables are presented as mean ± standard deviation, median. Median is reported for

variables that were not normally distributed. [a]Log10 transformed data. [b]hypersexuality: n=3, binge eating: n=1, compulsive shopping: n=1, punding: n=3; [c] hypersexuality + punding + compulsive shopping: n =2, hypersexuality + punding: n = 1, hypersexuality + compulsive shopping: n = 1 hypersexuality + binge eating: n = 1. [§|] Fisher-Freeman-Halton test. [§§]two-tailed Fisher exact test.

Design

This is a single-centre, cross-sectional, empirical single blind study of PwP, with and without ICBs, and HC. Flow diagram of the study is provided in Figure 3.2.

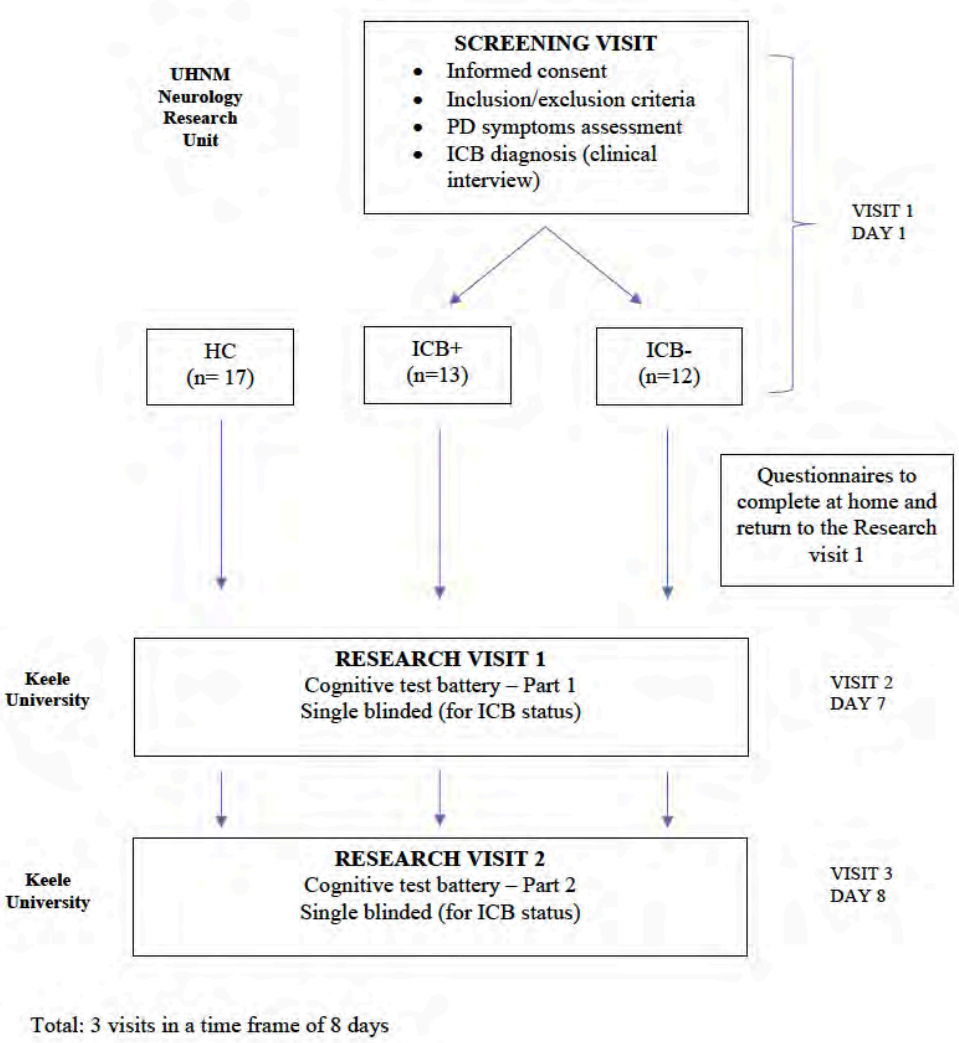


Figure 3. 2 The flow diagram of the study procedure. PD: Parkinson's disease; HC: healthy controls; ICB: impulsive-compulsive behaviour; ICB+: PwP with impulsive-compulsive behaviour; ICB-: PwP without impulsive-compulsive behaviour; UHNM: University Hospital of North Midlands.

Procedure

***Testing Session Procedure*.** Twenty-five PwP (ICB+: 13; ICB-: 12) attended two 60-90 minutes research visits on two consecutive days at the School of Psychology, Keele University. PwP were in an optimally medicated state (i.e., at least 120 minutes after having taken their first DRT of the day). To avoid performance bias, the assessor was blind to the ICBs status, but not to PD diagnosis.

During the research visits PwP completed measures of (i) incentive-driven decision-making, and (ii) cognitive processes associated with the four stages decision-making framework (Sinha et al., 2013). Assessments used during the research visits are listed in Table 3.3. PwP also completed questionnaires that provide subjective measures of (iii) affective and motivational factors. Questionnaires were provided at the end of the screening visit to complete at home and return at the first research visit.

Seventeen healthy controls attended the two research visits and completed the same tests and questionnaires as the PD groups. Questionnaires were provided at the end of the first research visit to complete at home and return at the second research visit. The order of the assessments on the two consecutive days was the same for all participants.

Table 3. 3 Cognitive assessments administered in each research session and questionnaire to complete at home.

Research Session 1 (90 mins testing PLUS breaks)	**Research Session 2 (90 mins testing PLUS breaks)**
TMT-A, TMT-B (5 mins)	WTAR (3 mins)
Logical Memory Immediate (10 mins)	CAMCOG (20 mins)
Divided Attention (25 mins)	BART (15 mins)
Go/No-Go task (5 mins)	Hayling Sentence Completion Task (10 mins)
Logical Memory Delayed (5 mins)	Brixton Spatial Anticipation Test (5 mins)
Questionnaires to complete at home (20 mins)	
Epworth Sleepiness Scale (3 mins)	
Barratt Impulsiveness Questionnaire (5 mins)	
Starkstein Apathy Scale (5 mins)	
Hospital Anxiety and Depression Scale (5 mins)	

Legend. TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; WTAR: Wechsler Test of Adult Reading; CAMCOG: Cambridge Cognitive Examination; BART: Balloon Analogue Risk Task.

Stimuli

Clinical Measures

Modified Hoehn and Yahr Staging Scale. The H&Y scale is a five-point scale to clinically describe PD stages, combining functional disability and objective signs of impairment (Goetz et al., 2004; Hoehn & Yahr, 1967). During the 1990s, a modified version including two intermediate stages was developed (Table 3.4). The modified H&Y scale (Appendix H) has been used in order to exclude PwP with severe PD (i.e., stages 4-5).

Table 3. 4 Original and modified Hoehn and Yahr Staging Scale.

Hoehn and Yahr Staging Scale	**Modified Hoehn and Yahr Staging Scale**
1: Unilateral involvement only usually with minimal or no functional disability	1: Unilateral involvement only
--	1.5: Unilateral and axial involvement
2: Bilateral or midline involvement without impairment of balance	2: Bilateral involvement without impairment of balance
--	2.5: Mild bilateral disease with recovery on pull test
3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	3: Mild to moderate bilateral disease; some postural instability; physically independent
4: Severely disabling disease; still able to walk or stand unassisted	4: Severe disability; still able to walk or stand unassisted
5: Confinement to bed or wheelchair unless aided	5: Wheelchair bound or bedridden unless aided

Unified Parkinson's Disease Rating Scale. PD-related disability and impairment over the disease progression has been assessed with the UPDRS (Appendix I) (Fahn & Elton, 1987). The scale is widely used in the clinical and research settings. It includes four sections evaluating mental, behaviour and mood

(UPDRS-I), activities of daily living (UPDRS-II), motor examination (UPDRS-III), and motor complications (UPDRS-IV). In this study, UPDRS-III and UPDRS-IV have been used.

The UPDRS-III comprises 14 items assessing severity of PD-related motor features such as speech, facial expression, tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movements of hands, leg agility, arising from chair, posture, gait, postural stability, body bradykinesia and hypokinesia. Items are scored from 0 (absent) to 4 (marked disability). The UPDRS-IV includes 11 items evaluating dyskinesias (duration, disability), motor fluctuations ("off" periods predictable or unpredictable, "off" periods come suddenly or not, proportion of the waking day in which PwP is "off"), and dystonia. Items can range from 0 (none, not disabling) to 4 (severe, completely disabled, e.g., 76-100% of the day).

Epworth Sleepiness Scale. The ESS (Johns, 1991) (Appendix J) is an 8-items self-report measure of daytime sleepiness. Participants are provided with 8 scenarios (e.g., "sitting and reading", "watching television") and they have to rate the chance of dozing for each situation on a 4 points scale, with 0 meaning "would never doze" and 3 meaning "high chance of dozing". Scores are summed to obtain a total score. As side effects of DRT, PwP might experience sleep disturbances and increased daytime sleepiness (Kaynak, Kiziltan, Kaynak, Benbir, & Uysal, 2005; Ondo et al., 2001), which in turn may affect cognitive performances (Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012). The ESS was included in this study to compare daytime sleepiness levels across groups.

Mini-Mental State Examination. For screening purposes only, global cognitive functioning was assessed using the MMSE (Folstein et al., 1975) (Appendix K), which is a brief, widely accepted instrument for screening of cognitive impairment and dementia. Although it has not been developed specifically for PD, it is extensively used in PD studies (Chou et al., 2010). The MMSE consists of five cognitive domains: orientation, registration and short-term recall, attention and concentration, language, and visuospatial function. It normally requires 10 minutes to be completed. Scores range from 0 to 30 (0-10 normal cognition, 11-20 moderate cognitive dysfunction, 21-26 mild cognitive dysfunction, and 27-30 normal cognitive function), and 24 is generally used as cutoff to screen dementia.

Cambridge Cognitive Assessment. The CAMCOG (Appendix L) is a comprehensive neuropsychological tests battery for the assessment of cognitive impairment in elderly that is part of the Cambridge Examination for Mental Disorders of Elderly (Roth et al., 1986). It consists of 67 items with a total score of 105 and subscores for orientation, language, memory, attention and calculation, praxis, abstract thinking, and perception. The assessment of executive function does not contribute to the total score, but it can be calculated as an additional score. Although the CAMCOG was developed to detect cognitive impairment in Alzheimer's disease, it has been recognized as a useful tool for screening dementia and cognitive impairments in PD as well (Hobson & Meara, 1999).

In this study, participants were administered both the MMSE and the CAMCOG. The MMSE was administered during the screening visit to exclude dementia and ascertain the ability to take part in the study (exclusion criteria), whilst CAMCOG was administered during the research visit to have a more comprehensive

and detailed cognitive profile since the MMSE demonstrates ceiling effects in subjects with mild cognitive impairments (Wind et al., 1997). CAMCOG total score has been included to characterize the cognitive profile of the sample, whilst executive function and memory subscores have been used as measures of option generation and learning stage, respectively (see "cognitive test battery" section).

Wechsler Test of Adult Reading. Premorbid intellectual functioning was assessed with the WTAR (Wechsler, 2009a) (Appendix M), that consists of 50 irregular words, which pronunciation cannot be inferred by the spelling rules (i.e., grapheme-phoneme translation), but relies on previous knowledge. Participants are asked to read each irregular word aloud. Each error is recorded and summed to obtain a scaled score (using normative scores and conversion tables provided in the manual). Reading abilities, compared to other skills, are relatively preserved in the presence of cognitive decline (Lezak, Howieson, Bigler, & Tranel, 2012). The WTAR was used to compare premorbid intellectual functioning levels between groups, which may account for differences in cognitive performance.

Incentive-driven decision-making task

The Balloon Analogue Risk Task. The BART (Appendix N) is a computerized risk-taking task related to incentive-driven decision-making, where choices are based on explicit probabilistic information (Lejuez et al. 2002). The BART was shown to be an ecologically valid and sensitive measure of risk-taking behaviour, as it positively correlates with both self-report impulsivity and real-world risky behaviours, such as number of sexual partners, alcohol, smoke and drug use (Hopko et al., 2006; Lejuez, Aklin, Jones, et al., 2003; Lejuez, Aklin, Zvolensky, et

al., 2003; Lejuez et al., 2002). The BART has good reliability properties. Risk-taking behaviour on the BART does not differ across days. Test-retest correlation across sessions is robust (r = +.77) (White, Lejuez, & de Wit, 2008).

During the BART, participants sit at 17'' computer screen and are instructed to sequentially click with the mouse on the box labelled "Click Here to Pump up the Balloon" to inflate a virtual blue balloon. Each click slightly pump the balloon and 5 pence are earned. However, if the balloon is inflated too much, it bursts and all the money collected so far are lost. To gain as much money as possible, participants had to stop inflating the balloon before it bursts and click the "Collect $$$" button. Money is then transferred to a virtual bank named "Total $$$" and an auditory feedback simulating slot machine reward sound is provided. The next trial commences when a new balloon appears following either a balloon burst or when money is banked. Each participant completes 30 trials. Balloons were pre-programmed to burst at a "break-point" in the range of 1-128 pumps. The probability that a balloon would burst was 1/128 for the first pump. If it did not explode, the probability for bursting was 1/127 for the second and so on. The average breakpoint was 64 pumps. The BART is illustrated in Figure 3.3.

Two dependent variables were recorded. The first was the average number of pumps in trials in which balloons were cashed. Higher risk-taking behaviour is associated with a higher number of pumps. The second was the average number of pumps for trials immediately preceding and immediately following a balloon burst (Claassen et al. 2011; Simioni et al. 2012). Lower number of pumps in trials that immediately follow a balloon burst compared to those that immediately precede a balloon burst indicates sensitivity toward negative feedback.

The BART was administered during the second research visit and participants were informed that no money was provided at the end of the task.

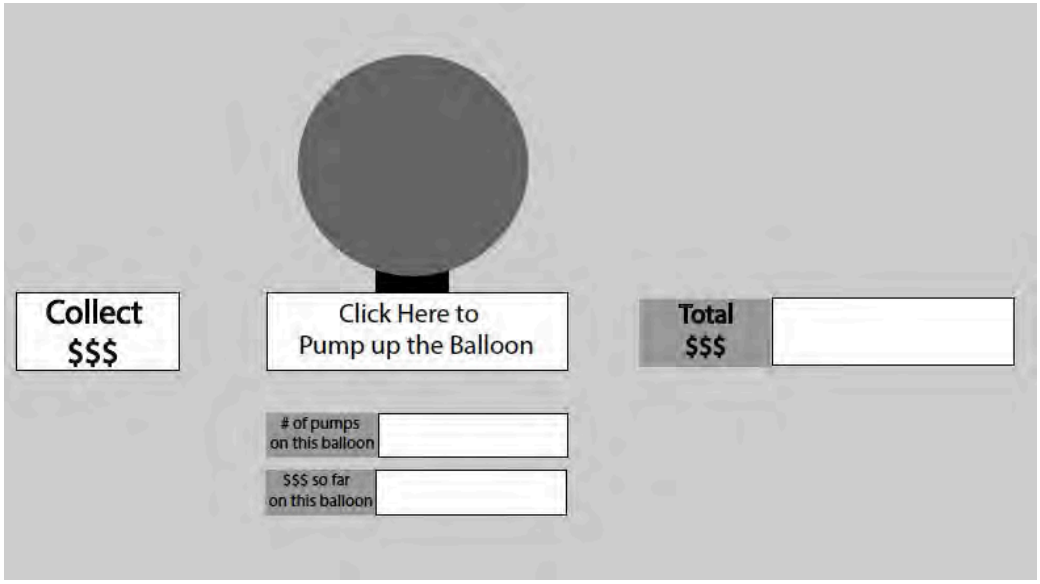


Figure 3. 3 The Balloon Analogue Risk Task (BART).

Cognitive Test Battery. A comprehensive cognitive test battery was administered to all participants on two consecutive days. The order was the same for all participants. The cognitive test battery included: divided attention task from the Test of Attentional Performance (Zimmermann and Fimm, 1995) and the Trail Making Test part A (TMT-A) (Reitan, 1958) as measures of divided and selective attention, respectively; Logical memory (immediate and delayed) from the Wechsler Memory Scale (Wechsler, 2009b) and CAMCOG memory subtests, as measures of memory; the Trail Making Test part B (TMT-B) (Reitan, 1958) as measure of set-shifting; the Hayling Sentence Completion Task-Section 1 (Burgess and Shallice, 1997) as measure of verbal generation; Go/No-Go task from the Test of Attentional Performance (Zimmermann and Fimm, 1995) and the Hayling Sentence Completion Task -Section 2 (Burgess and Shallice, 1997) as measures of motor and verbal

inhibitory control, respectively; CAMCOG executive function subtests as measure of executive function; Kirby Monetary Choice Questionnaire (to complete at home) (Kirby et al. 1999) scored according to (Myerson et al. 2014) as measure of temporal discounting; the Brixton Spatial Anticipation test (Burgess and Shallice, 1997) as measure of rule detection via feedback processing. The main outcome of each task was considered as a dependent variable.

To assess the four stages decision-making framework (Sinha et al. 2013), tasks were categorized as part of option generation (TMT-A, TMT-B, divided attention, Hayling Sentence Completion Task -Section 1, CAMCOG executive function subtests), option selection (Kirby Monetary Choice Questionnaire), action initiation and inhibition (Go/No-Go task, Hayling Sentence Completion Task-Section 2), and learning (Brixton Spatial Anticipation test, Logical memory, and the CAMCOG memory subtests).

Trail Making Test. The TMT (Reitan, 1958) (Appendix O) is a sheet-and-paper test which is formed by two parts. In the first part (TMT-A), participants are asked to draw a line to connect 25 circled numbers in ascending order. In the second part (TMT-B), participants are provided with both numbers and letters and they are instructed to draw a line to connect a number and a letter, in alternating and ascending order (i.e., 1-A-2-B-3-C, etc.). TMT-A is a measure of visuospatial search, selective attention and cognitive processing speed, whilst TMT-B also involves set-shifting. The number of errors in each part are considered as the main scores. The TMT-A and B have been used as measures of option generation, as attentional and executive mechanisms are important factors for option generation (Sinha et al., 2013).

Divided Attention. The Divided Attention test (Appendix P) is part of the Test of Attentional Performance (Zimmermann and Fimm, 1995), which is a computerized test battery assessing several dimensions of attention. The Divided Attention test is based on a "dual-task" paradigm, in which participants have to pay attention to two stimuli simultaneously. In the test, visual and auditory tasks have to be processed in parallel. In the visual task, crosses appear in the centre of the computer's screen in random order forming a 4x4 matrix. Participants press a computer key when four crosses form a small square. In the auditory task, two different tones (i.e., "high" tone and "low" tone) are presented in sequence. Participants have to press a computer key when two same tones appear twice in a row. The dual task is preceded by the two separated visual and auditory tasks in order to assure that participants are able to perform single tasks without difficulty. The main outcome is the number of correct responses minus false alarms (i.e., hit rates). The divided attention task has been used as a measure of option generation, as attentional mechanisms are important factors for option generation (Sinha et al., 2013).

Hayling Sentence Completion Task. The Hayling Sentence Completion Test (Appendix Q) (Burgess & Shallice, 1997) is divided in two subtests assessing verbal initiation (Hayling Sentence Completion Task Section 1: sensible completion) and verbal suppression (Hayling Sentence Completion Task Section 2: unconnected completion). In Section 1, participants are read 15 sentences with the last word missing from each of them (e.g., "he posted a letter without a"). As soon as the examiner finishes reading the sentence, participants have to give a word that

completes the sentence (e.g., “stamp”). The time needed to provide the word in each sentence is added and converted in a scale score using the table provided in the response sheet. Scale score of Section 1 provides a measure of response initiation. In Section 2, participants are read 15 sentences with the last word missing from each of them (e.g., “most cats see very well at”) and participants are asked to provide a word to complete the sentence that is completely unconnected in any way. This subtest requires the suppression of a strongly activated response (e.g., “night”) before the generation of the unconnected one (e.g., “banana”). The time needed to provide the word in each sentence is added and converted in a scale score using the table provided in the response sheet. Scale score of Section 2 provides a measure of verbal suppression. The Hayling Sentence Completion Task section 1 scaled score has been used as measure of option generation as proposed by Sinha et al. (2013). The Hayling Sentence Completion Task section 2 scaled score has been used as measure of action initiation and inhibition.

Kirby Monetary Choice questionnaire. Temporal discounting (i.e., the tendency to discount the value of delayed rewards) (Appendix R) was assessed with the 27-items self-administered Kirby Monetary Choice questionnaire (Kirby et al., 1999). For each item, participants chose between a smaller immediate reward or a larger one provided in the future. The amount of immediate and delayed rewards, as well as the number of days for receiving the delayed reward, change across items. Temporal discounting was assessed calculating the proportion of choices of the delayed rewards following Myerson et al. (2014), instead of the k-parameter of the hyperbolic discounting function proposed by Kirby et al. (1999). The k value method involves matching individual patterns of response to those predicted based on

individual differences in the rate parameter (k) of a hyperbolic discounting function: V= A/(1+*k*D), where V is the subjective value of reward amount A that it is available after a delay of D time units. Conversely, with the proportion method responses are scored as the proportion of questions on which the individual chose the delayed, larger reward over the immediate but smaller one (i.e., number of choices of a delayed reward divided by the number of questions). Individuals' scores calculated using the proportion method and the k values are very strongly correlated (rs > .97) (Myerson et al., 2014) but, conversely to the k value, the proportion method does not rely on assumptions regarding the mathematical form of the discounting function which may not be appropriate (Myerson et al., 2014). A simple hyperbola is not the best way to describe delay discounting functions at individual or group levels (Green & Myerson, 2004; Myerson & Green, 1995). The Kirby Monetary Choice questionnaire has been used as measure of option selection, as suggested by Sinha et al. (2013).

Go/No-Go. The Go/No-Go test (Appendix S) is part of the Test of Attentional Performance (Zimmermann & Fimm, 1995). The task assesses the ability to suppress unwanted motor responses. Participants have to respond to a specific stimulus ("Go-stimulus") and refrain from responding to another stimulus ("No-Go-stimulus"). Two types of stimuli (i.e., "+" and "x") appear in the centre of the computer's screen. Participants are instructed to press a computer key only when "x" appears. The main outcome is the number of false alarms (i.e., reactions to No-Go stimuli). The Go/No-Go task has been used as a measure of action initiation and inhibition (Kalis, Mojzisch, Schweizer, & Kaiser, 2008).

Brixton Spatial Anticipation Test. The Brixton Spatial Anticipation Test (Appendix T) (Burgess & Shallice, 1997) is a visuospatial sequencing task of rule detection via feedback. Participants are provided with a 56 pages stimuli book. Each page contains 10 circles with one coloured blue. The blue one moves position in each page according to various patterns that come and go without any warning. Participants are shown one page at time and asked to guess where the blue circle will be in the next page, inferring a rule based on what they saw in the previous pages. When the rule changes, participants have to find the new pattern. The errors are summed and converted in a scale score using the table provided in the scoring sheet. The Brixton Spatial Anticipation Test scale score has been used as measure rule detection via feedback processing which may be considered as part of the learning stage of Sinha et al. (2013)'s framework.

Logical Memory. The Logical Memory (Appendix U) subtests of the Wechsler Memory Scale IV edition (Wechsler, 2009b) are standardized tests of immediate and delayed free recall memory. In the Logical Memory I, which assesses immediate recall, participants are provided with two short stories (story A and B) made of 25 items each. For each story, participants are instructed to listen carefully and try to remember it as best as they can. Once the story has been read, participants have to recall it using the same words as far as it is possible (immediate recall). Logical memory I score is the number of items correctly recalled (maximum score is 75). Logical Memory II, which assesses delayed recall, is provided after a period of 30 minutes filled with non-verbal tasks to avoid interference effects. Participants are asked to recall both stories using the same word as far as it is possible. Logical memory II score is the number of items correctly recalled with a delay (maximum

score is 50). For the study, an immediate (Logical Memory I, story A plus first recall of Story B) and a delayed (Logical Memory II, story A plus story B) raw recall scores were considered.

Affective and Motivational measures

Barratt Impulsiveness Questionnaire. The Barratt Impulsiveness Questionnaire (BIS-11; (Patton et al. 1995)) (Appendix V) is a 30-items self-report questionnaire developed for assessing personality/behavioural construct of impulsiveness. The BIS-11 has been extensively used both in research and clinical settings (Stanford et al., 2009). In the BIS-11, impulsiveness is considered as a multi-dimensional construct comprising three sub-traits: attentional, motor, and non-planning impulsiveness. Attentional impulsiveness concerns the inability to focus attention (e.g., "I don't pay attention"), motor impulsiveness concerns acting without thinking (e.g., "I act on the spur of the moment"), and non-planning impulsiveness involves the lack of premeditation or future planning (e.g., "I am more interested in the present than in the future") (Stanford et al., 2009). Each item is scored on a 4-points scale with 1 meaning "rarely/never" and 4 meaning "almost always/always". Eleven of the 30 items are reverse scores. In order to describe the multi-dimensional aspects of impulsivity, both the total and the three sub-traits scores have been considered.

Starkstein Apathy Scale. The Starkstein Apathy Scale (SAS) (Starkstein et al., 1992) (Appendix W) is a 14-items self-report questionnaire developed for assessing apathy. The SAS has been specifically developed for PD as a short and less demanding version of the Apathy Evaluation Scale (Marin, Biedrzycki, &

Firinciogullari, 1991). A task force commissioned by the Movement Disorder Society (MDS) considered the SAS a recommended tool for screening and assessing apathy severity in PwP (Leentjens et al., 2008). In the SAS, each item is scored on a 4-points scale, ranging from "not at all" to "a lot". Items from 1 to 8 are scored considering "not at all" as the highest level of apathy (e.g., "are you interested on learning new things?"), whilst items from 9 to 14 are scored considering "not at all" as the lowest level of apathy (e.g., "are you indifferent to things?"). Each item is summed to obtain a total score, higher scores represent higher levels of apathy.

Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) (Appendix X) is a 14-items self-report scale composed by two subscales, one assessing depression (HADS-D) and one assessing anxiety (HADS-A). Seven items contribute to the HADS-D subscale scale (e.g., "I still enjoy the things I used to enjoy") and 7 items contribute to the HADS-A subscale (e.g., "I get sudden feelings of panic"). Each item is scored on a 4-points scale ranging from 0 to 3. Higher scores indicate higher anxiety and/or depression levels.

A task force commissioned by the MDS recommended the use of the HADS-D for screening depression in PD since the low number of somatic items included (Schrag et al., 2007). The evaluation of depression in PD is complicated by the presence of PD-related motor symptoms that may overlap with depression-related motor symptoms (e.g., agitation, retardation). The HADS-D should be cautiously used for assessing the degree of depressive states since it lacks items investigating most severe symptoms such as suicidal ideation or psychotic features (Schrag et al., 2007). The HADS-A has shown good psychometric characteristics in PD; it

demonstrates good reliability and it lacks floor and ceiling effects (Leentjens et al., 2011).

Statistical analysis. Data were analysed with Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp., 2012). Cohen's *d* effect sizes and 95% confidence intervals were analysed using JASP software version 0.10.2 (JASP Team, 2019), as Cohen's *d* effect sizes are not provided by SPSS.

For continuous variables, Shapiro-Wilks test was used to check normality of distribution. When variables were not normally distributed, log or square root transformation was applied. Normally distributed transformed variables were analysed using parametric tests. When transformation did not solve normality, both parametric and nonparametric analyses were used to compare groups. Results of both types of analysis were comparable, therefore only results of parametric tests were considered, as they assure greater statistical power. Bonferroni was used as a post hoc test when ANOVA yielded significant differences between the three groups. Fisher's exact test or Fisher-Freeman-Halton test were applied to categorical variables. $P < 0.05$ was set as a significance threshold for all the tests, except when Bonferroni correction for multiple comparisons was applied. Student t-test was applied to continuous variables for PD group's performances comparison. Missing data have been excluded pairwise.

For the BART, the average number of pumps on trials where balloons were cashed was compared between groups with a one-way ANOVA. Response to negative feedback was analysed with a 3x2 mixed-model ANOVA with the between-subjects factor group (ICB+, ICB-, healthy controls) and the within-subject factor condition (pre-burst, post-burst).

A composite score of memory was calculated (using z-scores) from the CAMCOG memory subtest, immediate and delayed logical memory. Performance on each of the ten cognitive measures was analysed separately with a series of one-way ANOVAs, and Bonferroni corrected $p < 0.005$.

An exploratory Spearman correlation analysis examined the relationship between a single discrepancy score, derived from the difference in the number of pumps pre- and post-balloon burst in the BART, and the separate measures of selective and divided attention, memory, executive function, set-shifting, temporal discounting, inhibitory control, and rule detecting via feedback processing. A smaller discrepancy score reflects smaller changes in risk-taking behaviour after balloon burst and loss of virtual money.

Results

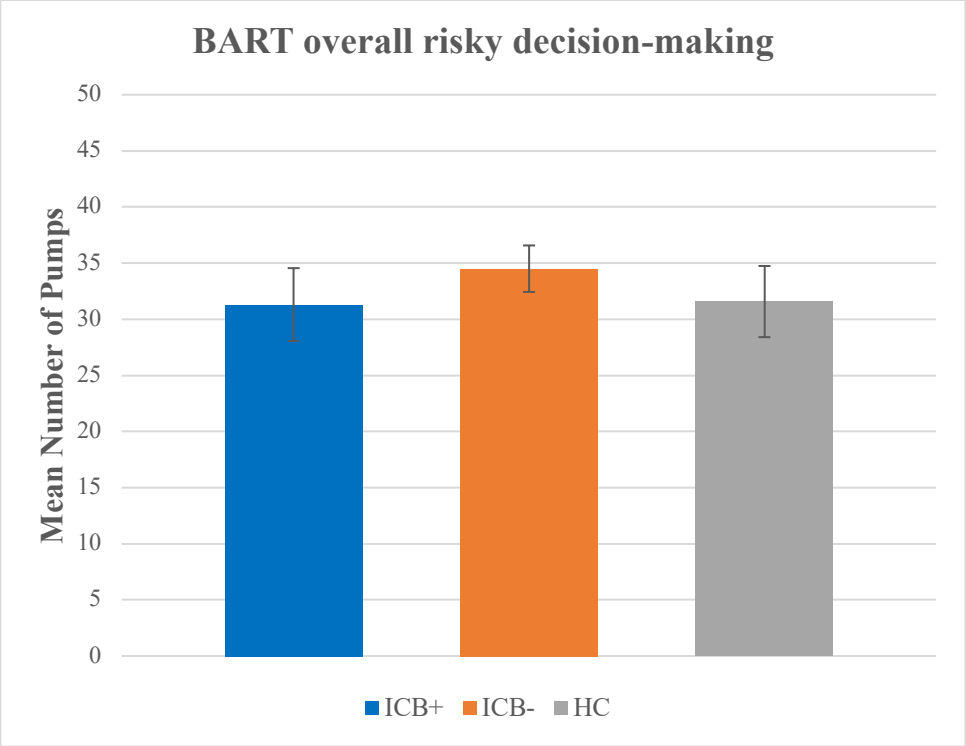
Incentive-driven decision-making task

In the BART, the three groups did not differ in the average number of pumps on trials where the balloon was cashed (ICB+: 31.32 ± 11.70; ICB-: 34.51 ± 7.17; HC: 35.58 ± 13.08; $F(2,39) <1$, $p = 0.73$, $\eta_p^2 = 0.02$; Table 3.5, Figure 3.4A).

A comparison of the number of balloon pumps pre- and post-burst revealed no main effect of group [$F(2,39) <1$, $p = 0.80$, $\eta_p^2 = 0.01$]. However, there was a main effect of feedback [$F(1, 39) = 11.23$, $p = 0.002$, $\eta_p^2 = 0.22$], indicating that the mean number of pumps was significantly lower post- vs. pre-burst (pre: 35.97 ± 2.11; post: 32.48 ± 2.26). The group x feedback interaction was also significant [$F(2, 39) = 3.31$, $p = 0.047$, $\eta_p^2 = 0.14$], reflecting the observation that both the HC and ICB- groups reduced their average number of pumps post-burst whereas the ICB+ group showed no change (Table 3.5, Figure 3.4B). The reduction of pumps post-

burst was significant for the HC [$t(16) = 4.30$, $p < 0.001$, $d = 1.04$, 95% CI [0.44, 1.63]] and for the ICB- group [$t(11) = 2.85$, $p = 0.02$, $d = 0.82$, 95% CI [0.15, 1.47]], but was not significant for the ICB+ group [$t(12) < 1$, $p = 0.89$, $d = -0.04$, 95% CI [-0.58, 0.51]].

A. Overall risky incentive-driven decision-making



B. Response to negative feedback

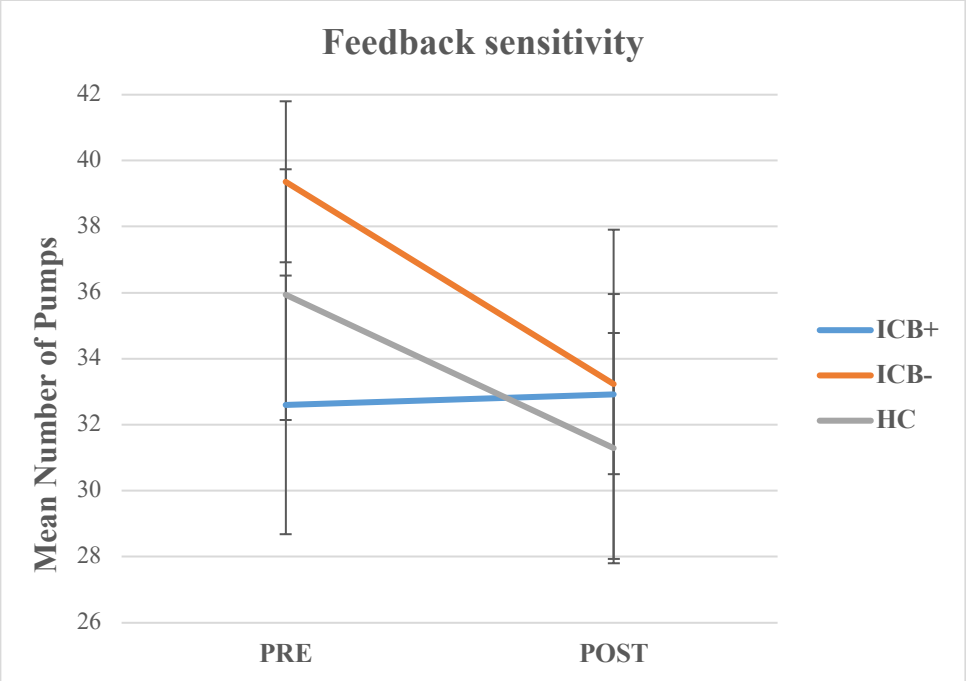


Figure 3. 4 Performances in the Balloon Analogue Risk Task (BART). A) Average number of pumps for cashed trials. The three groups did not differ in the average number of pumps, which reflects risk-taking behaviour. Higher scores represent

riskier behaviours. Error bars represent the standard error of the mean. B) Groups differ in the way they adjusted their behaviour after negative feedback. Negative feedback is expressed as the loss of money for trials in which a balloon burst. Both healthy controls (HC) and persons with Parkinson's disease (PwP) without impulsive-compulsive behaviours (ICBs) (ICB−) decreased the number of pumps after a negative feedback showing less risk-taking behaviour, whereas PwP with ICBs (ICB+) did not change their performance regardless of negative feedback. Error bars represent the standard error of the mean.

Table 3. 5 Performances in the Balloon Analogue Risk Task (BART) by groups and interactions.

Variables	**ICB+ (n=13)**	**ICB- (n=12)**	**HC (n=17)**	**F values**	***p***	**ES**
Average Adjusted Pumps	31.32 ± 11.70	34.51 ± 7.17	31.58 ± 13.08	$F(2,39) <1$	0.73	0.02
Negative feedback sensitivity	PRE: 32.6 ± 14.12	PRE: 39.36 ± 8.47	PRE: 35.94 ± 15.69	Main effect of feedback $F(1,39) = 11.23$	***0.002***	0.22
				Main effect of feedback*group $F(2,39) = 3.31$	***0.047***	0.14
	POST: 32.92 ± 18.01	POST: 33.23 ± 9.44	POST: 31.29 ± 14.38	Main effect of group $F(2,39) <1$	0.80	0.01

Legend. ICB+: Parkinson's PwP with ICBs; ICB-: Parkinson's PwP without ICBs history; HC: healthy controls; SD: standard deviation; Average Adjusted Pumps: average number of pumps in cashed balloons; PRE: number of pumps for trails that immediately precede a balloon burst; POST: number of pumps for trails that immediately follow a balloon burst; ES: partial eta-squared effect size. Data are presented as mean ± standard deviation.

Cognitive test battery

There were no significant differences between the three groups for any of the ten cognitive measures considered part of the four stages of incentive-driven decision-making using the strict Bonferroni corrected $p < 0.005$ (Table 3.6).

Table 3. 6 Results of the cognitive test battery.

Variables	ICB+ (n=13)	ICB- (n=12)	HC (n=17)	F values	*p*	ES
			(i) Option Generation Stage			
TMT-A	0.31 ± 0.48, 0	0 ± 0, 0	0.18 ± 0.39, 0	$F(2,39)=2.209$	0.12	0.10
Divided attention	25.08 ± 3.75, 24	26.08 ± 5.82, 27	28.65 ± 2.50, 30	$F(2,39)=3.056$[a]	0.06	0.14
TMT-B[§]	1.17 ± 1.53, 0.5	0.64 ± 0.67, 1	0.65 ± 0.93, 0	$F(2,37)<1$	0.39	0.05
Hayling section 1	5.46 ± 1.13, 6	4.75 ± 1.81, 6	5.65 ± 0.93, 6	$F(2,39)=1.206$[b]	0.32	0.01
CAMCOG EF	21.15 ± 2.97	20.83 ± 5.22	24.35 ± 2.37	$F(2,39)=6.109$[b]	0.008	0.14
			(ii) Option Selection Stage			
Kirby[§§]	0.47 ± 0.14	0.34 ± 0.12	0.49 ± 0.13	$F(2,38)=4.658$	0.02	0.20
			(iii) Action Initiation and Inhibition Stage			
GNG	1.15 ± 1.28, 1	1.08 ± 2.27, 0	0.47 ± 0.72, 0	$F(2,39)<1$	0.38	0.05
Hayling section 2	5.31 ± 1.11	5.92 ± 0.67	6.06 ± 0.56	$F(2,39)=3.519$	0.04	0.15
			(iv) Learning Stage			
Memory composite score	0.03 ± 0.83	-0.54 ± 1.05	0.35 ± 0.64	$F(2,39)=4.036$	0.03	0.17
Brixton	3.46 ± 2.37, 2	3.5 ± 2.54, 2	5.65 ± 2.29, 6	$F(2,39)=4.173$	0.02	0.18

Legend. ICB+: PwP with ICBs; ICB-: PwP without ICBs history; HC: healthy controls; TMT-A: Trail Making Test Part A number of errors; TMT-B: Trail Making Test Part B number of errors; Kirby: Kirby Monetary choice questionnaire total score; CAMCOG EF: Cambridge Cognitive Examination executive function subtest score; GNG: Go/No-Go false alarms; Hayling section 1: Hayling Sentence Completion task – section 1; Hayling section 2: Hayling Sentence Completion task – section 2; ES: partial eta-squared effect size (or adjusted omega squared when Welch's one-way ANOVA has been calculated). Data are presented as mean ± standard deviation, median. Median is reported for variables that were not normally distributed. [a]Log10 transformed data. [b]Welch test (Levene test statistically significant). [§]two PwP (one from the ICB+ and one from the ICB- groups) were excluded from the analysis because they were not able to complete the TMT-B task. [§§]one PwP from the ICB+ group refused to complete the Kirby Monetary Choice Questionnaire of temporal discounting and was excluded from the analysis.

Affective and motivational factors

HADS total score was significantly different [$F(2, 38) = 8.31$, $p = 0.001$, $\eta_p^2 = 0.30$]. Bonferroni's corrected post hoc t tests revealed higher scores in the ICB+ group (3.68 ± 0.80) compared to HC (2.12 ± 1.08, p=0.001, d = -1.80, 95% CI [-13.79, -3.36]), but no difference between the ICB+ and ICB- (3.05 ± 1.18) groups (p = 0.43, d = -0.54, 95% CI [-9.23, 2.07]) or between ICB- and healthy controls (p = 0.068, d = -0.88, 95% CI [-10.21, 0.22]; Table 3.7). Anxiety subscale score was significantly different [$F(2, 38) = 3.68$, $p = 0.035$, $\eta_p^2 = 0.16$]. ICB+ group showed higher scores (8.25 ± 3.74) than HC (4.12 ± 3.31, p=0.032, d = -1.18, 95% CI [-7.89, -0.37]), but there was no difference between ICB+ and ICB- (6.42 ± 5.26) groups (p = 0.837, d = -0.40, 95% CI [-5.90, 2.24]) or between ICB- and HC (p = 0.432, d = -0.54, 95% CI [-6.06, 1.46]; Table 3.7). Depression subscale score was significantly different [$F(2, 38) = 22.25$, $p = 0.00001$, $\eta_p^2 = 0.49$]. HC (1.47 ± 1.01) had lower scores than ICB+ (5.92 ± 2.35, p = 0.000002, d = -2.63, 95% CI [-6.25, -2.64]) and ICB- (4.17 ± 2.52, p = 0.002, d = -1.51, 95% CI [-4.50, -0.89]), but there was no difference between ICB + and ICB- (p = 0.106, d = -0.72, 95% CI [-3.71, 0.21]; Table 3.7). Scores for apathy and impulsivity from the SAS and the BIS-11, respectively, did not differ between the three groups (Table 3.7).

Table 3. 7 Affective and motivational characteristics by groups.

Variables	ICB+ (n=13)	ICB- (n=12)	HC (n=17)	F values	*p*	ES
HADS	14.17 ± 5.72, 15.5	10.58 ± 7.45, 9.5	5.59 ± 3.97, 5	$F(2,38)=8.313^{a}$	***0.001***§	0.30
HADS-A	8.25 ± 3.74	6.42 ± 5.26	4.12 ± 3.31	$F(2,38)=3.683$	***0.035***§	0.16
HADS-D	5.92 ± 2.35, 6.5	4.17 ± 2.52, 3.5	1.47 ± 1.01, 1	$F(2,38)=22.25^{b}$	***0.00001***§§	0.49
SAS	12.25 ± 4.75	11.66 ± 4.03	9.82 ± 2.94	$F(2,38)=1.593$	0.22	0.08
BIS-11	60.75 ± 10.28	58.33 ± 9.80	57.35 ± 10.59	$F(2,38)= <1$	0.68	0.02
BIS-11 Att	15.50 ± 3.45	14.58 ± 3.89	15.29 ± 3.50	$F(2,38)= <1$	0.80	0.01
BIS-11 Mot	21 ± 3.69	20.33 ± 3.60	20.24 ± 3.86	$F(2,38)= <1$	0.85	0.008
BIS-11 NP	24.25 ± 5.94	23.42 ± 5.25	21.82 ± 4.76	$F(2,38)= <1$	0.47	0.04

Legend. ICB+: PwP with ICBs; ICB-: PwP without ICBs history; HC: healthy controls; HADS: Hospital Anxiety and Depression scale total score; HADS-A: Hospital Anxiety and Depression scale anxiety subscale; HADS-D: Hospital Anxiety and Depression scale depression subscale; SAS: Starkstein Apathy scale; BIS-11: Barratt Impulsiveness questionnaire total score. BIS-11 Att: Barratt Impulsiveness questionnaire – attentional score; BIS-11 Mot: Barratt Impulsiveness questionnaire – motor score; BIS-11 NP: Barratt Impulsiveness questionnaire – non-planning score; ES: partial eta-squared effect size. One participant from the ICB+ group refused to complete the questionnaires. Data are

presented as mean ± standard deviation, median. [a]Squared root transformed data. [b]Welch test (Levene test statistically significant). [§]Post hoc comparison: HC < ICB+; HC = ICB-; ICB+ = ICB-. [§§] Post hoc comparison: HC < ICB+; HC < ICB-; ICB+ = ICB-.

Exploratory correlation analysis

The BART discrepancy score, reflecting the difference in the number of pumps pre- and post-burst, negatively correlated with the Go/No-Go false alarms [$r_s(42) = -0.34$, $p = 0.03$]. This finding suggests that the higher the sensitivity towards negative feedback, the fewer false alarms on the Go/No-Go task. No other correlations between BART discrepancy score and the cognitive outcomes were significant. Results for the full correlation matrix are presented in Table 3.8.

Table 3. 8 Correlation matrix.

Variable	TMT – A	TMT – B	DA	Hayling 1	CAMCOG EF	Kirby	GNG	Hayling 2	Brixton	Memory composite score
BART DS	0.85	0.20	0.10	0.18	0.55	0.47	***0.03***	0.65	0.22	0.62
TMT – A	—	***0.02***	0.22	0.79	0.17	0.29	0.15	0.64	0.72	0.82
TMT – B	—	—	0.11	0.35	***0.01***	0.90	***0.01***	0.81	0.49	0.47
DA	—	—	—	0.38	***< 0.0001***	0.35	***< 0.0001***	0.13	***< 0.0001***	***0.03***
Hayling 1	—	—	—	—	***< 0.0001***	***0.03***	0.87	0.14	0.25	***0.002***
CAMCOG EF	—	—	—	—	—	**0.06**	***0.02***	0.10	***< 0.0001***	***< 0.0001***
Kirby	—	—	—	—	—	—	0.43	0.67	0.62	***0.008***
GNG	—	—	—	—	—	—	—	0.71	***< 0.0001***	0.11
Hayling 2	—	—	—	—	—	—	—	—	0.33	**0.06**
Brixton	—	—	—	—	—	—	—	—	—	***0.03***

Legend. BART DS: Balloon Analogue Risk Task Discrepancy score; TMT-A: Trail Making Test Part A number of errors; TMT-B: Trail Making Test Part B number of errors; DA: Divided attention hit rate; CAMCOG – EF: Cambridge Cognitive Examination executive function subtest score; Kirby: Kirby Monetary choice questionnaire total score; GNG: Go/No-Go false alarms; Hayling 1: Hayling Sentence Completion task – section 1; Hayling 2: Hayling Sentence Completion task – section 2; Brixton: Brixton scaled score.

Discussion

This study investigated cognitive processes associated with incentive-driven decision-making in PwP with and without ICBs. The relationship between ICBs and previously identified affective and motivational features was also explored.

In relation to the primary aim, it was predicted that the cognitive profile of the ICB+ group would be marked by an incentive-driven decision-making deficit on the BART. The BART provides an ecologically valid estimate of risky incentive-driven decision-making, and this is supported by correlations between performance on the BART and self-reported impulsivity and risk-taking behaviours in daily life, such as drugs abuse, alcohol abuse, number of sexual partners (Hopko et al., 2006; Lejuez, Aklin, Zvolensky, et al., 2003; Lejuez et al., 2002). The analyses of the present work however, failed to support this prediction. When the three groups of participants were analysed together, incentive-driven decision-making performance did not significantly differ between ICB+, ICB- and HC.

These findings, however, can be reconciled with the previous reports of BART in PD with ICBs (Claassen et al., 2011; Rao et al., 2010; Ricciardi et al., 2017). Risky decision-making on the BART successfully discriminated between ICB+ and ICB- in PD in relation to striatal BOLD response, where activation was diminished in ICB+ compared to ICB- (Rao et al., 2010), but abnormal brain activation in ICB+ was not mirrored by increased behavioural risk-taking. Furthermore, a medication withdrawal study showed that DRT increased risk-taking behaviour in ICB+ reflecting an interaction between group and medication state, but there were no differences in incentive-driven decision-making behaviour between ICB+ vs. ICB- PwP (Claassen et al., 2011).

These previous negative findings were suggested to depend on the use of a modified BART version, since a reduced range of possible pumps was found to be less sensitive to individual variability in task performance and therefore diminished the likelihood of detecting differences in risk-related constructs and self-report real world behaviours (Lejuez et al., 2002).

The present BART data, which showed that risk-taking related incentive-driven decision-making is spared in the cohort of ICB+ in comparison to ICB- and HC, together with results of the cognitive battery, offers an alternative explanation. According to Sinha et al. (2013), incentive-driven decision-making is dependent on option generation, option selection, action initiation and inhibition, and learning stages. Therefore, the likelihood of incentive-driven decision-making impairment will depend on the nature and extent of impairments within and across these four stages. The present study showed that cognitive processes underlying option generation, selection, and action initiation and inhibition in ICB+ were not different from other groups. However, in the BART, an interaction between negative feedback and group was found, suggesting an impairment in the learning stage of incentive-driven decision-making process, that, despite being present, it is probably not by itself sufficient to affect overall performance. Interestingly, incentive-driven behaviour after negative feedback on the BART was significantly different in ICB+, but performance on the cognitive tasks related to learning did not differ across groups. Therefore, learning appears not to be abnormal in PwP with ICBs, unless reward is involved. The findings of the present study are in keeping with the notion that learning and reward are supported by two separate cortico-striatal-thalamocortical circuits: the associative and limbic circuits, respectively (Alexander, DeLong, & Strick, 1986; Chudasama & Robbins, 2006). The associative circuit links

the dorsolateral prefrontal cortex with the dorsal caudate nucleus, and the limbic circuit links the ventral striatum with the ventral medial prefrontal cortex, orbitofrontal cortex, dorsal anterior cingulate cortex, amygdala and hippocampus (Vriend, Pattij, et al., 2014). It could be speculated that there is a differential dopaminergic modulation of these two circuits in PwP.

Abnormal response to negative feedback deficit was frequently reported in PD (Di Rosa, Schiff, Cagnolati, & Mapelli, 2015; Frank et al., 2004; Jocham & Ullsperger, 2009; Volpato et al., 2016). The present study may extend this notion, by suggesting that this impairment is more severe in ICB+ PwP. According to Claassen et al. (2011), negative feedback processing was scored by comparing the number of pumps on the trials that immediately precede to those on trials immediately following a balloon burst. Sensitivity toward negative feedback should result in decrease in risk-taking behaviour after a burst. Interestingly, reduced sensitivity to negative feedback in ICB+ was found, while Claassen et al. (2011), failed to report differences between groups. As discussed above, these conflicting findings could be interpreted as due to differences on BART tasks used. Lower ranges of possible pumps could have decreased the variability across the overall score, as well as the trials considered for the negative feedback analysis.

According to event related potential studies, negative feedbacks in BART are processed in the anterior cingulate cortex (ACC) (Schultz, 1998, 2010), and are related to the reinforcement learning processes in the brain (Holroyd & Coles, 2002), and the phasic dopaminergic dip signals (Frank et al., 2004). The ACC uses this signal to learn which action should be selected and executed. This provides a mechanism through which actions and events are linked to their outcomes with the

goal of supporting decisions that maximize the opportunity to encounter reward in the future (Cockburn & Frank, 2011).

Every time an outcome is better than expected or an unpredicted reward is received, DA neurons increase their phasic firing activity and a positive prediction error is generated. Also, every time an outcome is worse than expected or predicted reward is not delivered, there is a phasic dip in the DA neurons firings and a negative prediction error is generated (Schultz, 1998, 2010). DRT could prevent the DA neurons dip associated with negative feedback, as PwP in "off" state are better when learning from negative than positive feedback, but they behave in the opposite way when "on" medication (Frank et al., 2004). In both cases, not correctly generated prediction errors might lead toward abnormal links between actions and outcomes and impulsive behaviours may be facilitated.

In the present study, the exploratory correlation analysis revealed a negative correlation between the BART discrepancy score and the number of false alarms in the Go/No-Go task supporting the importance of negative feedback processing for impulse control. The more participants decrease their risky behaviour after a negative feedback, the fewer false alarms they make on the motor impulsivity task.

It was also predicted that ICB+ would be characterized by increased impulsivity, and more symptoms of depression and anxiety but not apathy. Conversely from predictions, impulsivity levels were comparable between the three groups. BIS-11, which has not been validated in PD yet, may fail to differentiate between ICB- and ICB+ due to impulsivity presenting as a continuum of severity in PD despite the absence of clinical ICBs. Comparable BIS-11 total score between ICB+ and ICB- is in keeping with other reports (Antonini et al., 2011; Marín-Lahoz et al., 2018; Mosley et al., 2019; Tessitore, De Micco, et al., 2017). As BIS-11 is a

self-report tool, it is also possible that lack of awareness of impulsive behaviour in ICB+ may have resulted in comparable scores between PD groups.

Depression and anxiety were found to be significantly higher in the ICB+ group than in HC, but comparable between PD groups. The lack of differences between PD groups on the HADS score precludes any strong statement about the role of depression or anxiety in ICBs. Nonetheless, the fact that ICB+ and HC significantly differ on the HADS score may suggest one of two not mutually exclusive explanations. The first is that higher depression and anxiety levels might increase vulnerability toward ICBs in PD. Depression often precedes PD diagnosis by several years (Ishihara & Brayne, 2006; Tolosa, Gaig, Santamaría, & Compta, 2009) and both anxiety and depression symptoms are higher in PD than in the general population (Lieberman, 2006; Prediger, Matheus, Schwarzbold, Lima, & Vital, 2012). In a subset of vulnerable PwP, depression and anxiety symptoms could increase the risk of developing ICBs as coping mechanisms (Delaney, Leroi, et al., 2012; Delaney, Simpson, et al., 2012). This hypothesis is supported by retrospective studies that showed higher baseline depression scores on drug naïve PwP who later developed ICBs compared to PwP who did not (Marín-lahoz et al., 2019; Vriend, Nordbeck, et al., 2014). Second, depression and anxiety could result as a consequence of ICBs negative implications in PwP and caregivers, as supported by reports of reduced quality of life in PwP with ICBs (Erga et al., 2020; Leroi et al., 2011; Phu et al., 2014).

Limitations

First, the study is limited by small sample size and therefore low statistical power which may have reduced the likelihood to find the true effect. Therefore, any

interpretation of the study's findings should be cautiously done. Underpowered studies are frequent in the ICBs in PD literature, as supported by a meta-analysis in which the 50% of the studies included 20 or less participants in each group (Santangelo, Raimo, & Barone, 2017). There are several possible explanations for low recruitment rates. Participants are vulnerable individuals affected by a neurological condition, progressive in nature and associated with motor as well as affective and cognitive disabilities. ICBs may be perceived with a sense of guilt and embarrassment, making people less keen on taking part in research.

Second, in the BART not all the four components of the incentive-driven decision-making framework could be measured, but only risk-taking behaviour after negative feedback, which it was interpreted as part of the learning stage. The framework's components were assessed with the cognitive battery that was not significantly different between groups. The negative findings of the cognitive battery prevent any robust conclusion on the component(s) involved in the abnormal behaviour in PwP with ICBs. For example, ICB+ may not modify behaviour following negative feedback because of abnormal option selection mechanisms, such as increased salience of rewarding stimuli or hypersensitivity to reward (Drew et al., 2020). Further studies should include a task that can be broken down in the four different components of Sinha's framework. It is also possible that the tasks used do not provide adequate risk-reward valence to examine the processes associated with the incentive-driven decision-making stages (Yücel et al., 2018), or they may be insufficiently demanding for detecting between groups differences.

Third, healthy controls had significant higher scores in the WTAR, which is a measure of crystallized intelligence. This is unlikely to have affected the results since participants showed comparable performances in CAMCOG, an extensive

cognitive evaluation. Furthermore, since the comparable WTAR performances of the two PD groups it is unlikely that abnormal responses to negative feedback in PwP with ICBs were linked to crystallized intelligence.

Fourth, daytime sleepiness was significantly higher in PwP with ICBs than healthy controls. However, it is unlikely that sleepiness levels could have affected the study results, since comparable outcomes in cognitive evaluation were found. Increased daytime sleepiness has already been reported in PwP with ICBs (O'Sullivan, Loane, et al., 2011; Pontone et al., 2006; Scullin et al., 2013), probably because both represent side effects of DRT, especially DA agonists.

Fifth, ICBs were diagnosed with a semi-structured interview following diagnostic criteria. This point might make direct comparison to previous studies using QUIP-rs, a tool specifically validated in PD with ICBs, difficult. Nonetheless, the more conservative approach used in this study assured that only PwP with clinically relevant ICBs were categorized as PD with ICBs.

Conclusions

This study demonstrates that reduced negative feedback sensitivity is a cognitive feature of ICBs in PD which could account for impulsive behaviour in situations that involve both rewards and punishments. In addition, ICBs in PD are associated with increased anxiety and depression than the general population.

Conversely to predictions, no differences between groups were found in other cognitive measures. The low statistical power impedes any firm conclusion about the involvement of cognitive, affective and motivational processes in ICBs in PD. To overcome this limitation, a systematic review and meta-analysis has been done (Study 2). Furthermore, to test the robustness of the BART findings, replicability of

Study 1 has been tested in a separate larger sample of PwP (Study 3). Findings have been further extended exploring, in a subset of PwP taking part in Study 3, sensitivity toward negative feedback by combining two units of assessments, i.e., behaviour and neurophysiology (Study 4).

Key Findings

- Compared to ICB- and HC, ICB+ do not change their risky behaviour after a negative feedback;
- ICB+ show increased anxiety and depression levels than HC;
- Sensitivity toward negative feedback negatively correlates with motor inhibition as measured by the number of false alarms in the Go/No-Go task.

Study 2: Systematic review and meta-analysis of cognitive affective and motivational correlates of Impulsive-compulsive behaviours in Parkinson's disease[2]

Abstract

Background: Cognitive, affective and motivational correlates of ICBs in PwP under DRT are debated. In the previous study (Study 1), PwP with ICBs were found not to change their risky behaviour after a negative feedback. No between groups differences in the cognitive measures were found. Finally, PwP with ICBs show increased levels of anxiety and depression compared to healthy controls, which suggests that affective changes may increase vulnerability to ICBs or represent a consequence of ICBs. Although promising, findings are constrained by a small sample size which may have reduced the likelihood to find a real effect. This limitation has been overcome by the present study, which is a systematic review and meta-analysis of studies investigating cognitive, affective and motivational correlates of ICBs in PD.

Method: PubMed, Science Direct, ISI Web of Science, Cochrane, EBSCO databases were searched for studies published between January 1st 2000 and March 3rd 2017 comparing cognitive, affective and motivational measures in PwP with vs. without ICBs. Exclusion criteria were conditions other than PD, substance and/or alcohol abuse, dementia, drug naïve PwP, cognition assessed by self-report tools.

[2] Martini, A., Dal Lago, D., Edelstyn, N.M.J., Grange, J.A., Tamburin, S. (2018). Impulse control disorder in Parkinson's disease: a meta-analysis of cognitive, affective, and motivational correlates. *Frontiers in Neurology,* 9, 654

Results: 10,200 studies were screened (title, abstract), 79 full-texts were assessed, and 25 were included (ICB+: 625 PwP; ICB-: 938). Compared to ICB–, ICB+ showed worse performance in incentive-driven decision-making (SMD = 0.42 [0.02, 0.82], $p = 0.04$) and set-shifting tasks (SMD = −0.49 [95% CI −0.78, −0.21], $p = 0.0008$). ICBs in PD was also related to higher self-reported rate of depression (SMD = 0.35 [0.16, 0.54], $p = 0.0004$), anxiety (SMD = 0.43 [0.18, 0.68], $p = 0.0007$), anhedonia (SMD = 0.26 [0.01, 0.50], $p = 0.04$), and impulsivity (SMD = 0.79 [0.50, 1.09], $p < 0.00001$). Heterogeneity was low to moderate, except for depression ($I^2 = 61\%$) and anxiety ($I^2 = 58\%$).

Conclusions: ICBs in PD are associated with worse set-shifting and incentive-driven decision-making, and increased depression, anxiety, anhedonia and impulsivity, but not apathy.

Introduction

ICBs are recognized as side-effect of DRT, mainly DA agonists and levodopa (Weintraub et al., 2010), however their pathophysiology is unclear.

It has been hypothesised that, in vulnerable individuals, DRT used to restore DA levels in nigrostriatal circuit may overstimulate the less severely affected mesocorticolimbic circuitry (Cools & Robbins, 2004). Mesocorticolimbic overstimulation may disrupt prefrontal-dependent cognitive function, affect and motivation and thus increase vulnerability to ICBs. According to this view, in medicated PwP, we should expect a correlation between ICBs and cognitive, affective and motivational factors. However, data in the literature are inconclusive.

Studies on cognition, affective processing and motivation conducted in small cohorts of PwP with and without ICBs (i.e., n: 17-155 PwP) yielded inconsistent findings with respect to cognitive abilities in PwP with ICBs. Some studies reported worse performance in executive function, including set-shifting (Biundo et al., 2011, 2015; Santangelo et al., 2009; Tessitore et al., 2016; Tessitore, Santangelo, et al., 2017; Vitale et al., 2011), working memory (Djamshidian et al., 2010), concept formation and reasoning (Santangelo et al., 2009; Tessitore et al., 2016; Tessitore, Santangelo, et al., 2017), and incentive-driven decision-making (Djamshidian, O'Sullivan, Lees, et al., 2011; Housden et al., 2010; Leroi et al., 2013; Martini, Ellis, et al., 2018; Rossi et al., 2010; Voon, Gao, et al., 2011; Voon, Reynolds, et al., 2010) in PwP with vs. without ICBs. Conversely, other studies found similar performances for inhibition (Bentivoglio et al., 2013; Cera et al., 2014; Djamshidian, O'Sullivan, Lees, et al., 2011; Erga et al., 2017; Filip et al., 2018; Hlavatá et al., 2020; Marín-Lahoz et al., 2018; Martini, Ellis, et al., 2018; Ricciardi et al., 2017; Tessitore, Santangelo, et al., 2017), set-shifting (Mack et al., 2013; Martini, Ellis, et al., 2018;

Pineau et al., 2016), working memory (Bentivoglio et al., 2013; Biundo et al., 2011; Housden et al., 2010; Imperiale et al., 2018; Leroi et al., 2011; Piray et al., 2014), and incentive-driven decision-making (Bentivoglio et al., 2013; Biars et al., 2019; Cera et al., 2014; Joutsa et al., 2015; Pineau et al., 2016; Ricciardi et al., 2017). Finally, a single study reported better executive functions in PwP with ICBs (Siri et al., 2010).

Reports on affective factors are also inconclusive, as self-reported depression and anxiety were sometimes found to be associated with ICBs (Antonini et al., 2017; Biundo et al., 2017; Erga et al., 2017; Leroi et al., 2011; Marín-Lahoz et al., 2020; Navalpotro-Gomez et al., 2020; O'Sullivan, Loane, et al., 2011; Pineau et al., 2016; Pontieri et al., 2015; Santos Garcia et al., 2021; Vela et al., 2016; Wu et al., 2015), and sometimes not (Bentivoglio et al., 2013; Biundo et al., 2011, 2015; Cilia et al., 2008; Claassen et al., 2015; Filip et al., 2018; Mack et al., 2013; O'Sullivan, Djamshidian, et al., 2010; Piray et al., 2014; Tessitore et al., 2016; Verger et al., 2018; Vitale et al., 2011). Motivational factors such as self-reported apathy (Erga et al., 2017; Housden et al., 2010; Leroi et al., 2011; O'Sullivan, Loane, et al., 2011; Pontieri et al., 2015), anhedonia (Pettorruso et al., 2014; Pontieri et al., 2015), and impulsivity (Bentivoglio et al., 2013; Leroi et al., 2011; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Pettorruso et al., 2014; Pineau et al., 2016; Piray et al., 2014) appeared to be elevated in PwP with vs. without ICBs, although this has not been consistently reported (Marín-Lahoz et al., 2018; Martini, Ellis, et al., 2018; Mosley et al., 2019; Tessitore, De Micco, et al., 2017).

Inconsistency in previous studies' findings may be due to small sample size resulting in estimates of effects that are more biased than in large sample studies. A way to overcome this limitation is conducting a meta-analysis, which allows to

estimate effects in the population by combining the effect sizes from a variety of studies (Field & Gillet, 2010).

A recent meta-analysis identified several cognitive subdomains (i.e., concept formation, set-shifting, incentive-driven decision-making, and visuospatial abilities) to be worse in PwP with vs. without ICBs (Santangelo, Raimo, & Barone, 2017), but it included a mixed sample of medicated and drug naïve PwP that did not allow to explore the relationship between cognitive disturbances, DRT and ICBs. Moreover, it included PwP with comorbidities for substance abuse and/or dementia, two factors that could be independently associated with cognitive changes. Finally, cognitive but not affective and motivational factors were investigated, which impede to explore the relationship between cognition-emotion and cognition-motivation which is critical for understanding the broader context in which ICBs develop (Crocker et al., 2013; Sinha et al., 2013). This is supported by evidences of DA dysregulation in the pathophysiology of impulsivity, apathy, and anhedonia in gambling disorder, drug addiction, and PD (Bloomfield, Morgan, Kapur, Curran, & Howes, 2014; Clark et al., 2012; Sinha et al., 2013).

To overcome the limitation of small sample size of Study 1 (Martini, Ellis, et al., 2018) as well as reconcile discordant findings in the literature about cognitive, affective and motivational correlates of ICBs in medicated PwP, a systematic review and meta-analysis was conducted. Moreover, this work is meant to address the issues of a previous meta-analysis and to offer new information on this topic. To this aim, stricter inclusion and exclusion criteria were applied, by including only studies on PwP under DRT at the time of assessment and free from comorbid substance abuse and/or dementia. Moreover, studies investigating affective and motivational measures were also included, so that any cognitive change could be interpreted

within the broader context of cognition-emotion and cognition-motivation relationships (Crocker et al., 2013; Sinha et al., 2013). A clear understanding of cognitive, affective and motivational changes in ICBs may indirectly increase the understanding of ICBs pathophysiology and in turn its management.

Aims

This study aims to summarize published literature on ICBs in PD to understand which cognitive processes are associated with ICBs in medicated PwP. A secondary aim was to examine affective and motivational correlates of ICBs in PD.

Method

Study design, participants and comparators

A systematic review and meta-analysis were performed to identify cognitive, affective and motivational factors associated with ICBs in PD under DRT (ICB+). The comparator group was individuals with PD but no history of ICBs (ICB-).

Search strategy

On June 26th 2016, PubMed, Science Direct, ISI Web of Science, Cochrane, EBSCO were searched for peer-reviewed papers in English, Italian and Spanish published since January 2000, when the first report of ICBs development after dopaminergic medication initiation was reported (Seedat et al., 2000). The systematic review was further updated on March 8th 2017.

Studies were identified using the following string (Callesen, Scheel-Krüger, Kringelbach, & Møller, 2013) in PubMed: "(Parkinson's disease) AND (impulse control disorders OR impulsivity OR cognition OR decision-making)". The search

strategy for the other databases included (Parkinson's disease) AND (impulse control disorders), then (Parkinson's disease) AND (impulsivity), then (Parkinson's disease) AND (cognition), and (Parkinson's disease) AND (decision-making). A total of 40,672 papers were identified. After exclusion of duplicates, 10,200 papers were title and abstract screened.

Selection criteria

Studies were included if: a) PwP were under DRT; b) ICBs assessment was performed in a reliable manner with the QUIP, the QUIP-rs, the MIDI, clinical interview based on diagnostic criteria, or a combination of these; c) performances of ICB+ were compared with ICB-; d) cognitive, affective and/or motivational measures were reported. A further inclusion criterion was independence of samples. Only baseline data for prospective studies and the study with the largest sample for multiple studies published by the same author(s) were included.

Reviews, case studies, commentaries, letters, abstracts and dissertations, and postal surveys were excluded. Studies including drug naïve PwP were also excluded since the focus was on ICBs developed as a DRT side-effect. Studies in which PwP underwent non-pharmacological treatments such as Deep Brain Stimulation (DBS) were excluded. This criterion was based on controversial reports of either ICBs amelioration or ICBs appearance after DBS (Kim et al., 2018; Samuel et al., 2015), and the notion that DBS may worsen some cognitive outcomes (Combs et al., 2015). Studies including participants with dementia and drug/alcohol abuse were excluded, as these conditions might be independently associated with cognitive and neuropsychiatric changes (American Psychiatric Association, 2013; Fattore & Diana, 2016; Lee et al., 2015). Other exclusion criteria were: cognition assessed by self-

report measures or by general screening tools (e.g., MMSE) because of their limited specificity and sensitivity (Hoops et al., 2009). Finally, to ensure that the ICB- group was indeed ICB-free, studies where PwP were not screened for the presence of all types of ICBs were excluded.

Data extraction

Following exclusion of duplicate and irrelevant articles through title and abstract screening, 79 papers were included for full-text evaluation. Reference lists of these studies were manually searched to identify additional relevant articles, and two papers were included at this stage.

Two reviewers (AM, DDL) independently screened titles and abstracts using Rayyan software (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016), and three reviewers (AM, DDL, ST) independently evaluated papers selected for full-text examination. Disagreements were resolved through discussions. Disagreement concerned one paper (Merola et al., 2017) over the 75 selected for full-text examination (inter-rater agreement: 98.67%). Disagreement concerned the lack of a statement indicating that PwP with dementia were excluded. Twenty-five articles were included for quantitative analysis. The PRISMA diagram of the study is presented in Figure 3.5.

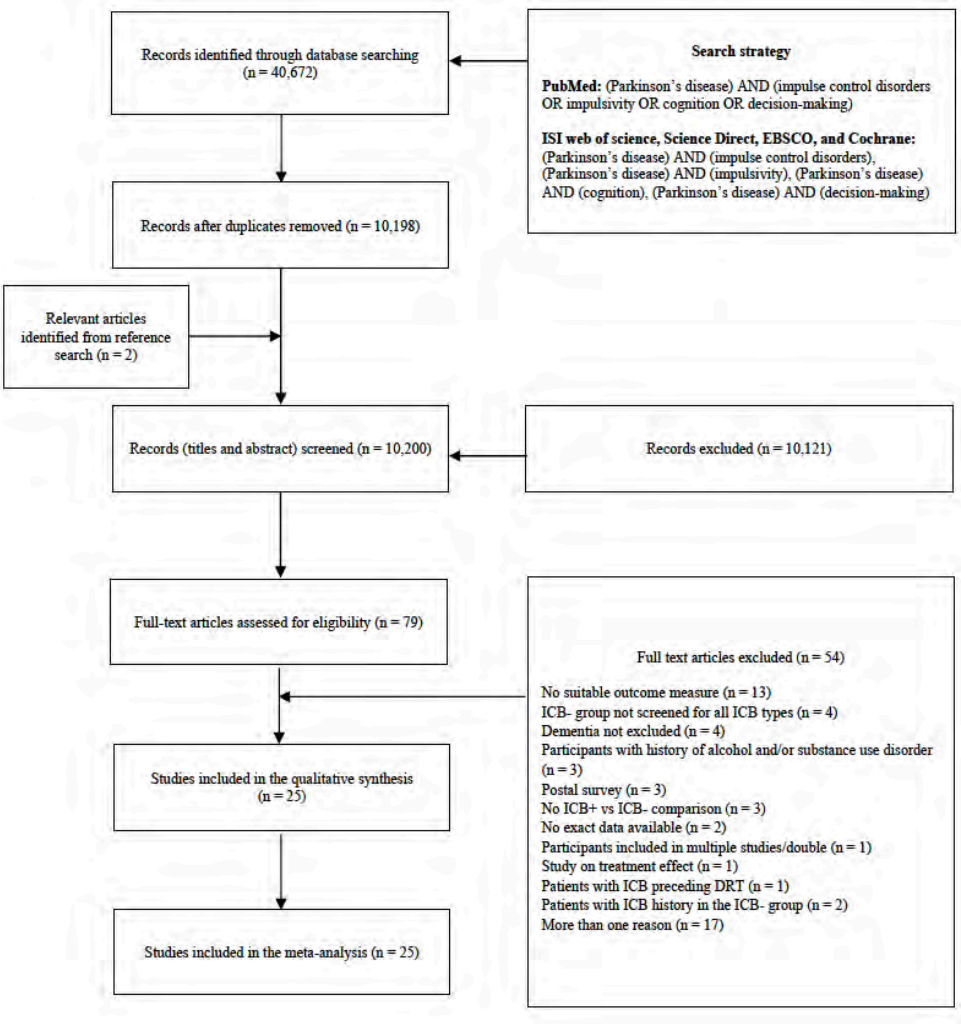


Figure 3. 5 PRISMA diagram of the study (www.prisma-statement.org). ICB: impulsive-compulsive behaviour; ICB+: persons with Parkinson's disease (PwP) and impulsive-compulsive behaviours; ICB-: PwP without impulsive-compulsive behaviours; DRT: dopamine replacement therapy.

Corresponding authors of five studies were contacted for exact data. Means and standard deviations were obtained for two studies, which reported median and interquartile ranges (Pineau et al., 2016; Vela et al., 2016), according to a proposed formula (Hozo, Djulbegovic, & Hozo, 2005). Two reviewers (AM, DDL) independently extracted the following data: sample size, age at evaluation, age at PD onset, PD duration, education (years), H&Y stage, UPDRS-III ON-medication, depression, antidepressants use, antipsychotics use, total LEDD (mg), levodopa LEDD (LD-LEDD, mg), dopamine agonist equivalent daily dose (DAED, mg), outcomes, ICBs screening tool, ICBs type, and statistics.

Primary outcomes were cognitive, affective and motivational scores. Cognitive tests were categorized on the basis of the main cognitive process involved (Lezak et al., 2012). The categories were 'memory' (short-term verbal and visuospatial memory, long-term verbal and visuospatial memory); 'working memory'; 'attention'; 'executive function' (concept formation and reasoning, concept formation sort and shift, set-shifting, inhibition, cognitive flexibility, incentive-driven decision-making); 'visuospatial abilities'; 'language'; 'apraxia'; 'novelty seeking'; 'incentive salience' and 'data gathering'. Concept formation and reasoning relates to the development of ideas based on the common properties of objects, events, or qualities using abstraction and generalization processes whilst concept formation sort and shift requires to form a sorting principle and apply it (sort), and then abandon it and switch to a different principle (shift) (Lezak et al., 2012). Affective and motivational measures were categorized as depression, anxiety, anhedonia, apathy and impulsivity.

Cognitive processes assessed in a single study (i.e., novelty seeking, incentive salience, data gathering, apraxia) were not included in the meta-analysis.

When a study reported multiple measures for the same outcome, the most relevant one was chosen by two reviewers with expertise on neuropsychological assessment (AM, DDL).

Data analysis

Data were analysed using ReviewManager v5.3 (The Nordic Cochrane Centre, 2014). Effect size was estimated as standardized mean difference (SMD), which is comparable to Hedges' adjusted g value. Effect sizes of 0.2, 0.5 and 0.8 or more are considered as small, moderate and large, respectively (Cohen, 1977). Cochran's Q (χ^2) was used to test heterogeneity between studies. The degree of heterogeneity was quantified by I^2, values of which range between 0% and 100%. I^2 percentages of 25, 50, 75 are considered as low, moderate and high, respectively (Higgins, Thompson, Deeks, & Altman, 2003). Random-effect model was applied, as PwP differ in clinical (e.g., UPDRS-III ON medication range: 10.9 - 36.7) and demographic characteristics (e.g., age range: 54.6 – 71.4), therefore the true effect may vary from study to study. In contrast to fixed-effect models, random-effect models consider both within and between study variances. As heterogeneity was moderate to high for some outcomes (i.e., working memory, depression, anxiety, and apathy), the consequences of applying a fixed-effect model, which does not consider between studies variance, may result in type I error rate inflation (Field & Gillet, 2010). Conversely, if random-effect models are applied with effect sizes that vary only due to sampling error as when heterogeneity is low (i.e., short-term visuospatial memory, attention, concept formation reasoning, anhedonia), the consequences are less dramatic (e.g., using Hedges' method, the additional between-study effect size variance used in the random effect method becomes zero when sample effect sizes

are homogeneous, yielding the same result as the fixed effect method) (Field & Gillet, 2010). Moreover, following this approach, studies were not excluded because of their small sample size, because in random-effect models effect sizes are weighed by their variance, which is higher in smaller studies.

Two authors independently explored funnel plots for publication bias (AM, DDL), and incongruences were resolved by discussion with two other authors (ST, JAG). A funnel plot is a scatter plot of the effect estimates from individual studies against some measure of each study's size or precision (e.g., standard error) (Sterne et al., 2011). When there are no bias and high between study heterogeneity, the scatter plot will be due to sampling variation alone and it will resemble a symmetrical inverted funnel (Sterne et al., 2011). Funnel plots of outcomes with less than ten studies were not inspected since the power is too low to discriminate publication bias's asymmetry from chance (Sterne et al., 2011). Blinding of assessors (performance bias) and incomplete data outcome (attrition bias) were independently assessed for each study as "low risk", "high risk" or "unclear" by two reviewers (AM, DDL) following Cochrane Collaboration recommendations. Sensitivity analysis was performed by excluding one study at time and verifying its impact on the overall effect size. Sensitivity analysis was not performed for outcomes with two studies. Moderator analysis via meta-regression was performed using SPSS version 21.0 (IBM Corp., 2012). The underlying hypothesis was that variation among studies in effect size was associated with differences in age, years of education, disease duration, UPDRS-III score, H&Y score, total LEDD, LD-LEDD, and DAED. Moderator analysis was conducted only for outcomes in which there were at least ten studies to one covariate (Borenstein, 2009).

Results

After removal of duplicates, 10,200 records were screened by title and abstract, 79 full-text articles were assessed for eligibility, and 54 were excluded (Figure 3.5). Twenty-five studies were included in the meta-analysis. Demographic and clinical characteristics of the studies included in the meta-analysis is provided in Table 3.9. List of studies excluded at the full-text screening stage with reasons for exclusions is provided in the Appendix Y.

Table 3. 9 Characteristics of the studies included in the meta-analysis.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Education (y)*	H&Y	UPDRS-III (ON)*	Depression†	Antidep (N)
Bentivoglio et al. (2013)	ICB+: 17 (14) ICB-: 17 (11)	ICB+: 62.0 (10.1) ICB-: 63.9 (9.2)	NR	ICB+: 6.9 (3.8) ICB-: 7.3 (4.4)	ICB+: 8.7 (3.7) ICB-: 10.2 (4.4)	ICB+: 2.0 (0.8) ICB-: 2.3 (0.5)	ICB+: 23.8 (11.0) ICB-: 22.5 (6.9)	NO	ICB+: 2 ICB-: 4
Biundo et al. (2011)	ICB+: 33 (18) ICB-: 24 (17)	ICB+: 61.3 (10.2) ICB-: 70.4 (6.8)	ICB+: 53.2 (10.6) ICB-: 60.5 (10.0)	ICB+: 8.8 (4.8) ICB-: 8.9 (5.4)	ICB+: 11.8 (3.9) ICB-: 10.4 (4.8)	NR	ICB+: 30.2 (13.2) ICB-: 32.3 (12.8)	NO	NR
Biundo et al. (2015)	ICB+:58 (38) ICB-:52 (32)	ICB+: 60.3 (9.3) ICB-: 63.1 (10.2)	ICB+: 50.1 (12.1) ICB-: 54.7 (11.6)	ICB+: 9.0 (5.5) ICB-: 8.0 (5.7)	ICB+: 10.9 (4.3) ICB-: 11.3 (4.7)	ICB+: 2.4 (0.7) ICB-: 2.3 (0.7)	ICB+: 26.7 (16.5) ICB-: 28.5 (12.3)	NO	NR
Cera et al. (2014)	ICB+:9 (6) GD:10 (7) ICB-:14 (7)	ICB+: 59.3 (6.8) GD: 60.6 (6.8) ICB-: 59.0 (9.5)	NR	ICB+: 29.0 (8.5)‡ GD: 28.2 (12.3) ICB-: 27.2 (8.4)	ICB+: 10.3 (3.2) GD: 11.7 (2.6) ICB-: 11.7(1.9)	ICB+: 1.7 (0.3) GD: 1.9 (0.2) ICB-: 1.7 (0.0)	ICB+: 21.4 (4.2) GD: 20.5 (6.8) ICB-: 21.6 (6.9)	NO	NR
Cilia et al. (2008)	ICB+: 11 (10) ICB-: 40 (27)	ICB+: 57.4 (5.8) ICB-: 55 (7)	ICB+: 49.5 (4.7) ICB-: 46.4 (7.2)	ICB+: 8.4 (3.4) ICB-: 8.4 (5.1)	NR NR	ICB+: 2.1 (0.6) ICB-: 2.3 (0.8)	ICB+: 18.0 (11.0) ICB-: 19.1 (8.5)	YES	NO
Claassen et al. (2015)	ICB+: 12 (8) ICB-:12 (6)	ICB+: 59.4 (5.5) ICB-: 60.8 (7.2)	NR	ICB+: 6.5 (4.7) ICB-: 6.1 (3.8)	ICB+: 17.1 (2.7) ICB-: 16.3 (2.8)	NR	ICB+: 15.9 (6.6) ICB-: 15.7 (8.3)	YES	NO
Djamshidian et al. (2010)	ICB+:18 (13) ICB-:12 (9)	ICB+: 55 (2.1) ICB-: 63.6 (2.2)	ICB+: 43.9 (2.1) ICB-: 50.9 (2.2)	ICB+: 10.9 (1.2) ICB-: 12.7 (2.1)	ICB+: 12.2 (0.9) ICB-: 14.2 (1.3)	NR	ICB+: 18.0 (2.2)§ ICB-: 13.0 (1.4)	NO	NR

Table 3. 9 (continued) Characteristics of the studies included in the meta-analysis.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Education (y)*	H&Y	UPDRS-III (ON)*	Depression†	Antidep (N)
Djamshidian et al. (2011)	ICB+: 28 (21) ICB-:24 (21)	ICB+: 54.6 (9.2) ICB-: 64.2 (10.1)	ICB+: 44.5 (8.7) ICB-: 52.5 (9.6)	ICB+: 10.1 (5.5) ICB-: 11.7 (7.2)	ICB+: 13.4 (3.0) ICB-: 14.7 (3.6)	NR	ICB+: 15.5 (8.3) ICB-: 14.4 (5.8)	NO	ICB+: 4 ICB-: 2
Erga et al. (2017)	ICB+: 38 (26) ICB-:87 (49)	ICB+: 67.9 (7.7) ICB-: 71.4 (9.8)	NR	ICB+: 7.4 (1.6) ICB-: 7.4 (1.9)	NR	ICB+: 2.2 (0.5) ICB-: 2.2 (0.6)	ICB+: 23.8 (10.5) ICB-: 22.2 (10.7)	NO	ICB+: 5 ICB-:11
Housden et al. (2010)	ICB+: 18 (11) ICB-:18 (12)	ICB+: 62.3 (7.6) ICB-: 67.7 (5.5)	NR	ICB+: 13.9 (9.0) ICB-: 12.9 (8.3)	NR	ICB+: 2.5 (0.6) ICB-: 2.5 (0.7)	ICB+: 20.0 (6.6) ICB-: 21.3 (10.4)	YES	NR
Joutsa et al. (2015)	ICB+:9 (9) ICB-:8 (8)	ICB+: 59.3 (8.4) ICB-: 60.1 (5.9)	ICB+: 53.1 (8.7) ICB-: 55.3 (5.1)	ICB+: 6.1 (1.8) ICB-: 5.1 (2.0)	NR	NR	ICB+: 31.7 (4.9) ICB-: 30.1 (10.7)	YES	NR
Leroi et al. (2011)	ICB+: 35 ICB-:38	NR	NR	NR	NR	NR	ICB+: 26.9 (10.0) ICB-: 24.1 (10.4)	NO	NR
Mack et al. (2013)	ICB+: 17 (11) ICB-:17 (8)	ICB+: 61.1 (7.5) ICB-: 63.8 (8.5)	ICB+: 48.1 (5.2) ICB-: 53.7 (10.0)	ICB+: 13.1 (6.9) ICB-: 10.2 (5.6)	NR	ICB+: 2.8 (1.0) ICB-: 2.4 (1.3)	ICB+: 36.7 (16.1) ICB-: 28.5 (15.2)	NO	YES
Merola et al. (2017)	ICB+: 8 (8) ICB-: 113 (60)	NR	ICB+: 48.2 (9.4) ICB-: 46.6 (7.3)	ICB+: 13.4 (7.8) ICB-: 13.1 (4.4)	NR	NR	ICB+: 14.3 (6.7) ICB-: 15.5 (7.8)	NO	NR

Table 3. 9 (continued) Characteristics of the studies included in the meta-analysis.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Education (y)*	H&Y	UPDRS-III (ON)*	Depression†	Antidep (N)
O'Sullivan et al. (2010)	ICB+:39 (31) ICB-:61 (44)	ICB+: 59.3 (9.1) ICB-: 66.6 (9.5)	ICB+: 45.8 (10.3) ICB-: 55.9 (11.7)	ICB+: 12.0 (6.0) ICB-: 9.6 (7.1)	NR	ICB+: 2.6 (0.5) ICB-: 2.2 (0.5)	ICB+: 16.3 (7.5) ICB-: 18.5 (8.8)	NO	NR
O'Sullivan et al. (2011)	ICB+: 30 (26) ICB-: 62 (46)	ICB+: 58.9 (8.5) ICB-: 66.4 (9.7)	ICB+: 46.2 (10.1) ICB-: 55.8 (12.0)	ICB+: 11.5 (5.9) ICB-: 9.5 (7.0)	NR	ICB+: 3 (2-3)¶ ICB-: 2 (2-3)	NR	NO	YES
Pettorruso et al. (2014)	GD: 11 (8) ICB+: 23 (18) ICB-: 120 (60)	GD: 64.9 (10.9) ICB+: 62.0 (9.1) ICB-: 67.7 (9.4)	GD: 56.6 (10.6) ICB+: 53.2 (9) ICB-: 60.6 (9.2)	GD: 8.3 (3.2) ICB+: 8.8 (6) ICB-: 7.0 (5.4)	GD: 10 (4.2) ICB+: 11.3 (4.4) ICB-: 11 (5.2)	NR	GD: 20.4 (12.3) ICB+: 18.4 (8.5) ICB-: 20.4 (8.4)	NO	NR
Pineau et al. (2016)	ICB+: 17 (14) ICB-: 20 (13)	ICB+: 55 (37–69)‖ ICB-: 55 (40-62)	ICB+: 48 (32–65)‖ ICB-: 48 (35–55)	ICB+: 7 (2–10)‖ ICB-: 5.5 (4–12)	ICB+: 7 (3–7)‖ ICB-: 7 (3–7)	NR	ICB+: 7 (0–23)‖ ICB-: 8.5 (0–34)	NO	NR
Piray et al. (2014)	ICB+: 16 (14) ICB-: 15 (12)	ICB+: 64.4 (3.3) ICB-: 63.3 (4.0)	NR	ICB+: 9.6 (2.5) ICB-: 8.9 (3.1)	NR	ICB+: 2.5 (0.5) ICB-: 2.4 (0.6)	ICB+: 19.0 (5.3) ICB-: 19.6 (6.4)	NO	NR
Pontieri et al. (2015)	GD: 21 ICB+: 36 ICB-: 98	GD: 58 (9) ICB+: 64 (8) ICB-: 66 (9)	GD: 51 (8) ICB+: 57 (10) ICB-: 61 (9)	GD: 8 (5) ICB+: 7 (4) ICB-: 5 (3)	GD: 10 (4) ICB+: 11 (4) ICB-: 10 (4)	GD: 2.0 (0.5) ICB+: 1.9 (0.8) ICB-: 1.8 (0.5)	GD: 21.5 (11.6) ICB+: 19.1 (12.7) ICB-: 19.0 (11.9)	NO	GD: 4 ICB+: 7 ICB-: 26

Table 3. 9 (continued) Characteristics of the studies included in the meta-analysis.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Education (y)*	H&Y	UPDRS-III (ON)*	Depression†	Antidep (N)
Rossi et al. (2010)	ICB+: 7 (6) ICB-: 13 (10)	ICB+: 61.4 (6.9) ICB-: 65.1 (3.8)	ICB+: 52.0 (5.6) ICB-: 58.3 (6.9)	NR	ICB+: 13.8 (4.1) ICB-: 11.9 (5.5)	ICB+: 2.2 (0.7) ICB-: 2.0 (0.7)	ICB+: 17.0 (9.1) ICB-: 14.7 (6.7)	NO	NR
Tessitore et al. (2016)	ICB+: 15 (13) ICB-: 15 (12)	ICB+: 62.9 (8.6) ICB-: 63.1 (8.0)	NR	ICB+: 5.3 (2.9) ICB-: 6.6 (3.9)	ICB+: 9.8 (5) ICB-: 12.9 (8)	ICB+: 1.3 (0.5) ICB-: 1.4 (0.6)	ICB+: 10.9 (4.5) ICB-: 12.1 (4.4)	NO	NO
Vela et al. (2016)	ICB+: 49 (28) ICB-: 35 (23)	ICB+: 48 (44–52)¶ ICB-: 46 (42–52)	NR	ICB+: 7 (3−11)¶ ICB-: 3 (1−10)	NR	ICB+: 2 (2–2)¶ ICB-: 2 (1–2)	ICB+: 16(10−22)¶ ICB-: 17 (11–24)	NO	NO
Vitale et al. (2011)	HS: 13 (13) M-ICB: 10 (9) ICB-: 14	HS: 68.7 (5.4) M-ICB: 62.2 (7.5) ICB-: 61.3 (8.2)	HS: 59.5 (5.6) M-ICB: 55.5 (5.3) ICB-: 53.2 (9.1)	HS: 8.5 (3.9) M-ICB: 8.1 (4.5) ICB-: 7.6 (4.4)	HS: 9.5 (5) M-ICB: 8.2 (2.8) ICB-: 13 (4)	HS: 1.8 (0.5) M-ICB: 1.5 (0.7) ICB-: 1.8 (0.8)	HS: 15.1 (6.5) M-ICB: 13 (7.1) ICB-: 11.7 (6)	NO	HS: 1 M-ICB: 2 ICB-: 0
Wu et al. (2015)	S-ICB: 7 M-ICB: 10 ICB-: 9	S-ICB: 62.3 (3.9) M-ICB: 58.1 (2.8) ICB-: 60.2 (3.2)	S-ICB: 51.7 (4.0) M-ICB: 43.8 (3.4) ICB-: 50.3 (3.4)	S-ICB: 10.6 (2.0) M-ICB: 14.3 (11.2) ICB-: 9.9 (2.1)	NR	NR	NR	NO	NR

Table 3.9 (continued). Characteristics of the studies included in the meta-analysis.

Ref	Antipsy: N	LEDD (mg)			Outcomes	ICB	
		Total LEDD*	LD-LEDD*	DAED*		Diagnosis**	Type: N
Bentivoglio et al. (2013)	ICB+: 3	ICB+: 606.1 (319.2) ICB-: 616.2 (367.8)	ICB+: 539 (264.3) ICB-: 455.7 (299.0)	ICB+: 172.9 (112.2) ICB-: 192.5 (88.5)	Digit span forward; CBTT; Immediate visual memory; RAVLT; Digit span backward; Double barrage; FAB; MWCST; RCPM; Stroop; Fluency (semantic, phonological); IGT; Apraxia (ideomotor, orofacial, constructional); Oral confrontation naming (nouns, verbs); HAM-D; HAM-A; BIS-11	Clinical interview (DSM-IV)	HS: 8; CS: 2; GD: 10; BE: 6; M-ICB: 7
Biundo et al. (2011)	NR	ICB+: 556.8 (304.6) ICB-: 497.4 (341.2)	NR	ICB+: 186.5 (149.3) ICB-: 165.8 (108.8)	Digit span forward; CBTT; RAVLT; ROCF (copy, delayed); Digit span backward; TMT A; FAB; TMT B; RCPM; Similarities for abstract verbal reasoning; Stroop; Fluency (semantic, phonological); BDI	MIDI; DSM-IV-TR; interview (caregivers); additional clinical interview	HS: 11; CS: 9; GD: 1; punding: 2; M-ICB: 12
Biundo et al. (2015)	NR	ICB+: 923.1 (474.1) ICB-: 722.6 (498.5)	NR	ICB+: 163.7 (111.3) ICB-: 148.9 (105.0)	Digit span forward; CBTT; Prose (immediate, delayed); ROCF; Digit ordering test; TMT-A; TMT B; Stroop; Fluency (semantic, phonological); Naming; VOSP; Clock drawing test; BDI	QUIP-rs; MIDI; clinical interview (PwP and carergiver)	HS: 6; CS: 7; GD: 2; hoarding: 2; impulsive aggression: 1; M-ICB: 40
Cera et al. (2014)	NO	ICB+: 283.3 (132.9) GD: 294.5 (123.1) ICB-: 307 (96.3)	NR	NR	Stroop test; Emotional Stroop test; Monetary risk tasking task	DSM-IV, QUIP-rs, SOGS	GD:10; M-ICB: 9

Table 3.9 (continued). Characteristics of the studies included in the meta-analysis.

Ref	Antipsy: N	LEDD (mg)			Outcomes	ICB	
		Total LEDD*	LD-LEDD*	DAED*		Diagnosis**	Type: N
Cilia et al. (2008)	NO	ICB+: 811.8 (229.0) ICB-: 877.3 (289.3)	NR	ICB+: 289.1 (57.5) ICB-: 340.1 (157.2)	FAB; RPM; GDS	Diagnostic criteria; SOGS	GD:1; GD+HS: 5; GD+BE: 2; GD+CS: 2; GD+IA: 1
Claassen et al. (2015)	NO	ICB+: 618.7 (361.9) ICB-: 520.3 (314.9)	ICB+: 408.2 (349.6) ICB-: 319.7 (318.9)	ICB+: 293.8 (167.4) ICB-: 200.6 (116.8)	Stop signal task; CESD	QUIP; clinical interview	HS: 5; CS: 5; BE: 6; hobbism: 9
Djamshidian et al. (2010)	NR	ICB+: 971 (183)§ ICB-: 732 (203)	ICB+: 752 (109)§ ICB-: 604 (73)	NR	Digit span backward; Risk Task; Learning task.	Diagnostic criteria	GD: 10; HS:9; CS: 5; BE: 7; DDS: 6; punding: 2; kleptomania: 1
Djamshidian et al. (2011)	NR	ICB+: 832 (425) ICB-: 821 (400)	NR	NR	Stroop	Diagnostic criteria	GD: 11; HS: 13; CS: 8; punding:4; kleptomania:1
Erga et al. (2017)	NR	ICB+: 730.6 (343.3) ICB-: 658.4 (275.9)	ICB+: 505.2 (279.1) ICB-: 408.7 (266.7)	ICB+: 293.7 (132.4) ICB-: 289.5 (150.0)	CLVT-II; Stroop; Fluency (phonological); VOSP; MADRS	QUIP	M-ICB: 36 (GD: 2; HS: 7; CS:6; BE:14; punding:12; hobbyism:13; DDS: 3)
Housden et al. (2010)	NR	ICB+: 891.5 (432.1) ICB-: 804.8 (358.5)	ICB+: 643.5 (254.1) ICB-: 634.2 (301.7)	ICB+: 248 (301.3) ICB-: 170.5 (159.3)	Digit span forward; Digit span backward; KDT; WTAR; SAT; BDI; STAI-state	Structured interview (diagnostic criteria)	GD:9; BE: 9; HS: 7; CS: 6; DDS: 4; punding: 8

Table 3. 9 (continued). Characteristics of the studies included in the meta-analysis

Ref	Antipsy: N	LEDD (mg)			Outcomes	ICB	
		Total LEDD*	LD-LEDD*	DAED*		Diagnosis[g]	Type: N
Joutsa et al. (2015)	NR	ICB+: 628 (186) ICB-: 762 (269)	NR	ICB+: 173 (80) ICB-: 216 (67)	KDT	Diagnostic criteria	GD: 5; HS: 4; BE: 1
Leroi et al. (2011)	NR	NR	NR	NR	n-back; Fluency (phonological); HADS-D; HADS-A; AES-C; BIS-11	Diagnostic criteria; SOGS	GD: 12; HS: 9; CS: 5; BE: 3; DDS: 3; punding: 3
Mack et al. (2013)	NR	ICB+: 1,677.9 (893.0) ICB-: 1,269.3 (560.7)	NR	NR	Digit span; HVLT-R; TMT-A; TMT-B; Fluency (semantic, phonological); NART; BDI	Semistructured interview (diagnostic criteria)	NR
Merola et al. (2017)	NR	ICB+: 1576.4 (397.6) ICB-: 1216.2 (403.0)	NR	ICB+: 344.4 (314.5) ICB-: 297.2 (235.3)	Digit span forward; Bi-syllabic words repetition test; CBTT; Paired associate learning; TMT-A; Digit cancellation test; FAB; TMT-B; MWCST; RCPM; Fluency (semantic, phonological); BDI; STAI-state; AES-C	Clinical interview (diagnostic criteria)	GD, HS, CS, punding, DDS
O'Sullivan et al. (2010)	NR	ICB+: 927 (658) ICB-: 742 (477)	ICB+: 684 (512) ICB-: 588 (418)	ICB+: 259 (472) ICB-: 139 (200)	HADS-D; HADS-A; BSCS; Impulse buying tendency;	Semistructured interview (diagnostic criteria)	Punding: 20; BE: 14; HS: 12; GD: 11; CS: 11; DDS: 11

Table 3. 9 (continued). Characteristics of the studies included in the meta-analysis.

Ref	Antipsy: N	LEDD (mg)			Outcomes	ICB	
		Total LEDD*	LD-LEDD*	DAED*		Diagnosis[g]	Type: N
O'Sullivan et al. (2011)	NR	ICB+: 981 (651) ICB-: 645 (443)	ICB+: 701 (508) ICB-: 543 (399)	ICB+: 201 (0-284)[¶] ICB-: 0 (0-201)	HADS-D; HADS-A	Semistructured interview (diagnostic criteria)	HS: 12; GD: 11; CS: 8; BE: 8; punding: 15
Pettorruso et al. (2014)	NR	GD: 712 (373) ICB+: 654 (380) ICB-: 575 (420)	GD: 592 (404) ICB+: 458 (376) ICB-: 445 (386)	GD: 120 (99) ICB+: 196 (113) ICB-: 130 (112)	FAB; HAM-D; HAM-A; SHAPS; BIS-11	Interview (diagnostic criteria)	S-ICB: 24; M-ICB: 10 (GD: 11; HS: 20; BE: 9; CS: 5)
Pineau et al. (2016)	NR	ICB+: 897.5 (299.9–1247.3)[‖] ICB-: 1049.9 (527.1–1549.8)	NR	ICB+: 299.9 (77–718.0)[‖] ICB-: 340.2 (66.7–700.0)	Conner's performance test; TMT B-A; MWCST; Fluency (phonological); IGT; MADRS; Starkstein apathy scale; BIS-11	Semistructured interview; ASBPD	GD: 6; HS: 1; CS: 2; CE: 2; M-ICB: 6
Piray et al. (2014)	NR	NR	NR	NR	Digit span forward; Digit span backward; Probabilistic reward learning task; NAART; BDI; BIS-11	Interview	S-ICB: 4; M-ICB: 12 (CS: 10; HS: 9; GD: 6; BE: 4)
Pontieri et al. (2015)	GD: 2 ICB+: 3 ICB-:4	GD: 794 (603) ICB+: 704 (509) ICB-: 416 (304)	GD: 487 (625) ICB+: 388 (278) ICB-: 251 (279)	GD: 307 (275) ICB+: 316 (374) ICB-: 166 (197)	RAVLT (immediate, delayed); ROCF (immediate, delayed); MWCST; Stroop; Fluency (semantic, phonological); HAM-D; HAM-A; SHAPS; Starkstein apathy scale	Diagnostic criteria; QUIP	GD: 21 (GD only:10; GD and other ICB:11); HS:16; CS:3; BE:10;M-ICB: 7
Rossi et al. (2010)	NR	ICB+: 935.9 (548.6) ICB-: 698.2 (474.6)	NR	ICB+: 201.9 (78.0) ICB-: 223.9 (136.8)	FAB; MWCST; Go/No-Go; Stroop; IGT; Game of dice; Investment task; Social cognition; Reversal and extinction learning; MADRS	Interview (diagnostic criteria); MIDI; SOGS;	GD: 7; HS: 2; CS: 2; DDS:2

Table 3. 9 (continued). Characteristics of the studies included in the meta-analysis.

Ref	Antipsy: N	LEDD (mg)			Outcomes	ICB	
		Total LEDD*	LD-LEDD*	DAED*		Diagnosis[g]	Type: N
Tessitore et al. (2016)	NO	ICB+: 477.3 (222.9) ICB-: 532.1 (207.2)	NR	ICB+: 243.3 (82.1) ICB-: 243.3 (90.2)	CBTT; RAVLT (immediate, delayed); Attentional matrices; TMT-B; WCST; RCPM; Stroop; Fluency (semantic, phonological); ROCF; HAM-D; HADS	MIDI	HS:13; BE:8; GD: 1
Vela et al. (2016)	NO	ICB+: 543 (248–1039)¶ ICB-: 460 (133–700)	ICB+: 300 (0–675)¶ ICB-: 300 (0–600)	ICB+: 210 (168–308)¶ ICB−: 180 (0−300)	BDI	QUIP	GD: 9; HS: 20; CS: 13; BE: 17; hobbyism: 25; punding: 15; walkabout: 4
Vitale et al. (2011)	HS: 2 M-ICB: 0 ICB-: 0	HS: 727.3 (254.3) M-ICB: 808.3 (292.2) ICB-: 630.3 (311.8)	NR	HS: 200 (130.4) M-ICB: 207.1 (159.2) ICB-: 267.1 (201.3)	WCST; ROCF copy; TMT B-A; Attentional matrices; Stroop; RAVLT (immediate, delayed); HAM-D; HADS-A; HADS-D	MIDI; clinical interview	HS: 13; M-ICB: 10
Wu et al. (2015)	NR	S-ICB: 782.3 (83.5) M-ICB: 724.0 (99.0) ICB-: 831.9 (119.2)	S-ICB: 538.0 (83.4) M-ICB: 268.5 (84.9) ICB-: 666.3 (129.0)	S-ICB: 244.3 (51.4) M-ICB: 244.0 (55.4) ICB-: 165.6 (48.9)	BDI	Semistructured interview	HS: 4; GD: 3; M-ICB: 10

Legend. AES-C: Apathy evaluation scale by a clinician; ASBPD: Antidep: antidepressant; Antipsy: antipsychotic; Ardouin scale of behaviour in Parkinson's disease; BDI: Beck depression inventory; BE: binge eating; BIS-11: Barratt impulsiveness questionnaire; BSCS: Brief self-control

scale CBTT: Corsi's block-tapping test; CESD: Center for Epidemiological Studies-Depression scale; CLVT-II: California verbal learning test II; CS: compulsive shopping; DAED: dopamine agonist equivalent daily dose; DDS: Dopamine dysregulation syndrome; DSB: digit span backward; DSF: digit span forward; DSM-IV: diagnostic and statistical manual of mental disorders, fourth edition; DSM-IV-TR: diagnostic and statistical manual of mental disorders, fourth edition, text revision; FAB: frontal assessment battery; GDS: Geriatric depression scale; HADS-A: Hospital anxiety and depression scale – anxiety subscale; HADS-D: Hospital anxiety and depression scale – depression subscale; HAM-A: Hamilton rating scale for anxiety; HAM-D: Hamilton rating scale for depression; H&Y: Hoehn & Yahr score; HS: hyper-sexuality; HVLT-R: Hopkins verbal learning test revised; IA: internet addiction; ICBs: impulsive-compulsive behaviours; ICB+: PwP with ICB; ICB-: PwP without ICBs; IGT: Iowa gambling task; KDT: Kirby Monetary Choice Questionnaire of temporal discounting; LEDD: levodopa equivalent daily dosage (mg); LD: levodopa; MADRS: Montgomery-Asberg depression rating scale; M-ICBs: multiple ICBs; MIDI: Minnesota impulsive disorder interview; MMSE: mini-mental state examination; MWCST: Modified Wisconsin card sorting test; N: number of PwP; NAART: North American adult reading test; NART: The National adult reading test; NR: not reported. PD: Parkinson's disease; PwP: persons with Parkinson's disease; GD: gambling disorder; Pts: PwP; QUIP: questionnaire for impulsive-compulsive disorders in Parkinson's disease; QUIP-rs: questionnaire for impulsive-compulsive disorders in Parkinson's disease rating scale; RAVLT: Rey's auditory verbal learning test; RCPM: Raven's coloured progressive matrices; Ref: reference number; ROCF: Rey-Osterrieth complex figure test; RPM: Raven's progressive matrices; SAT: salience attribution test; SHAPS: Snaith-Hamilton pleasure scale; S-ICB: single ICBs; SOGS: South oaks gambling screen; STAI-state:

state-trait anxiety inventory; TMT-A: Trail making test part A; TMT-B: Trail making test part B; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; VOSP: visual object and space perception battery; WCST: Wisconsin card sorting test; WTAR: Wechsler test of adult reading; y: years. [*]Mean (SD) unless otherwise stated. [†]Depression as an exclusion factor. [‡]Data reported in months. [§]Mean (SEM). [¶]Median (interquartile range). [‖]Median (lower–upper quartile). [**]Questionnaire or method used to screen and/or diagnose ICBs.

Four studies investigated cognitive performance without affective and motivational outcomes (Cera et al., 2014; Djamshidian et al., 2010; Djamshidian, O'Sullivan, Lees, et al., 2011; Joutsa et al., 2015), seventeen studies included both cognitive, affective and motivational outcomes (Bentivoglio et al., 2013; Biundo et al., 2011, 2015; Cilia et al., 2008; Claassen et al., 2015; Erga et al., 2017; Housden et al., 2010; Leroi et al., 2011; Mack et al., 2013; Merola et al., 2017; Pettorruso et al., 2014; Pineau et al., 2016; Piray et al., 2014; Pontieri et al., 2015; Rossi et al., 2010; Tessitore et al., 2016; Vitale et al., 2011), and four studies included affective and motivational data only (O'Sullivan, Djamshidian, et al., 2010; O'Sullivan, Loane, et al., 2011; Vela et al., 2016; Wu et al., 2015).

Three studies divided ICB+ in two groups: PwP with gambling disorder and those with ICBs other than gambling disorder (Cera et al., 2014; Pettorruso et al., 2014; Pontieri et al., 2015), and one study divided the ICB+ in multiple and single ICBs groups (Wu et al., 2015). As the comparison between ICBs subtypes was not relevant in this meta-analysis, sub-groups were merged by calculating the pooled means and standard deviations. In one study (Vitale et al., 2011) ICB+ group was divided in gambling disorder, binge eating, hypersexuality and multiple ICBs sub-groups. Since seven PwP belonging to either the gambling disorder or the binge eating sub-groups developed ICBs before DRT initiation, only data from hypersexuality and multiple ICBs sub-groups were extracted and merged as described above. Six studies focused on neuroimaging outcomes but also provided affective (Wu et al., 2015) and cognitive measures (Biundo et al., 2011, 2015; Cilia et al., 2008; Joutsa et al., 2015; Tessitore et al., 2016). One study retrospectively investigated persistent, remitting, and new-onset ICBs before and after subthalamic nucleus DBS (STN-DBS) (Merola et al., 2017). For this study, only pre-STN-DBS

data of persistent and never experienced ICBs were included in the meta-analysis. Despite the fact that dementia was not explicitly excluded (Merola et al., 2017), data were included because STN-DBS is performed in non-demented PwP only.

The meta-analysis includes 1563 subjects. The ICB+ group was composed of 625 PwP (mean age range: 54.6–68.7 years; mean PD duration: 2.4–14.3 years; mean H&Y: 1.3–2.8; mean UPDRS-III score ON medication: 10.9–36.7). The ICB- group included 938 PwP (mean age range: 55–71.4 years; mean PD duration: 2.3–13.1 years; mean H&Y stage: 1.4–2.5; mean UPDRS-III score ON medication: 11.7–32.3).

Fourteen meta-analyses were performed to compare cognitive outcomes and five to compare affective and motivational measures in ICB+ compared to ICB- groups.

The following cognitive outcomes were explored: short-term verbal and visuospatial memory, long-term verbal and visuospatial memory, working memory, attention, set-shifting, concept formation (reasoning, sort and shift), inhibition, cognitive flexibility, incentive-driven decision-making, visuospatial abilities, and language. Cognitive subdomains and related cognitive tasks are provided in Table 3.10.

Table 3. 10 Cognitive subdomains and tasks used in the studies included in the meta-analysis.

Cognitive subdomain	**Cognitive tasks**	**References**
Short-term verbal memory	CVLT-II immediate	Erga et al. (2017)
	Digit Span Forward	Bentivoglio et al. (2013); Biundo et al. (2011); Biundo et al. (2015); Housden et al. (2010); Merola et al. (2017); Piray et al. (2014)
	RAVLT - immediate	Pontieri et al. (2015); Tessitore et al. (2016); Vitale et al. (2011)
Short-term visuospatial memory	CBTT	Bentivoglio et al. (2013); Biundo et al. (2011); Biundo et al. (2015); Merola et al. (2017); Tessitore et al. (2016)
Long-term verbal memory	CVLT-II delayed HVLT-R delayed Paired associate learning Prose Memory	Erga et al. (2017) Mack et al. (2013) Merola et al. (2017) Biundo et al. (2015)
	RAVLT- delayed	Bentivoglio et al. (2013); Biundo et al. (2011); Pontieri et al. (2015); Tessitore et al. (2016); Vitale et al. (2011)
Long-term visuospatial memory	ROCF – delayed	Biundo et al. (2011); Biundo et al. (2015); Pontieri et al. (2015)
Working memory	Digit Ordering Test	Biundo et al. (2015)
	Digit Span Backward	Bentivoglio et al. (2013); Biundo et al. (2011); Djamshidian et al. (2010); Housden et al. (2010); Piray et al. (2014)
	n-Back	Leroi et al. (2011)

Table 3. 10 (continued) Cognitive subdomains and tasks used in the studies included in the meta-analysis.

Cognitive subdomain	**Cognitive tasks**	**References**
Attention	Attentive Matrices	Tessitore et al. (2016); Vitale et al. (2011)
	Conner's Performance Test	**Pineau et al. (2016)**
	Double barrage – accuracy	Bentivoglio et al. (2013)
	TMT-A	**Biundo et al. (2011); Biundo et al. (2015); Mack et al. (2013); Merola et al. (2017)**
Set-shifting	TMT-B	**Biundo et al. (2011); Biundo et al. (2015); Mack et al. (2013); Merola et al. (2017); Tessitore et al. (2016)**
	TMT- B-A	**Pineau et al. (2016); Vitale et al. (2011)**
Concept formation (sort and shift)	MWCST – categories	Bentivoglio et al. (2013); Merola et al. (2017); Pineau et al. (2016)**;** Pontieri et al. (2015); Rossi et al. (2010)
	WCST – global score	**Tessitore et al. (2016); Vitale et al. (2011)**
Concept formation (reasoning)	RCPM RPM	Bentivoglio et al. (2013); Biundo et al. (2011); Merola et al. (2017); Tessitore et al. (2016) Cilia et al. (2008)
Inhibition	Go/No-Go – errors	**Rossi et al. (2010)**
	Stop Signal Task	Claassen et al. (2015)
	Stroop errors	**Bentivoglio et al. (2013); Biundo et al. (2011); Biundo et al. (2015); Djamshidian et al. (2011);** Vitale et al. (2011)
	Stroop time	**Cera et al. (2014); Erga et al. (2017); Pontieri et al. (2015); Tessitore et al. (2016)**

Table 3. 10 (continued) Cognitive subdomains and tasks used in the studies included in the meta-analysis.

Cognitive subdomain	**Cognitive tasks**	**References**
Cognitive flexibility	Phonological Fluency	Bentivoglio et al. (2013); Biundo et al. (2011); Biundo et al. (2015); Erga et al. (2017); Leroi et al. (2011); Mack et al. (2013); Merola et al. (2017); Pineau et al. (2016); Pontieri et al. (2015); Tessitore et al. (2016)
Incentive-driven decision-making	IGT	**Bentivoglio et al. (2013);** Pineau et al. (2016); **Rossi et al. (2010)**
	KDT	Housden et al. (2010); Joutsa et al. (2015)
	Monetary risk taking	Cera et al. (2014)
	Probabilistic Reward	Piray et al. (2014)
	Risk Task	Djamshidian et al. (2010)
Visuospatial abilities	Constructional apraxia	Bentivoglio et al. (2013)
	ROCF – copy	Biundo et al. (2011); Biundo et al. (2015); Pontieri et al. (2015); Tessitore et al. (2016); Vitale et al. (2011)
	VOSP - silhuette	Erga et al. (2017)
Language	Naming	Biundo et al. (2015)
	Oral Verbal Naming	Bentivoglio et al. (2013)

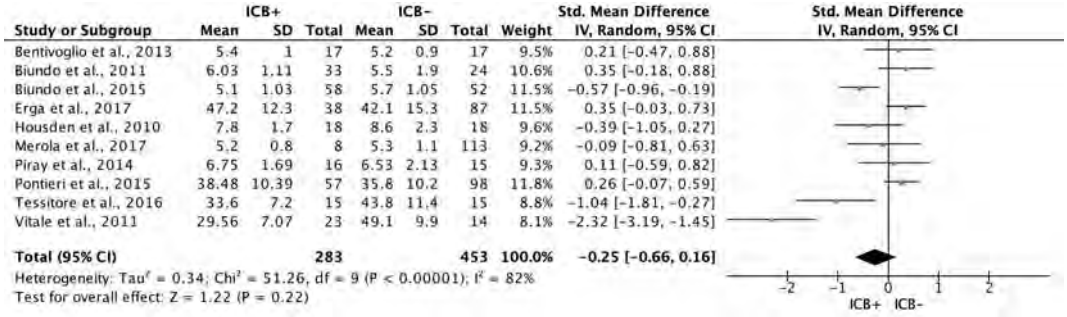
Table 3. 10 (continued) Cognitive subdomains and tasks used in the studies included in the meta-analysis.

Affective and Motivational	**Self-report measures**	**References**
Depression	BDI	Biundo et al. (2011); Biundo et al. (2015); Housden et al. (2010); Mack et al. (2013); Merola et al. (2017); Piray et al. (2014); Vela et al. (2016); Wu et al. (2015)
	CESD	Claassen et al. (2015)
	GDS	Cilia et al. (2008)
	HADS-D	Leroi et al. (2011); O'Sullivan et al. (2010); O'Sullivan et al. (2011); Vitale et al. (2011)
	HAM-D	Bentivoglio et al. (2013); Pettorruso et al. (2014); Pontieri et al. (2015); Tessitore et al. (2016)
	MADRS	Erga et al. (2017); Pineau et al. (2016); Rossi et al. (2010)
Anxiety	HADS-A	Leroi et al. (2011); O'Sullivan et al. (2010); O'Sullivan et al. (2011); Tessitore et al. (2016); Vitale et al. (2011)
	HAM-A	Bentivoglio et al. (2013); Pettorruso et al. (2014); Pontieri et al. (2015)
	STAI-state	Housden et al. (2010); Merola et al. (2017)
Anhedonia	SHAPS	Pettorruso et al. (2014); Pontieri et al. (2015)
Apathy	AES-C	Leroi et al. (2011); Merola et al. (2017)
	Starkstein Apathy Scale	Pineau et al. (2016); Pontieri et al. (2015)
Impulsivity	BIS-11	Bentivoglio et al. (2013); Leroi et al. (2011); Pettorruso et al. (2014); Pineau et al. (2016); Piray et al. (2014)
	BSCS	O'Sullivan et al. (2010)

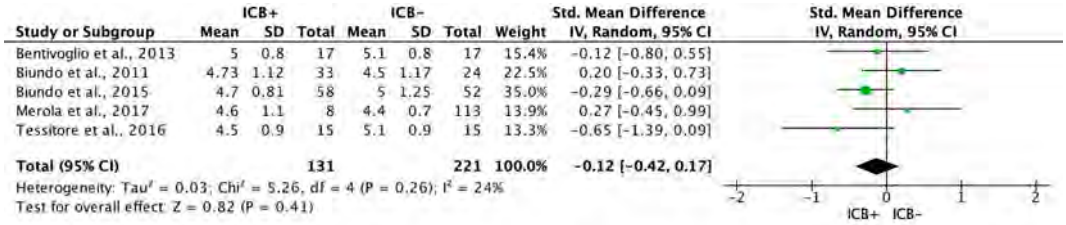
Legend. AES-C: Apathy evaluation scale by a clinician; BDI: Beck depression inventory; BIS-11: Barratt impulsiveness questionnaire; BSCS: brief self-control scale; CBTT: Corsi's block-tapping test; CVLT-II: California verbal learning test II; CESD: Centre for Epidemiological Studies-Depression scale; GDS: Geriatric depression scale; HADS-A: Hospital anxiety and depression scale-anxiety subscale; HADS-D: Hospital anxiety and depression scale-depression subscale; HAM-A: Hamilton rating scale for anxiety; HAM-D: Hamilton rating scale for depression; HVLT-R: Hopkins verbal learning test revised; IGT: Iowa gambling task; KDT: Kirby Monetary Choice Questionnaire of temporal discounting; MADRS: Montgomery-Asberg depression rating scale; MWCST: modified Wisconsin card sorting test; RAVLT: Rey's auditory verbal learning test; RCPM: Raven's colored progressive matrices; ROCF: Rey-Osterrieth complex figure test; RPM: Raven's progressive matrices; SHAPS: Snaith-Hamilton pleasure scale; STAI-state: state-trait anxiety inventory; TMT-A: trail making test part A; TMT-B: trail making test part B; VOSP: visual object and space perception battery; WCST: Wisconsin card sorting test. In bold scores that have been reversed in order to obtain scores with the same meaning (e.g., higher scores better performances).

ICB+ showed worse performance in set-shifting (SMD = -0.49; 95% CI: -0.78, -0.21; Z = 3.37; $p = 0.0008$) and incentive-driven decision-making (SMD = 0.42; 95% CI: 0.02, 0.82; Z = 2.05; $p = 0.04$). The heterogeneity was low-to-moderate for set-shifting ($\chi^2 = 9.32$, $p = 0.16$, $I^2 = 36\%$) and moderate for incentive-driven decision-making ($\chi^2 = 15.50$, $p = 0.03$, $I^2 = 55\%$). Effect sizes for the other cognitive outcomes did not differ significantly between groups. Heterogeneity was low for short-term visuospatial memory, attention, concept formation (reasoning), moderate for cognitive flexibility, concept formation (sort and shift), and language, high for short-term verbal memory, long-term verbal memory, long-term visuospatial memory, visuospatial abilities, and inhibition, moderate-to-high for working memory. Forest plots for cognitive outcomes are provided in Figures 3.6, 3.7, 3.8, 3.9, 3.10.

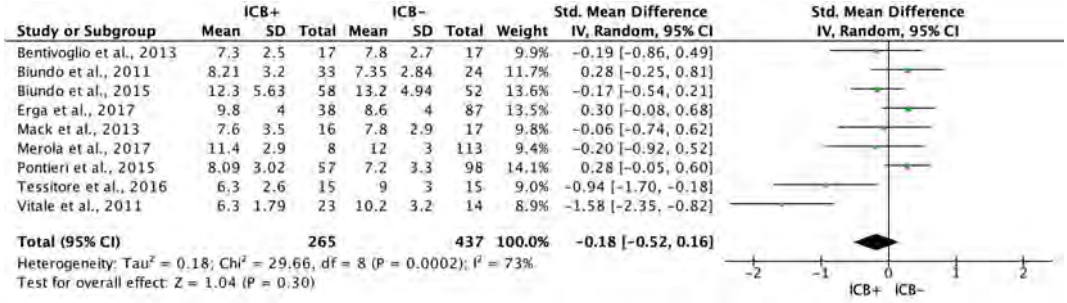
A. Short-term memory (verbal)



B. Short-term memory (visuo-spatial)



C. Long-term memory (verbal)



D. Long-term memory (visuo-spatial)

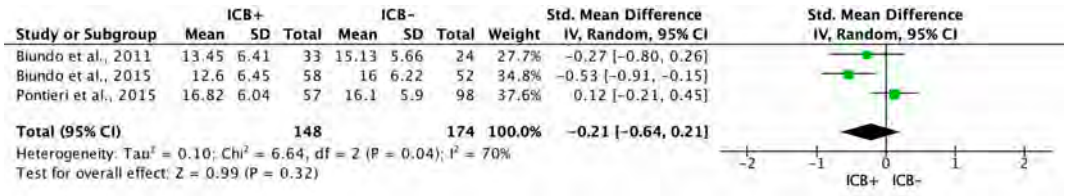
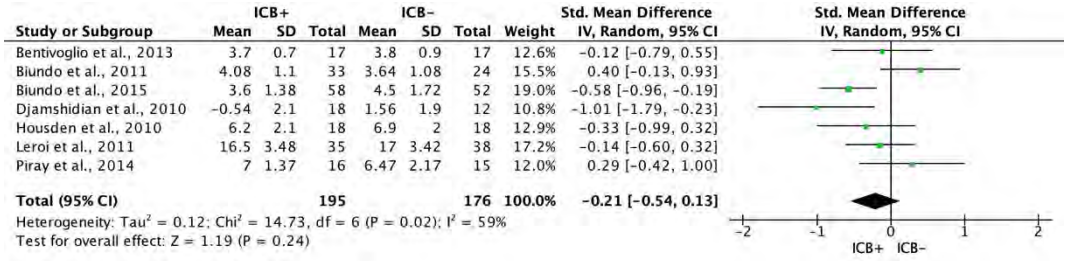


Figure 3. 6 Forest plots for memory. Here are reported forest plots for short-term (verbal, (A) visuospatial, (B) and long-term (verbal, (C); visuospatial, (D) memory outcomes. Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative

effect sizes indicate worse performance in Persons with Parkinson's disease (PwP) with ICBs (ICB+) in comparison to those without ICB (ICB–). ICBs, impulsive-compulsive behaviours.

A. Working memory



B. Attention

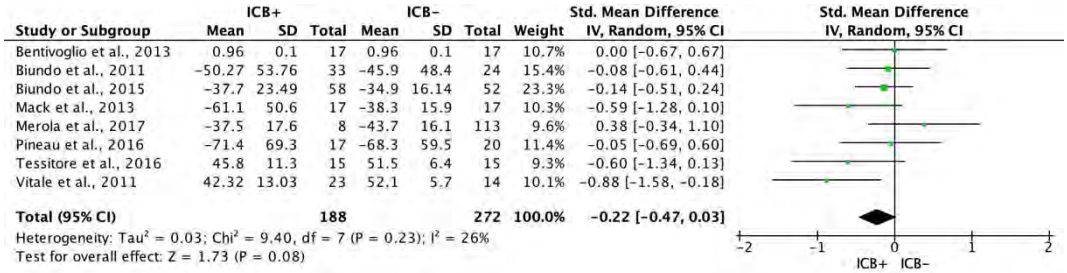
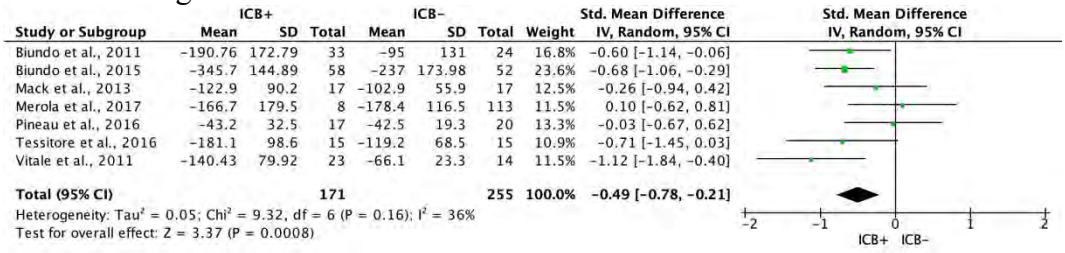
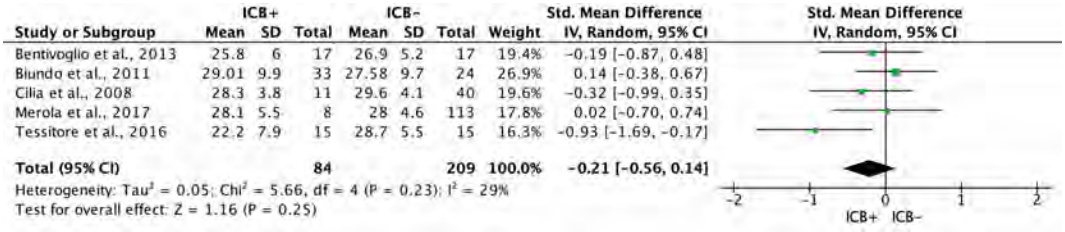


Figure 3. 7 Forest plots for working memory and attention. Here are reported forest plots for working memory (A) and attention (B). Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in Persons with Parkinson's disease (PwP) with ICBs (ICB+) in comparison to those without ICBs (ICB−). ICBs, impulsive-compulsive behaviours.

A. Set-shifting



B. Concept formation (reasoning)



C. Concept formation (sort and shift)

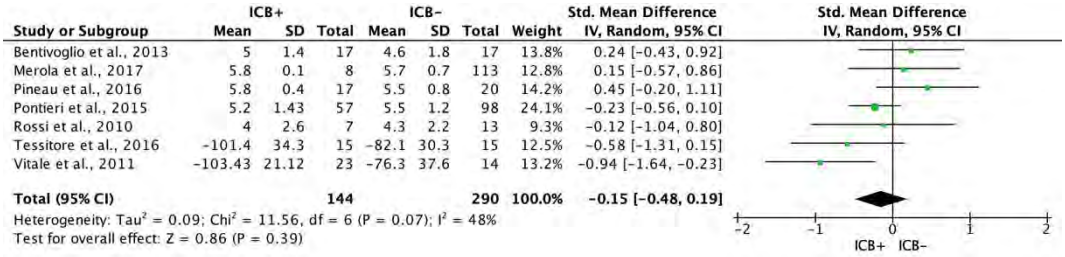
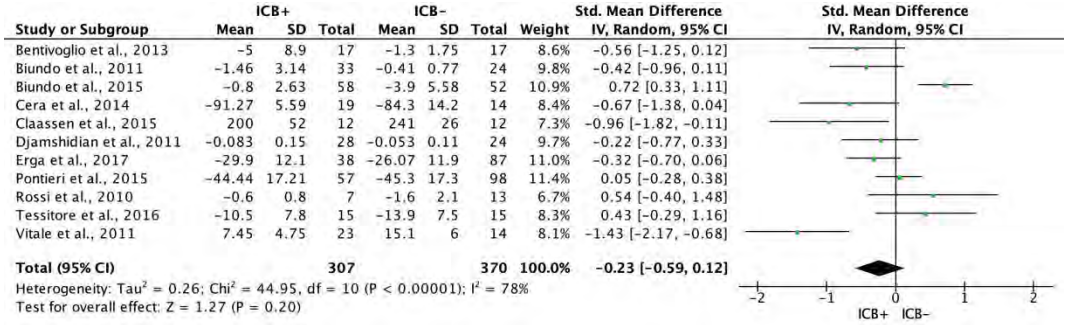
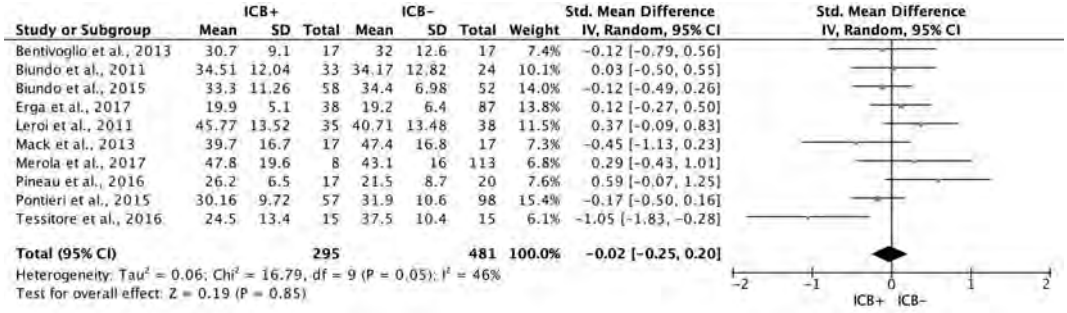


Figure 3. 8 Forest plots for executive functions set-shifting and concept formation. Here are reported forest plots for set-shifting (A), and concept formation (reasoning, B; sort and shift, C). Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in Persons with Parkinson's disease (PwP) with ICBs (ICB+) in comparison to those without ICBs (ICB−). ICBs, impulsive-compulsive behaviours.

A. Inhibition



B. Cognitive flexibility



C. Incentive-driven decision-making

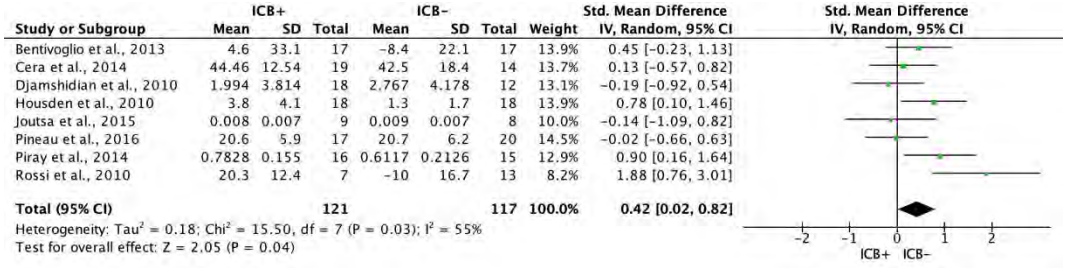
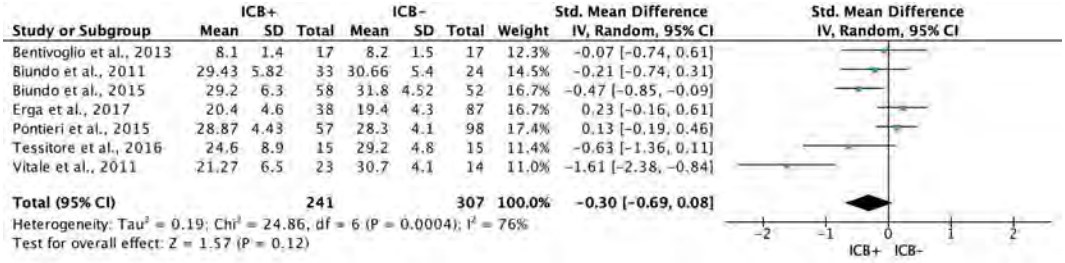


Figure 3. 9 Forest plots for executive functions inhibition, cognitive flexibility, and incentive-driven decision-making. Here are reported forest plots for inhibition (A), cognitive flexibility (B), and incentive-driven decision-making (C). Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in Persons with Parkinson's disease (PwP) with ICBs (ICB+) in comparison to those without ICBs (ICB–). ICBs, impulsive-compulsive behaviours.

A. Visuospatial abilities

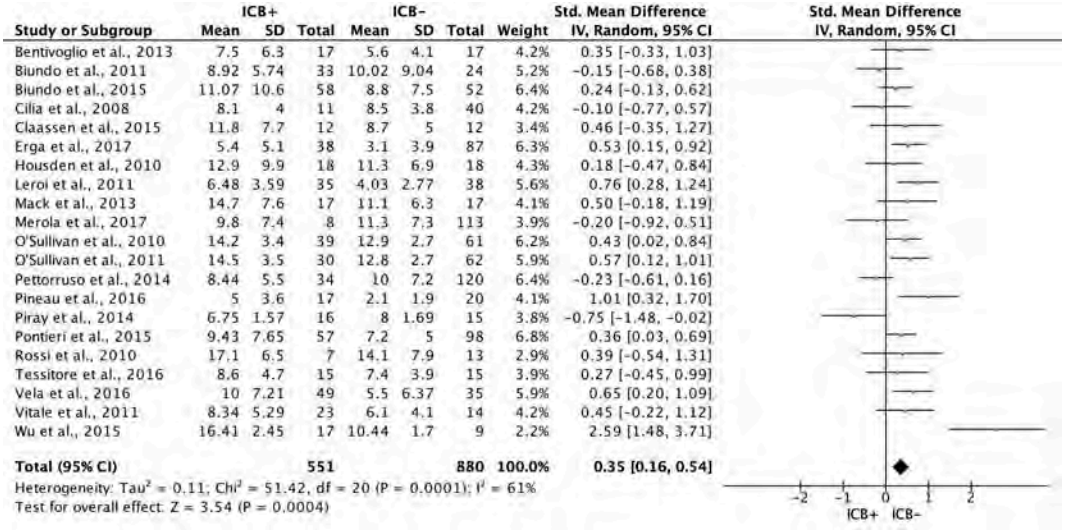


B. Language

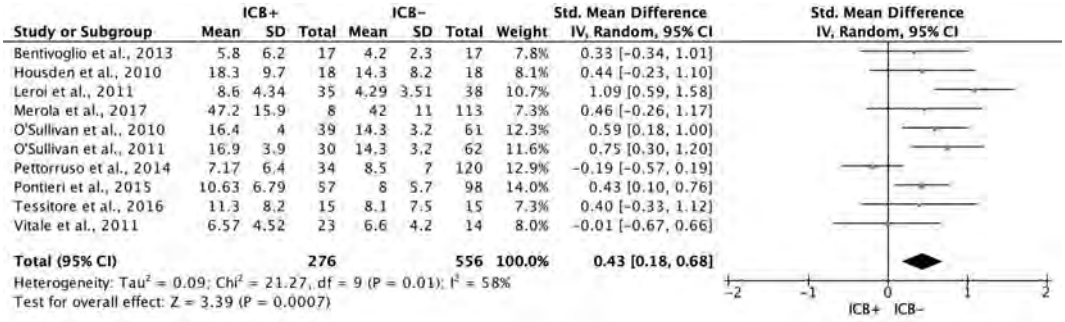
Figure 3. 10 Forest plots for visuospatial abilities and language. Here are reported forest plots for visuospatial abilities (A) and language (B). Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in Persons with Parkinson's disease (PwP) with ICBs (ICB+) in comparison to those without ICBs (ICB−). ICBs, impulsive-compulsive behaviours.

The following self-reported affective and behaviour outcomes were explored: depression, anxiety, anhedonia, apathy and impulsivity. ICB+ showed increased depression (SMD = 0.35; 95% CI: 0.16, 0.54; Z = 3.54; $p = 0.0004$), anxiety (SMD = 0.43; 95% CI: 0.18, 0.68; Z = 3.39; $p = 0.0007$), anhedonia (SMD = 0.26; 95% CI: 0.01, 0.50; Z = 2.01; $p = 0.04$), and impulsivity (SMD = 0.79; 95% CI: 0.50, 1.09; Z = 5.26; $p < 0.00001$), but comparable apathy symptoms. Heterogeneity was low for anhedonia ($\chi^2 = 0.01$, $p = 0.94$, $I^2 = 0\%$), moderate for impulsivity ($\chi^2 = 8.89$, $p = 0.11$, $I^2 = 44\%$), and moderate-to-high for depression ($\chi^2 = 51.42$, $p = 0.0001$, $I^2 = 61\%$), anxiety ($\chi^2 = 21.27$, $p = 0.01$, $I^2 = 58\%$), and apathy ($\chi^2 = 9.09$, $p = 0.03$, $I^2 = 67\%$). Forest plots for affective and motivational outcomes are provided in Figure 3.11. Results of the meta-analyses are summarized in Table 3.11.

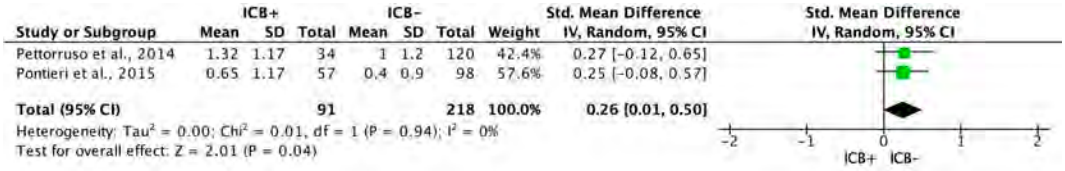
A. Depression



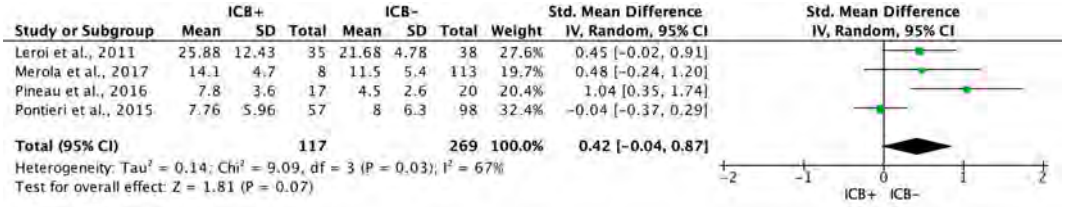
B. Anxiety



C. Anhedonia



D. Apathy



E. Impulsivity

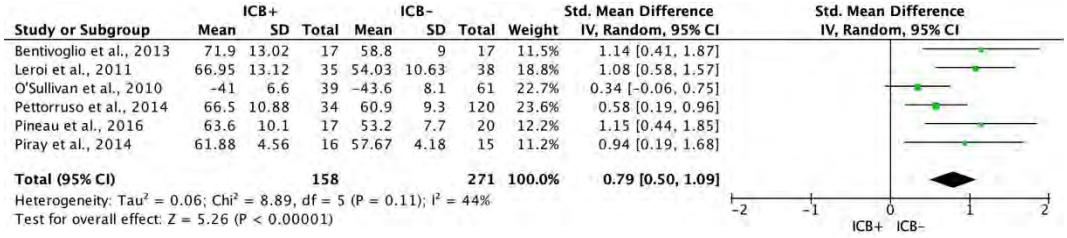


Figure 3. 11 Forest plots for affective and motivational outcomes. Here are reported forest plots for depression (A), anxiety (B), anhedonia (C), apathy (D), and impulsivity (E). Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate worse performance in Persons with Parkinson's disease (PwP) with ICBs (ICB+) in comparison to those without ICBs (ICB−). ICBs, impulsive-compulsive behaviours.

Table 3. 11 Results of the meta-analyses.

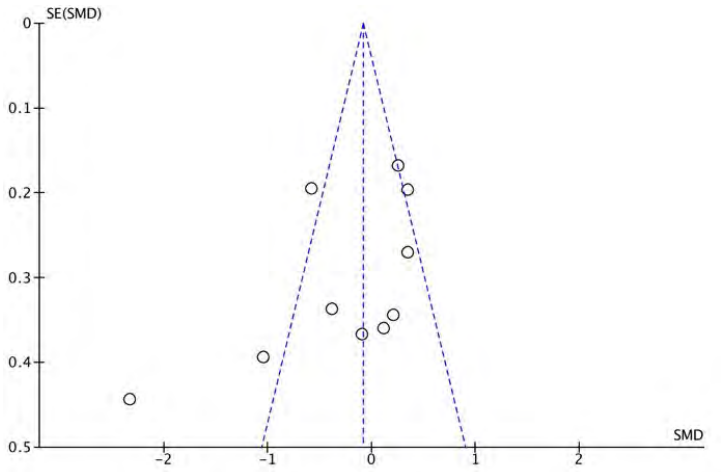
			Random-effect model results				Heterogeneity		
Outcome	**K**	**N**	**SMD**	**[95% CI]**	**Z**	***p***	X^2	***p***	I^2
Short-term verbal memory	10	736	-0.25	[-0.66, 0.16]	1.22	0.22	51.26	*<0.00001*	82%
Short-term visuospatial memory	5	352	-0.12	[-0.42, 0.17]	0.82	0.41	5.26	0.26	24%
Long-term verbal memory	9	702	-0.18	[-0.52, 0.16]	1.04	0.30	29.66	*0.0002*	73%
Long-term visuospatial memory	3	322	-0.21	[-0.64, 0.21]	0.99	0.32	6.64	*0.04*	70%
Working memory	7	371	-0.21	[-0.54, 0.13]	1.19	0.24	14.73	*0.02*	59%
Attention	8	460	-0.22	[-0.47, 0.03]	1.73	0.08	9.40	0.23	26%
Set-shifting	7	426	-0.49	[-0.78, -0.21]	3.37	*0.0008*	9.32	0.16	36%
Concept formation (sort and shift)	7	434	-0.15	[-0.48, 0.19]	0.86	0.39	11.56	0.07	48%
Concept formation (reasoning)	5	293	-0.21	[-0.56, 0.14]	1.16	0.25	5.66	0.23	29%
Inhibition	11	677	-0.23	[-0.59, 0.12]	1.27	0.20	44.95	*<0.00001*	78%
Cognitive flexibility	10	776	-0.02	[-0.25, 0.20]	0.19	0.85	16.79	*0.05*	46%
Reward-related decision-making	8	238	0.42	[0.02, 0.82]	2.05	*0.04*	15.50	*0.03*	55%
Visuospatial abilities	7	548	-0.30	[-0.69, 0.08]	1.57	0.12	24.86	*0.0004*	76%
Language	2	144	-0.35	[-0.87, 0.17]	1.31	0.19	1.96	0.16	49%
Depression	21	1431	0.35	[0.16, 0.54]	3.54	*0.0004*	51.42	*0.0001*	61%
Anxiety	10	832	0.43	[0.18, 0.68]	3.39	*0.0007*	21.27	*0.01*	58%
Anhedonia	2	309	0.26	[0.01, 0.50]	2.01	*0.04*	0.01	0.94	0%
Apathy	4	386	0.42	[-0.04, 0.87]	1.81	0.07	9.09	*0.03*	67%
Impulsivity	6	429	0.79	[0.50, 1.09]	5.26	*<0.00001*	8.89	0.11	44%

Legend. K*:* number of studies; N: number of participants; SMD: standardized mean difference; CI: confidence interval. *P* values below the significance level ($p<0.05$) are reported in italics.

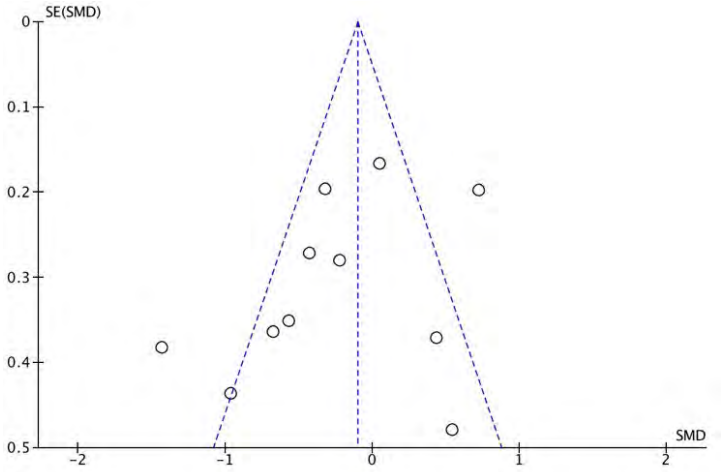
Risk of bias

Visual exploration of funnel plots did not suggest possible publication bias for short-term verbal memory, inhibition, cognitive flexibility, depression, and anxiety that were the only outcomes with at least ten studies; that is, small studies spread across both sides of the plot. Funnel plots are provided in Figure 3.12. Risk of performance bias was unclear with only 2/25 studies indicating assessors blinding procedures (Housden et al., 2010; O'Sullivan, Djamshidian, et al., 2010). Attrition bias was low, with 4/25 studies with missing data (Joutsa et al., 2015; Mack et al., 2013; O'Sullivan, Djamshidian, et al., 2010; Piray et al., 2014). Risk of performance and attrition biases graph is provided in Figure 3.13.

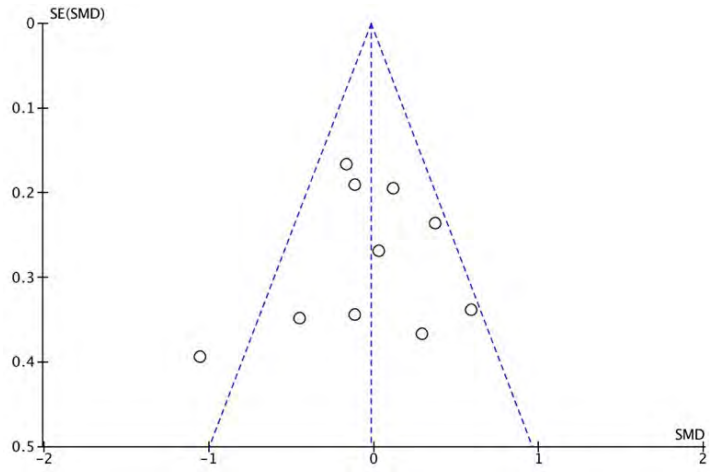
A. Funnel plot for short-term verbal memory



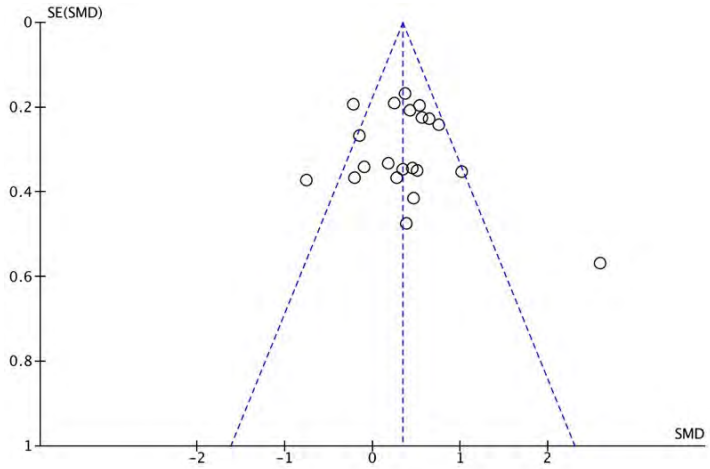
B. Funnel plot for inhibition



C. Funnel plot for cognitive flexibility



D. Funnel plot for depression



E. Funnel plot for anxiety

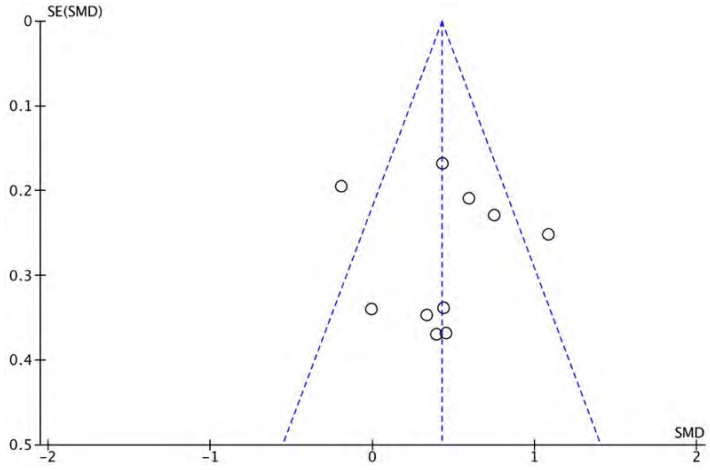


Figure 3. 12 Funnel plots for cognitive, affective and motivational outcomes. Here are reported funnel plots for short-term verbal memory (A), inhibition (B), phonological fluency (C), depression (D), and anxiety (E). There is no evidence to suggest publication bias. Small studies spread across both sides of the plot (A-E). High heterogeneity might account for a scattered shape of the funnel plot (A, B, D, E).

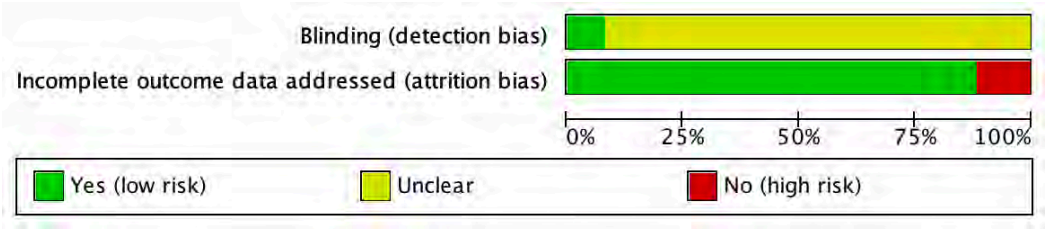


Figure 3. 13 Risk of performance and attrition biases graph. Review authors' judgements about detection and attrition biases presented as percentages across all included studies.

Sensitivity analysis and moderator analysis

Sensitivity analysis showed that after removing Pontieri et al. (2015), the overall effect size of long-term visuospatial memory became significant (SMD = -0.44; 95% CI: -0.75, -0.13; Z = 2.81; $p = 0.005$) and the heterogeneity changed from high ($\chi^2 = 6.64$, $p = 0.04$, $I^2 = 70\%$) to low ($\chi^2 = 0.62$, $p = 0.43$, $I^2 = 0\%$). After removing Biundo et al. (2011), the overall effect size of working memory became significant (SMD = -0.32; 95% CI: -0.63, -0.01; Z = 2.05; $p = 0.04$) and the heterogeneity changed from high ($\chi^2 = 14.73$, $p = 0.02$, $I^2 = 59\%$) to moderate ($\chi^2 = 8.41$, $p = 0.13$, $I^2 = 41\%$). The overall effect size of attention became significant after removing Merola et al. (2017) (SMD = -0.27; 95% CI: -0.50, -0.04; Z = 2.29; $p = 0.02$), but heterogeneity remained low. The overall effect size of inhibition became significant after removing Biundo et al. (2015) (SMD = -0.34; 95% CI: -0.65, -0.03; Z = 2.18; $p = 0.03$) and heterogeneity changed from high to moderate-to-high ($\chi^2 = 24.18$, $p = 0.004$, $I^2 = 63\%$). The overall effect size of incentive-driven decision-making lost significance after removing Bentivoglio et al. (2013) (SMD = 0.42; 95% CI: -0.05, 0.89; Z = 1.75; $p = 0.08$), Housden et al. (2010) (SMD = 0.36; 95% CI: -0.08, 0.81; Z = 1.59; $p = 0.11$), Piray et al. (2010) (SMD = 0.35; 95% CI: -0.08,

0.78; Z = 1.58; $p = 0.11$), and Rossi et al. (2010) (SMD = 0.29; 95% CI: -0.03, 0.61; Z = 1.78; $p = 0.07$). After removing Rossi et al. (2010), heterogeneity changed from moderate ($\chi^2 = 15.50$, $p = 0.03$, $I^2 = 55\%$) to low ($\chi^2 = 8.27$, $p = 0.22$, $I^2 = 27\%$). Including or excluding the other studies did not change heterogeneity. The overall effect size of apathy became significant after removing Pontieri et al. (2015) (SMD = 0.60; 95% CI: 0.25, 0.95; Z = 3.38; $p = 0.0007$) and heterogeneity changed from high ($\chi^2 = 9.09$, $p = 0.03$, $I^2 = 67\%$) to low ($\chi^2 = 2.07$, $p = 0.35$, $I^2 = 4\%$).

Moderator analysis was performed for short-term verbal memory, inhibition, cognitive flexibility, and depression, which were the only outcomes that included at least ten studies each (Borenstein, 2009). Anxiety did not undergo moderator analysis, because none of the covariates of interest were assessed in at least ten studies. Moderator analysis showed no effect of age, education, PD duration, H&Y, UPDRS-III, and total LEDD, LD-LEDD, DAED on short-term verbal memory, inhibition, cognitive flexibility, and depression. Results of the moderator analysis are provided in Table 3.12.

Table 3. 12 Results of the moderator analysis.

	Short-term Verbal Memory			Inhibition			Cognitive Flexibility			Depression			Anxiety		
Moderators	K	β	*p*	K	β	*p*	K	β	*p*	K	β	*p*	K	β	*p*
Age	9[a]	--	--	11	-0.003	0.97	8[a]	--	--	19	-0.03	0.18	8[a]	--	--
Education	8[a]	--	--	10	-0.05	0.67	6[a]	--	--	10	-0.05	0.33	6[a]	--	--
PD Duration	8[a]	--	--	10	0.04	0.64	9[a]	--	--	19	-0.01	0.81	8[a]	--	--
H&Y Stage	8[a]	--	--	8[a]	--	--	6[a]	--	--	14	-0.15	0.57	7[a]	--	--
UPDRS-III	10	0.07	0.08	11	0.02	0.58	10	-0.005	0.80	19	-0.01	0.56	9[a]	--	--
Total LEDD	9[a]	--	--	10	0.002	0.20	9[a]	--	--	19	0.000	0.99	9[a]	--	--
DAED	9[a]	--	--	9[a]	--	--	8[a]	--	--	18	0.001	0.43	9[a]	--	--
LD-LEDD	4[a]	--	--	5[a]	--	--	3[a]	--	--	10	0.000	0.75	6[a]	--	--

Legend. PD: Parkinson's disease; H&Y: Hoehn & Yahr score; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; LEDD: levodopa equivalent daily dosage (mg); DAED: dopamine agonist equivalent daily dosage (mg); LD: levodopa; K: number of studies. [a]not included in the moderator analysis because k<10.

Discussion

The primary aim of this meta-analysis of 25 studies was to describe the pattern of cognitive function in DRT-medicated ICB+ compared to ICB-. A stricter set of inclusion criteria was applied than used previously (Santangelo, Raimo, & Barone, 2017), to achieve a more homogenous ICB+ group, and a better understanding of the relationship between ICBs and cognition in medicated PD. A secondary aim was to examine affective and motivational correlates of ICBs, as emotion-cognition and motivation-cognition relationships are receiving increasing attention to understand psychopathology and improve pharmacological and psychological treatments (Crocker et al., 2013).

The findings of the present meta-analysis suggest ICBs to be associated with worse performance on a set of executive function measures assessing set-shifting (Trail Making Test part B, and B-A) and incentive-driven decision-making (Iowa Gambling Task, Monetary Risk Task, Kirby Monetary Choice Questionnaire), with relative sparing of other executive tasks that assess concept formation and reasoning (Raven's progressive matrices standard and coloured versions), concept formation sort and shift (Wisconsin card sorting test standard and modified versions), inhibition (Stroop, Stop Signal Task, Go/No-Go), and cognitive flexibility (phonological fluency), as well as memory, working memory, attention, visuospatial abilities, and language.

Set-shifting and incentive-driven decision-making abilities are important determinants of advantageous behaviour, serving to translate goals into action planning, as well as monitoring response and errors (Gläscher et al., 2012; Sinha et al., 2013).

Structural and functional neuroimaging outcomes were not included in this meta-analysis, but neuroanatomical findings in PwP with abnormalities in set-shifting and incentive-driven decision-making may help speculate on brain areas that may undergo DRT overdose in PD. Lesion-symptom mapping studies suggest incentive-driven decision-making to rely upon an anatomical network composed of the ventromedial, orbitofrontal and frontopolar cortices. In particular, set-shifting, which is one of the processes underlying cognitive control involved in option generation stage of the incentive-driven decision-making framework (Sinha et al., 2013), depends on rostral ACC functioning (Gläscher et al., 2012). These brain areas form part of the mesocorticolimbic system that, in the early stages of PD, undergo less dopaminergic damage than the dorsal striatal pathways.

According to the 'overdose hypothesis', the DRT amount required to control motor symptoms in PD has the potential to move the same PwP away from the optimum for certain cognitive functions (Rowe et al., 2008). The relationship between the efficiency of neuronal activity and the state of dopaminergic modulation is represented by a Yerkes-Dodson inverted U-shaped curve with cognitive functions declining with deviation away from optimum DA levels, indicated by the centre of the curve (Cools & Robbins, 2004). Extrapolating this model to set-shifting and incentive-driven decision-making implies that DRT has the capacity to both improve and impair these executive functions depending on baseline DA levels in the underlying neural circuitry. For PwP with low baseline DA levels in the mesocorticolimbic system, DRT may optimize activity as supported by improved set-shifting and incentive-driven decision-making when assessed in an optimally medicated state compared to the same PwP assessed following DRT withdrawal (Boller et al., 2014; Cools et al., 2001). By the same token, if PwP starts out with

higher mesocorticolimbic baseline levels of DA, DRT causes DA over-activity in the mesocorticolimbic system. This view is consistent with evidence that DA agonists increase frontal cortex blood flow (Claassen et al., 2017), and enhance incentive-driven risk-taking behaviour in ICB+ compared to ICB- (Claassen et al., 2011). Furthermore, preserved brain metabolism has been observed in ICB+ compared to ICB- (Marín-Lahoz et al., 2020).

A recent meta-analysis of case-control studies on the prevalence of ICBs in PD provides indirect evidence of dopaminergic over-activity, as being medicated for PD and disease duration were both factors that increased the risk of ICBs (Molde et al., 2018). As disease duration advances, the dopaminergic degeneration spreads to brain areas that were spared in the early stages of the disease, such as the prefrontal cortex (Marinus et al., 2018). The progressive involvement of brain areas during PD progression may have two consequences. The first is a dysregulation of brain regions involved in the top-down mechanisms of cognitive control of behaviour (Cilia et al., 2011), that are important for the option generation, option selection, and action initiation or inhibition stages of the incentive-driven decision-making (Sinha et al., 2013). The second is the need to increase DRT dosage to compensate motor symptoms and the consequent overstimulation of less damaged brain areas. However, the relationship between ICBs and DRT dosage is not well established; some studies report no difference between DRT doses and ICBs (Avanzi et al., 2006; Erga et al., 2017; Isaias et al., 2008; Vela et al., 2016), with others reporting an association between ICBs and DA agonists doses (Biundo et al., 2017; Corvol et al., 2018; Joutsa, Martikainen, Vahlberg, & Kaasinen, 2012; Perez-Lloret, Rey, Fabre, Ory, Spampinato, Brefel-Courbon, et al., 2012; Valença et al., 2013; Zhang, He, Li, Chen, & Liu, 2017). This meta-analysis lacked the power for conducting moderator

analysis for disease duration, total LEDD, LD-LEDD, and DAED in incentive-driven decision-making and set-shifting leaving this question unanswered.

Data from reported here meta-analysis may help reconcile the debate whether ICBs in PD is associated with frontal lobe dysfunction (Djamshidian et al., 2014; Siri et al., 2015; Steeves et al., 2009; van Eimeren et al., 2010). The discrepancy between previous reports is likely due to differences in the tasks and the underlying executive function subdomains investigated. The data of this meta-analysis indicate that some frontal tasks and related subdomains may not be affected by ICBs. Therefore, neuropsychological evaluation of ICB+ should include a broad range of executive function tasks, encompassing both incentive-driven decision-making and set-shifting, and not be limited to a general frontal screening test, such as the Frontal Assessment Battery, which does not include those subdomains.

The profile of executive dysfunction found in the present work confirms the conclusions of a previous meta-analysis (Santangelo, Raimo, & Barone, 2017) that also reported reduced abstraction/concept formation and visuospatial abilities in ICB+. The discrepancy between the two meta-analyses can be ascribed to the inclusion of two reports (Erga et al., 2017; Merola et al., 2017) not available at the time of the former one, and by stricter exclusion criteria. Six studies included by Santangelo et al. (2017) were excluded in this meta-analysis (Cerasa et al., 2014; Leroi et al., 2013; Santangelo et al., 2009; Voon, Gao, et al., 2011; Voon, Reynolds, et al., 2010; Yoo, Yun, et al., 2015), because of a) the ICB- group included PwP with hypersexuality and compulsive shopping (Santangelo et al., 2009), b) dementia not excluded (Leroi et al., 2013), c) previous or current drug abuse or dependence (Voon, Gao, et al., 2011; Voon, Reynolds, et al., 2010), and d) PwP screened for

gambling disorder (Cerasa et al., 2014) or punding (Yoo, Yun, et al., 2015) only, thereby the presence of other ICBs in the ICB- group could not be ruled out.

The secondary aim was to explore affective and motivational outcomes associated with ICBs, as evidence indicates a role for DA dysregulation in the pathophysiology of impulsivity, apathy, and anhedonia in gambling disorder, drug addiction, and ICB+ (Bloomfield et al., 2014; Clark et al., 2012; Sinha et al., 2013). The present study found increased rates of self-reported depression, anxiety, anhedonia, and impulsivity, but not apathy in ICB+ compared to ICB-.

Impulsivity and apathy have been suggested to represent opposite ends of a dopaminergic continuum, where the former and the latter are associated with hyper and hypodopaminergic states, respectively (Sinha et al., 2013). According to this view, DRT mesocorticolimbic overstimulation increases impulsivity that, in turn, may enhance incentive-driven behaviour that, over time, may become addictive in nature (Antonini & Cilia, 2009). The association between ICB+ and impulsivity but not apathy in this meta-analysis is consistent with this model and the evidence that the DA agonist pramipexole improves apathy in PwP without ICBs (Leentjens et al., 2009) but also increases impulsivity (Weintraub et al., 2010).

Anhedonia is defined as the decreased ability to experience pleasure from positive stimuli (American Psychiatric Association, 2013). Pramipexole may reduce anhedonia in ICB-, suggesting its hypodopaminergic nature (Lemke, Brecht, Koester, Kraus, & Reichmann, 2005). The co-occurrence of hypodopaminergic anhedonia with hyperdopaminergic ICBs is surprising. One possible explanation is that ICB+ may have decreased ability to experience pleasure when not engaged in ICBs. This hypothesis is supported by the evidence that people addicted to alcohol or drugs experience anhedonia during withdrawal syndrome, a feature that may

facilitate relapse (Hatzigiakoumis, Martinotti, Di Giannantonio, & Janiri, 2011). However, the relationship between anhedonia and dopaminergic states is not so straightforward and anhedonia is also recognized as one of the overlapping symptoms between apathy and depression (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015). The association with anhedonia may be confounded by the presence of depression, which in some cases might be serotoninergically mediated (Boileau et al., 2008). However, there are only two studies investigating anhedonia and further investigation is needed.

The pathophysiology of depression and anxiety in PD is likely to be multifactorial including reaction to disease diagnosis and anxiety about its future course. Depression and anxiety are present in the premorbid PD stage (Ishihara & Brayne, 2006), therefore suggesting they may represent a core feature of PD. In this meta-analysis depression and anxiety levels were higher in ICB+ compared to ICB-. ICBs may have a negative impact on the quality of life (Leroi et al., 2011; Vela et al., 2016), and in turn increase depression and anxiety levels. Conversely, at least in some PwP, depression and anxiety could increase the risk of developing ICBs as coping mechanisms (Delaney, Leroi, et al., 2012; Delaney, Simpson, et al., 2012). Also, as the mesocorticolimbic pathway dysfunction may be involved in depression, anxiety and ICBs, they might co-occur as epiphenomena of shared neural correlates (Vriend, Pattij, et al., 2014).

Limitations

First, this meta-analysis is constrained by a small number of studies, most of which with small samples that might have contributed to high heterogeneity for some of the outcomes explored. This consideration could be reflected in the

sensitivity analysis data for long-term visuospatial memory, working memory, attention, inhibition, incentive-driven decision-making, apathy, and it suggests caution in the interpretation of the results for these outcomes. For example, long-term visuospatial memory become significant excluding Pontieri et al. (2015), in which participants were under antipsychotic and antidepressant and had lower UPDRS-III score and higher DAED compared to the other two studies included in the domain (Biundo et al., 2011, 2015). This is also the case for attention, that become significant after excluding Merola et al. (2017) in which participants had lower UPDRS-III score and higher DAED compared to the other studies included (Biundo et al., 2011, 2015; Mack et al., 2013).

Second, the inclusion in the same domains of tasks that might involve different cognitive processes could have contributed to the high heterogeneity and the low stability of some results. However, considering the single cognitive task would have resulted in a reduction of the power, because of the low number of studies using the same tasks. Moreover, in some cases different versions of the same task has been used, which may explain the low stability of working memory, inhibition and incentive-driven decision-making results when sensitivity analysis was performed. Different versions may be differently sensitive to cognitive changes. For example, as measure of working memory, Biundo et al. (2011) used a version of the digit span backword that is different from the versions used in the other studies included (Bentivoglio et al., 2013; Djamshidian et al., 2010; Housden et al., 2010). As measure of inhibition, the Stroop task used differ between studies, with 2/5 studies using a different version of the task (Djamshidian, O'Sullivan, Lees, et al., 2011; Vitale et al., 2011). As measure of incentive-driven decision-making, Pineau et al. (2016) used a version of the Iowa Gambling Task in which participants received instructions with a

hint (i.e., explicit knowledge that there are advantageous decks), compared to the study of Bentivoglio et al. (2013) in which this information was not disclosed to participants. Conversely, in Rossi et al. (2010) no enough information was provided about the version of the Iowa Gambling Task used. Future studies should provide detailed information about the tasks used, which may account for differences between studies' findings. Furthermore, providing detailed information is crucial for allowing replicability studies conducted by other research groups.

Third, it was not possible to perform separate analyses for DA agonists and LD, as the majority of the studies included PwP who were under both types of DRT. Due to the small number of studies, moderator analysis for total LEDD, LD-LEDD and DAED was performed for depression only, which showed no effect. This is not surprising, as in the larger study published so far, ICBs were found to be associated either with DA agonists or, to a lesser extent, with levodopa (Weintraub et al., 2010). These data are in keeping with the notion that both levodopa and DA agonists can interfere with the phasic and tonic activity of dopaminergic neurons (Voon et al., 2017) that, by facilitating neuroadaptive changes in dopaminergic system functioning, may predispose to ICBs.

Fourth, the inclusion of cross-sectional studies impedes the exploration of the direction of the cause-effect relationship between cognitive, affective and motivational outcomes and ICBs; therefore, multicentre and longitudinal studies are needed.

Fifth, 23/25 studies did not mention assessors to be blind to the ICBs status and this might have affected tools administration and scoring. Future studies should be conducted following blinding procedures.

Sixth, QUIP, a validated screening instrument with high sensitivity (94%) but low specificity (72%) to ICBs in PD (Weintraub et al., 2009) was used as the main

screening tool in two studies (Erga et al., 2017; Vela et al., 2016), possibly leading to false positive and/or subclinical ICBs inclusion.

Conclusions

ICBs in PD are associated with worse set-shifting and incentive-driven decision-making, and increased depression, anxiety, anhedonia and impulsivity, but not apathy. Replicability of these findings, together with the findings of Study 1 of this thesis, have been tested in a large cross-sectional multicentre study (Study 3).

Key Findings

- ICB+ perform worse than ICB- in set-shifting and incentive-driven decision-making tasks;
- ICB+ have higher depression, anxiety, anhedonia and impulsivity levels than ICB-;
- ICB+ and ICB- have comparable apathetic levels.

Study 3: A multicentre empirical investigation of cognitive, affective and motivational correlates of Impulsive-compulsive behaviours in Parkinson's disease

Abstract

Background: Study 2 of this thesis shows that ICBs in PD are associated with poorer set-shifting and incentive-driven decision-making, as well as increased depression, anxiety, anhedonia and impulsivity, but not apathy. In Study 1, PwP with ICBs did not change their risky behaviour after a negative feedback in the BART, an incentive-driven decision-making task. Study 1 was constrained by small sample size therefore findings need to be replicated in a larger cohort of PwP. The aim of the present multicentre cross-sectional study is to replicate and confirm Study 1 BART findings of negative feedback impairments in a larger sample of PwP with and without ICBs and healthy controls. To offer information on the neurobiological underpinnings of the findings, the study has been further extended by combining two units of assessments (i.e., behavioural and neurophysiology) (Study 4) and data are provided in Chapter 4.

Method: An Italian cohort of 63 PwP (ICB+: 28; ICB-: 35) and 30 HC were assessed with a test battery including the BART as well as cognitive, affective and motivational measures.

Results: The study failed to replicate previous findings, in that all groups decreased their risky behaviour after negative feedback in the BART. As in Study 1, there was no main effect of group [$F(2, 87) <1$, $p = 0.68$, $\eta_p^2 = 0.01$] and feedback [$F(1, 87) = 1.42$, $p = 0.24$, $\eta_p^2 = 0.02$]. Conversely from Study 1, there was no group x feedback interaction [$F(2, 87) <1$, $p = 0.38$]. ICB+ showed increased

false alarms in the Go/No-Go task compared to both ICB- and HC [$F(2, 89) = 7.41$, $p = 0.001$, $\eta_p^2 = 0.14$; ICB+ vs. ICB-: $p = 0.001$, $d = 0.81$, 95% CI [0.05, 2.25]; ICB+ vs. HC: $p = 0.02$, $d = 0.64$, 95% CI [0.13, 2.08]; ICB- vs. HC: $p = 1.00$, $d = -0.37$, 95% CI [-1.18, 0.63]]. A main effect of group was found for depression [$F(2, 88) = 5.52$, $p = 0.006$, $\eta_p^2 = 0.11$], with higher symptoms in ICB+ vs. HC [ICB+ vs. HC: $p = 0.005$, $d = 1.02$, 95% CI [0.82, 5.35]].

Conclusions: The BART, which is a sensitive measure of risky behaviours in non-PD populations, is not a reliable measure of ICBs in PD. Conversely, impulsive behaviours in PD seem to be associated with abnormal response inhibition and higher levels of depression. These results call for caution against using the BART for assessing behavioural performances in ICBs in PD, which is a task that is sensitive to changes in healthy, but not necessarily in clinical populations.

Introduction

ICBs in PD seem to be characterized by specific impairments in the processes involved in incentive-driven decision-making. In Study 1 of this thesis, PwP with ICBs failed to change risky behaviour after negative feedback during incentive-driven decision-making (i.e., the BART). Despite being documented, this impairment was not by itself sufficient to affect overall risky decision-making performance on the BART. These results are in keeping with those from a systematic review and meta-analysis of cognitive studies (Study 2) that showed that impairments in PwP with ICBs are not only found in tasks assessing incentive-driven decision-making, but also in tasks assessing set-shifting. Set-shifting is a process related to cognitive control (Gläscher et al., 2012), which is important for the option generation stage of the incentive-driven decision-making framework (Sinha et al., 2013) (Figure 3.1).

Albeit promising, BART findings of Study 1 are limited by small sample size and limited statistical power. Here, we aimed to explore the robustness of previous findings by replicating them in a separate and larger sample of PwP.

Replication studies aim to establish reproducibility of a finding with new data. Reproducibility is a core principle of scientific progress (Open Science Collaboration, 2015); this is because, in the scientific process, new evidence is collected based on previous findings; however, findings from rigorous and high-quality research may not be reproduced due to random or systematic errors. Replication studies may highlight the low reliability of the data (Open Science Collaboration, 2015). Replication research in behavioural sciences is not so common (Koole & Lakens, 2012; Makel, Plucker, & Hegarty, 2012), although substantial efforts have been made to promote it (Open Science Collaboration, 2015).

In the current study, a larger PwP sample was used to test replicability of Study 1's findings. Apart from the BART, another incentive-driven decision-making task was used to explore whether findings are consistent across measures. Finally, a comprehensive neuropsychological, affective and motivational test battery was administered to explore whether ICBs in PD are associated with worse cognitive control and increased depression, anxiety and impulsivity, as found in Study 2. In a subset of PwP, findings of reduced sensitivity toward negative feedback have been further supported by combining two units of assessments (i.e., behavioural and neurophysiology) and data are provided in Chapter 4 (Study 4).

Aims and Predictions

The primary aim of this study is to explore the robustness of preliminary evidence that PwP with ICBs do not adjust their risky behaviour after negative feedback by replicating previous results (Study 1) in a separate and larger cohort of PwP.

In agreement with the results of the meta-analysis on cognitive, affective and motivational correlates of ICBs in PD (Study 2), it was further predicted that PwP with ICBs, compared to PwP without ICBs would show:

1. Increased risk-taking behaviour related to reward decision-making and reduced set-shifting abilities (in agreement with Studies 1 and 2);
2. Increased levels of depression, anxiety and impulsivity, but not apathy (in agreement with Study 2).

Demographically matched healthy adults have been included to provide baseline control data for cognitive and affective variables.

Method

Peer Review and Ethic Approval

The study has been peer reviewed before submission to the ethic committee (Appendix Z). It has been approved in March 2017 by the *Ethical Review Panel of Keele University* following the submission of a complete protocol, participants' consent forms and information sheets, validate and non-validated questionnaires and neuropsychological assessments (Appendix AA). The study has also been approved by the *Ethical Review Panel of Verona and Rovigo Territory* in May 2018 (Appendix AB) and by the *Ethical Review Panel of the Venice Territory* in September 2018 (Appendix AC).

Participants

Sample Size calculation (power analysis). A sample size of 96 participants (32 in each group: ICB+, ICB-, and HC) has been estimated using G*Power. This has been done with an a priori power analysis for a one-way ANOVA, a statistical power of 0.80, an alpha of 0.05 and effect size of 0.32. The effect size has been calculated using the means (number of pumps) and SD of the BART pre- and post-explosions discrepancy scores from Study 1 (ICB+: M= -0.31, SD=8.20, n=13; ICB-: M= 6.13, SD= 7.47, n=12; HC: M= 4.65, SD=4.46, n=17) (Martini, Ellis, et al., 2018). A further 5-6 participants were scheduled to be recruited taking into account a drop-out rate of 5% (Martini, Ellis, et al., 2018), which resulted in an overall sample size of 102 participants (34 in each group: ICB+, ICB-, and HC). An effect size of 0.32 is obtained using mean and SD from a previous study (Martini, Ellis, et al., 2018) where PwP diagnosed with ICBs showed a different performance in a measure of risk-taking behaviour (the BART), compared to PwP without ICBs and HC.

In this study, data from a total sample of 93 participants (ICB+: N=28; ICB-: N=35; HC: N=30) will be presented, as the target number of PwP to be recruited was not reached. Effect sizes have also been provided as, unlike p-values, they are independent of sample size (Sullivan & Feinn, 2012).

Persons with Parkinson's disease

Identification (Pre-screening). In the first site (University Hospital of Verona), identification of eligible PwP with a diagnosis of idiopathic mild to moderate PD diagnosed according to the UKPDSBB Diagnostic Criteria (1992) was coordinated by the CI/PI. In the second site (S. Camillo Hospital of Venice), identification of eligible PwP was coordinated by the second site PI. In both sites, databases and clinic lists were used to identify eligible PwP.

Recruitment. In both sites, eligible PwP were approached, at the end of the routine clinic visit, by a member of the research team. Participants were informed about the study and provided with the information sheet (Appendix AD). If they were interested in taking part in the study, the screening visit was scheduled.

Screening visit. Sixty-six PwP attended the screening visit. The screening visit took place in the Neurology Unit of Policlinico G.B. Rossi (University Hospital of Verona) (for the first site) and in the Parkinson's research Unit of S. Camillo Hospital of Venice (for the second site), and lasted 60-90 minutes. Mental capacity to consent was assessed by CI/PI or Alice Martini before PwP signed consent forms. Capacity to provide informed consent was based on MMSE minimum score of 25 or more plus functional assessment of mental capacity with the Four Stage Assessment

of Functional Capacity Questionnaire. In the first site, during the screening visit, CI/PI or Alice Martini were responsible for (1) reviewing inclusion/exclusion criteria; (2) clinical assessment of PD symptoms (modified H&Y Scale, UPDRS motor subsection and motor complications subsection); (3) medical history record; and (4) assessment of ICBs presence and severity using the clinical interview and the QUIP-rs (Appendix AE). The clinical interview includes the same adapted diagnostic criteria for gambling disorder, binge eating disorder, compulsive shopping, hypersexuality, punding/hobbyism, and DDS as Study 1. If present, the caregiver was independently interviewed to confirm the outcome of the clinical interview. In case of discrepancies, the caregiver's interview outcome was considered. At the end of the ICBs screening interview, PwP who were experiencing clinically significant ICBs were allocated to the ICB+ group and PwP with no history of ICBs were allocated to the ICB- group. PwP who did not experience ICBs now but in the past (i.e., remitters) were not enrolled in the study. It should be noted that PwP in this study had ICBs of such severity that they were deemed by the neurologist to be clinically significant.

At the end of the screening visit, participants signed the consent form (Appendix AF). No study procedure initiated until participants provided written informed consent. The same procedure was followed in the second site, where PwP were screened by a Research Neurologist and ICBs were assessed by a neuropsychologist with expertise on ICBs.

Inclusion/exclusion criteria. The same inclusion/exclusion criteria of Study 1 were followed (see section "inclusion/exclusion criteria", page 92). PwP could be currently medicated with the same medication as Study 1 and/or levodopa/carbidopa

intestinal gel infusion. Since the assessments are validated in an Italian population, participants who were not Italian native speakers were excluded, in line with Study 1.

Persons with Parkinson's disease Participants. Sixty-six PwP with idiopathic non-dementing PD were enrolled in the study (34 enrolled in the first site, 32 enrolled in the second site), but 3 of them were excluded during the screening visit as their ICBs was fully remitted (2 in the first site, 1 in the second site). Therefore, 63 PwP (47 males, 16 females; mean age = 62.73, SD = 9.92) completed the study. All PwP were in the mild to moderate stages of PD (H&Y mean score = 1.91, SD = 0.54). Summary of PwP recruitment is listed in table 3.13.

Table 3. 13 Summary of eligible PwP identified and recruited.

Stage of recruitment	**Number of PwP**
Identified as eligible (pre-screening)	66
Excluded during the screening	3
Excluded during the research visit (withdrawn)	0
Participated in the study	63

Legend. PwP: persons with Parkinson's disease.

PwP were divided in two subgroups: 28 PwP (24 males, 4 females) with active ICBs were allocated to the ICB+ group, and 35 PwP (23 males, 12 females) with no ICBs history were allocated to the ICB- group[3].

[3] One of the PwP included in the ICB+ group denied any ICBs, however his behaviour during his permanence in the hospital was indicative of ICBs. The PwP was therefore included in the ICB+ group.

The ICB+ and ICB- subgroups had comparable age [$t(61) < 1$, $p = 0.22$, $d = -0.32$, 95% CI [-0.81, 0.18]], sex [Fisher-Freeman-Halton test, $p = 0.09$], education [$t(61) < 1$, $p = 0.61$, $d = -0.13$, 95% CI [-0.63, 0.37]], current levels of functioning [MMSE: $t(61) < 1$, $p = 0.37$, $d = 0.23$, 95% CI [-0.27, 0.73]], disease severity stage [H&Y: $t(61) < 1$, $p = 0.50$, $d = 0.17$, 95% CI [-0.33, 0.67]], motor functioning [UPDRS-III: $t(37.54) = 1.64$, $p = 0.11$, $d = 0.45$, 95% CI [-0.08, 0.99]], and motor complications [UPDRS-IV: $t(34.54) = 1.32$, $p = 0.19$, $d = 0.37$, 95% CI [-0.17, 0.90]].

ICB+ had longer disease duration [$t(61) = 2.20$, $p = 0.03$, $d = 0.56$, 95% CI [0.05, 1.06]][4], younger age at PD onset [$t(61) < 1$, $p = 0.02$, $d = -0.60$, 95% CI [-1.11, -0.09]], and higher ICBs severity [QUIP-rs total score: $t(28.66) = 6.77$, $p < 0.00001$, $d = 1.80$, 95% CI [1.11, 2.47]].

DA agonist use was comparable between groups [Fisher-Freeman-Halton test, $p = 0.74$]. Total LEDD [$t(43.12) = 2.72$, $p = 0.009$, $d = 0.71$, 95% CI [0.18, 1.22]] was higher in ICB+ vs. ICB- group. Conversely, DAED [$t(61) = 1.67$, $p = 0.10$, $d = 0.42$, 95% CI [-0.08, 0.92]] and LD-LEDD [$U = 353.5$, $p = 0.06$, $r_{rb} = 0.28$, 95% CI [-0.003, 0.52]] did not differ between ICB+ and ICB- groups. Total LEDD, LD-LEDD and DAED have been calculated following published formula (Tomlinson et al., 2010). The new drugs Safinamide and Opicapone have been converted following the proposed formula (Schade, Mollenhauer, & Trenkwalder, 2020), as they were not available at the time the study of Tomlinson et al. (2010) was performed. Melevodopa was converted as Levodopa (1 mg Melevodopa = 1 mg levodopa).

[4] Sex, education, MMSE, H&Y, UPDRS-III and IV, disease duration, Total LEDD, LD-LEDD, and DAED are not normally distributed. When the results were comparable for both parametric t test and for the non-parametric Mann U Whitney, results of parametric tests were provided, as they assure greater statistical power.

Clinical and demographic characteristics by centre. PwP from the first site (N = 32), compared to PwP from the second site (N = 31), were younger [first site: M = 60.50, SD = 10.46; second site: M = 65.87, SD = 9.34; $t(61) < 1$, $p = 0.04$, $d = -0.54$, 95% CI [-1.04, -0.04]], had worse motor functioning [UPDRS-III score first site: M = 31.47, SD = 14.76; second site: M = 21.08, SD = 10.37; $t(54.46) = 3.12$, $p = 0.003$, $d = 0.81$, 95% CI [0.27, 1.36]], and higher DAED levels [first site: M = 268.13, SD = 234.90; second site: M = 133.87, SD = 91.29; $t(40.41) = 3.01$, $p = 0.005$, $d = 0.75$, 95% CI [0.23, 1.27]].

Sex [Fisher-Freeman-Halton test, $p = 0.57$], education [$t(61) < 1$, $p = 0.36$, $d = 0.23$, 95% CI [-0.26, 0.73]], current levels of functioning [MMSE: $t(61) < 1$, $p = 0.33$, $d = 0.25$, 95% CI [-0.25, 0.74]], disease duration [$t(53.70) < 1$, $p = 0.82$, $d = 0.06$, 95% CI [-0.44, 0.55]], age at PD onset [$t(61) < 1$, $p = 0.06$, $d = -0.47$, 95% CI [-0.97, 0.03]], disease severity stage [H&Y: $t(61) < 1$, $p = 0.58$, $d = -0.14$, 95% CI [-0.63, 0.35]], motor complications [UPDRS-IV: $t(49.09) = 1.58$, $p = 0.12$, $d = 0.41$, 95% CI [-0.12, 0.93]], DA agonist use [Fisher-Freeman-Halton test, $p = 1.00$], dopaminergic medication levels [Total LEDD, mg: $t(61) < 1$, $p = 0.62$, $d = 0.12$, 95% CI [-0.37, 0.62]; LD- LEDD, mg: $t(61) < 1$, $p = 0.50$, $d = -0.17$, 95% CI [-0.66, 0.32]], and ICBs severity [QUIP-rs total score: $t(61) = 1.35$, $p = 0.18$, $d = 0.34$, 95% CI [-0.16, 0.84]] did not differ between the PwP of the two sites. The number of PwP allocated to the ICB+ group did not differ between sites [first site: N = 15; second site: N = 13; $X^2(1, N = 63) = 0.16$, $p = 0.69$].

Healthy controls

Recruitment. In both sites, eligible HC contact details were gathered from (1) a list of participants who have taken part in previous studies and agreed to be

contacted again about participation in future research or (2) word of mouth. Also, (3) volunteers who provided contact details following talks about the study to local PD and non-PD associations were recruited. Thirty eligible HC were contacted via email or sent the information sheet (Appendix AG).

Screening visit. Thirty HC were screened. In the first site, the screening visit for HC took place in the Neurology Unit of the University Hospital of Verona. In the second site, the screening visit for healthy controls took place in the Parkinson's Unit of the S. Camillo Hospital. The screening visit lasted 60 minutes. Mental capacity to consent was assessed by CI/PI or Alice Martini (in the first site) and by a Research Neurologist (in the second site) before PwP signed consent forms. Capacity to provide informed consent was based on a combination of MMSE minimum score of 25 or more plus functional assessment of mental capacity with the Four Stage Assessment of Functional Capacity Questionnaire. During the screening visit, the CI/PI or Alice Martini (in the first site) or a Research Neurologist (in the second site), was responsible for reviewing inclusion/exclusion criteria, and taking consent (Appendix AH). The CI/PI or Alice Martini (in the first site) or a neuropsychologist (in the second site) was responsible for administering the clinical interview to confirm presence/absence of ICBs. As no cut-off for sensitivity and specificity in the general population has been validated yet, the QUIP-rs was not administered to HC in agreement with previous studies (Navalpotro-Gomez et al., 2020; Tessitore, De Micco, et al., 2017). HC experiencing ICBs either at the time of the screening visit or in the past were excluded from the study. No study procedure initiated until participants provided written informed consent.

Inclusion/exclusion criteria. The same inclusion/exclusion criteria of Study 1 were followed (see section "inclusion/exclusion criteria", page 95). Since the assessments are validated in the Italian population, participants who were not Italian native speakers were excluded, in line with Study 1.

Healthy controls Participants. Thirty healthy older adults (18 males, 12 females; mean age = 61.87, SD = 9.41) were enrolled in the study.

Matching Parkinson's disease subgroups and healthy controls

ICB+ and ICB- were matched to the HC for age [$F(2,90) <1$, $p = 0.38$, $\eta_p^2 = 0.02$] and sex [X^2 (2, N=93) = 5.01, $p = 0.08$]. Years of education was comparable between PD groups [ICB+: M = 10.96, SD = 3.51; ICB-: M = 11.51, SD = 4.69; $p = 1.00$, $d = -0.13$, 95% CI [-2.99, 1.90]] but significantly higher in HC [M = 14.80, SD = 3.70; HC vs. ICB+: $p = 0.002$, $d = -1.06$, 95% CI [-6.37, -1.30]; HC vs. ICB-: $p = 0.005$, $d = -0.77$, 95% CI [-5.69, -0.88]]. Therefore, years of education was included as covariate in all the analysis for the following reasons: (i) individuals with higher levels of education perform at a higher level of cognitive functioning compared to individuals with lower levels of educational attainment (Lenehan, Summers, Saunders, Summers, & Vickers, 2015) and (ii) the responses to affective and motivational questionnaires may correlate with education (Santangelo, Raimo, Siciliano, et al., 2017).

The current level of functioning, as assessed with the MMSE, was comparable between PD groups [ICB+: M = 28.32, SD = 1.61; ICB-: M = 27.94, SD = 1.68; $p = 0.51$, $d = 0.28$, 95% CI [-0.33, 1.25]], and between ICB+ and HC [HC: M

= 29.40, SD = 0.81; p = 0.51, d = -0.40, 95% CI [-1.39, 0.37]], but significantly lower in ICB- vs. HC [p = 0.02, d = -0.72, 95% CI [-1.79, -0.15]].

Daytime sleepiness, measured with the Epworth Sleepiness Scale (ESS) (Johns, 1991) was higher in the ICB+ compared to both ICB- and HC [ICB+: M = 8.00; SD = 5.17; ICB-: M = 5.23; SD =3.22; HC: M = 4.37; SD = 2.88; ICB+ vs. ICB-: p = 0.01, d = 0.67, 95% CI [0.48, 5.14]; ICB+ vs. HC: p = 0.001, d = 0.96, 95% CI [1.38, 6.51]], with no differences between ICB- and HC [p = 0.78, d = 0.37, 95% CI [-1.25, 3.53]]. ESS data have been collected during the research visits (see section “Procedure”, page 210). Table 3.14 shows baseline and clinical characteristics of the study sample.

Table 3. 14 Baseline data and clinical characteristics of the study sample.

Variables	**ICB+ (n=28)**	**ICB- (n=35)**	**HC (n=30)**	**F, t, χ^2 values**	***p***	***Post hoc***
Age (y)	61.36 ± 9.18	64.57 ± 10.88	61.87 ± 9.41	$F(2,90) <1$	0.38	
Male, n (%)	24 (85.7%)	23 (65.7%)	18 (60%)	$X^2 (2, N=93) = 5.01$	0.08	
Education (y)	10.96 ± 3.51, 11	11.51 ± 4.69, 12	14.80 ± 3.70, 14	$F(2,90) = 7.85$	***0.001***	ICB+ = ICB-; ICB+ < HC; ICB- < HC
ESS	8.00 ± 5.17, 7	5.23 ± 3.22, 5	4.37 ± 2.88, 3.5	$F(2,88)=7.33$[‖]	***0.001***	ICB+ > ICB-; ICB+ > HC; ICB- = HC
MMSE	28.31 ± 1.58, 29	27.94 ± 1.68, 28	29.40 ± 0.81, 30	$F(2,89)=3.99$[‖]	***0.02***	ICB+ = ICB-; ICB+ = HC; ICB- < HC
PD features						
Age at diagnosis	50.64 ± 10.94	57.40 ± 11.34	NA	$t(61) <1$	***0.02***	
PD Duration	10.88 ± 6.68, 10.5	7.48 ± 5.61, 6	NA	$t(61) = 2.20$	***0.03***	
UPDRS-III	30.63 ± 16.6, 29.5	24.21±11.10, 22	NA	$t(37.54) = 1.64$	0.11	
UPDRS-IV	2.42 ± 3.49, 1	1.36 ± 2.06, 0	NA	$t(34.54) = 1.32$	0.19	
H&Y	1.96 ± 0.59, 2	1.87 ± 0.51, 2	NA	$t(61) <1$	0.50	
Total LEDD (mg)	995.36 ± 587.30, 902.5	649.06 ± 366.51, 600	NA	$t(43.12) = 2.72$	***0.006***	
LD-LEDD (mg)	715.89 ± 535.26, 500	445.06 ± 394.03, 400	NA	$U= 353.5$	0.06	
DAED (mg)	246.25 ± 229.69, 195	166.71 ± 145.67, 150	NA	$t(61) = 1.67$	0.10	
DA use, n (%)	24 (85.71%)	28 (80%)	NA		0.74[§]	

Table 3. 14 (continued) Baseline data and clinical characteristics of the study sample.

Variables	**ICB+ (n=28)**	**ICB- (n=35)**	**HC (n=30)**	**F, t, χ^2 values**	***p***	***Post hoc***
QUIP-rs score	20.29 ± 14.60, 16	1.31 ± 2.86, 0	NA	$t(28.66) = 6.77$	***<0.00001***	
ICB type						
Single ICB	1 / 5 / 2 / 2 / 2 / 2 [a]	0	0			
Multiple ICB	14[b]	0	0			

Legend. ICB+: PwP with ICB; ICB-: PwP without ICBs history; HC: healthy controls; Education: years of formal education; ESS: Epworth sleepiness scale; MMSE: Mini-mental state examination; UPDRS-III: Unified Parkinson's disease rating scale part III (motor score); UPDRS-IV: Unified Parkinson's disease rating scale part IV (complications); H&Y: Hoehn-Yahr disease severity rating scale; LEDD: Levodopa Equivalent Daily Dosage; LD: levodopa; DAED: dopamine agonist equivalent daily dose; DA: dopamine agonist; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – Rating Scale total score; NA: not available; [a]Single ICB: gambling disorder: n = 1, hypersexuality: n = 5, binge eating: n = 2, compulsive shopping: n = 2, hobbyism: n = 2, punding: n = 2; [b]Multiple ICBs: gambling disorder + hypersexuality: n = 3, gambling disorder + binge eating: n = 1, gambling disorder + compulsive shopping: n = 1, gambling disorder + punding: n=1, hypersexuality + binge eating: n = 1, hypersexuality + compulsive shopping: n = 1, gambling disorder + hypersexuality + binge eating: n = 1, gambling disorder + hypersexuality + punding: n = 2, gambling disorder + hypersexuality + DDS: n = 1, gambling disorder + hypersexuality

+ binge eating + compulsive shopping: n = 1, hypersexuality + binge eating + compulsive shopping +hobbyism + punding: n =1. ‖ANCOVA model with education as covariate. §| Fisher-Freeman-Halton test.

Design

This is a multicentre, cross-sectional, empirical study of 28 PwP with ICBs diagnosed after PD onset, 35 PwP without ICBs history, and 30 HC matched to the PD groups for age and sex.

Procedure

Testing session procedure. There are two sites involved. In both sites, participants attended a screening visit and two research visits (i.e., research visits 1: BART assessment; research visit 2: neuropsychological assessment). When possible, the first research visit was completed the same day as the screening visit, at the end of the screening visit. During the second research visit participants completed measures of (i) incentive-driven decision-making, (ii) cognitive processes associated with the four stages decision-making framework (Sinha et al., 2013), and (iii) affective and motivation. During all research visits, PwP were in an optimally medicated state (i.e., at least 120 minutes after having taken their first DRT of the day). Flow diagram of the study procedure is provided in Figure 3.14. Assessments used during the research visits 1 and 2 are listed in Table 3.15.

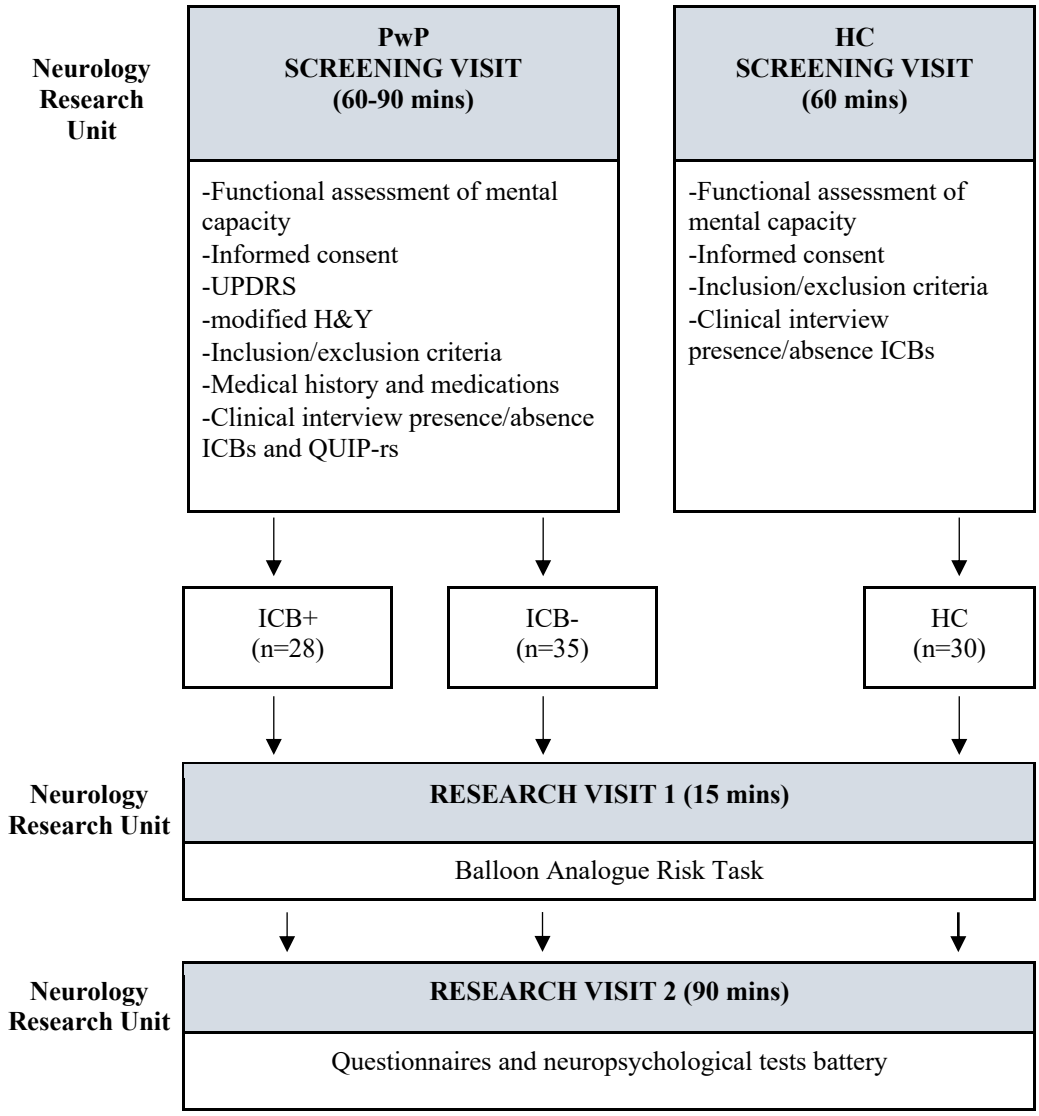


Figure 3. 14 The Flow diagram of the study procedure. HC: healthy controls; UPDRS: Unified Parkinson's disease Rating Scale; H&Y: Hoehn and Yahr Scale; ICBs: impulsive-compulsive behaviours; ICB+: PwP with impulsive-compulsive behaviour; ICB-: PwP without impulsive-compulsive behaviour; PwP: persons with Parkinson's disease; QUIP-rs: Questionnaire for impulsive-compulsive disorders in Parkinson's disease – rating scale.

Table 3. 15 Assessments administered in each research session.

Research Session 1 (15 mins testing)	Research Session 2 (90 mins testing PLUS breaks)
BART	ROCF copy
	Phonological fluency
	DSS
	ROCF delay
	Prose Memory Immediate
	TMT-A
	TMT-B
	Prose Memory delayed
	Go/No-Go task
	Stroop task
	IGT
	Brixton Spatial Anticipation Test
	Kirby Monetary Choice Questionnaire
	I-DAS
	HADS
	BIS-11
	ESS

Legend. BART: Balloon Analogue Risk Task; ROCF: Rey-Osterrieth complex figure test; DSS: Digit span sequencing task; TMT-A: Trail Making Test – part A; TMT-B: Trail Making Test – part B; IGT: Iowa Gambling Task; I-DAS: Italian Dimensional Apathy Scale; HADS: Hospital Anxiety Depression Scale; BIS-11: Barratt Impulsiveness questionnaire; ESS: Epworth sleepiness scale.

Stimuli

Clinical Measures

Modified Hoehn and Yahr Staging Scale. See page 102.

Unified Parkinson's Disease Rating Scale. See page 102.

Epworth Sleepiness Scale. See page 103.

Mini-Mental State Examination. See page 104.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – Rating Scale. See page 73.

Incentive-driven decision-making tasks

The Balloon Analogue Risk Task. A version of the BART was programmed in e-prime v2.0 (Pleskac & Wershbale, 2014). The e-prime BART version is comparable to the BART version used in Study 1, but it was programmed to be also used during electroencephalography (EEG) acquisition (see Study 4, Chapter 4).

Participants sat in front of a 17''computer screen and were instructed to press the V key on a QWERTY keyboard to inflate the balloon. Each click slightly pumps the balloon and 5 pence are earned. If the balloon is inflated too much, it bursts, and then the visual feedback "I am sorry, the balloon burst" appears in the middle of the screen for 1 second. If the balloon bursts, all the money collected for that trial is lost. To gain as much money as possible, participants had to stop inflating the balloon before it bursts and press the N key on a QWERTY keyboard. When they press N,

the visual feedback “congratulation, you have won XX$ money for this balloon” appears in the middle of the screen for 1 second, together with an auditory feedback that simulates slot machine reward, and money is transferred to a virtual bank. After each trial (either a balloon burst or when money is banked), a fixation cross appears in the middle of the screen for 1 second and then the next trial begins. Each participant completed 30 trials, as adding additional trials has been shown to result in little change in pumping rates (Wallsten, Pleskac, & Lejuez, 2005). At the beginning of the task, a practice trial was provided in order to familiarize with the task. The practice trial was pre-programmed to burst at a “break-point” in the range of 1-64 pumps; for the practice trial, a reduced break-point range was chosen in order to reduce between-subjects variability as the experience in the first balloons may impact the subsequent risk-taking behaviour (Koscielniak, Rydzewska, & Sedek, 2016). In the task, balloons were pre-programmed to burst at a break-point in the range of 1-128 pumps. The probability that a balloon would burst was 1/128 for the first pump. If it did not explode, the probability for bursting was 1/127 for the second and so on. The average break-point was 64 pumps. The e-prime BART version is illustrated in Figure 3.15.

Two dependent variables were recorded. The first was the average number of pumps in trials in which balloons were cashed. Higher risk-taking behaviour is associated with a higher number of pumps. The second was the average number of pumps for trials immediately preceding and immediately following a balloon burst (Claassen et al., 2011; Martini, Ellis, et al., 2018; Simioni et al., 2012). Lower number of pumps in trials that immediately followed a balloon burst compared to those that immediately preceded it indicates sensitivity toward negative feedback.

The BART was administered during the first research visit and participants were informed that no money was provided at the end of the task.

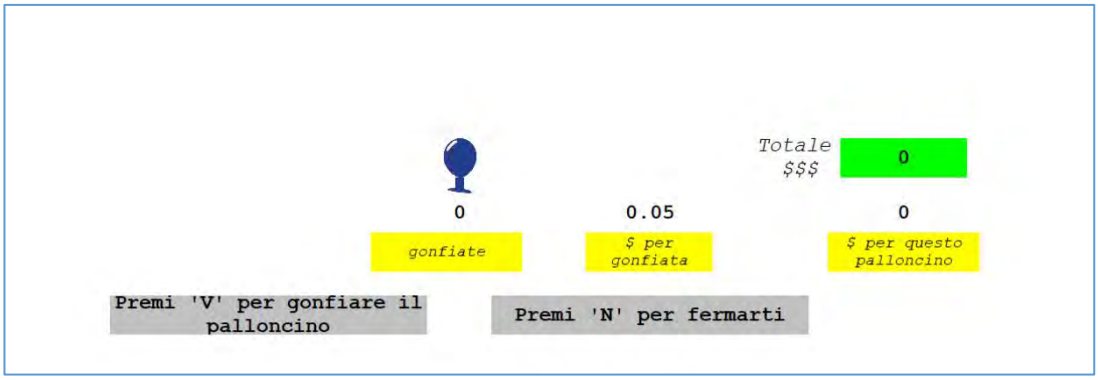


Figure 3. 15 The Balloon Analogue Risk Task (BART).

The Iowa Gambling Task. The Iowa Gambling task (IGT) (Appendix AI) is a task that simulates real-life decision-making in ambiguous situations where outcome probabilities are unknown, conversely to decision-making under risk tasks where outcome probabilities are known or calculable. The PsyToolkit web-based version has been used (Stoet, 2017), as it is free and easily accessible in both hospitals. Participants sat at a 17'' computer screen where there are four decks of cards, two of them are disadvantageous in the long run as they offer high virtual rewards but also high virtual losses, whilst the other two are advantageous as they offer smaller virtual rewards but also smaller virtual losses leading to overall gains. Participants were warned that some decks are more advantageous than others, in agreement with other studies (Balconi, Siri, Meucci, Pezzoli, & Angioletti, 2018); when participants receive instructions with a hint (i.e., explicit knowledge that there are advantageous decks), the reinforcer type (i.e., real vs. virtual reward) does not affect performance (Fernie & Tunney, 2006).

Participants have to choose 100 cards in total, one at the time. Each time they choose a card, they get feedback about winning money. Sometimes, they also lose money. After trials and errors, participants should learn which decks are advantageous (Bechara, Damasio, Damasio, & Anderson, 1994). Decks A and B always yield $100, but there is a 50% chance of also losing $250. Decks C and D always yield $50, but there is a 50% chance of also losing $50. A total score (i.e., net score) was calculated by means of the difference between the overall number of cards selected in advantageous decks (C and D) minus those chosen in disadvantageous ones (A and B). Furthermore, a learning score was calculated according to previous reports (Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005; Kobayakawa, Tsuruya, & Kawamura, 2010; Mapelli, Di Rosa, Cavalletti, Schiff, & Tamburin, 2014; Pagonabarraga et al., 2007). The 100 choices were divided into five blocks of 20 consecutive card selections. For each block, the difference between advantageous and disadvantageous choices was calculated, obtaining 5 scores for each participant. An increased value from the first to the last block is indicative of learning of correct response strategy.

***Cognitive Test Battery*.** A comprehensive cognitive test battery was administered to all participants. The order was the same for all participants. The cognitive test battery included: the TMT-A and TMT-B (Arcara, Bisiacchi, Mapelli, Mondini, & Vestri, 2011; Reitan, 1958) as measures of selective attention and set-shifting, respectively; prose memory (immediate and delayed) (Arcara et al., 2011) and the Rey-Osterrieth complex figure test (ROCF) delayed recall (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002; Osterreith, 1994; Rey, 1941) as measures of memory; the digit span sequencing task (DSS) subtest of the Wechsler Adult Intelligence Scale fourth edition (WAIS-IV) (Wechsler, 2008) as measure of

working memory; the phonological fluency test (Novelli et al., 1986) as measure of verbal generation; Go/No-Go task (Stoet, 2017) and the Stroop Color and Word Test (Scarpina & Tagini, 2017; Stroop, 1935) as measures of motor and verbal inhibitory control, respectively; Kirby Monetary Choice Questionnaire (Kirby et al., 1999) as measure of temporal discounting; the Brixton Spatial Anticipation test (Burgess & Shallice, 1997) as measure of rule detection via feedback processing. The main outcome of each task was considered as a dependent variable.

According to the four stages decision-making framework (Sinha et al., 2013), tasks were categorized as part of option generation (TMT A and B, Phonological fluency, DSS), option selection (Kirby Monetary Choice Questionnaire), action initiation and inhibition (Go/No-Go task, Stroop Color and Word Test), and learning (Prose memory, ROCF delay, and the Brixton Spatial Anticipation test).

Trail Making Test. See page 108.

Phonological fluency. The phonological fluency test assesses verbal ability and executive control (Novelli et al., 1986) (Appendix AL). Participants are given 1 minute to produce as many words as possible starting with a given letter (i.e., F, L, P). All words are accepted, except proper names. The total score is the number of correct words correctly produced for the three letters. In this study, phonological fluency has been used as a measure of option generation, according to Kalis et al. (2008).

Digit span sequencing task. The DSS is a subtest of the WAIS-IV (Wechsler, 2008), which assesses working memory (Appendix AM). The WAIS-IV has been

validated in the Italian population. The examiner reads lists of digits of increasing length to the participants who have to repeat the digits in ascending order, immediately after the presentation (e.g., "2-3-1" to be repeated as "1-2-3"). The digits are read at the pace of one per second. When a string is repeated correctly, the examiner read the next longer sequence. The task ends when participants fail a pair of series of digits of the same length, or when participants correctly repeat a string of 9 digits. The total score is the number of lists of digits correctly repeated (maximum score = 16).

Kirby Monetary Choice questionnaire. See page 110.

Go/No-Go. The Go/No-Go task assesses the ability to suppress unwanted motor responses. The computerized Neuropsydia version has been used (Makowski & Dutriaux, 2017), as it is free and easily accessible in both hospitals. In this task, participants are placed in front of a computer and they are instructed to respond to a specific stimulus ("Go-stimuli") and refrain from responding to another stimulus ("No-Go-stimuli"). Two types of stimuli (i.e., "green circle" and "red circle") appear in the centre of the computer's screen. Participants are instructed to press the spacebar key only when the green circle appears. There are a total number of 100 trials, with an inter-stimulus interval of 1 second. The main outcome is the number of false alarms. The Go/No-Go task has been used as a measure of action initiation and inhibition.

Stroop Color and Word Test. The Stroop Color and Word Test is a neuropsychological task extensively used to assess the ability to inhibit cognitive

interference, which occurs when the processing of a stimulus feature affects the simultaneous processing of another attribute of the same stimulus (Scarpina & Tagini, 2017; Stroop, 1935) (Appendix AN). The task is divided in three parts; in the first part participants are instructed to read the names of 30 colours-words printed in black ink (W), whilst in the second part participants are instructed to name as fast as possible the colour of 30 coloured circles (C). Those two conditions are "congruent conditions". In the last part, named "incongruent condition", participants are provided with a list of 30 colour-words printed with a different colour (e.g., the word "blue" printed in green ink) and they have to name as fast as possible the colour of the ink (CW). Therefore, the subjects have to perform a less automated task (i.e., naming ink colour) while inhibiting the interference arising from a more automated task (i.e., reading the word). The difficulty in inhibiting the more automated process is named Stroop effect. The time interference effect score is the time required to perform the CW condition minus the time required to perform C and W conditions [CW_t-((C_t+W_t)/2)]. The error interference effect score is the number of errors in performing the CW condition minus the number of errors in performing C and W conditions [CW_e-((C_e+W_e)/2)]. In this study, the main outcome is the error interference score. The Stroop task has been used as a measure of action initiation and inhibition.

Brixton Spatial Anticipation Test. See page 112.

Prose Memory. The Prose Memory subtests of the Esame Neuropsicologico Breve (ENB-2) (Arcara et al., 2011) are standardized tests of immediate and delayed free recall memory (Appendix AO). In the first part, which assesses immediate

recall, participants are provided with a short story formed by 28 items. Participants are instructed to listen to the story carefully and try to remember it as best as they can. Once the story has been read, participants have to recall it using the same words as possible (immediate recall). Prose memory immediate recall score is the number of items correctly recalled (maximum score is 28). After the first recall, the story is read for a second time. Participants are instructed to try to remember the story as best as they can, as it will be asked again in the future. After a period of 10 minutes, filled with non-verbal tasks to avoid interference effects, participants are asked to recall the story using the same word as possible. Prose memory delayed recall score is the number of items correctly recalled (maximum score is 28). Prose memory has been used instead of Logical Memory subtest of the Wechsler Memory Scale IV edition (Wechsler, 2009b), as both are validated in the Italian population, but the former is routinely used as part of the neuropsychological assessment in the hospitals where the study is based.

Rey-Osterrieth complex figure test. The ROCF is a standardized measure of non-verbal memory (i.e., ROCF delayed recall), as well as visuospatial and visuoconstructional abilities (i.e., ROCF copy) (Osterreith, 1994; Rey, 1941) (Appendix AP). Participants are provided with a complex bidimensional figure to copy as accurately as possible. When the copy is completed, the figure is removed from the sight. Without forewarning, after a period of 10 minutes filled with verbal tasks to avoid interference effects, participants are asked to reproduce the figure from the memory. The 10 minutes interval was chosen in agreement with ROCF validation study in the Italian population (Caffarra et al., 2002), as well in agreement with the time interval used for Prose memory immediate and delayed recall (see

section “Prose memory”, page 219). The ROCF includes 18 elements. For each element, two points are given if the element is correctly reproduced, 1 point if the reproduction is incomplete but placed properly, or complete but misplaced, 0.5 point if the reproduction is incomplete and misplaced. A zero score is given if the element is absent or not recognisable. The maximum score for both the copy and the free recall conditions is 36.

Affective and Motivational measures

Barratt Impulsiveness Questionnaire. See page 113.

Italian Dimensional Apathy Scale. The Italian Dimensional Apathy Scale (I-DAS) (Santangelo, Raimo, Siciliano, et al., 2017) is the Italian version of the self-report questionnaire Dimensional apathy scale (Radakovic & Abrahams, 2014), which was developed to assess subtypes of apathy minimizing the effect of motor dysfunction (Appendix AQ). It consists of 24 items rated on a 4-points Likert scale, with a total score ranging from 0 to 72, and an optimal cutoff of 28.5 (Santangelo, D’Iorio, et al., 2017). There are three subscales: executive subscale assessing apathetic impairments associated with planning, attention or organisation; emotional subscale assessing apathy associated with altered emotion integration; and behavioural/cognitive initiation subscale assessing apathy associated with loss of self-generation of behaviours or cognition. I-DAS raw scores are affected by formal education level but not by age or gender (Santangelo, D’Iorio, et al., 2017); however, education has been included as covariate in the analysis.

Hospital Anxiety and Depression Scale. See page 114.

Statistical analysis

Data were analysed with SPSS version 21.0 (IBM Corp., 2012). Cohen's *d* effect sizes and 95% confidence intervals were analysed using JASP software version 0.10.2 (JASP Team, 2019), as Cohen's *d* effect sizes are not provided by SPSS.

For continuous variables, normality of distribution was explored with the Shapiro–Wilks test. For variables not normally distributed, both parametric and nonparametric analyses were used to compare groups. When the results were comparable for both types of analysis, results of parametric tests were considered, as they assure greater statistical power. As education level was not comparable between groups, cognitive, affective and motivational variables were compared between groups using ANCOVA models adjusting for years of education. Since this is a replication study, for comparative purposes data have also been analyses removing education as covariate, in line with Study 1. Bonferroni was used as a post-hoc test when ANCOVA yielded significant differences between the three groups. Fisher's exact test or Fisher–Freeman–Halton test was applied to categorical variables. The significance threshold for all the tests was set at $p < 0.05$ (two-tailed), except when Bonferroni correction for multiple comparisons was applied.

For the BART, the average number of pumps on trials where balloons were cashed was compared between groups with a one-way ANCOVA with education as covariate. Response to negative feedback was analysed with a 3 × 2 mixed-model ANCOVA with the between- subjects factor group (ICB+, ICB−, and HC), the within-subject factor feedback (pre-, post-burst), and education as covariate. For the IGT, the net score was compared between groups with a one-way ANCOVA, with

education as covariate. Learning across the IGT task was analysed with a 3 x 5 mixed-model ANCOVA, with the between- subjects factor group (ICB+, ICB−, and HC), the within-subject factor block (block 1, block 2, block 3, block 4, and block 5), and education as covariate. A composite score of memory was calculated (using z-scores) from the immediate and delayed logical memory and the ROCF delay.

Performance on each of the nine cognitive measures was analysed separately with a series of one-way ANCOVAs with education as covariate, and Bonferroni corrected $p < 0.006$. Affective and motivational measures were analysed separately with a series of one-way ANCOVAs with education as covariate, and Bonferroni corrected $p < 0.012$.

An exploratory Spearman correlation analysis examined the relationship between severity of ICBs (QUIP-rs) and cognitive, affective and motivational measures.

Results

Incentive-driven decision-making tasks

On the BART, the three groups did not differ in the average number of pumps where the balloon was cashed [ICB+: 38.67 ± 18.00; ICB−: 32.48 ± 17.25; HC: 36.77 ± 17.23; $F(2, 89) = 1.61$, $p = 0.21$, $\eta_p^2 = 0.03$; Table 3.16 and Figure 3.16A]. Without adjusting for education, the results of the comparison did not change [$F(2, 90) = 1.05$, $p = 0.35$, $\eta_p^2 = 0.23$]. When the average number of balloon pumps pre- and post-burst was compared, there was no main effect of group [$F(2, 87) < 1$, $p = 0.68$, $\eta_p^2 = 0.01$], feedback [$F(1, 87) = 1.42$, $p = 0.24$, $\eta_p^2 = 0.02$], nor group x feedback interaction [$F(2, 87) < 1$, $p = 0.38$, $\eta_p^2 = 0.02$] (see Figure 3.16B). Leaving out education from the model, only the main effect of feedback became

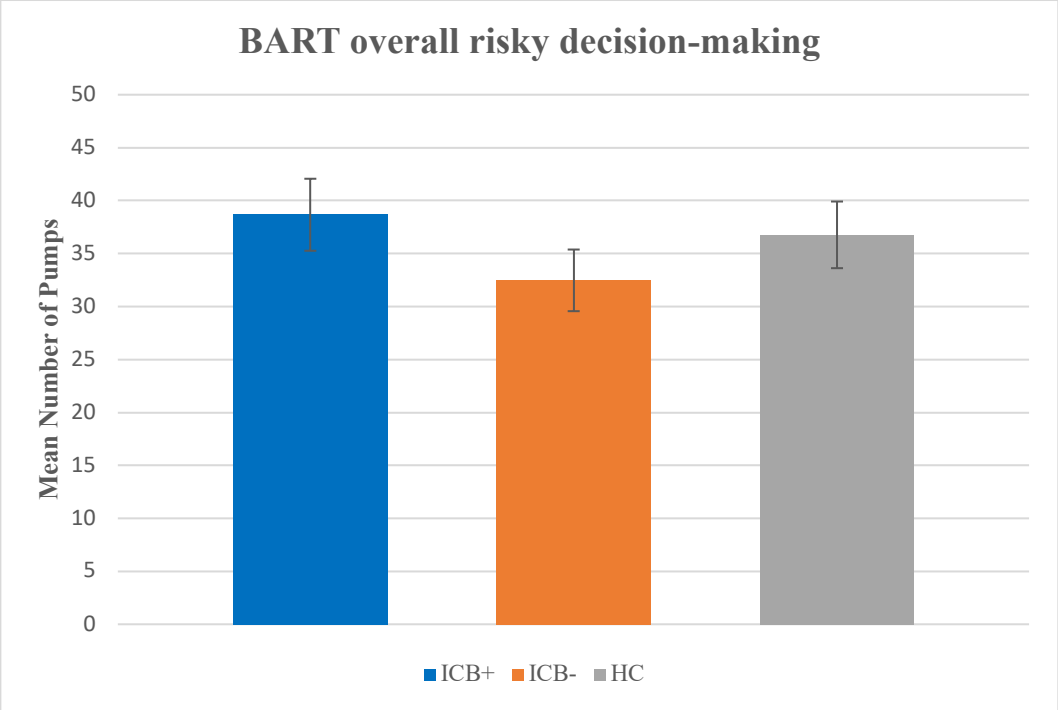
significant [$F(1, 88) = 24.89$, $p = 0.000003$, $\eta_p^2 = 0.22$], indicating that the average number of pumps was significantly lower before than after burst (PRE: 36.70 ± 17.15; POST: 32.86 ± 17.04). The main effect of group [$F(2, 88) < 1$, $p = 0.62$, $\eta_p^2 = 0.01$] and group x feedback interaction [$F(2, 88) < 1$, $p = 0.39$, $\eta_p^2 = 0.02$] remained not significant.

Table 3. 16 Performances in the BART by groups and interactions in the ANCOVA model.

	ICB+ (n=28)	**ICB- (n=35)**	**HC (n=30)**	**F values**	***p***	**ES**
Average adjusted pumps	38.67 ± 18.00	32.48 ± 17.25	36.77 ± 17.23	$F(2, 89) = 1.61$	0.21	0.03
Negative feedback sensitivity	PRE: 37.76±15.28 POST: 32.57 ± 15.00	PRE: 34.76 ± 18.52 POST: 30.75 ± 18.35	PRE: 38.06 ± 17.38 POST: 35.57 ± 17.31	Main effect of feedback $F(1, 87) = 1.42$ Main effect of feedback x group $F(2, 87) < 1$ Main effect of group $F(2, 87) < 1$	0.24 0.38 0.68	0.02 0.02 0.01

Legend. Data are presented as mean ± standard deviation. Significant p values ($p < 0.05$) are given in bold. ICB+: persons with Parkinson's disease (PwP) with impulsive-compulsive behaviours (ICBs); ICB−: PwP without ICBs history; HC: healthy controls; Average adjusted pumps: average number of pumps in cashed balloons; PRE: number of pumps for trials that immediately precede a balloon burst; POST: number of pumps for trials that immediately follow a balloon burst; ES: partial eta-squared effect size.

A. Overall risky incentive-driven decision-making



B. Response to negative feedback

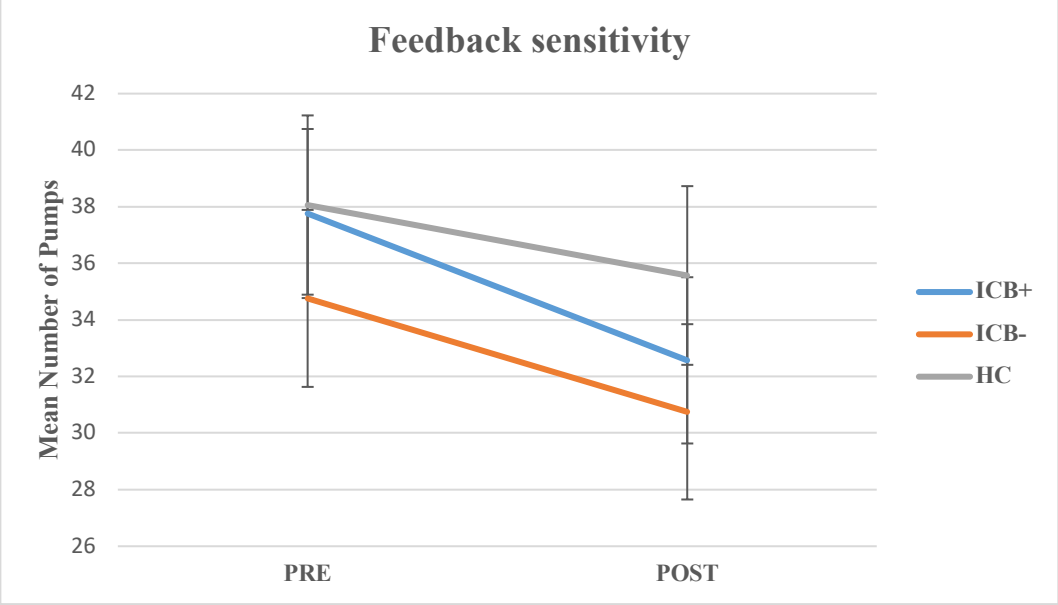


Figure 3. 16 Performances in the Balloon Analogue Risk Task (BART). A) Average number of pumps for cashed trials. The three groups [persons with Parkinson's

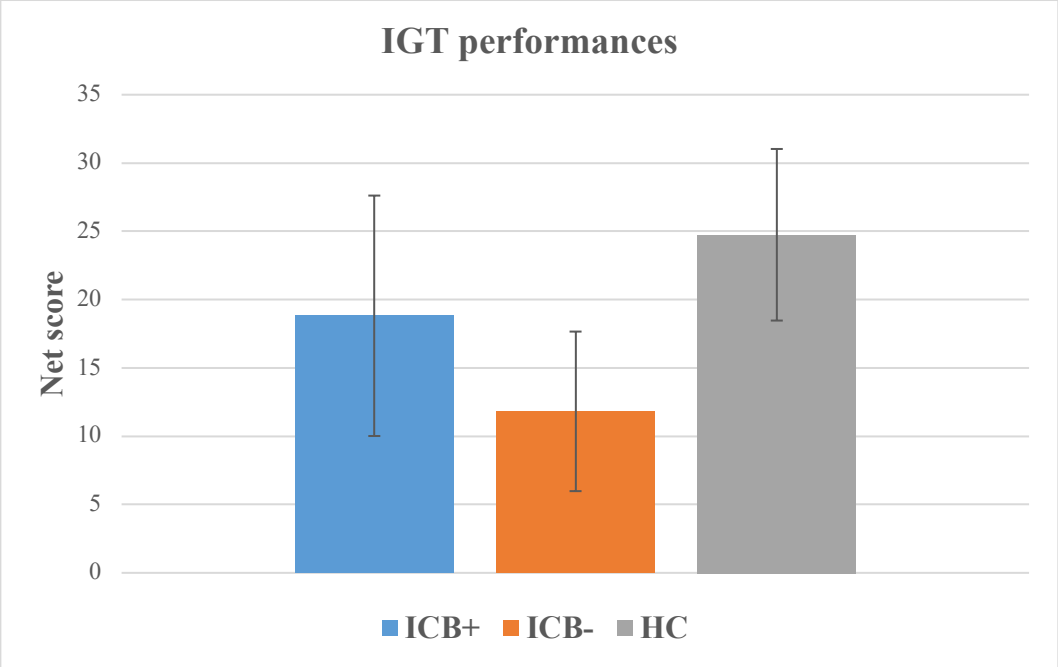
disease and impulsive-compulsive behaviours (ICB+), persons with Parkinson's disease but not impulsive-compulsive behaviours (ICB-), and healthy controls (HC)] did not differ in the average number of pumps, which reflects risk-taking behaviour. Higher scores represent riskier behaviours. Error bars represent the standard error of the mean. B) Groups did not differ in the way they adjusted their behaviour after negative feedback. Negative feedback is expressed as the loss of money for trials in which a balloon burst. All groups decreased the number of pumps after a negative feedback showing less risk-taking behaviour. Error bars represent the standard error of the mean.

Performance on the IGT did not differ between groups [IGT Net score: ICB+: 18.82 ± 46.58; ICB−: 11.83 ± 34.57; HC: 24.75 ± 33.25; $F(2, 87) < 1$, $p = 0.47$, $\eta_p^2 = 0.02$] (Figure 3.17A). Leaving out education from the model, results did not change [$F(2, 88) < 1$, $p = 0.41$, $\eta_p^2 = 0.02$].

A 3 (group) x 5 (block) ANCOVA on the net scores found no main effect of group [$F(2, 87) < 1$, $p = 0.77$, $\eta_p^2 = 0.01$] and block [$F(3.44, 299.2) = 1.11$, $p = 0.35$, $\eta_p^2 = 0.01$], but a trend toward significant block x group interaction [$F(6.88, 299.2) = 1.89$, $p = 0.07$, $\eta_p^2 = 0.04$][5] (Figure 3.17B). Leaving out education from the model, the main effect of block [$F(3.44, 302.74) = 14.68$, $p < 0.0001$, $\eta_p^2 = 0.14$] and block x group interaction [$F(6.88, 302.74) = 2.40$, $p = 0.02$, $\eta_p^2 = 0.05$] become significant, with no changes for the main effect of group [$F(2,88) < 1$, $p = 0.56$, $\eta_p^2 = 0.01$].

[5] Greenhouse -geisser corrections applied, as the Mauchy's test of sphericity indicated that the assumption of sphericity has been violated [$X^2(9) = 24.84$, $p = 0.003$].

A. Overall performances on the IGT



B. IGT Block x group interaction

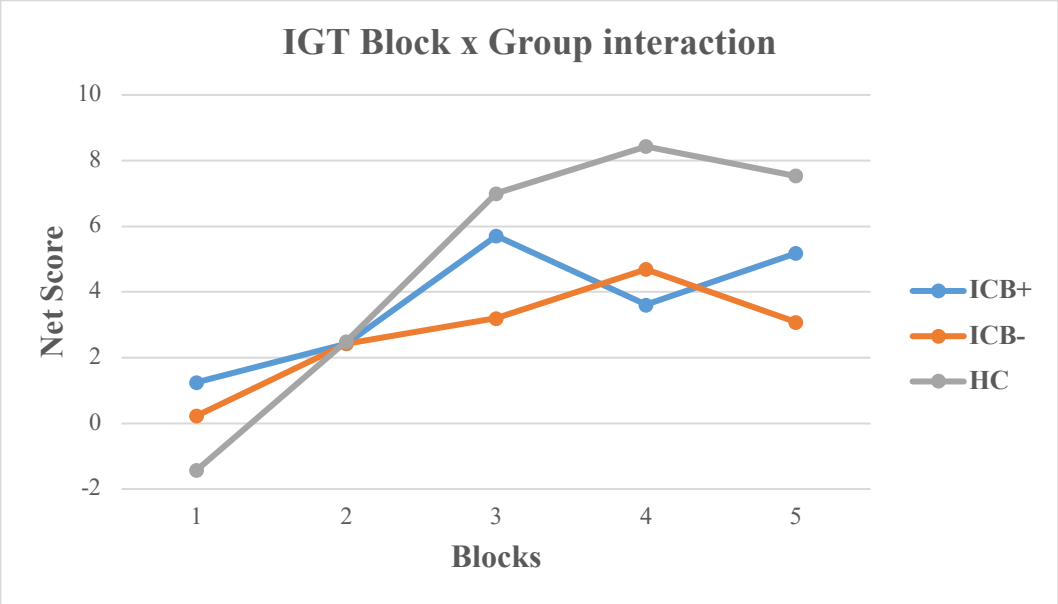


Figure 3. 17 Performances in the Iowa Gambling Task (IGT). A) Average net score. The three groups [persons with Parkinson's disease and impulsive-compulsive behaviours (ICB+), persons with Parkinson's disease but not impulsive-compulsive behaviours (ICB-), and healthy controls (HC)] did not differ in the average net score.

Higher scores represent better incentive-driven decision-making abilities. Error bars represent the standard error of the mean. B) Groups did not differ in the way they behave across blocks. Performances improved across blocks in all groups. Error bars represent the standard error of the mean.

The two PD groups were not clinically matched, therefore ANCOVA models with disease duration, age at PD onset, and total LEDD as covariates were performed to compare PD groups performances on the BART and IGT tests. Including clinical variables as covariates did not change the results [BART main score: $F(1, 58) = 1.69$, $p = 0.20$, $\eta_p^2 = 0.03$; IGT net score: $F(1, 58) = 2.50$, $p = 0.12$, $\eta_p^2 = 0.04$]. When the average number of balloon pumps pre- and post-burst was compared including disease duration, age at PD onset, and Total LEDD as covariates, there was no main effect of group [$F(1, 56) < 1$, $p = 0.68$, $\eta_p^2 = 0.003$] and group x feedback interaction [$F(1, 56) < 1$, $p = 0.45$, $\eta_p^2 = 0.01$], but a trend toward significant effect of feedback [$F(1, 56) = 3.97$, $p = 0.051$, $\eta_p^2 = 0.07$]. When the IGT net scores was compared across blocks including disease duration, age at PD onset, and total LEDD as covariates, there was no main effect of group [$F(1, 58) < 1$, $p = 0.38$, $\eta_p^2 = 0.01$], block [$F(4, 232) < 1$, $p = 0.72$, $\eta_p^2 = 0.009$], nor group x block interaction [$F(4, 232) < 1$, $p = 0.42$, $\eta_p^2 = 0.02$].

Cognitive Test Battery

The three groups differed for the Go/No-Go false alarms [ICB+: 1.86 ± 2.40; ICB−: 0.45 ± 0.78; HC: 0.60 ± 0.67; $F(2, 89) = 7.41$, $p = 0.001$, $\eta_p^2 = 0.14$; Table 3.17]. In particular, the ICB+ group shows a significantly higher number of false alarms than the ICB- [$p = 0.001$, $d = 0.81$, 95% CI [0.05, 2.25]] and the HC [$p =$

0.02, d = 0.64, 95% CI [0.13, 2.08]], with no differences between ICB- and HC [p = 1.00, d = -0.37, 95% CI [-1.18, 0.63]]. The other cognitive measures considered part of the four stages of the incentive-driven decision-making framework did not differ between the three groups when a stringent Bonferroni correction of $p < 0.006$ was used. Results of the cognitive test battery are presented in Table 3.17.

When PD groups were compared including disease duration, age at PD onset, and total LEDD as covariates, between groups differences in the Go/No-Go did not reach the stringent Bonferroni corrected p-value threshold [$F(1, 58) = 5.74$, $p = 0.02$, $\eta_p^2 = 0.09$]. The other cognitive measures did not differ between the three groups.

Table 3. 17 Results of the cognitive test battery.

Variables	ICB+ (n=28)	ICB- (n=35)	HC (n=30)	F values	*p*	ES
		(i) Option Generation Stage				
TMT-A errors	0.18 ± 0.47, 0	0.9 ± 0.28, 0	0.7 ± 0.25, 0	$F(2,89) <1$	0.45	0.02
TMT-B errors	0.96 ± 1.48, 0	1.12 ± 1.45, 1	0.43 ± 0.73, 0	$F(2,85) <1$	0.57	0.01
Phonol fluency	35.04 ± 16.64	33.97 ± 15.06	47.37 ± 9.03	$F(2,88)= 3.61$	0.03	0.08
DSS	7.89 ± 2, 8	7.35 ± 2, 7	8.93 ± 2, 9	$F(2,87)= 2.12$	0.13	0.05
		(ii) Option Selection Stage				
Kirby total[6]	0.34 ± 0.14, 0.37	0.37 ± 0.22, 0.37	0.42 ± 0.22, 0.41	$F(2,88) <1$	0.68	0.01
		(iii) Action Initiation and Inhibition Stage				
Go/No-Go FA	1.86 ± 2.40, 1	0.45 ± 0.78, 0	0.60 ± 0.67, 0.5	$F(2, 89) = 7.41$	***0.001***†	0.14
Stroop INT errors	1.77 ± 2.99, 0	1.77 ± 3.83, 0	0.50 ± 1.73, 0	$F(2,88) <1$	0.57	0.01
		(iv) Learning Stage				
Memory composite score	-0.08 ± 0.93, -0.03	-0.33 ± 0.68, -0.32	0.44 ± 0.60, 0.58	$F(2,88)= 4.17$	0.02	0.09
Brixton scaled score	4.85 ± 2.54, 6	4.6 ± 2.43, 5	4.90 ± 2.06, 6	$F(2,86) <1$	0.62	0.01

[6] Exploratory 3 (group: ICB+ vs. ICB- vs. HC) x 3 (reward: small vs. medium vs. large) ANCOVA with education as covariate showed that the main effect of magnitude is significant [$F(2,176) = 3.14$, $p = 0.046$], but the main effect of group [$F(2,88) = 0.32$, $p = 0.73$], and group x magnitude interaction [$F(4,176) = 0.25$, $p = 0.91$] are not significant. All groups showed higher temporal discounting for small > medium > large rewards.

Legend. ICB+: persons with Parkinson's disease (PwP) and impulsive-compulsive behaviours (ICBs); ICB-: PwP without ICBs history; HC: healthy controls; TMT-A errors: Trail Making Test Part A number of errors; TMT-B errors: Trail Making Test Part B number of errors; DSS: Digit span sequencing test; Kirby total: Kirby Monetary choice questionnaire total score; Go/No-Go FA: Go/No-Go false alarms; Phonol fluency: Phonological fluency; Stroop INT errors: Stroop interference number of errors; ES: partial eta-squared effect size. Data are presented as mean ± standard deviation, median. Median is reported for variables that were not normally distributed. Significant *p* values ($p < 0.006$) are given in bold.

[†]Post-hoc comparison: ICB+ > ICB-; ICB+ >HC; ICB- = HC.

Affective and Motivational measures

HADS depression subscale score significantly differs between groups [F(2, 88) = 5.52, p = 0.006, η_p^2 = 0.11; Table 3.18]. Bonferroni's corrected post-hoc t tests revealed higher scores in the ICB+ group (5.78 ± 3.67) compared to HC [2.73 ± 2.29, p = 0.005, d = 1.02, 95% CI [0.82, 5.35]], but no difference between ICB+ and ICB- [4.80 ± 3.80; p = 0.77, d = 0.26, 95% CI [-1.07, 3.04]], and a trend toward significance in the comparison ICB- and HC [p = 0.06, d = 0.66, 95% CI [-0.003, 4.21]]. Conversely, HADS anxiety subscale score was not significant [F(2, 88) = 1.51, p = 0.23, η_p^2 = 0.03]. Using the stringent Bonferroni corrected $p < 0.012$, I-DAS total score showed a trend toward significance [F(2, 87) = 4.57, p = 0.013, η_p^2 = 0.09]. Bonferroni's corrected post-hoc t tests revealed higher scores in the ICB+ group (24.54 ± 8.18) compared to HC [17.96 ± 5.87, p = 0.01, d = 0.87, 95% CI [1.31, 11.09]], with no differences between ICB+ and ICB- groups [21.77 ± 7.31, p = 0.37, d = 0.37, 95% CI [-1.55, 7.28]] and between ICB- and HC [p = 0.26, d = 0.50, 95% CI [-1.23, 7.89]]. The BIS-11 total score shows a trend toward significance [F(2, 88) = 4.14, p = 0.019, η_p^2 = 0.08]. Bonferroni's corrected post-hoc t tests revealed higher scores in the ICB+ group (61.07 ± 8.77) compared to ICB- [55.60 ± 7.18 p = 0.02, d = 0.68, [0.73, 10.09]], with no differences between ICB+ and HC [55.97 ± 7.21 p = 0.10, d = 0.58, [-0.51, 9.84]] and between ICB- and HC [p = 1.00, d = -0.10, [-5.59, 4.10]].

When PD groups were compared including disease duration, age at PD onset, and total LEDD as covariates (and the stringent Bonferroni corrected $p < 0.012$), impulsivity showed a trend toward significance in the ICB+ vs. ICB- [BIS-11: F(1, 58) = 4.44, p = 0.04, η_p^2 = 0.07]. Conversely, depression [HADS-D: F(1, 57) <1, p = 0.52, η_p^2 = 0.007], anxiety [HADS-A: F(1, 57) <1, p = 0.41, η_p^2 = 0.01], and apathy

[I-DAS: $F(1, 57) = 1.35$, $p = 0.25$, $\eta_p^2 = 0.02$] levels did not differ between PD groups.

Table 3. 18 Affective and motivational characteristics by groups.

Variables	ICB+ (n=28)	ICB- (n=35)	HC (n=30)	F values	*p*	ES	*Post hoc*
HADS-A	5.15 ± 3.52, 4	3.89 ± 3.02, 4	3.97 ± 2.59, 3.5	$F(2, 88) = 1.51$	0.23	0.03	
HADS-D	5.78 ± 3.67, 6	4.80 ± 3.80, 4	2.73 ± 2.29, 2	$F(2, 88) = 5.52$	***0.006***	0.11	ICB+ = ICB-; ICB+ > HC; ICB- = HC
I-DAS[7]	24.70 ± 8.29	21.77 ± 7.31	17.96 ± 5.87	$F(2, 87) = 4.57$	0.013	0.09	
BIS-11[8]	61.07 ± 8.77, 61	55.60 ± 7.18, 55	55.97 ± 7.21, 54	$F(2,88) = 4.14$	0.019	0.08	

Legend. ICB+: persons with Parkinson's disease (PwP) and impulsive-compulsive behaviours (ICBs); ICB-: PwP without ICBs history; HC: healthy controls; HADS-A: Hospital Anxiety and Depression scale anxiety subscale; HADS-D: Hospital Anxiety and Depression scale depression subscale; I-DAS: Italian Dimensional Apathy scale; BIS-11: Barratt Impulsiveness questionnaire total score; ES: partial eta-squared effect size. Data are presented as mean ± standard deviation, median. Median is reported for variables that were not normally distributed. Significant *p* values ($p < 0.012$) are given in bold.

[7] Exploratory ANCOVA models with education as covariate on the I-DAS subscales scores showed significant differences between groups in the I-DAS behavioural/cognitive initiation subscale score [$F(2, 87) = 5.87$, $p = 0.004$]. Bonferroni's corrected post-hoc t tests showed higher scores in the ICB+ vs. HC groups ($p = 0.003$), but not in the ICB+ vs. ICB- groups ($p = 0.18$), and in the ICB- and HC ($p = 0.21$). I-DAS executive [$F(2, 87) = 0.64$, $p = 0.53$] and emotional [$F(2, 87) = 2.21$, $p = 0.11$] subscales scores did not differ between groups.

[8] Exploratory ANCOVA models with education as covariate on the BIS-11 subscale scores showed significant between groups differences in the BIS-11 non planning subscales score $F(2, 89) = 5.08$, $p = 0.008$]. Bonferroni's corrected post-hoc t tests showed higher scores in the ICB+ vs. ICB- groups ($p = 0.01$) and in the ICB+ vs. HC groups ($p = 0.047$), but no differences between ICB- and HC ($p = 1.00$). BIS-11 attentional [$F(2, 89) = 1.08$, $p = 0.34$] and BIS-11 motor $F(2, 89) = 2.29$, $p = 0.11$] subscales scores did not differ between groups.

Exploratory correlation analysis

The QUIP-rs total score positively correlated with the Go/No-Go false alarms [$r_s(63) = 0.38$, $p = 0.002$], the HADS depression subscale score [r_s (62) = 0.27, p = 0.03], the HADS anxiety subscale score [r_s (62) = 0.33, p = 0.008], and the BIS-11 total score [r_s (63) = 0.38, p = 0.002]. No other correlations between the QUIP-rs and the cognitive, affective and motivational outcomes were significant.

The Go/No-Go false alarms positively correlated with the QUIP-rs total score [r_s (63) = 0.38, p = 0.002], the STROOP interference errors [r_s (92) = 0.31, p = 0.002], and showed a trend toward a significant negative correlation with the IGT Net score [r_s (91) = -0.19, p = 0.06]. No other correlations between the Go/No-Go false alarms and the cognitive, affective and motivational outcomes were significant. Results for the full correlation matrix are presented in Table 3.19.

Table 3. 19 Correlation matrix.

Var	BART	IGT	TMT-A	TMT-B	Phon Flu	DSS	Kirby	GNG	STROOP	MEM	Brixton	HADS-D	HADS-A	I-DAS	BIS-11	ESS
QUIP-rs	0.11	0.69	0.52	0.20	0.63	0.26	0.87	***0.001***	0.93	0.32	0.49	***0.03***	***0.007***	0.38	***0.002***	0.11
BART	—	0.85	0.68	0.14	0.54	0.15	0.86	0.20	0.40	0.052	0.12	0.70	0.63	0.71	***0.008***	0.17
IGT	—	—	0.31	***0.03***	0.99	0.39	0.42	0.06	***0.006***	0.38	0.67	0.07	0.60	0.15	0.55	0.07
TMT-A	—	—	—	0.38	0.82	0.42	0.19	0.63	0.058	0.74	***0.02***	***0.02***	0.85	0.13	0.16	0.62
TMT-B	—	—	—	—	***0.001***	***<0.001***	0.54	0.22	***<0.001***	***<0.001***	***0.001***	0.67	0.30	***0.005***	0.31	0.52
Phonol Flu	—	—	—	—	—	***<0.001***	0.39	0.46	***<0.001***	***<0.001***	***<0.001***	***0.04***	0.82	***<0.001***	0.054	0.70
DSS	—	—	—	—	—	—	0.46	0.10	***<0.001***	***<0.001***	***<0.001***	0.49	0.98	***0.003***	0.23	0.23
Kirby	—	—	—	—	—	—	—	0.29	0.44	0.59	0.29	0.60	0.82	0.83	0.06	0.70
GNG	—	—	—	—	—	—	—	—	***0.004***	0.63	0.38	0.20	0.67	0.52	0.13	0.32
STROOP	—	—	—	—	—	—	—	—	—	***<0.001***	***0.008***	0.51	0.50	0.06	***0.03***	0.22
MEM	—	—	—	—	—	—	—	—	—	—	***0.01***	0.27	0.96	***0.01***	0.20	0.20
Brixton	—	—	—	—	—	—	—	—	—	—	—	0.40	0.95	***0.005***	0.27	0.59
HADS-D	—	—	—	—	—	—	—	—	—	—	—	—	***<0.001***	***<0.001***	***0.007***	***0.03***
HADS-A	—	—	—	—	—	—	—	—	—	—	—	—	—	0.21	0.12	***0.05***
I-DAS	—	—	—	—	—	—	—	—	—	—	—	—	—	—	***<0.001***	0.07
BIS-11	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.06

Legend. QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – Rating Scale total score; BART: Balloon Analogue Risk Task main score; IGT: Iowa Gambling Task net score; TMT-A: Trail Making Test Part A number of errors; TMT-B: Trail Making Test Part B number of errors; Phonol Flu: Phonological Fluency; DSS: Digit span sequencing test; Kirby: Kirby Monetary choice questionnaire total score; Brixton: Brixton scaled score; MEM: Memory composite score; GNG: Go/No-Go false alarms; Stroop: Stroop interference number of errors; HADS-A: Hospital Anxiety and Depression scale anxiety subscale; HADS-D: Hospital Anxiety and Depression scale depression subscale; I-DAS: Italian Dimensional Apathy scale; BIS-11: Barratt Impulsiveness questionnaire total score. Significant *p* values ($p<0.05$) are given in bold.

Discussion

The main aim of the present study was to replicate Study 1 findings of comparable overall risky behaviour, but reduced sensitivity toward negative feedback in the BART in ICB+ compared to ICB- and HC (Martini, Ellis, et al., 2018). To this aim, a larger sample of PwP with and without ICB, and HC was recruited.

The first key finding of the present study is that comparable overall risky behaviour between ICB+, ICB- and HC in the BART was replicated. This suggests that the overall score, which is a sensitive measure of risky behaviour in non-PD populations (Hopko et al., 2006; Lejuez, Aklin, Jones, et al., 2003; Lejuez, Aklin, Zvolensky, et al., 2003), might not be a sensitive measure of ICBs in PD, at least when only the overall behavioural score is considered. For example, DA agonists increase risk-taking behaviour in the BART of PwP with but not without ICBs, albeit the overall score did not differ between groups (average number of pumps in cashed trials: ICB+: 5.3; ICB-: 4.8) (Claassen et al., 2011). Another study found diminished BOLD activity in the right ventral striatum of PwP with ICBs compared to PwP without ICBs despite comparable behavioural performances (average number of pumps in cashed trials: ICB+: 5.6; ICB-: 5.8) (Rao et al., 2010). This study adds on the general BART literature showing that the overall score is not sensitive to ICBs in PD regardless of the BART version used. Previous studies used modified versions with reduced number of pumps and therefore reduced sensitivity toward individual variability in task performance [i.e., maximum number of pumps was either 16 or 8 (Ricciardi et al., 2017), 12 (Rao et al., 2010), and 14 or 7 (Claassen et al., 2011), whilst in the original task version the maximum number of pumps is 128 (Lejuez et al., 2002)]. However, in Study 1 the original BART version was used in a small

sample of PwP with and without ICBs and HC (Martini, Ellis, et al., 2018), and negative findings have been replicated here, with a larger PwP sample, using the same version of the task. Other than being replicated, Study 1 findings have also been generalized across PD populations, being the sample of this study recruited in another country (i.e., Italy).

The second key finding of the present study is that it failed to replicate Study 1 finding of reduced sensitivity toward negative feedback; in Study 1, PwP with ICBs compared to both PwP without ICBs and HC have been found to not change their risky behaviour after balloon burst and money loss (Martini, Ellis, et al., 2018), which suggested an impairment in the learning stage of the incentive-driven decision-making framework (Sinha et al., 2013). Albeit being promising, those findings have not been replicated here. In the present study, all groups decreased their risky behaviour after a negative feedback but this was significant only when education was not included as covariate. It could be suggested that including education as covariate may have reduced the statistical power therefore diminishing the likelihood of finding a true positive effect. This finding is aligned with another study in which a modified BART version was used (Claassen et al., 2011). It could be argued that differences between studies in the PwP populations may have accounted for discrepancy findings; in Study 1, PwP were matched for clinical PD-related characteristics whilst in this study ICB+ had younger age at PD onset, longer disease duration, and higher total LEDD compared to ICB-. These characteristics are commonly associated with ICBs in PD in Italian (Antonini et al., 2017) as well as in non-Italian PD populations (Callesen et al., 2014; Weintraub et al., 2010), therefore suggesting that this sample is representative of ICBs in PD. It is unlikely that those variables might have accounted for discrepancy in the BART findings; when age at

PD onset, disease duration and total LEDD were included in the model as covariates, the results did not change. Conversely, findings suggest that risky behaviour after negative feedback is not a reliable indicator of ICBs in PD and question its use as a measure of ICBs in PD. Although surprising, the present study underscores the need for replication studies, uncommon in PD literature.

The unreliability of psychological findings is a concerning, well-known issue. In a collaborative research project, 100 experimental and correlation studies (97% with statistically significant results) published on three important psychology journals were replicated and only the 36% of them had statistically significant results (Open Science Collaboration, 2015). Replication studies are important as "innovation points out paths that are possible; replication points out paths that are likely; progress relies on both. (…) Replication can increase certainty when findings are reproduced and promote innovation when they are not" (Open Science Collaboration, 2015, pp. 949).

The third key finding is that ICBs are associated with failure to inhibit inappropriate responses; in the Go/No-Go task, which assesses motor inhibitory control, ICB+ compared to both ICB- and HC committed a higher number of false alarms. Motor inhibitory control, which is conceptualized as part of the action initiation and inhibition stage of the incentive-driven decision-making (Sinha et al., 2013), requires subjects to refrain from on-going movements. Abnormal response inhibition has been frequently reported in PD (Gauggel, Rieger, & Feghoff, 2004; Nombela, Rittman, Robbins, & Rowe, 2014; Obeso et al., 2011). The present study may extend this notion, suggesting that this impairment is more severe in ICB+ than ICB- PwP.

Previous evidence of inhibitory control impairments in PwP with ICBs is conflicting; most of the studies show no differences between PwP with vs. without ICBs in the Go/No-Go (Filip et al., 2018; Hlavatá et al., 2020; Martini, Ellis, et al., 2018; Rossi et al., 2010; Yoo, Yun, et al., 2015) or in other inhibition tasks (Djamshidian, O'Sullivan, Lees, et al., 2011; Leroi et al., 2013; Marín-Lahoz et al., 2018). However, there is also evidence of worse performance in ICB+ vs. ICB- (Palermo et al., 2017; Vitale et al., 2011). Variability in findings may be due to the version of the Go/No-Go task used across studies (e.g., differences in stimulus complexity, high vs. low probability Go/No-Go stimuli ratio) (Criaud & Boulinguez, 2013), with some task versions being insufficiently demanding for detecting between-groups differences.

A meta-analysis of fMRI studies in healthy individuals found that No-Go signals activates a right-lateralized network that includes the dorsolateral and inferior frontal cortices, the inferior parietal lobule, the supplementary motor cortex, the ACC and the insula (Criaud & Boulinguez, 2013).

It could be speculated a different involvement of brain regions for the response inhibition impairments in ICB+. Dorsal striatum, which receives predominantly sensorimotor afferents and has greater dopaminergic innervation, facilitates habit-formation and association of stimuli to rewards (Balleine & O'Doherty, 2010). In contrast, ventral striatum, which has limbic connections and relatively sparse dopaminergic input, is implicated in goal-directed behaviour via acquisition of stimulus-action-outcome associations. Ventral striatum is therefore crucial for option selection stage, but when habits have formed, it becomes bypassed by dorsal striatum with a direct connection between option generation and action initiation (Sinha et al., 2013). This is supported by a recent study showing decreased

Go/No-Go task connectivity of ventral striatum to the left dorsolateral prefrontal cortex and to the cingulate gyrus in ICB+ vs. ICB- (Filip et al., 2018). DRT mesocorticolimbic overstimulation increases impulsivity that, in turn, may enhance incentive-driven behaviour that, over time, may become a habit (Antonini & Cilia, 2009). Once ICBs become a habit, impairments in inhibitory control may promote addictive behaviours. This is supported by the association between Go/No-Go false alarms and ICBs severity in the QUIP-rs. However, the impairment in action initiation and inhibition stage of the incentive-driven decision-making seems not be by itself sufficient to affect overall incentive-driven decision-making performance in the BART and IGT tasks.

The fourth key finding is that PwP with ICBs showed higher depression and a trend toward higher apathy compared to healthy controls, and a trend toward higher impulsivity compared to ICB-. Higher depression and impulsivity levels in ICB+ were not surprising and are in line with Study 2 (Martini, Dal Lago, Edelstyn, Grange, et al., 2018; Martini, Ellis, et al., 2018). Depression may precede ICBs onset and increase the risk of further developing ICBs (Marín-lahoz et al., 2019). However, depression can also be a reaction to ICBs development, as these behaviours are associated with reduced quality of life and higher caregiver burden (Erga et al., 2020; Leroi, Harbishettar, et al., 2012; Phu et al., 2014).

Conversely, the co-occurrence of a trend toward higher impulsivity and trend toward higher apathy is surprising as they are considered as the opposite sides of a dopaminergic continuum with hyper dopaminergic levels facilitating impulsivity and hypo dopaminergic levels facilitating apathy (Sinha et al., 2013). However, there are reports of higher impulsivity (Martini, Dal Lago, Edelstyn, Grange, et al., 2018; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Voon, Sohr, et al., 2011) as

well as higher apathy levels (Antonini et al., 2017; Baig et al., 2019) in PwP with ICBs. It could be speculated about two possible reasons for the co-occurrence of a trend toward higher apathy and impulsivity in ICB+. First, apathy and impulsivity share the same neurobiological substrate [i.e., disrupted ventromedial prefrontal, orbitofrontal and anterior cingulate cortices functioning (Leroi, Andrews, et al., 2012)] and it is possible that those two states fluctuate during the day. If this is true, questionnaires used to investigate motivational correlates within a temporal window of one or few weeks may be not sensitive to assess these fluctuations. Secondly, in line with the broad addiction literature, PwP with ICBs show a high drive for reward-based activities and they may lose interest for all the other non-reward related activities.

It should be noted that findings related to apathy and impulsivity only reached a trend toward significance, therefore any interpretation on the role of impulsivity and apathy in ICBs in PD should be carefully considered. For example, the measure of impulsivity used in this study (i.e., BIS-11) has not been validated in PD yet, therefore may not be a sensitive measure of ICBs in PD due to impulsivity presenting as a continuum of severity in PD despite the absence of clinical ICBs. This finding also opens up the issue of the translation of surrogate markers to clinical meaningfulness. For example, the same task may be sensitive for detecting pathological gambling in those who perform online sports betting but not in those engaging in trading online. At the same time, a gambling task may be sensitive to detect ICBs in individuals with pathological gambling but not in those with compulsive shopping or binge-eating. At the moment, the only way for the clinicians to ascertain ICBs presence in PD is by interviewing PwP and their carers. In the

future, the development of validated surrogate markers that may be used in the clinical setting is required.

Limitations

The study is constrained by several limitations that should be acknowledged.

First, although the target number of participants was very closed to be achieved, 4 ICB+ and 2 HC were not recruited. Compared to Study 1, a different recruitment strategy (i.e., approaching PwP at the end of the clinic visit vs. postal invitation) as well as multicentre design were implemented. These strategies allowed to increment the recruitment rate, although this was not enough. PwP with ICBs may be reluctant in taking part to studies directly investigating a condition that is associated with social stigma, lack of awareness and shame, and healthy older adults with low education levels may be less keen to take part in studies involving cognitive tasks. Since the target number of participants was not met, effect sizes have been provided as, unlike p-values, they are independent of sample size (Sullivan & Feinn, 2012).

Second, the sample of this study is not simply a larger group of PD patients compared to Study 1. In this study part of the sample comprises inpatients while in Study 1 all PwP participants were outpatients. Inpatients may differ as they would be more actively supervised during some time of the historical ICBs reporting period (1-3 months) and therefore less likely to perform, or have a desire to perform ICBs. Also, being an inpatient may alter the perception or the desire to complete questionnaires. Therefore, the lack of replicability of Study 1 findings may be related to differences in the studies samples rather than reliability of BART measures.

Future studies should further investigate replicability of both Study 1 and 3 findings in separate and homogeneous samples of inpatients and outpatients.

Third, PwP were not matched for clinical characteristics. Being unable to recruit the target number of PwP, it was not possible to select the sample for matching purposes. However, BART results did not change including clinical variables as covariate. Furthermore, ICB+ were characterized by variables commonly associated with ICBs (Antonini et al., 2017; Biundo et al., 2017; Erga et al., 2020; Weintraub et al., 2010), therefore suggesting that the sample of the present study is a good representation of ICBs in the general PD population.

Fourth, PwP were not well balanced between sites, with PwP recruited in Venice being older, with less severe motor symptoms, and lower DAED levels. This could be explained by most of participants being inpatients in Venice site and outpatients in Verona sites. Inpatients are usually older and, residing for weeks in the hospital with their medication being adjusted and undertaking physiotherapy, their motor symptoms may be better controlled. Despite increasing variability, multicentre studies provide a more realistic situation.

Fifth, QUIP-rs has not been validated in the Italian population yet, therefore findings concerning QUIP-rs should be considered cautiously. However, recent QUIP-rs validations in other European countries show high concordance (Marques et al., 2019; Probst et al., 2014). In this study, QUIP-rs was only used as a measure of ICBs severity and diagnosis was done in agreement with the clinical interview. The QUIP-rs was not administered to HC, this is because it has not been validated in the general non-PD population yet, in any country. It should be noted that all HC have been screened for ICBs presence by clinical interview.

Sixth, no blinding procedures were followed therefore increasing the risk of performance bias. Blinding was not feasible as the research visit assessor was also involved in the ICBs assessment. Due to clinic practice, it was not possible for the PI/CI in the first site to be always involved in all screening procedures. Negative results are unlikely to be affected by performance bias, therefore the lack of between groups differences in the BART and in the other cognitive tasks are not related to assessor biases. Additionally, impairments in inhibitory control in ICB+ are also unlikely to be affected by performance bias as the task was computerized and responses recorded automatically. Finally, questionnaires were filled by the participant with no help by the assessors.

Finally, it cannot be excluded that ICB- with disease duration < 5 years may have not developed ICBs now but they will in the future, as previous studies show that ICBs may be developed up to 5 years after DRT initiation (Corvol et al., 2018). These individuals may differently perform showing cognitive, affective and motivational vulnerabilities predating ICBs compared to PwP who will never develop ICBs.

Conclusions

This study demonstrates that reduced negative feedback in the BART is not a reliable measure of ICBs in PD. PwP with ICBs show reduced inhibitory control, compared to both PwP without ICBs and HC. In addition, ICBs in PD are associated with increased depression and a trend toward increased apathy than in the healthy population. Compared to PwP without ICBs, PwP with ICBs show a trend toward increased impulsivity.

Key Findings

- PwP with ICBs show comparable overall risky behaviour in the BART;
- PwP with ICBs reduce their risky behaviour after balloon burst and money loss, therefore Study 1's finding of reduced sensitivity toward negative feedback was not replicated;
- PwP with ICBs show poorer inhibitory control compared to both PwP without ICBs and healthy controls;
- PwP with ICBs vs. healthy controls show higher depression.

Interim Conclusion

In this chapter, behavioural correlates (i.e., cognitive, affective and motivation) have been investigated using an incentive-driven decision-making framework (Sinha et al., 2013).

The first study shows that, within all the cognitive processes involved in incentive-driven decision-making, negative feedback processing impairment seems to be a potential driver for PwP with ICBs. Furthermore, PwP with ICBs showed higher depression and anxiety levels than HC, although no difference between PD groups were found.

The first study was limited by small sample size. In order to overcome this limitation, a systematic review and meta-analysis of cognitive, affective and motivation correlates of ICBs has been performed (Study 2). The systematic review and meta-analysis confirmed worse performance of PwP with ICBs in tasks assessing incentive-driven decision-making, but also evidenced lower performances in task assessing set-shifting, which is a process involved in cognitive control, and important for the option generation stage of the incentive-driven decision-making framework (Sinha et al., 2013). The systematic review and meta-analysis further evidenced higher depression, anxiety, anhedonia and impulsivity levels in PwP with ICBs vs. PwP without ICBs.

In the meta-analysis, there were no studies using the BART. Therefore, Study 1 needed to be replicated in a larger study (Study 3). The third study failed to replicate the BART findings of impairments in the negative feedback processing. However, PwP with ICBs showed worse inhibitory abilities (performance in the Go/No-Go task expressed as number of false alarms). In line with Study 1, PwP with ICBs showed higher depression levels than healthy controls.

Taken together, cognitive findings suggest that impairments in the ICB+ are evident across incentive-driven decision-making. What are the specific incentive-driven decision-making processes involved is still unclear, as there was no consistency in findings across studies (i.e., negative feedback processing in Study 1, set-shifting in Study 2, and motor inhibition in Study 3). Furthermore, the BART overall and discrepancy scores seem to not be reliable indicators of ICBs in PD and their use in the clinical practice should be questioned.

Taken together, affective and motivational findings suggest that depression is a consistent feature of ICBs in PD. Whether anxiety, anhedonia and impulsivity are reliable indicators of ICBs in PD is unclear, as they were found to differ between PD groups in the meta-analysis but not in the empirical studies. Apathy seems not to be associated with ICBs in PD, as supported by the three behavioural studies.

Still unanswered questions include whether behavioural performance in the BART is mirrored by neurophysiological changes. This has been explored in a subset of PwP who took part in this study and data are presented in Chapter 4, Study 4. Furthermore, whether ICBs in PD are associated with neuroanatomical and/or neurofunctional brain changes has been explored in Chapter 5, which includes (i) a systematic review of structural and functional brain imaging studies of PwP with and without ICBs (Study 5) and (i) a systematic review and meta-analysis of PET and SPECT striatal studies (Study 6).

Despite being underpowered and with a more powerful study with the same design reported, Study 1 has been included in this thesis because it provides the starting point of this programme of research. Subsequent studies have been designed in order to overcome Study 1 limitations (e.g., small sample size and low statistical power – Studies 2 and 3; lack of brain imaging measures – Studies 5 and 6) and

extend its findings (e.g., neurophysiological measure of negative feedback processing – Study 4).

Chapter 4 Neurophysiological Feature

This chapter presents a pilot investigation of a possible neurophysiological feature of impulsive-compulsive behaviours (ICBs) in Parkinson's disease (PD). Participants included in this study were enrolled in the large multicentre empirical investigation (Study 3, Chapter 3). This pilot study took place in one of the two centres (i.e., San Camillo Hospital of Venice, Italy) in order to keep electroencephalography (EEG) machine and investigators the same for every participant, therefore reducing variability and possible confounders.

Study 4: Feedback-related negativity in Parkinson's disease and Impulsive-compulsive behaviours

Abstract

Background: Previous EEG studies in neurologically healthy and non-PD clinical populations show that the 'feedback-related negativity event-related potential' (FRN) occurs 200-300 msec after negative feedback on the Balloon Analogue Risk Task (BART), that is, when a balloon bursts and accumulated winnings are lost. FRN is a measure of negative feedback processing which indicates that performance is worse than expected. Blunted FRN have been reported in individuals with behavioural and substance addictions. The status of the FRN has not been explored in PwP with ICBs before. This is an important clinical and research question, as differences in FRN amplitudes between persons with Parkinson's disease (PwP) with and without ICBs may be a clinical marker of ICBs. In this pilot study, negative feedback processing has been investigated using two levels of assessments: behaviour and neurophysiology. The first aim is to explore whether PwP, irrespective of ICBs, shows an association between FRN amplitude and risky behaviour in the BART, which has been observed in other populations. The secondary aim was to obtain pilot data of FRN in PwP with and without ICBs whilst performing the BART to power a larger study.

Methods: 18 PwP (ICB+: 8; ICB-: 10) underwent EEG whilst completing the BART. The FRN was recorded from anterior and posterior frontocentral scalp positions (Fz and Cz electrodes, respectively). Clinical, cognitive, affective and motivational characteristics were collected as part of Study 3. Two dependent

variables were measured: (i) FRN amplitude in the 200-300 msec following a balloon burst; and (ii) the number of pumps following a previous balloon burst.

Results: At the group level, there was a positive correlation between FRN amplitude in Cz and decreased number of pumps after balloon bursts [$r_s(18) = 0.52$, $p = 0.03$]. However, FRN amplitude did not discriminate PwP with and without ICBs as there was no main effect of electrode [$F(1, 15) = 1.32$, $p = 0.27$, $d = 0.03$, 95% CI [-0.92, 1.06]], no main effect of group [$F(1, 15) < 1$, $p = 0.50$, $d = -0.16$, 95% CI [-7.59, 3.85]], and no effect of group x electrode interaction [$F(1, 15) < 1$, $p = 0.80$]. Behaviourally, both groups decreased the number of pumps after balloon bursts, as there was main effect of feedback [$F(1, 16) = 11.18$, $p = 0.004$, $d = 0.82$, 95% CI [2.04, 8.36]], but no main effect of group [$F(1, 16) < 1$, $p = 0.59$, $d = -0.13$, 95% CI [-13.41, 7.90]], nor group x feedback interaction [$F(1, 16) = 1.17$, $p = 0.29$]. No other between groups differences in the cognitive, affective and motivational measures were observed. The small number of participants impedes power analysis calculation.

Conclusions: The preliminary evidence suggests that when two groups are collapsed into a single group there is an association between neurophysiology and behaviour. However, PwP with ICBs show similar neurophysiological and behavioural performance as PwP without ICBs, at least in the cohort of PwP investigated. Due to the small sample size, findings should be considered cautiously and no firm conclusion can be drawn. The small sample size prevents any a-priori power analysis for a fully powered study.

Introduction

Persons with Parkinson's disease (PwP) with clinically significant Impulsive-compulsive behaviours (ICBs) (i.e., those requiring medical intervention to reduce the impact of the ICBs on their and their carers lives) have cognitive deficits in set-shifting and incentive-driven decision-making abilities, according to a recent systematic review and meta-analysis (Martini, Dal Lago, Edelstyn, Grange, et al., 2018) (Study 2, Chapter 3). The clinical effect of these research cognitive findings is currently undetermined.

Incentive-driven decision-making involves several cognitive processes that, if affected, can result in imbalanced reward-seeking attitude. Within these processes, external feedback detection and evaluation is important for adapting goal- and reward-oriented behaviours (Sinha et al., 2013). This is supported by evidence of negative feedback impairments in the development, maintenance and later relapse of addictive behaviours (Fridberg et al., 2010; Parvaz et al., 2015; Verdejo-Garcia, Chong, Stout, Yücel, & London, 2018; Yücel et al., 2018). For example, binge-eaters continue in their overeating behaviours despite increasing weight and malnutrition, and gamblers continue to bet despite incurring huge losses.

Negative and positive feedback are associated, respectively, with phasic decrease and increase of dopaminergic activity in the midbrain, which in turn generates a signal to the anterior cingulate cortex (ACC). This signal is used to update the incentive-driven decision-making process for improving task performance (Holroyd & Coles, 2002).

In PD, dopaminergic replacement therapy (DRT) may prevent the normal dopaminergic neurons dip after negative feedback resulting in blunted negative

feedback-related ACC activity. When “off” their medication, persons with Parkinson’s disease (PwP) are better at learning to avoid choices that lead to negative outcomes than they are at learning from positive outcomes, however, medication reverses this bias, making PwP more sensitive to positive vs. negative feedback (Frank et al., 2004).

In the context of ICBs, PwP who develop ICBs may be individuals who are more vulnerable to the effect of DRT on the dopaminergic neurons during negative feedback, therefore affecting negative feedback processing. This is supported by a previous study of this thesis (Study 1, Chapter 3) showing that PwP with ICBs do not reduce their risky behaviour after negative feedback in an incentive-driven decision-making task (i.e., the Balloon Analogue Risk Task - BART) (Martini, Ellis, et al., 2018).

Over the variety of incentive-driven decision-making tasks, the BART has the advantages of being an ecological measure as it mimics many real-world risks, where probability of loss is initially small but grows persisting in the behaviour (e.g., substance abuse) (Lejuez et al., 2002; Schonberg et al., 2011). The BART has been extensively used with healthy as well as clinical populations, and performances in the task correlate with risky behaviours in real life such as drug abuse, smoking behaviour, sexual promiscuity and risky traffic behaviour (Hopko et al., 2006; Lejuez, Aklin, Jones, et al., 2003; Lejuez et al., 2002; Raymond et al., 2020; Vaca et al., 2013).

During the BART, participants are provided with several virtual balloons to pump up, one at time. With each pump money is earned; however, each balloon has a maximum unknown capacity over which additional pumps would result in balloon burst and money loss. Participants have to decide how much to inflate the balloon,

trying to stop before it bursts in order to save the money. As in real life, feedback detention (balloon bursts) is important for adjusting risky behaviour (number of pumps in the following balloon).

Negative feedback processing can be investigated with electroencephalography (EEG), measuring 'the feedback-related negativity' (FRN) which is a component of the brain electrical event-related activity (ERPs) (Gehring & Willoughby, 2002; Holroyd & Coles, 2002; Miltner, Braun, & Coles, 1997). The FRN is a frontocentral negative deflection generated in the ACC (Gehring & Willoughby, 2002; Miltner et al., 1997) that occurs 200–300 ms after a negative feedback of any modality is presented (Holroyd & Coles, 2002; Talmi, Atkinson, & El-Deredy, 2013). The FRN is thought to mirror rapid feedback evaluation and phasic dopaminergic changes in activity between the basal ganglia and the ACC (Holroyd & Coles, 2002).

In neurologically healthy populations, it has been shown that a FRN can be elicited 200–300 ms after balloon burst in the BART (Kessler, Hewig, Weichold, Silbereisen, & Miltner, 2017; Kóbor et al., 2015). Furthermore, blunted FRN during the BART has been observed in methamphetamine dependent (Zhong et al., 2020) and in adolescent with problematic internet use (Yau, Potenza, Mayes, & Crowley, 2015), whilst in alcoholics smaller FRN amplitudes from the BART have been associated with a greater family history of alcohol abuse (Fein & Chang, 2008). There are no PD studies assessing FRN amplitude during BART performance.

Furthermore, whether FRN is reduced in PwP with ICBs is unknown, as, no study has investigated the neurophysiological correlates of negative feedback processing in this population before. This is an important clinical and research

question as blunted FRN may represent a signature of ICBs which could be used in the clinical setting for identifying PwP at risk of ICBs.

This pilot study is the first study to examine FRN during incentive-driven decision-making in PwP with and without ICBs. Negative feedback processing has been investigated using two levels of assessment: behavioural and neurophysiology. This is important as in some cases abnormalities in neurophysiology may not manifest in abnormal behaviour. In other words, changes at neurophysiological levels may be subtle and not by themselves sufficient for affecting behaviour. Neurophysiological measures may be more sensitive and therefore have the potential of being used in the clinical setting as clinical markers of ICBs in PD. As there are no FRN studies on PwP with ICBs in the literature, data of this pilot study will be used to inform a-priori power analysis. Performing pilot studies to obtain estimates of effect size to perform power analysis for subsequent studies is a common approach in the literature (Fritz, Morris, & Richler, 2012; Sullivan & Feinn, 2012). For example, the Reproducibility Project which involved the replication of 100 psychological studies relied on the effect sizes of the original works to perform power analysis (Open Science Collaboration, 2015).

Aims

The primary aim of this study is to explore whether PwP, irrespective of ICBs, show an association between FRN amplitude and risky behaviour in the BART.

The secondary aim is to investigate FRN amplitude in PwP with and without ICBs providing data for calculating sample size for a fully powered study.

Method

Peer Review and Ethic Approval

See page 198.

Participants

Persons with Parkinson's disease

Identification (Pre-screening). See page 199.

Recruitment. See page 199.

Screening visit. This pilot study was performed in the second site only, in order to keep EEG machine and investigators the same for every participant therefore reducing variability and possible confounders. The same screening visit procedure of Study 3 was followed (see page 199, Chapter 3), but PwP were also screened for capability to perform EEG. In particular, EEG exclusion criteria were (i) dyskinesia as the movements create artifacts preventing analysis and (ii) epilepsy. PwP who disclose contraindications to perform EEG were not included in this study but continued with the study procedure involving data taken outside the EEG (data provided in chapter 3, Study 3).

Inclusion/exclusion criteria. See page 200.

Participants. Twenty-one idiopathic non-dementing PwP were enrolled in the study from a larger cohort of participants who took part in Study 3 of this thesis (Chapter 3).

Data of 3 participants (ICB+: 2; ICB-: 1) could not be analysed because of an insufficient number of negative-feedback events (ICB+: N_{loss} = 9, N_{loss} = 13; ICB-: N_{loss} = 8). In agreement with a previous study, an a priori threshold of 15 negative-feedback events was used for FRN analyses (Yau et al., 2015).

Therefore, 18 PwP (15 males, 3 females; mean age = 66.50, SD = 8.15) completed the study. All PwP were in the mild to moderate stages of PD (modified Hoehn and Yahr (H&Y) mean score = 1.92, SD = 0.57). PwP were divided in two subgroups: 8 PwP (8 males, 0 females) with ICBs were allocated to the ICB+ group, and 10 PwP (7 males, 3 females) with no ICBs history were allocated to the ICB- group. Information on the number of PwP assessed for eligibility (together with reasons for exclusion), allocation and the complete datasets analysed are presented in a CONSORT diagram in Figure 4.1.

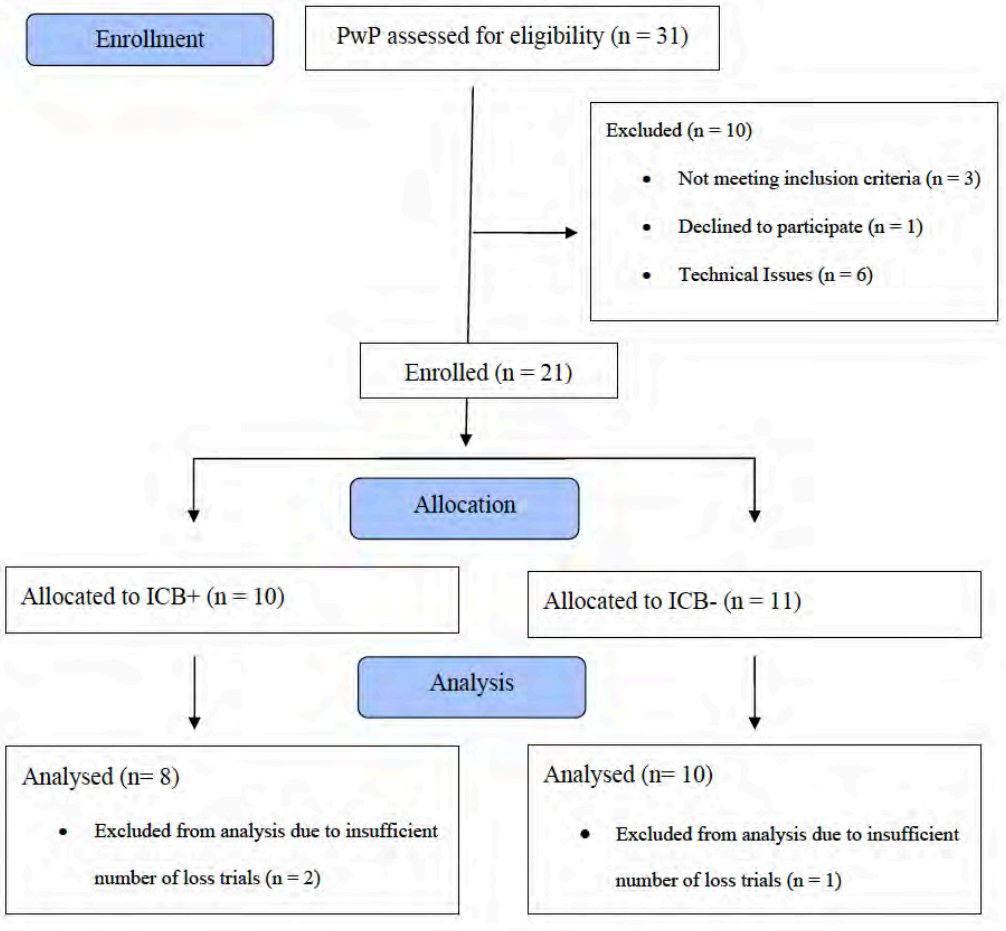


Figure 4. 1 The CONSORT diagram showing the number of PwP assessed for eligibility, allocation and complete datasets analysed. PwP: persons with Parkinson's disease; ICB+: PwP with impulsive-compulsive behaviour; ICB-: PwP without impulsive-compulsive behaviour.

The two groups were matched for age [$t(16) < 1$, $p = 0.28$, $d = -0.53$, 95% CI [-1.47, 0.43]], sex [Fisher-Freeman-Halton test, $p = 0.22$], education [$t(16) < 1$, $p = 0.39$, $d = -0.42$, 95% CI [-1.35, 0.53]], age at PD onset [$t(16) < 1$, $p = 0.24$, $d = -0.75$, 95% CI [-1.52, 0.38]], disease duration [$t(16) < 1$, $p = 0.94$, $d = 0.04$, 95% CI [-0.89, 0.97]], disease severity stage [H&Y: $t(16) < 1$, $p = 0.28$, $d = -0.52$, 95% CI [-1.46, 0.43]], motor functioning [Unified Parkinson's disease rating scale part III (UPDRS-

III): $t(8.19) < 1$, $p = 0.95$, $d = -0.03$, 95% CI [-1.02, 0.96]], motor complications [Unified Parkinson's disease rating scale part IV (UPDRS-IV): $t(8.05) = 1.01$ $p = 0.34$, $d = 0.53$, 95% CI [-0.50, 1.54]], and levels of daytime sleepiness [Epworth Sleepiness scale (ESS): $t(16) < 1$, $p = 0.55$, $d = 0.29$, 95% CI [-0.65, 1.22]]. Total L-Dopa equivalent daily dosage [Total LEDD, mg: $U = 20$, $p = 0.08$, $r_{rb} = 0.50$, 95% CI [-0.002, 0.80]], L-Dopa equivalent daily dosage [LD-LEDD, mg: $t(10.21) = 1.72$, $p = 0.12$, $d = 0.84$, 95% CI [-0.18, 1.82]] and dopamine (DA) agonist use [Fisher-Freeman-Halton test, $p = 0.22$] were equivalent between groups, although DA agonist equivalent daily dose [DAED, mg: $t(16) = 2.27$, $p = 0.04$, $d = 1.10$, 95% CI [0.06, 2.06]] was significantly higher in the ICB+ vs. ICB- groups. As the DRT may modulate reward and punishment learning, the DAED was included as covariate in the ERP analysis. Total LEDD, DAED and LD-LEDD have been calculated based on published formulae (Schade et al., 2020; Tomlinson et al., 2010). The current level of functioning was higher in ICB+ vs. ICB- groups [MMSE: $t(16) = 2.85$, $p = 0.01$, $d = 1.35$, 95% CI [0.29, 2.37]]. Demographic and clinical characteristics of the PwP included in the EEG analysis are provided in Table 4.1.

Table 4. 1 Baseline data and clinical characteristics of the study sample.

Variables	**PwP overall (n=18)**	**ICB+ (n=8)**	**ICB- (n=10)**	**t, U, χ^2 values**	***p***
Age (y)	66.50 ± 8.15	64.13 ± 10.19	68.4 ± 5.98	$t(16) < 1$	0.28
Male, n (%)	15 (83.3%)	8 (100%)	7 (70%)		0.22[§|]
Education (y)	11.39 ± 4.86	10.25 ± 3.84	12.30 ± 5.58	$t(16) < 1$	0.39
ESS	7.44 ± 4.12	8.12 ± 4.39	6.90 ± 4.04	$t(16) < 1$	0.55
MMSE	27.83 ± 1.65	28.88 ± 1.13	27 ± 1.56	$t(16) = 2.85$	***0.01***
PD features					
Age at onset	58.17 ± 8.06	55.62 ± 8.72	60.20 ± 7.30	$t(16) < 1$	0.24
PD Duration	8.67 ± 3.96	8.75 ± 4.43	8.60 ± 3.78	$t(16) < 1$	0.94
UPDRS-III	22.81 ± 12, 17.5	22.57 ±16.55, 16	23.00 ± 8.03, 21	$t(8.19) < 1$	0.95
UPDRS-IV	1.69 ± 1.92, 1.5	2.29 ± 2.56, 1	1.22 ±1.20, 2	$t(8.05) = 1.01$	0.34
H&Y	1.91 ± 0.57	1.75 ±0.65	2.05 ± 0.50	$t(16) < 1$	0.28
LEDD Tot (mg)	812.27 ± 431.41, 670	1047.87 ±506.59, 960	623.80 ±251.30, 590	$U = 20$	0.08
LEDD LD (mg)	639.50 ± 381.96	812.25 ± 461.61	501.30 ± 249.20	$t(10.21) = 1.72$	0.12
DAED (mg)	141.11 ± 101.64	195.62 ± 87.89	97.50 ± 93.54	$t(16) = 2.27$	***0.04***
DA use, n (%)	15 (83.3%)	8 (100%)	7 (70%)		0.22[§|]
QUIP-rs	7.50 ± 9.18, 3.5	16.00 ± 7.31, 16.50	0.7 ± 1.49, 0	$t(7.47) = 5.82$	***0.001***

Table 4. 1 (continued). Baseline data and clinical characteristics of the study sample.

Variables	PwP overall (n=18)	ICB+ (n=8)	ICB- (n=10)	t, U, χ^2 values	*p*
ICB type					
Single ICB		2/ 1[a]	0		
Multiple ICBs		1/1/1/1/1[b]	0		

Legend. PwP: persons with Parkinson's disease; ICBs: impulsive-compulsive behaviours; ICB+: PwP with ICBs; ICB-: PwP without ICBs; Education: years of formal education; ESS: Epworth sleepiness scale; MMSE: Mini-mental state examination; UPDRS-III: Unified Parkinson's disease rating scale part III (motor score); UPDRS-IV: Unified Parkinson's disease rating scale part IV (motor complications); H&Y: Hoehn-Yahr disease severity rating scale; LEDD: Levodopa Equivalent Daily Dosage; LD: levodopa; DAED: dopamine agonist equivalent daily dose; DA: Dopamine agonist; QUIP-rs: Questionnaire for impulsive-compulsive disorders in Parkinson's disease – total score. Continuous variables are presented as mean ± standard deviation, median. Median is reported for variables that were not normally distributed. [a]hypersexuality: n=2, hobbyism: n=1; [b]hypersexuality + binge eating: n = 1, hypersexuality + compulsive shopping: n = 1, hypersexuality + gambling disorder: n = 1, hypersexuality + gambling disorder + punding: n = 1, gambling disorder + punding: n = 1. [§|] Fisher-Freeman-Halton test.

Procedure

Participants attended one screening visit and two research visits (i.e., 1: BART assessment during EEG recording; 2: neuropsychological assessment). During the second research visit PwP completed measures of (i) incentive-driven decision-making, (ii) cognitive processes associated with the four stages decision-making framework (Sinha et al., 2013), and (iii) affective and motivation. PwP were tested in the morning in the "on" state (i.e., at least 120 minutes after having taken their first DRT of the day), in their usual medication. Flow diagram of the study illustrating study procedure is provided in Figure 4.2. Assessments used during the research visits 1 and 2 are listed in Table 4.2.

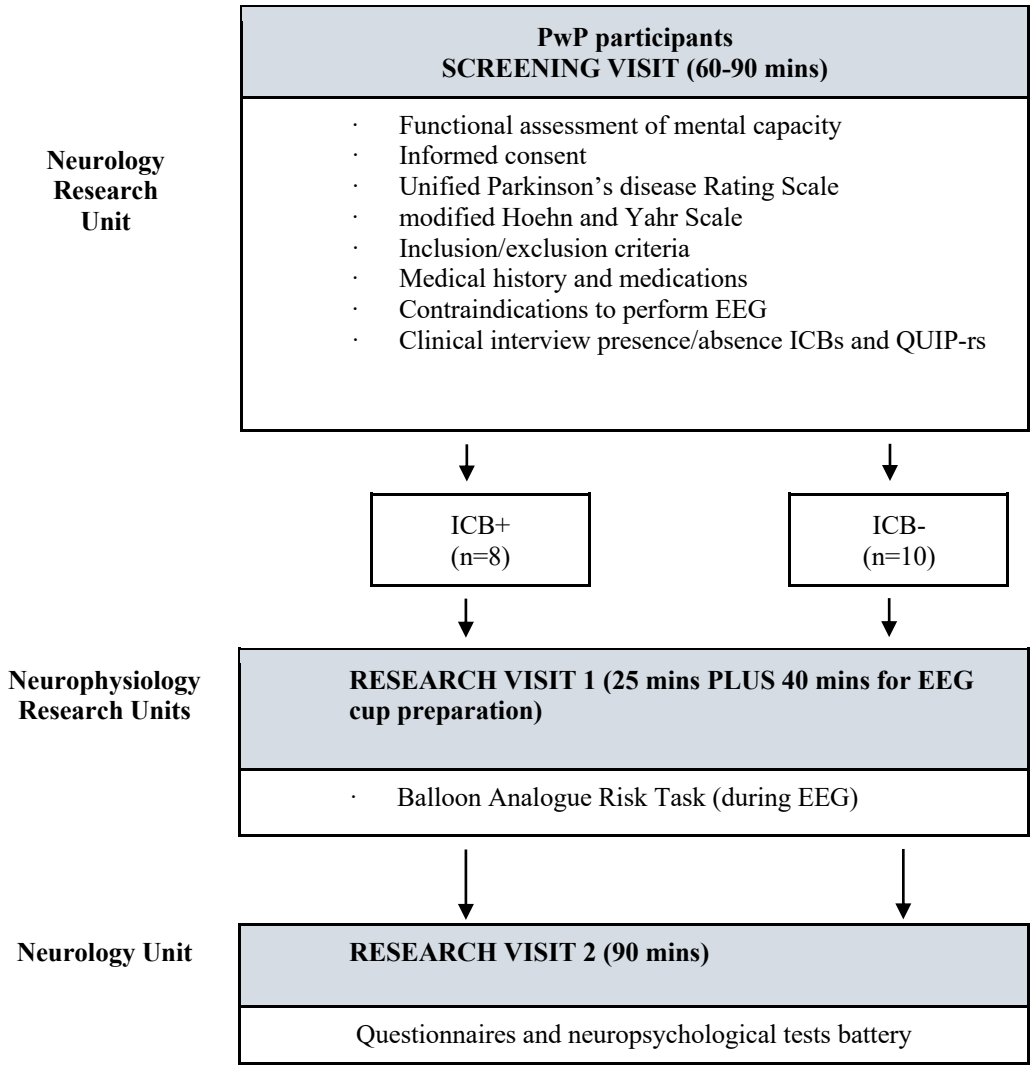


Figure 4. 2 Flow diagram illustrating study procedure. PwP: persons with Parkinson's disease; ICBs: impulsive-compulsive behaviours; ICB+: PwP with impulsive-compulsive behaviour; ICB-: PwP without impulsive-compulsive behaviour; QUIP-rs: Questionnaire for impulsive-compulsive disorders in Parkinson's disease – rating scale; EEG: EEG: electroencephalography.

Table 4. 2 Assessments administered in each research session.

Research Session 1 (25 mins testing PLUS 40 mins for EEG cup)	Research Session 2 (90 mins testing PLUS breaks)
BART	ROCF copy Phonological fluency DSS ROCF delay Prose Immediate TMT-A TMT-B Prose Memory Delay Go/No-Go task Stroop task IGT Brixton Spatial Anticipation Test Kirby Monetary Choice Questionnaire I-DAS HADS BIS-11 ESS

Legend. BART: Balloon Analogue Risk Task; ROCF: Rey Complex Figure; DSS: Digit span sequencing task; TMT-A: Trail Making Test – part A; TMT-B: Trail Making Test – part B; IGT: Iowa Gambling Task; I-DAS: Italian Dimensional Apathy Scale; HADS: Hospital Anxiety Depression Scale; BIS-11: Barratt Impulsiveness questionnaire; ESS: Epworth sleepiness scale; EEG: electroencephalography.

Stimuli

Clinical Measures

Modified Hoehn and Yahr Staging Scale. See page 102.

Unified Parkinson's Disease Rating Scale. See page 102.

Epworth Sleepiness Scale. See page 103.

Mini-Mental State Examination. See page 104.

Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – Rating Scale. See page 73.

Cognitive measures

The Balloon Analogue Risk Task. See page 213.

The Iowa Gambling Task. See page 215.

Trail Making Test. See page 108.

Phonological fluency. See page 217.

Digit span sequencing task. See page 217.

Kirby Monetary Choice Questionnaire. See page 110.

Go/No-Go. See page 218.

Stroop Color and Word Test. See page 218.

Brixton Spatial Anticipation Test. See page 112.

Prose Memory. See page 219.

Rey-Osterrieth complex figure test. See page 220.

Affective and motivational measures

Barratt Impulsiveness Questionnaire. See page 113.

Italian Dimensional Apathy Scale. See page 221.

Hospital Anxiety and Depression Scale. See page 114.

EEG acquisition and preprocessing

Participants performed the BART while 63-channels electroencephalogram (International 10-20 system) was recorded using BrainAmp MR plus amplifiers and BrainVision recorder 2.0 (Brain Products GmbH, Gilching, Germany). Participants completed two sessions of 60 trials each for a total number of 120 trials[9]. Usually, the number of trials provided in the BART is 30 (Wallsten et al., 2005); however, providing participants with 120 trials allowed to increase the number of negative feedback epochs available for averaging, although the breaking point remained unchanged from the original BART version for behavioural analyses. Negative feedback-locked waveforms were based on no less than 15 epochs per subject (whole sample: M=26.61, SD=9.22) in agreement with a previous study (Yau et al., 2015). To avoid participants fatigue, a 10-mins break was scheduled between the

[9] The first three participants (all from the ICB- group) performed only one session of 60 trials. In order to decrease the risk of having a small number of negative feedback trials, a second session of 60 trials was introduced for the following participants. Participants who performed 60 trials only were not discarded from the analyses as their FRN amplitudes were similar to the ones observed in the other participants (i.e., their z scores were within ± 1.5 SD from the group mean).

two sessions. Audio feedback typically used in the BART was removed from positive and negative feedback as it could have induced unwanted startle responses and muscle artefacts.

ERPs were time-locked to the onset of negative-loss feedback. Ag/AgCl active electrodes were mounted on an elastic cap, according to the International 10-20 system. The ground electrode was located at Oz, and FCz served as reference. Data were collected with a sampling rate of 512 Hz. Continuous data were filtered offline with an IIR Butterworth band-pass filter to reject frequencies below 0.1 Hz (0.1 half-amplitude filter, 12 dB/oct) and above 30 Hz (30 Hz half-amplitude, 12 dB/oct). Parks-McClellan Notch filter was applied at 50 Hz. After filtering, data were resampled at 256 Hz. Bad channels were identified visually and interpolated (whole sample: M=1.79, SD= 1.93). Continuous data were segmented into epochs of 1000 ms (200 ms before and 800 ms after feedback onset), and then baseline corrected at 200 ms before feedback onset (i.e., -200 to 0). Blinks and eye movements artefacts were corrected via Independent Component Analysis (Makeig, Bell, Jung, & Sejnowski, 1996). After artefact rejection, data were re-referenced to linked mastoids (electrodes TP9/TP10), and then averaged separately for each participant, and electrode. FRN was calculated from the mean amplitude between 200-300 ms at the midline electrodes Fz and Cz. Mean amplitude across an interval is an unbiased measure which means that it is equally likely to be larger or smaller than the true value and is not more likely to produce consistently larger values in noisier waveforms (Luck, 2014). Increasing the noise, mean amplitude will increase the variance and decrease statistical power, but it will not become larger. Furthermore, compared to other ERPs measures, such as peak amplitude, it can be

used when the number of trials differ between participants and/or when comparing groups with different levels of noise (Luck, 2014).

Statistical analysis

Data were analysed with Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp., 2012). Cohen's *d* effect sizes and 95% confidence intervals were analysed using JASP software version 0.10.2 (JASP Team, 2019), as Cohen's *d* effect sizes are not provided by SPSS.

Normality of distribution was explored with the Shapiro–Wilks test. For variables not normally distributed, both parametric and nonparametric analyses were used to compare groups. When the results were comparable for both types of analysis, results of parametric tests were considered, as they assure greater statistical power.

Continuous variables were analysed using t test or the non-parametric equivalent Mann-Whitney. Fisher's exact test or Fisher–Freeman–Halton test was applied to categorical variables. $p < 0.05$ (two-tailed) was set as the significance threshold for all the tests, except when Bonferroni correction for multiple comparisons was applied. Behavioural performance in the BART were analysed with a 2x2 mixed-model ANOVA with the between-subjects factor group (ICB+, ICB-) and the within-subject factor feedback (pre-, post-burst).

For the first aim, a Spearman correlation analysis examined the relationship between FRN for negative-loss feedback in Fz and Cz, and a BART discrepancy score (derived from the difference in the number of pumps pre- and post- balloon burst), cognitive, motivational and affective measures.

For the second aim, FRN values were analysed via mixed model repeated ANCOVA with mean amplitude of ERP responses for negative feedback as dependent variables, between-subject factors group (ICB+, ICB-) and within-subject factors electrode (Fz, Cz), and DAED as covariate. ERP responses for positive feedback have not been analysed as, using the original task version, the knowledge of win outcome is clear earlier in the positive feedback condition (i.e., participants know they have won the money once they decide to collect the money, before pressing the N key and seeing the visual positive feedback), therefore creating a shift in the average waveforms.

The small number of participants prevents any power analysis for subsequent studies. This is because small sample size may provide poor estimate of effect sizes, if the effect is highly variable across participants (Albers & Lakens, 2018). Therefore, no power analysis calculation will be provided in the results section.

For exploratory purposes, z scores were calculated from FRN scores of each participant, both at Fz and Cz electrodes, to identify (i) whether there are individuals performing 2 SD above the mean (i.e., abnormal FRN) and, if so, (ii) whether those individuals share some clinical and demographic characteristics.

Results

Correlation analysis

Spearman correlation analysis found a significant positive correlation between the FRN amplitude in Cz and the BART discrepancy score [$r_s(18) = 0.52$, $p = 0.03$; 95% CI [0.07, 0.80]]. This finding suggests that the more the negative feedback is processed, the more PwP adjust their risky behaviour after a negative feedback. No other correlations between FRN in Fz and Cz electrodes and the

cognitive, affective and motivational measures investigated were found. The correlation matrix is presented in Table 4.3. Correlation plots of significant correlations are provided in Figure 4.3.

Table 4. 3 Exploratory correlation analysis.

Variable	QUIP-rs	BART Main	BART DS	IGT	TMT-A	TMT-B	DSS	Phon Flu	Kirby	GNG	Stroop
FRN Fz	0.71	0.80	0.15	1.00	0.33	0.34	0.33	0.55	0.13	0.59	0.97
FRN Cz	0.40	0.46	***0.03***	0.96	0.69	0.27	0.90	0.15	0.29	0.61	0.72

Table 4. 3 (continued) Exploratory correlation analysis.

Variable	Mem	Brixton	MMSE	HADS-A	HADS-D	I-DAS	BIS-11
FRN Fz	0.94	0.24	0.94	0.94	0.11	0.94	0.13
FRN Cz	0.68	0.36	1.00	0.70	0.21	0.51	0.33

Legend. FRN: Feedback-related negativity; MMSE: Mini-mental state examination; QUIP-rs Tot: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – Rating Scale total score; BART: Balloon Analogue Risk Task main score; BART DS: BART discrepancy score; IGT: Iowa Gambling Task net score; TMT-A: Trail Making Test Part A number of errors; TMT-B: Trail Making Test Part B number of errors; DSS: Digit span sequencing test; Phon Flu: phonological fluency; Kirby: Kirby Monetary choice questionnaire total score; GNG: Go/No-Go false alarms; Stroop: Stroop interference number of errors; Brixton: Brixton scaled score; Mem: memory composite score; HADS-A: Hospital Anxiety and Depression scale anxiety subscale; HADS-D: Hospital Anxiety and Depression scale depression subscale; I-DAS: Italian Dimensional Apathy scale total score; BIS-11: Barratt Impulsiveness questionnaire total score. Significant *p* values ($p<0.05$) are given in bold.

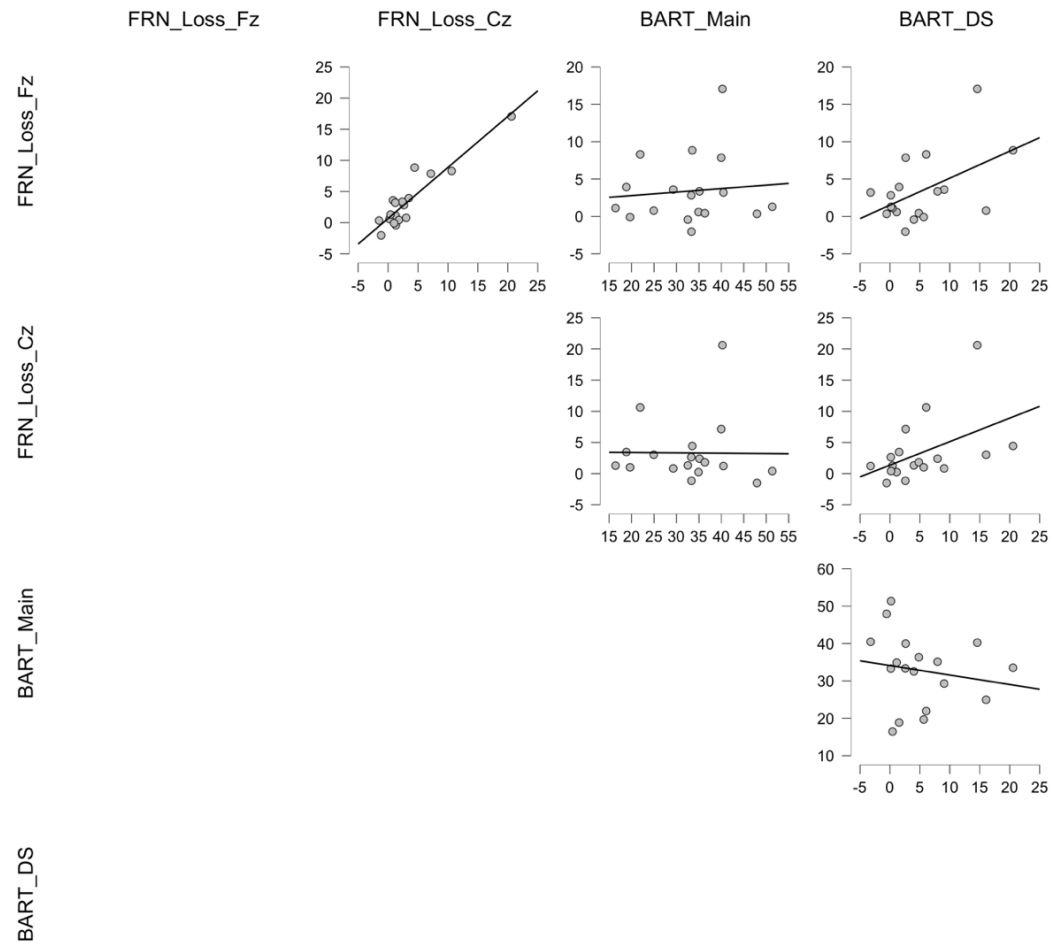


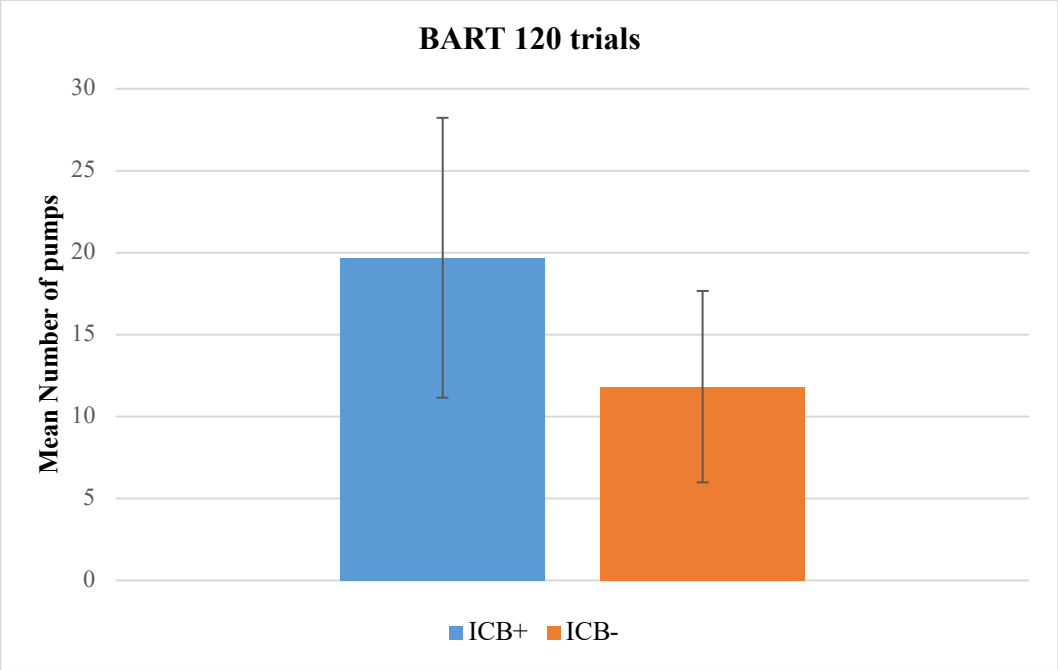
Figure 4. 3 Correlation Plots. FRN_Loss_Fz: Feedback-related negativity for negative-loss feedback at the electrode Fz; FRN_Loss_Cz: Feedback-related negativity for negative-loss feedback at the electrode Cz; BART_Main: Balloon Analogue Risk Task main score; BART_DS: Balloon Analogue Risk Task discrepancy score.

The Balloon Analogue Risk Task

Considering the performance on the whole 120 trials, the two groups did not differ in the average number of adjusted pumps where the balloon was cashed [$t(16) < 1$, $p = 0.58$, $d = -0.26$, 95% CI [-1.19, 0.67]] (see Figure 4.4A). When the average number of adjusted balloon pumps pre- and post-burst was compared, the main effect of feedback was significant [$F(1, 16) = 11.18$, $p = 0.004$, $d = 0.82$, 95% CI [2.04, 8.36]], although there was no main effect of group [$F(1, 16) < 1$, $p = 0.59$, $d = -0.13$, 95% CI [-13.41, 7.90]], nor group x feedback interaction [$F(1, 16) = 1.17$, $p = 0.29$; ICB+ vs. ICB- PRE: $p = 1.00$, $d = -0.20$, 95% CI [-19.84, 11.08]; ICB+ vs. ICB- POST: $p = 1.00$, $d = -0.05$, 95% CI [-16.59, 14.33]] (see Figure 4.4B).

For comparative purposes with Study 1, performance in the first 30 trials only was also analysed. The two groups did not differ in the average number of adjusted pumps where the balloon was cashed [$t(16) < 1$, $p = 0.73$, $d = -0.17$, 95% CI [-1.09, 0.77]]. When the average number of adjusted balloon pumps pre- and post-burst was compared, the main effect of feedback was significant [$F(1, 16) = 6.22$, $p = 0.02$, $d = 0.62$, 95% CI [1.07, 9.82]], although there was no main effect of group [$F(1, 16) < 1$, $p = 0.53$, $d = -0.15$, 95% CI [-15.76, 8.43]], nor group x feedback interaction [$F(1, 16) < 1$, $p = 0.50$; ICB+ vs. ICB- PRE: $p = 1.00$, $d = -0.20$, 95% CI [-22.91, 12.65]; ICB+ vs. ICB- POST: $p = 1.00$, $d = -0.08$, 95% CI [-19.98, 15.59]].

A. Overall risky incentive-driven decision-making



B. Response to negative feedback

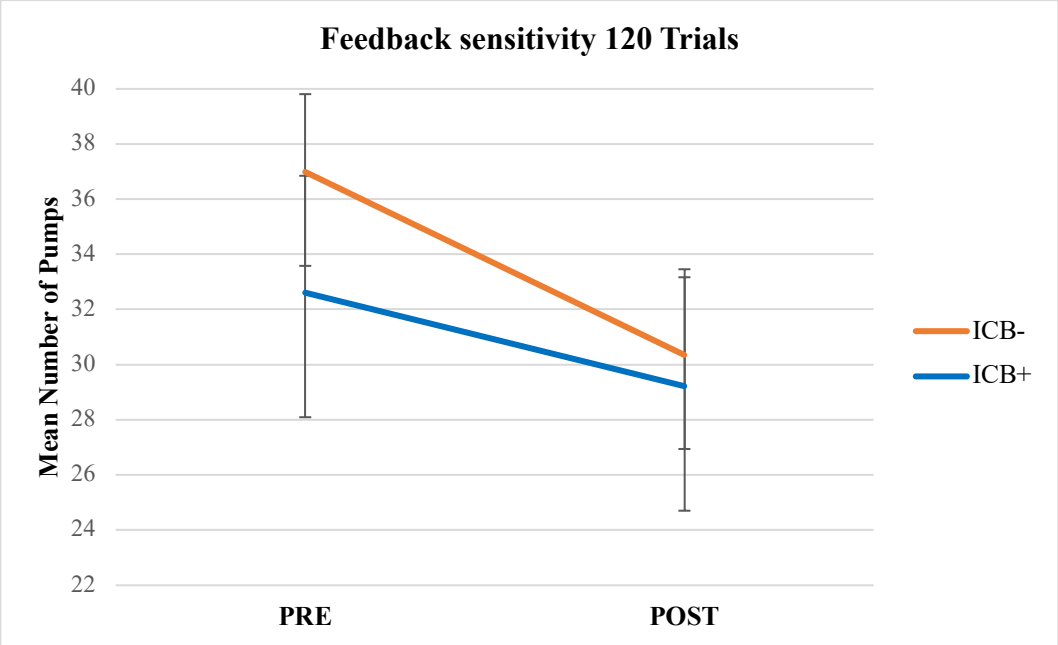


Figure 4. 4 Performance in the 120 trials of the Balloon Analogue Risk Task (BART). A) Average number of pumps for cashed trials. The two groups did not differ in the average number of pumps, which reflects risk-taking behaviour. Higher scores represent riskier behaviours. Error bars represent the standard error of the

mean. B) Both groups decreased the number of pumps after a negative feedback showing less risky behaviour. Negative feedback is expressed as the loss of money for trials in which a balloon burst. Error bars represent the standard error of the mean. ICB+: persons with Parkinson's disease and impulsive-compulsive behaviours; ICB-: persons with Parkinson's disease without impulsive-compulsive behaviours; PRE: average number of pumps in the balloons immediately preceding a balloon burst; POST: average number of pumps in the balloons immediately following a balloon burst.

Cognitive, affective and motivational measures

There were no significant differences between the two groups for any of the cognitive, affective and motivational measures assessed, using the stringent Bonferroni corrected *p*-values [Iowa Gambling Task (IGT) net score: $p < 0.05$; Trail Making test part A and Trail Making test part B errors (TMT-A and TMT-B), Phonological fluency, Kirby Monetary choice questionnaire total, Go/No-Go false alarms, Stroop interference errors, Memory composite score, Brixton scaled score: $p < 0.006$; Hospital Anxiety and Depression scale depression (HADS-D) and anxiety (HADS-A) subscales scores, Italian Dimensional Apathy scale score (I-DAS), Barratt Impulsiveness Scale total score (BIS-11): $p < 0.012$]. Cognitive, affective and motivational performances are provided in Tables 4.4 and 4.5.

Table 4. 4 Cognitive performances of PwP.

Variables	PwP overall (n=18)	ICB+ (n=8)	ICB- (n=10)	t values	*p*	ES	95% CI
		Incentive-driven decision-making task					
IGT Net	6.67 ± 31.41	18 ± 37.26	-2.4 ± 24.03	$t(16) = 1.41$	0.18	0.67	-0.30, 1.62
		(i) Option Generation Stage					
TMT-A errors	0.17 ± 0.38, 0	0.13 ± 0.35, 0	0.20 ± 0.42, 0	$t(16) <1$	0.69	-0.19	-1.12, 0.74
TMT-B errors	1.11 ± 1.37, 1	1 ± 1.31, 0.5	1.20 ± 1.48, 1	$t(16) <1$	0.77	-0.14	-1.07, 0.79
Phonol fluency	39.89 ± 17.42, 40	44.62 ± 17.38, 42.5	36.10 ± 17.40, 32.5	$t(16) = 1.03$	0.32	0.49	-0.46, 1.43
DSS	7.82 ± 2.35	8.62 ± 2.39	7.11 ± 2.20	$t(15) = 1.36$	0.19	0.66	-0.33, 1.63
		(ii) Option Selection Stage					
Kirby total	0.36 ± 0.17	0.27 ± 0.12	0.43 ± 0.18	$t(16) <1$	0.05	-1.03	-2.01, -0.02
		(iii) Action Initiation and Inhibition Stage					
Go/No-Go FA	0.39 ± 0.70, 0	0.62 ± 0.92, 0	0.20 ± 0.42, 0	$t(9.36) = 1.21$	0.25	0.62	-0.34, 1.57
Stroop INT	1.92 ± 4.74, 0	1.5 ± 4.25, 0	2.25 ± 5.30, 0	$t(16) <1$	0.75	-0.15	-1.08, 0.78
		(iv) Learning Stage					
Memory	-0.18 ± 1.11, -0.22	0.37 ± 1.37, 0.21	-0.60 ± 0.63, -0.60	$t(16) = 2.00$	0.06	0.94	-0.05, 1.92
Brixton	4.94 ± 2.71	6 ± 2.14	4.20 ± 2.10	$t(16) = 1.33$	0.20	0.63	-0.33, 1.58

Legend. PwP: persons with Parkinson's disease; ICB+: PwP with ICB; ICB-: PwP without ICB history; IGT: Iowa Gambling Task; TMT-A: Trail Making Test Part A number of errors; TMT-B: Trail Making Test Part B number of errors; Phonol fluency: Phonological fluency test; DSS: Digit span sequencing test; Kirby total: Kirby Monetary choice questionnaire total score; Stroop INT: Stroop interference number of errors; Memory: memory composite score; Brixton: Brixton scaled score; ES: Cohen's *d* effect size; CI: confidence interval. Data are presented as mean ± standard deviation, median. Median is reported for variables that were not normally distributed. Significant *p* values (IGT Net: $p < 0.05$; TMT-A errors, TMT-B errors, Phonological fluency, Kirby total, Go/No-Go FA, Stroop INT errors, Memory composite score, Brixton scaled score: $p < 0.006$) are given in bold.

Table 4. 5 Affective and motivational performances of PwP.

Variables	PwP overall (n=18)	ICB+ (n=8)	ICB- (n=10)	t values	*p*	ES	95% CI
HADS-A	4.17 ± 2.99	5.25 ± 3.01	3.30 ± 2.83	$t(16) < 1$	0.18	0.67	-0.30, 1.62
HADS-D	5.72 ± 4.15	5 ± 3.62	6.30 ± 4.62	$t(16) < 1$	0.52	-0.31	-1.24, 0.63
I-DAS	23.06 ± 8.58	23.37 ± 10.01	22.80 ± 7.81	$t(16) < 1$	0.89	0.06	-0.87, 0.99
BIS-11	57.44 ± 6.89	57.75 ± 7.30, 56	57.20 ± 6.92, 56	$t(16) > 1$	0.87	0.08	-0.85, 1.01

Legend. PwP: persons with Parkinson's disease; ICB+: PwP with ICB; ICB-: PwP without ICB history; HADS-A: Hospital Anxiety and Depression scale anxiety subscale; HADS-D: Hospital Anxiety and Depression scale depression subscale; I-DAS: Italian Dimensional Apathy scale; BIS-11: Barratt Impulsiveness questionnaire total score; ES: Cohen's *d* effect size; CI: confidence interval. Data are presented as mean ± standard deviation, median. Median is reported for variables that were not normally distributed. Significant *p* values ($p < 0.012$) are given in bold.

Feedback-related negativity amplitude

Mixed model repeated ANCOVA with mean amplitude of ERP responses for negative feedback as dependent variables showed no main effect of electrode type [$F(1, 15) = 1.32$, $p = 0.27$, $d = 0.03$, 95% CI [-0.92, 1.06]], no main effect of group [$F(1, 15) < 1$, $p = 0.50$, $d = -0.16$, 95% CI [-7.59, 3.85]], and no effect of group x electrode interaction [$F(1, 15) < 1$, $p = 0.80$; ICB+ vs. ICB- in Fz: $p = 1.00$, $d = -0.15$, 95% CI [-9.96, 6.50]; ICB+ vs. ICB- in Cz: $p = 1.00$, $d = -0.17$, 95% CI [-10.24, 6.21]] (see Table 4.6, and Figures 4.5 - 4.7). Leaving out DAED levels from the model, the results did not change; there was no main effect of electrode type [$F(1, 16) < 1$, $p = 0.92$, $d = 0.03$, 95% CI [-0.92, 1.06]], no main effect of group [$F(1, 16) < 1$, $p = 0.84$, $d = -0.05$, 95% CI [-5.43, 4.50]], and no effect of group x electrode interaction [$F(1, 16) < 1$, $p = 0.68$; ICB+ vs. ICB- in Fz: $p = 1.00$, $d = -0.07$, 95% CI [-7.79, 6.46]; ICB+ vs. ICB- in Cz: $p = 1.00$, $d = -0.03$, 95% CI [-7.39, 6.86]].

Table 4. 6 FRN mean amplitude by electrode x group interaction.

	PwP overall (n=18)	**ICB+ (n=8)**	**ICB- (n=10)**	**F values**	***p***
FRN	Fz: 3.39 ± 4.60, 2 Cz: 3.32 ± 5.19, 1.5	Fz: 3.02 ± 3.35, 2 Cz: 3.17 ± 3.86, 2.2	Fz: 3.68 ± 5.57, 2.1 Cz: 3.43 ± 6.26, 1.3	Main effect of electrode $F(1, 15) = 1.32$ Main effect of electrode x group $F(1, 15) = 0.07$ Main effect of group $F(1, 15) = 0.48$	0.27 0.80 0.50

Legend. FRN: feedback related negativity mean amplitude; ICB+: persons with Parkinson's disease and impulsive-compulsive behaviours; ICB-: persons with Parkinson's disease without impulsive-compulsive behaviours; Data are presented as mean ± standard deviation. Significant *p* values (<0.05) are given in bold.

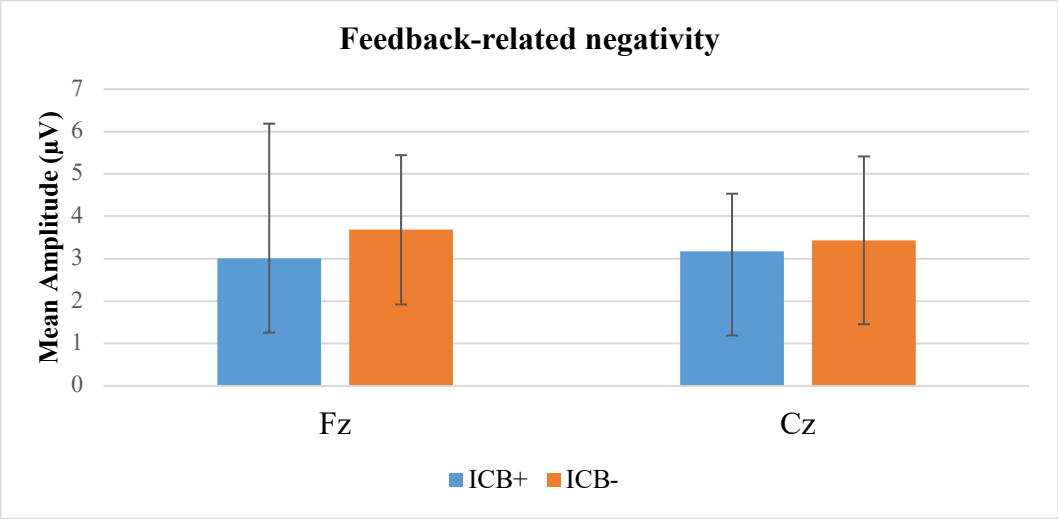


Figure 4. 5 Feedback-related negativity mean amplitude recorded at Fz and Cz electrodes in time window 200-300 ms for ICB+ and ICB- groups. ICB+: persons with Parkinson's disease and impulsive-compulsive behaviours; ICB-: persons with Parkinson's disease without impulsive-compulsive behaviours.

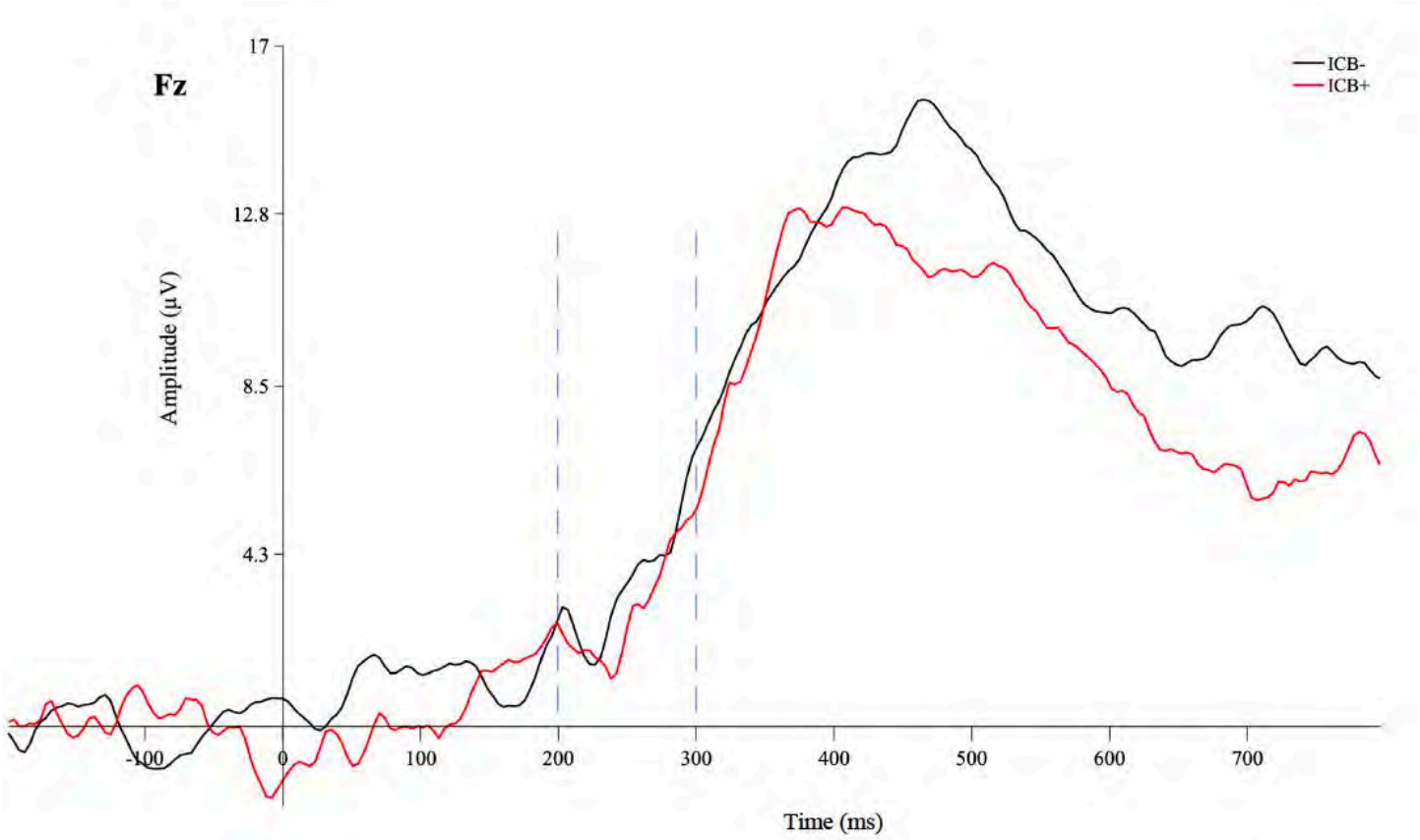


Figure 4. 6 Grand average FRN for negative-feedback trials for ICB+ and ICB- groups at the electrode Fz. Average waveforms are first computed across trials for each subject at electrode site Cz, and then the waveforms are averaged across subjects of each group.

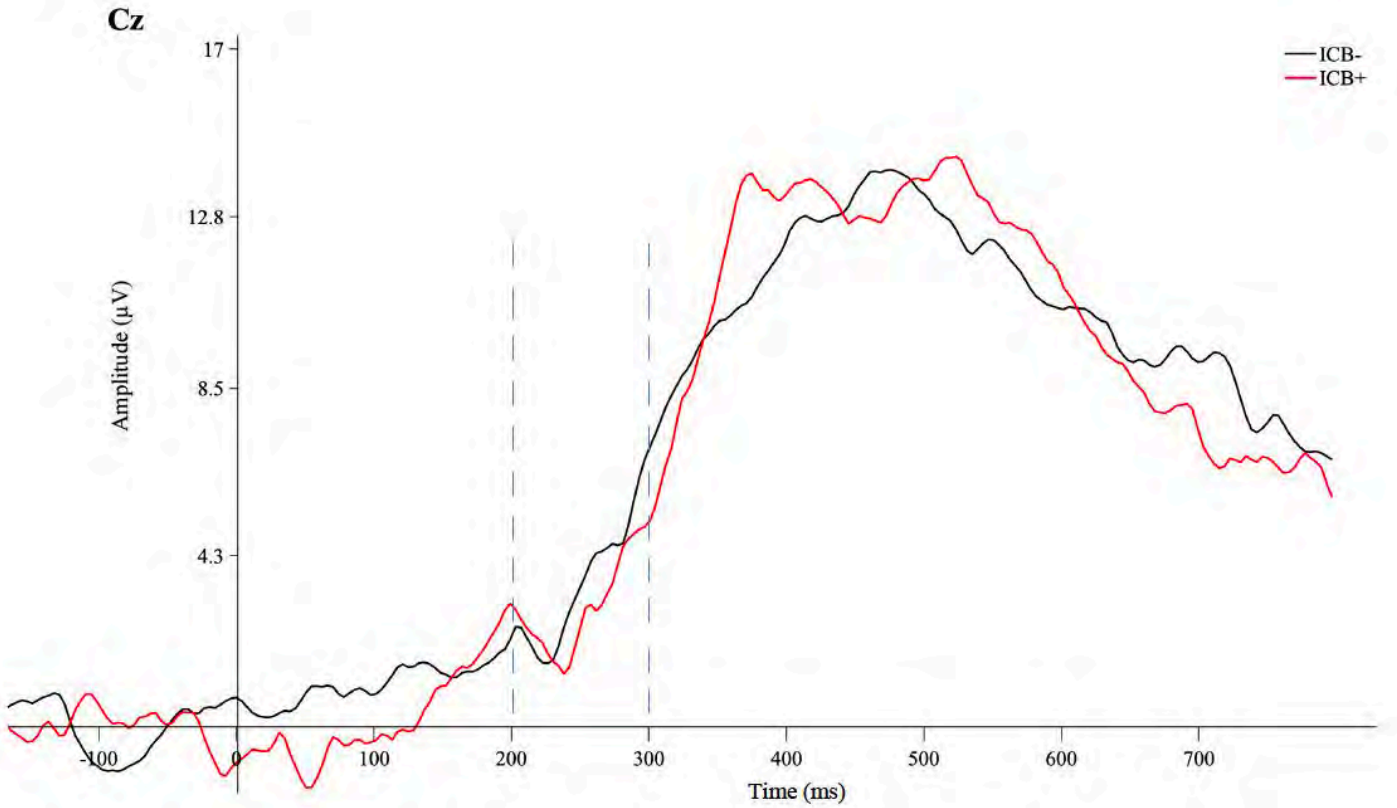


Figure 4. 7 Grand average FRN for negative-feedback trials for ICB+ and ICB- groups at the electrode Cz. Average waveforms are first computed across trials for each subject at electrode site Cz, and then the waveforms are averaged across subjects of each group.

Z scores

FRN scores of each participant have been converted as z scores, using means and SDs of the whole group of PwP (N=18). This allows to explore performance of each participant to identify whether there is a subgroup of PwP with similar clinical and demographic characteristics who shows blunted FRN. If FRN is a specific feature of a subgroup of individuals, differences between PwP with and without ICBs may not be evident.

None of the PwP showed FRN amplitude 2 SD below the mean, therefore reflecting higher blunted FRN compared to the rest of the group. In both Fz and Cz electrodes, one participant of the ICB- group (participant 9, see Figures 4.8 and 4.9) showed FRN amplitude 2 SD above the mean, therefore reflecting higher FRN amplitude compared to the rest of the sample. All the other participants performed within ± 1.5 SD from the group mean. FRN z scores of each participant at Fz and Cz electrodes are presented in Figures 4.8 and 4.9.

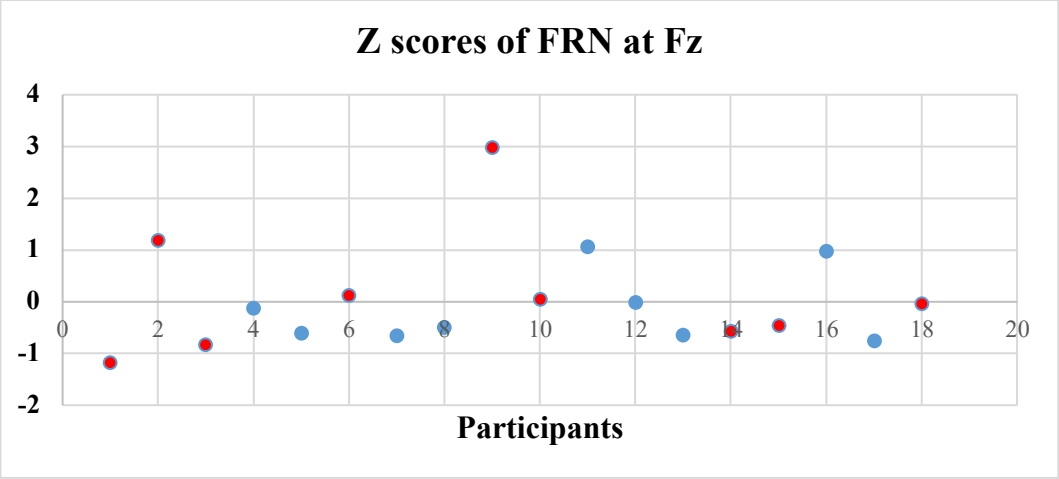


Figure 4. 8 Feedback-related negativity (FRN) Z score for each participant at the electrode Fz. Blue dots represent persons with Parkinson's disease and impulsive-compulsive behaviours. Red dots represent persons with Parkinson's disease but not impulsive-compulsive behaviours.

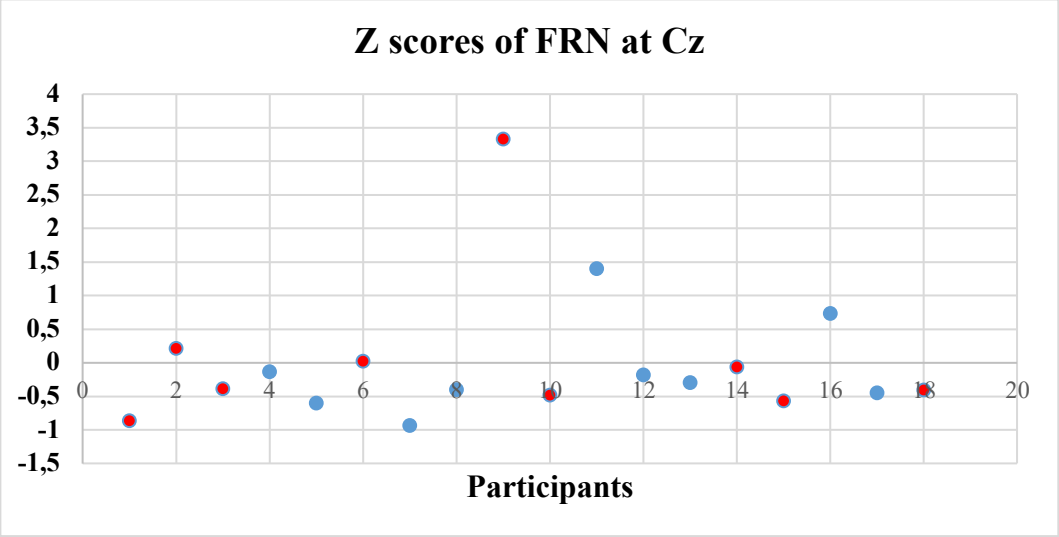


Figure 4. 9 Feedback-related negativity (FRN) Z score for each participant at the electrode Cz. Blue dots represent persons with Parkinson's disease and impulsive-compulsive behaviours. Red dots represent persons with Parkinson's disease but not impulsive-compulsive behaviours.

Discussion

The main aim of the present pilot study was to explore whether PwP, irrespective of ICBs, show an association between FRN amplitude and risky behaviour in the BART. The secondary aim was to investigate, for the first time, FRN amplitude in PwP with and without ICBs providing data for calculating sample size for a fully powered study.

The first key finding of this pilot study is that, when the two groups are merged together, FRN amplitude at Cz is positively correlated with the BART discrepancy score. This means that the more participants decreased their risky behaviour after a negative feedback, the larger was their FRN wave. It should be noted that ERP amplitude can be affected by trials number, in that fewer trials can lead to more extreme amplitude; therefore, it is possible that this association is mediated by trial number differences across sample. However, this is unlikely as FRN were calculated as mean amplitude within an interval, which is an unbiased measure. This means that mean amplitude is not more likely to produce consistently larger values in noisier waveforms (Luck, 2014).

Using different paradigms, literature provides inconsistent findings about FRN during negative feedback in PD. During performance in the IGT, blunted FRN during negative feedback was reported in PwP (without distinguishing between ICB+ and ICB-) compared to healthy controls (Mapelli et al., 2014). Conversely, another study found preserved FRN during performance of a gambling task in PwP without apathy compared to healthy controls (Martinez-Horta et al., 2014). The present study cannot reconcile previous discrepant findings related to FRN amplitude in PD vs. non-PD population (Mapelli et al., 2014; Martinez-Horta et al., 2014), as a healthy older adults control group was not included in the study.

Nonetheless, the present study adds to the broad literature indicating that, even if FRN during negative feedback may be blunted in PwP, they are able to process negative feedback in order to reduce risky behaviour during incentive-driven decision-making, as higher FRN are associated with reduction in risky behaviour after balloon burst.

Interestingly, there were no associations between FRN and affective and motivational measures, although blunted FRN have been reported among depressed and nonclinical adults with high trait anxiety, and in apathetic PwP (Keren et al., 2018; Martinez-Horta et al., 2014; Takács et al., 2015). Discrepancies with previous findings can be reconciled suggesting that, in PwP, associations between FRN and affective and motivational measures are only evident in groups with clinically significant affective and motivational changes. Separate analysis for PwP with and without depression, anxiety and apathy was not possible due to the low number of individuals with scores above the cut-offs (i.e., 4 PwP for depression, 2 for anxiety, and 6 for apathy).

The second key finding is that, conversely from predictions, FRN amplitude during negative feedback does not differ between ICB+ and ICB-. The lack of between groups differences at the neurophysiological level were mirrored by comparable BART performances at the behavioural level, as both groups reduced their risky behaviour after negative feedback. The negative behavioural BART findings were evident regardless of considering the first 30 trials (as in the Studies 1 and 3, Chapter 3) or the whole 120 trials. This is the first evidence of FRN amplitude in ICBs in PD, and this is in contrast with the wider addiction literature showing blunted FRN during the BART in individuals with behavioural addiction and substance abuse (Fein & Chang, 2008; Yau et al., 2015; Zhong et al., 2020). Blunted

FRN have been observed regardless of comparable behavioural performances, suggesting a higher sensitivity of the neurophysiological assessments compared to behavioural ones (Kóbor et al., 2015; Yau et al., 2015).

There are at least two explanations for similar FRN in PwP with and without ICBs.

The first explanation is that blunted FRN is an endophenotypic neurophysiological alteration of PD but not ICBs, which may be related to neural degeneration, to DRT, or both. This is supported by some (Mapelli et al., 2014), but not all studies (Holroyd, Praamstra, Plat, & Coles, 2002; Martinez-Horta et al., 2014). DRT might prevent the dopaminergic dip during negative feedback, therefore impairing learning from negative feedback and promoting learning from positive feedback (Frank et al., 2004). It could be speculated that the DRT effect on negative feedback might be independent of ICBs. If this hypothesis is true, blunted FRN may not be by itself sufficient for preventing risky behaviour adjustments as supported by the association, in the present study, between FRN amplitude and risky behaviour in the BART. Future studies should investigate this hypothesis including ICB+, ICB- and healthy controls groups.

The second explanation is that ICBs in PD are driven by enhanced sensitivity toward rewards instead of reduced sensitivity toward negative consequences. Previous studies show that PwP with ICBs make more risky choices in the gain vs. in the loss conditions (Voon, Gao, et al., 2011) and show increased ventral striatal dopaminergic released when exposed to reward-related visual cues (Wu et al., 2015). Heightened sensitivity toward rewards both “on” and “off” DRT has been documented in PwP with ICBs, whereas in those without ICBs sensitivity toward rewards is reduced when “off” DRT (Drew et al., 2020).

Positive feedback processing can be investigated looking at the P300, which is an ERP component characterized by a positive deflection peaking ~300 – 450 ms post-feedback. P300 reflects reward evaluation (Hajcak, Holroyd, Moser, & Simons, 2005; Sato et al., 2005; Yeung & Sanfey, 2004); in particular, P300 seems to be sensitive to feedback valence, although other studies find that it encodes reward magnitude (Sato et al., 2005; Yeung & Sanfey, 2004). Unfortunately, the BART version used here prevents any analyses of positive feedback processing (e.g., by assessing P300 amplitudes for gain trials). Conversely from the losses that were unpredictable and known only through feedback, gains are known before the positive feedback is provided. In other words, when participants are exposed to the positive feedback (i.e., "congratulations, you have won XX$ money for this balloon") they are already aware of the positive outcome of their action which is evident when participants decide to press the key to secure money in the bank. Knowledge of win is therefore clear earlier in the positive feedback conditions, creating a shift in the average waveforms. Furthermore, it is neither possible to analyse the specific moment in which the participants decide to stop inflating the balloon and taking the gain for the specific trial. This is because that decision is supported by a set of mental processes, which exacting timing is not possible to be identified and triggered for analysis. One of the advantages of EEG/ERP is the good temporal resolution. This means that they provide measurement of brain activity from one millisecond to the next (Woodman, 2010), which different time moments associated with different cognitive processes. Previous ERPs studies implemented a modified BART version that allows to analyse positive and negative feedback (Euser, van Meel, Snelleman, & Franken, 2011; Yau et al., 2015). However, in these modified versions participants do not consequently inflate the balloon but just type the target number of

pumps at the beginning of each trial. These modified versions miss the escalating feeling of risk that participants perceive when they accumulate greater potential rewards and are exposed to increasing possible losses by sequentially pumping the balloon (Schonberg et al., 2011). This is supported by evidence of brain activity reduction in the ventromedial prefrontal cortex when participants further extend the balloon (Schonberg et al., 2012).

The secondary aim of providing data for calculating a-priori power analysis for a subsequent investigation of FRN in ICBs in PD was not met due to the small number of participants included in the study. Effect sizes estimates from small sample studies may be inaccurate leading to unpowered design (Albers & Lakens, 2018; Leon, Davis, & Kraemer, 2011). Running pilot studies before larger studies is still crucial as they can identify modifications needed in the design of larger hypothesis testing studies (Leon et al., 2011). Small effect sizes estimate from small pilot studies should not preclude follow-up studies, and more investigations are needed to understand whether ICBs in PD are associated with blunted FRN. The tendency of researchers to not follow-up on pilot studies when facing small effect sizes estimates is named *follow-up bias.* Alternative approach to design future FRN studies in ICBs in PD may involve sequential analyses, which allows researchers to analyse the data multiple times (e.g., after 20, 40, 60, etc. participants have been collected) whilst controlling Type I error rates (Albers & Lakens, 2018; Lakens, 2014).

Limitations

There are several limitations that should be acknowledged.

First, the study is limited by small sample size and therefore low statistical power which may have reduced the likelihood to find the true effect. Any interpretation of the results should be cautiously considered. In the PD literature, underpowered studies investigating FRN are frequent, with the smallest study including 9 PwP and 9 healthy controls (Holroyd et al., 2002) and the largest including 40 PwP (20 apathetic and 20 non-apathetic) and 11 healthy controls (Martinez-Horta et al., 2014). In the context of ICBs, recruitment is even harder as ICBs are a condition characterized by a feeling of shame making individuals reluctant in taking part in research. Furthermore, dyskinesias, which create artifacts in the EEG signal and may represent a reason for exclusion, is frequently reported in PwP with ICBs (Biundo et al., 2017; Voon et al., 2017) making recruitment even harder. These reasons may explain, at least in part, the paucity of EEG studies in PwP with ICBs. For example, there are only three studies using EEG in PwP with ICBs (Carriere et al., 2016; Meyer et al., 2020; Spay et al., 2019) and none of them investigated FRN.

Second, the original BART version used prevents any FRN analysis in the positive trials. Future studies should investigate both positive and negative feedback processing, in the same PwP cohort with and without ICBs, using a task that does not eliminate the dynamic of the ongoing decision while increasing the risk; this is important as loss aversion and expectancy valence in the BART may change within a single trial during the pumping phase, which in turn may impact the ongoing risky behaviour (Euser et al., 2011).

Third, the study lacks a control group of healthy older adults that could have provided baseline data for comparing data of PwP participants.

Finally, motor-related negative central cortical EEG potential (e.g., Bereitscshaftpotential) can occur 1-3 seconds before a self-initiated movement (Di Russo et al., 2017). It is unlikely that the FRN recorded in this study reflect pre-motor Bereitscshaftpotential because FRN are recorded 1 second after a voluntary movement. Nonetheless, there was no limb EMG recording to ascertain that participants were not tense, or moving or clenching muscles at the time of the FRN or immediately after. Future study should also include EMG recording to exclude the possible confounding effect of pre-motor activity.

Conclusions

This pilot study shows that in PD reduced risky behaviour after loss is associated with higher FRN amplitude. However, when data of ICB+ and ICB- were analysed separately, FRN amplitudes did not differ between groups. The small sample size prevents a-priori power analysis. However, FRN during negative feedback in PwP with ICBs should be further investigated in follow-up studies, possibly using sequential analyses approach (Albers & Lakens, 2018; Lakens, 2014). This pilot study identified a modification needed in the design of a larger neurophysiological study, which is the implementation of a task that allows both positive and negative feedback processing. This is important for ascertain whether ICBs in PD may result from enhanced sensitivity toward rewards instead of reduced sensitivity toward punishments.

Key Findings

- FRN amplitude in Cz positively correlates with sensitivity toward negative feedback, as measured by the difference between the average number of pumps pre- and post-balloons burst.
- FRN during negative feedback does not differ between PwP with and without ICBs.
- BART behavioural performance does not differ between PwP with and without ICBs.

Chapter 5 Brain Imaging Correlates

This chapter presents the following two studies investigating brain imaging correlates of impulsive-compulsive behaviours (ICBs) in Parkinson's disease (PD):

1) Study 5: A systematic review of 30 structural and functional brain imaging studies comparing persons with Parkinson's disease (PwP) with and without ICBs;
2) Study 6: A systematic review and meta-analysis of 9 PET and SPECT studies comparing striatal functioning of PwP with and without ICBs;

The final section of this chapter will present an interim conclusion of the main results integrated across the two studies. Both studies have been published (Martini, Dal Lago, Edelstyn, Salgarello, et al., 2018; Martini et al., 2020).

Study 5: Brain correlates of Impulsive-compulsive behaviours in Parkinson's disease: a systematic review of neuroimaging studies[10]

The study presented in this chapter has been published (Martini et al., 2020) and is reproduced with permission of the copyright holder.

Abstract

Background: In Parkinson's disease (PD), impulsive-compulsive behaviours (ICBs) may develop as side-effect of dopaminergic medications. Abnormal incentive-driven decision-making, which is supported by the cognitive control and motivation interaction, may represent an ICBs signature. This systematic review explored whether structural and/or functional brain differences between persons with PD (PwP) with vs. without ICBs encompass incentive-driven decision-making networks.

Methods: Structural and functional neuroimaging studies comparing PwP with and without ICBs, either drug naïve or medicated, were included.

Results: Thirty articles were identified. No consistent evidence of structural alteration both in drug naïve and medicated PwP were found. Differences in connectivity within the default mode, the salience and the central executive networks predate ICBs development and remain stable once ICBs are fully developed. Medicated PwP with ICBs show increased metabolism and cerebral blood flow in orbitofrontal and cingulate cortices, ventral striatum, amygdala, insula, temporal and supramarginal gyri during resting-state, and increased activity in ventral striatum,

[10] Martini, A., Tamburin, S., Biundo, R., Weis, L., Antonini, A., Pizzolo, C., Leoni, G., Chimenton, S. & Edelstyn, N. M. (2020). Incentive-driven decision-making networks in de novo and drug-treated Parkinson's disease patients with impulsive-compulsive behaviors: A systematic review of neuroimaging studies. *Parkinsonism & Related Disorders, 78*, 165-177.

cingulate cortex, ventromedial prefrontal and orbitofrontal cortices, subthalamic nucleus and inferior frontal gyrus during reward-based task performance. Reduced frontostriatal and increased mesolimbic connectivity was reported in PwP with ICBs.

Discussion: Functional brain signatures of ICBs in PD encompass areas involved in cognitive control and motivational encoding networks of the incentive-driven decision-making. Functional alterations predating ICBs may be related to abnormal synaptic plasticity in these networks.

Introduction

Individuals with ICBs are unable to resist or have diminished control over an appetitive urge, such as craving, to engage in behaviours that include gambling, sexual activity, eating, shopping. Engaging in such behaviours gives rise to feelings of pleasure or hedonia, but, left uncontrolled, can lead to relationship breakdown, financial difficulties, and health problems (American Psychiatric Association, 2013). Despite the pervasive nature of ICBs in PD and their negative impact, much remains to be elucidated about their neural correlates.

Incentive-driven decision-making, which refers to decision made to engage in a hedonic activity, is a result of weighing up the predicted benefits of following that particular goal, traded-off against the effort involved in achieving the goal, the risk involved and the time to outcome delivery, versus the alternative option(s) that are not pursued (Botvinick & Braver, 2015; Sinha et al., 2013). There is a consensus of opinion that incentive-driven decision-making is supported by cognitive control and motivation, which are intrinsic and closely interrelated aspects, and will therefore impact on the extent to which the goal directed behaviour is regulated, or not as in the case of ICBs (Botvinick & Braver, 2015).

Cognitive control reflects the ability to flexibly organise and control the selection and deployment of on-going cognitive processes that include attention, memory, action-planning, and co-ordinate their activity to ensure successful delivery of goals in multitask environments (Badre & Nee, 2018). Once options are generates, cognitive control is crucial for the 'option selection' and 'action initiation or inhibition' stages of the incentive-driven decision-making (Sinha et al., 2013).

Motivation can be defined as follows 'when an external or internal incentive alters the biological system (i.e., generates a 'motivated state') to stimulate an

observable change in behaviour' (Yee & Braver, 2018). In other words, motivational states can be induced by offering rewards or negative incentives that lead to changes in cognitive control and influence behaviour (Cubillo, Makwana, & Hare, 2019). This highly dynamic and (two-way) interactive relationship is further influenced by individual differences in sensitivity to reward and punishment (Capa & Bouquet, 2018; Cubillo et al., 2019) and by modulation of the dopaminergic system (e.g., by dopamine replacement therapy (DRT)) (Pessiglione et al., 2006).

Evidence from cognitive neuroscience research suggests that incentive-driven decision-making reflect interactions between at least two brain networks: the central one is involved in cognitive control and the other one governs the intensity of control conveying motivational signals (i.e., reward value) (Yee & Braver, 2018).

In a recent review, Badre and Nee (2018) suggest that cognitive control relies on frontal regions that interact via a local and global hierarchical structure. At the lowest level of the hierarchy, projections between the mid-dorsolateral prefrontal cortex (mid-DLPFC) and premotor to motor cortex, and frontal eye fields support sensory-motor control. Rostrolateral prefrontal cortex occupies the intermediate level and has responsibility for domain-specific control of behaviour, forming 'schema' from specific episodic information. At the apex of the hierarchy, and residing between caudal and rostral lateral prefrontal cortex, lies the mid-DLPFC that supports domain-general control based on abstract rules and concepts (Badre & Nee, 2018).

A parallel dopaminergic network, which comprises the ventral striatum, the anterior cingulate cortex and, minimally, the dorsomedial frontal cortex has been suggested to govern the intensity of control amongst the networks conveying motivational signals (Botvinick & Braver, 2015). Dorsomedial frontal cortex

interacts with rostrolateral and DLPFC during performance monitoring and prediction error detection, implying that the two systems work together in 'deciding' whether the salience or value of the incentives are worth increasing the strength of control and accepting the greater subjective cost that control involves (Frank & Claus, 2006; Kurniawan et al., 2010; Zarr & Brown, 2016).

Thus, returning to PD, individuals with ICBs show impairment in incentive-driven decision-making (Study 2) (Martini, Dal Lago, Edelstyn, Grange, et al., 2018; Martini, Ellis, et al., 2018; Rossi et al., 2010), that are evident in diminished control over reward-seeking behaviours in real life. Therefore, we may expect abnormal structural changes and/or functional activation in rostrolateral prefrontal cortex, mid-DLPFC cortex, dorsomedial prefrontal cortex, ventral striatum and anterior cingulate cortex in ICBs compared to non-ICBs PwP. If present in drug naïve PwP, then, these differences may represent indicators of vulnerability to ICBs.

Aim

The aim of this study was to systematically review structural and functional brain imaging studies to investigate whether ICBs in PD are associated with changes in the incentive-driven decision-making networks. The presence of these abnormalities were also explored in drug naïve PwP as indicator of vulnerability trait. This systematic review included magnetic resonance imaging (MRI) and perfusion brain positron emission tomography (PET) or single-photon emission computed tomography (SPECT) imaging studies. Neuropharmacological PET or SPECT studies were not included as they provide neuropharmacological instead of anatomical data. Furthermore, Neuropharmacological PET or SPECT studies' findings are explored in the following study of this thesis (Study 6).

Method

Study design, participants and comparators

A systematic review was conducted to verify whether ICBs in PD are associated with changes in the incentive-driven decision-making brain networks. Studies were selected if they compared PwP with one or more ICBs (ICB+) to those without any ICBs (ICB-). Findings are presented separately for drug naïve PwP and those treated with DRT.

Search strategy

On the 10th of August 2018, PubMed, Cochrane, EBSCO, and ISI Web of Science databases were searched for peer-reviewed papers in English, Spanish or Italian published since database inception. The search was further updated on the 30th of March 2020. The protocol of the systematic review was pre-registered in PROSPERO (ID: CRD42018106365).

Each database was searched twice for structural and functional imaging studies. For structural studies the following search string was used: (Parkinson's disease) AND (impulse control disorders OR impulse control disorder OR impulsive compulsive behaviors OR impulsive compulsive behaviours OR impulsive compulsive behavior OR impulsive compulsive behaviour OR ICD OR ICB)) AND (voxel-based OR morphometry OR VBM OR MRI OR structural magnetic resonance imaging OR diffusion spectrum imaging OR diffusion MRI OR DTI OR DSI OR diffusion magnetic resonance imaging).

For functional studies the following search string was used: ((Parkinson's disease) AND (impulse control disorders OR impulse control disorder OR impulsive

compulsive behaviors OR impulsive compulsive behaviours OR impulsive compulsive behavior OR impulsive compulsive behaviour OR ICD OR ICB)) AND (fMRI OR functional magnetic resonance imaging OR functional MRI OR neuroimaging OR PET OR SPECT OR Positron emission tomography OR Single Photon Emission Computed Tomography OR FDG OR ASL).

Selection criteria

The following inclusion criteria were applied: 1) between-group comparison between ICB+ and ICB- PwP; 2) ICBs status determined using clinical interviews based on published or proposed criteria and/or rating scales with evidenced construct validity, and defined rates of sensitivity and specificity; 3) neuroimaging studies reporting grey matter structure using voxel-based morphometry (VBM) performed on structural MRI (sMRI), white matter connectivity using diffusion tensor imaging/ diffusion weighted imaging analysis (DTI)/(DWI) performed on sMRI, functional activation and functional connectivity using blood oxygen level dependent (BOLD) signal in functional MRI (fMRI), or brain perfusion using PET or SPECT at rest to investigate changes in regional cerebral blood flow.

The following exclusion criteria were applied: 1) studies including PwP with dementia; 2) other neurological conditions other than PD; 3) alcohol or any substance use disorder either at the moment when PwP were tested or in the past, because these conditions might be independently associated with structural and functional brain changes. Finally, 4) studies not screening for the absence of all ICBs types in the ICB- groups were not included.

Data extraction

The following demographic and clinical data, if available, were extracted: age at participation, age at PD onset, PD duration, Hoehn and Yahr (H&Y) PD stage, antidepressant use, medication status (drug naïve or treated). The following information were also extracted: total dopaminergic medication equivalent daily dose (total LEDD), levodopa LEDD (LD-LEDD), dopamine agonist LEDD (DAED), and motor symptom severity "on" and/or "off" medication using the Unified Parkinson's Disease Rating Scale motor section (UPDRS-III), type of ICB, ICBs screening tools, variables that were matched between groups, and criteria used for defining "on" and "off" medication state (for functional studies only).

The main outcomes for the structural imaging studies were the differences between ICB+ and ICB- groups in cortical and subcortical grey matter density measured with VBM, cortical thickness (Cth), and subcortical white matter tract metrics assessed using DTI/DWI.

The main outcomes for the functional studies were the differences between ICB+ and ICB- groups in connectivity during resting state fMRI (rs-fMRI), brain perfusion during resting state, using PET or SPECT and brain activation during task performance using fMRI.

Results

Search results

The search terms turned up 720 papers. Four hundred and twenty-three of these papers were identified as duplicates and removed. The title and abstract of the remaining 299 papers were screened, independently, by two reviewers (AM and SC in the first search, AM and CP in the updating) using Rayyan software (Ouzzani et

al., 2016). A final subset of thirty-nine papers were identified for full-text reading. The reference lists of these papers were also hand searched for relevant papers. A further nine papers were excluded, leaving a final set of 30 papers to go forward into the systematic review. The inter-rater agreement between the two reviewers was 100%.

Of the final 30 papers, 12 evaluated structural alterations (Biundo et al., 2011, 2015; Canu et al., 2017; Hammes et al., 2019; Hlavatá et al., 2020; Mosley et al., 2019; Pellicano et al., 2015; Prasad et al., 2019; Ricciardi et al., 2018; Tessitore et al., 2016; Yoo, Lee, et al., 2015; Zadeh, Ashraf-Ganjouei, Sherbaf, Haghshomar, & Aarabi, 2018), 12 evaluated functional alterations (Cilia et al., 2011, 2008; Claassen et al., 2017; Frosini et al., 2010; Girard et al., 2019; Loane et al., 2015; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Petersen et al., 2018; Politis et al., 2013; Tessitore, Santangelo, et al., 2017; Verger et al., 2018), and 6 included both structural and functional measures (Carriere et al., 2015; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Ruitenberg et al., 2018; Tessitore, De Micco, et al., 2017). The study of Hammes et al. (2019) was included in the structural section only, as no between groups analysis was performed for functional alteration analysis. The study of Tessitore, Santangelo et al. (2017) was included in the functional section only as the sample and the structural alteration analysis were the same as Tessitore et al. (2016). List of studies excluded at the full-text screening stage with reasons for exclusions is provided in the Appendix AR. The PRISMA diagram of the systematic review is shown in Figure 5.1.

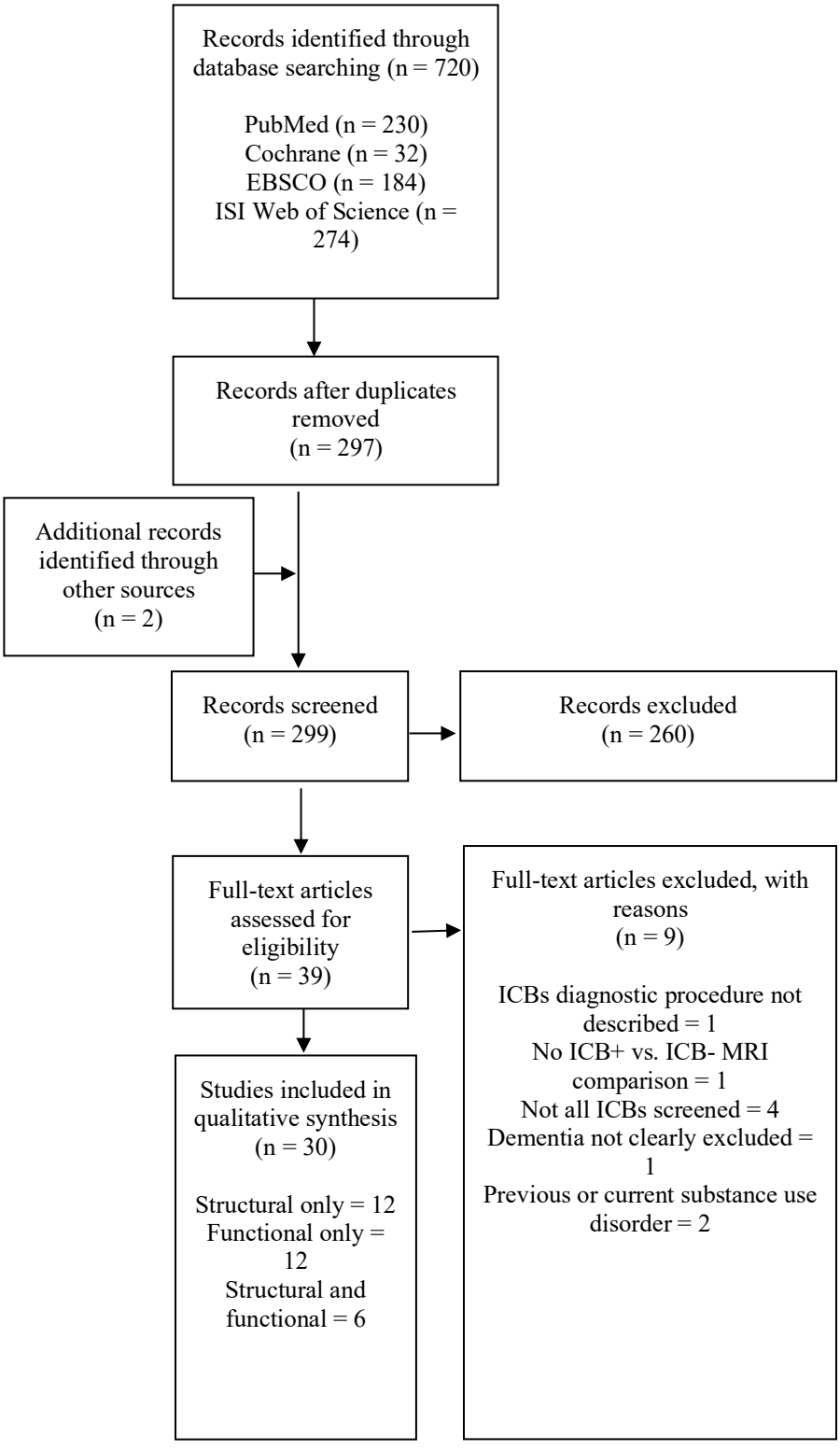


Figure 5. 1 PRISMA diagram of the study (www.prisma-statement.org). ICBs: impulsive-compulsive behaviours. ICB+: persons with Parkinson's disease and ICBs; ICB-: persons with Parkinson's disease without ICBs; MRI: magnetic resonance imaging.

Structural studies

Drug naïve Persons with Parkinson's disease. Three studies examined ICBs in drug naïve PwP. Two were longitudinal (Ricciardi et al., 2018; Tessitore, De Micco, et al., 2017), and the other one was cross-sectional in design (Zadeh et al., 2018).

The two longitudinal studies examined differences in local grey matter density using VBM (Ricciardi et al., 2018; Tessitore, De Micco, et al., 2017). Ricciardi et al. (2018) also measured Cth. Zadeh et al. (2018) examined subcortical white matter tracts using DTI.

Demographic and clinical characteristics. In the cross-sectional study, the groups were matched for age, PD duration and PD stage, and motor symptoms severity (UPDRS-III) (Zadeh et al., 2018). Retrospective analysis of the baseline data for the drug naïve PwP who went on to developed ICBs at follow-up versus those who did not were also well matched for clinical and demographic characteristics (Ricciardi et al., 2018; Tessitore, De Micco, et al., 2017). Demographic and clinical characteristics of the three studies are provided in Table 5.1.

Table 5. 1 Demographic and clinical characteristics of the structural studies on drug naïve PwP.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	H&Y*	UPDRS-III (OFF)*	Antidepressant (N)
Longitudinal							
Ricciardi el al. (2018)	ICB+: 42 (28) ICB–: 42(30)	ICB+: 62.6 (9.6) ICB–: 62.2 (9.1)	NR	ICB+: 43.8 (17.3) ** ICB–: 61.7 (29.5) **	ICB+: 1.8 (0.5) ICB–: 1.7 (0.5)	ICB+: 22.3 (9.6) ICB–: 20.6 (9.8)	NR
Tessitore, De Micco et al. (2017)	ICB+: 15 (5) ICB–: 15 (6)	ICB+: 57 (9.7) ICB–: 58.2 (7.3)	NR	ICB+: 1.4 (0.5) ICB–: 1.3 (0.5)	ICB+: 1.1 (0.3) ICB–: 1.2 (0.4)	ICB+: 15.7 (6) ICB–: 16.4 (6)	NR
Cross-sectional							
Zadeh et al. (2018)	ICB+: 21 (14) ICB–: 68 (44)	ICB+: 57.7 (9.8) ICB–: 59.1 (9.5)	NR	ICB+: 10.4 (10.5) ICB–: 5.8 (5.3)	ICB+: 1.6 (0.5) ICB–: 1.6 (0.5)	ICB+: 21.1 (8.5) ICB–: 21.4 (8.8)	NR

Legend. H&Y: Hoehn & Yahr score; ICBs: impulsive-compulsive behaviours; ICB+: PwP with ICBs; ICB-: PwP without ICBs; N: number of PwP; NR: not reported; PD: Parkinson's disease; PwP: persons with Parkinson's disease; Pts: PwP; Ref: reference; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score assessed in unmedicated drug naïve PwP; y: years. *Mean (SD) unless otherwise stated **months.

Cortical and subcortical volume. Baseline and follow-up VBM measures did not dissociate between groups of drug naïve PwP who went on to develop ICBs from those who did not (Ricciardi et al., 2018; Tessitore, De Micco, et al., 2017).

Cortical thickness. There was no difference in Cth at either baseline or follow-up between groups of drug naïve PwP who went on to develop ICBs from those who did not (Ricciardi et al., 2018).

Subcortical diffusion tensor imaging study. The single cross-sectional study evidenced decreased bilateral white matter connectivity in the cortico-thalamic tract, the cortico-pontine tract, the corticospinal tract, the superior cerebellar peduncle, and the middle cerebellar peduncle in drug naïve ICB+ compared to ICB- PwP (Zadeh et al., 2018).

Key details of the three studies including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome are provided in Table 5.2.

Table 5. 2 Results of the three structural studies on drug naïve PwP.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matching variables	Unmatching variables	Differences in brain regions	Findings: ICB+ vs. ICB-
Longitudinal								
Ricciardi el al. (2018)	VBM, Cth	ICB+: 42 ICB-: 42	QUIP	NR	Sex, age, education, PD duration, H&Y, UPDRS-III, DAED, GDS	Total LEDD: ICB+>ICB-; MoCA: ICB+<ICB-; Anxiety (STAI): ICB+>ICB-	No differences	ICB+ = ICB-
Tessitore, De Micco et al. (2017)	VBM	ICB+: 15 ICB-: 15	QUIP-rs; clinical interview	HS:6; BE:5; GD:2; CS:2	Sex, age, education, PD duration, H&Y, UPDRS-III, total LEDD; DAED, BDI-II, MMSE	NR	No differences	ICB+ = ICB-
Cross-sectional								
Zadeh et al. (2018)	Diffusion MRI connectometry	ICB+: 21 ICB–: 68	QUIP	HS: 1; CS: 1; BE: 8; HB: 2; Punding: 5; walking/driving+ HS: 2; BE+ punding: 1; CS+HS: 1; CS+BE+punding: 1	Sex, age, education, PD duration, H&Y, UPDRS-III, MoCA score	Depression (GDS): ICB+<ICB-	Decreased bilateral white matter connectivity in the cortico-thalamic tract, the cortico-pontine tract, the corticospinal tract, the superior and middle cerebellar peduncles	ICB+ ↓

Legend. BDI-II: Beck depression inventory II; BE: binge eating; CS: compulsive shopping; Cth: cortical thickness; GD: gambling disorder; GDS: geriatric depression scale; HB: hobbyism; HC: healthy controls; H&Y: Hoehn & Yahr score; HS: hypersexuality; ICBs: impulsive compulsive behaviours; ICB+: PwP with ICBs; ICB-: PwP without ICBs; Total LEDD: levodopa equivalent daily dose total; DAED: dopamine agonists equivalent daily dose; MoCA: Montreal cognitive assessment; MRI: magnetic resonance imaging; NR: not reported; PwP: persons with Parkinson's disease; ref.: reference; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; STAI: State-Trait anxiety inventory; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; VBM: voxel-based morphometry.

Dopaminergic replacement therapy-medicated Persons with Parkinson's disease. A total of 15 cross-sectional studies reported sMRI findings associated to ICBs in medicated PwP. Three studies reported grey matter cortical volume using VBM (Biundo et al., 2011; Ruitenberg et al., 2018; Tessitore et al., 2016). Eight reports explored subcortical volumes for a set of a priori regions of interest using sMRI (Biundo et al., 2015; Hlavatá et al., 2020; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Pellicano et al., 2015; Prasad et al., 2019; Ruitenberg et al., 2018). Cth was reported in 10 studies (Biundo et al., 2015; Carriere et al., 2015; Hammes et al., 2019; Hlavatá et al., 2020; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Pellicano et al., 2015; Prasad et al., 2019; Tessitore et al., 2016), and subcortical white matter changes using DTI/DWI were described in further four studies (Canu et al., 2017; Imperiale et al., 2018; Mosley et al., 2019; Yoo, Lee, et al., 2015).

Demographic and clinical characteristics. ICB+ and ICB- were matched for age at evaluation (Canu et al., 2017; Carriere et al., 2015; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Pellicano et al., 2015; Prasad et al., 2019; Ruitenberg et al., 2018; Tessitore et al., 2016; Yoo, Lee, et al., 2015), age at PD onset (Canu et al., 2017; Imperiale et al., 2018; Markovic et al., 2017; Pellicano et al., 2015; Prasad et al., 2019; Ruitenberg et al., 2018), PD duration (Biundo et al., 2011; Canu et al., 2017; Carriere et al., 2015; Hlavatá et al., 2020; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Prasad et al., 2019; Ruitenberg et al., 2018; Tessitore et al., 2016; Yoo, Lee, et al., 2015) and PD stage (Biundo et al., 2015; Canu et al., 2017; Carriere et al., 2015; Hlavatá et al., 2020; Imperiale et al., 2018; Markovic et al., 2017; Prasad et al., 2019; Tessitore et al.,

2016; Yoo, Lee, et al., 2015), motor symptoms severity (Biundo et al., 2011, 2015; Canu et al., 2017; Carriere et al., 2015; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Prasad et al., 2019; Ruitenberg et al., 2018; Tessitore et al., 2016; Yoo, Lee, et al., 2015), total LEDD (Biundo et al., 2011; Canu et al., 2017; Carriere et al., 2015; Hlavatá et al., 2020; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Pellicano et al., 2015; Prasad et al., 2019; Ruitenberg et al., 2018; Tessitore et al., 2016; Yoo, Lee, et al., 2015), LD-LEDD (Markovic et al., 2017; Prasad et al., 2019) and DAED (Biundo et al., 2011, 2015; Carriere et al., 2015; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Pellicano et al., 2015; Tessitore et al., 2016; Yoo, Lee, et al., 2015). In the remaining studies, ICB+ and ICB- groups were either not matched for a subset of clinical or key demographic characteristics (see points i-iv) below, or clinical information was not reported (see points v).

i. ICB+ compared to ICB- were younger and they had a younger age at PD onset but they were matched for PD duration, motor symptom severity, and total and DAED. Age was included as covariate in the analyses (Biundo et al., 2011).

ii. ICB+ vs. ICB- were younger, had earlier PD onset, longer PD duration, and higher total LEDD, but comparable PD stage, motor symptoms severity and DAED. Age at evaluation, PD duration and total LEDD were included as covariates in the analysis (Biundo et al., 2015).

iii. ICB+ had longer PD duration, advanced disease stage and worse motor symptoms severity than ICB- group (Pellicano et al., 2015).

iv. ICB+ had higher DAED compared to ICB- but were comparable age at evaluation, age at PD onset, disease duration, PD stage, motor symptoms in "off" condition, total LEDD and LD-LEDD (Prasad et al., 2019).

v. No demographic or clinical characteristics were reported in two studies (Hammes et al., 2019; Hlavatá et al., 2020), while in seven studies the following information was omitted: age at PD onset (Carriere et al., 2015; Mosley et al., 2019; Tessitore et al., 2016; Tessitore, Santangelo, et al., 2017; Yoo, Lee, et al., 2015), PD stage (Biundo et al., 2011; Ruitenberg et al., 2018) and DAED (Canu et al., 2017; Mosley et al., 2019; Ruitenberg et al., 2018).

Demographic and clinical characteristics of the 15 studies are provided in Table 5.3.

Table 5. 3 Demographic and clinical characteristics of the fifteen structural studies on DRT PwP.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	H&Y*	UPDRS-III*	Antidepressant (N)
Cross-sectional							
Biundo et al. (2011)	ICB+: 33 (18) ICB–: 24 (17)	**ICB+: 61.3 (10.2)** **ICB–: 70.4 (6.8)**	**ICB+: 53.2 (10.6)** **ICB–: 60.5 (10.0)**	ICB+: 8.8 (4.8) ICB–: 8.9 (5.4)	NR	ON: ICB+: 30.2 (13.2) ICB-: 32.3 (12.8) OFF: NR	NR
Biundo et al. (2015)	ICB+: 58 (38) ICB–: 52 (32)	**ICB+: 60.3 (9.3)** **ICB–: 63.1 (10.2)**	**ICB+: 50.1 (12.1)** **ICB–: 54.7 (11.6)**	**ICB+: 9.0 (5.5)** **ICB–: 8.0 (5.7)**	ICB+: 2.4 (0.7) ICB–: 2.3 (0.7)	ON: ICB+: 26.7 (16.5) ICB–: 28.5 (12.3) OFF: NR	NR
Canu et al. (2017)	ICB+: 21(18) ICB–: 28 (19)	ICB+: 63.8 (8.8) ICB-: 63.6 (6.5)	ICB+: 54.3 (9.9) ICB-: 53.9 (8.0)	ICB+: 9.4 (5.4) ICB-: 9.7 (5.4)	ICB+: 2.5 (0.9) ICB-: 2.6 (0.5)	ON: ICB+: 43.9 (13.5) ICB-: 47.3 (8.2) OFF: NR	NR
Carriere et al. (2015)	ICB+: 19 (15) ICB–: 17 (13)	ICB+: 57.4 (8.9) ICB–: 57.4 (8)	NR	ICB+: 6.9 (3.8) ICB–: 7.2 (4.2)	ICB+: 2.4 (0.6) ICB–: 2.3 (0.5)	ON: ICB+: 20.5 (7.7) ICB–: 19.6 (7.9) OFF: NR	ICB+: 1 ICB-: 2 (SSRI)
Hammes et al. (2019)	ICB+: 18 (NR) ICB-: 44 (NR)	NR	NR	NR	NR	NR	NR
Hlavatà et al. (2020)§	ICB+: 15 (11) ICB–: 22 (10)	**ICB+: 59.27 (8.88)** **ICB-: 69.18 (5.47)**	**ICB+: 50.80 (9.64)** **ICB-: 62.55 (6.25)**	ICB+: 8.87 (4.17) ICB-: 6.95 (4.63)	ICB+: 2.53 (0.64) ICB-: 2.48 (0.66)	NR	NR

Table 5.3 (continued) Demographic and clinical characteristics of the fifteen structural studies on DRT PwP.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	H&Y*	UPDRS-III*	Antidepressant (N)
Imperiale et al. (2018)	ICB+: 35 (30) ICB–: 50 (36)	ICB+: 62.0 (10.4) ICB–: 61.5 (8.9)	ICB+: 52.5 (10.4) ICB–: 52.5 (8.2)	ICB+: 9.5 (5.2) ICB–: 9.0 (6.1)	ICB+: 2.7 (0.8) ICB–: 2.5 (0.7)	ON: ICB+: 47.2 (15.5) ICB–: 43.5 (12.4) OFF: NR	NR
Marìn-Lahoz et al. (2020)	ICB+: 9 (5) ICB–: 15 (8)	ICB+: 70.2 (8.4) ICB-: 70.8 (6.8)	NR	ICB+: 4.5 (2.5) ICB-: 6.1 (2.2)	NR	ON: ICB+: 29.0 (6.7) ICB-: 28.7 (9.6) OFF: NR	NR
Markovic et al. (2017)	ICB+: 22(19) ICB–: 30 (21)	ICB+: 63.1 (9.2) ICB–: 63.9 (6.6)	ICB+: 54.0 (9.8) ICB–: 54.0 (7.8)	ICB+: 9.1 (5.4) ICB–: 9.9 (5.3)	ICB+: 2.5 (0.9) ICB–: 2.6 (0.5)	ON: ICB+: 43.1 (13.7) ICB–: 47.2 (8.0) OFF: NR	NR
Mosley et al. (2019)	ICB+: 17 (NR) ICB-: 40 (NR)	NR	NR	NR	NR	NR	NR
Pellicano et al. (2015)	ICB+: 18 (16) ICB–: 18 (14)	ICB+: 56.6 (9) ICB–: 55.8 (8)	ICB+: 46.2 (10) ICB–: 49.4 (8)	**ICB+: 10.4 (4.8)** **ICB–: 6.4 (4.8)**	**ICB+: 2.3 (0.5)**** **ICB–: 1.9 (0.5)****	ON: NR OFF: **ICB+: 43 (11)** **ICB–: 28 (10)**	NR
Prasad et al. (2019)	ICB+: 11 (8) ICB–: 15 (12)	ICB+: 57.18 (7.90) ICB–: 54.20 (7.60)	ICB+: 49.54 (6.84) ICB–: 50.06 (8.90)	ICB+: 7.63 (2.49) ICB–: 6.45 (2.3)	ICB+: 2.09 (0.41) ICB-: 1.90 (0.50)	ON: NR OFF: ICB+: 37.54 (10.43) ICB-: 30.9 (8.17)	NR

Table 5.3 (continued) Demographic and clinical characteristics of the fifteen structural studies on DRT PwP.

Ref	**Pts (males)**	**Age (y)***	**PD onset (y)***	**PD duration (y)***	**H&Y***	**UPDRS-III***	**Antidepressant (N)**
Ruitenberg et al. (2018)	ICB+: 21 (14) ICB–: 30 (19)	ICB+: 60 (5) ICB–: 62 (8)	ICB+: 55.9 (6.2) ICB–: 58.1 (8.4)	ICB+: 57.3 (30.7) *** ICB–: 44.2 (37.7) ***	NR	ON: ICB+: 25.9 (9.9) ICB–: 25.3 (9.5) OFF: NR	NR
Tessitore et al. (2016)	ICB+: 15 (13) ICB–: 15 (12)	ICB+: 62.9 (8.6) ICB–: 63.1 (8)	NR	ICB+: 5.3 (2.9) ICB–: 6.6 (3.9)	ICB+: 2.5 (0.6) ICB-: 2.5 (0.7)	ON: ICB+: 10.9 (4.5) ICB–: 12.1 (4.4) OFF: NR	No
Yoo et al. (2015)	ICB+: 10 (7) ICB–: 9 (6)	ICB+: 54.5 (6.2) ICB–: 59.6 (8.6)	NR	ICB+: 10.2 (7.3) ICB–: 10.6 (3.9)	ICB+: 2.4 (0.5) ICB–: 2.2 (0.4)	ON: ICB+: 14.6 (11.5) ICB–: 14.4 (8.0) OFF: NR	NR

Table 5.3 (continued). Demographic and clinical characteristics of the fifteen structural studies on DRT PwP.

Ref	Total LEDD*	LD-LEDD*	DAED*
Biundo et al. (2011)	ICB+: 556.8 (304.6) ICB–: 497.4 (341.2)	NR	ICB+: 186.5 (149.3) ICB–: 165.8 (108.8)
Biundo et al. (2015)	**ICB+: 923.1 (474.1)** **ICB–: 722.6 (498.5)**	NR	ICB+: 163.7 (111.3) ICB–: 148.9 (105.0)
Canu et al. (2017)	ICB+: 908.8 (342.5) ICB-: 936.4 (303.8)	NR	NR
Carriere et al. (2015)	ICB+: 908 (492) ICB–: 817 (463)	NR	ICB+: 243 (114) ICB–: 336 (223)
Hammes et al. (2019)	NR	NR	NR
Hlavatà et al. (2020)	ICB+: 1289.75 (543.97) ICB-: 1025.46 (567.18)	NR	NR
Imperiale et al. (2018)	ICB+: 966.3 (438.7) ICB–: 800.8 (414.6)	NR	ICB+: 228.1 (164) ICB–: 255.5 (191.2)
Marìn-Lahoz et al. (2020)	ICB+: 634.2 (352.4) ICB-: 627.1 (205.5)	NR	ICB+: 175.3 (91.1) 135.6 (118.3)
Markovic et al. (2017)	ICB+: 887.9 (348.3) ICB–: 934.8 (302.8)	ICB+: 644 (411.5) ICB–: 415 (397.3)	ICB+: 269.1 (141.2) ICB–: 315.7 (177.8)

Table 5.3 (continued). Demographic and clinical characteristics of the fifteen structural studies on DRT PwP.

Ref	Total LEDD*	LD-LEDD*	DAED*
Mosley et al. (2019)	NR	NR	NR
Pellicano et al. (2015)	ICB+: 789 (370) ICB–: 560 (418)	NR	ICB+: 154 (144) ICB–: 124 (125)
Prasad et al. (2019)	ICB+: 735.59 (247.12) ICB-: 610.60 (220.75)	ICB+: 502.75 (120.95) ICB-: 541.15 (191.49)	**ICB+: 253.88 (124.18)** **ICB-: 109.50 (65.89)**
Ruitenberg et al. (2018)	ICB+: 561 (322) ICB–: 486 (332)	NR	NR
Tessitore et al. (2016)	ICB+: 477.3 (222.9) ICB–: 532.1 (207.2)	NR	ICB+: 243.3 (82.1) ICB–: 243.3 (90.2)
Yoo et al. (2015)	ICB+: 924.6 (362.1) ICB–: 861.8 (440.6)	NR	ICB+: 255.0 (177.6) ICB–: 170.0 (89.2)

Legend. DA: dopamine agonists; DRT: drug replacement therapy; H&Y: Hoehn & Yahr score; ICBs: impulsive-compulsive behaviours; ICB+: PwP with ICBs; ICB-: PwP without ICBs; total LEDD: levodopa equivalent daily dosage total (mg); DAED: dopamine agonist equivalent daily dosage (mg); LD-LEDD: : levodopa equivalent daily dosage levodopa only (mg); N: number of PwP; NR: not reported; PD: Parkinson's disease; PwP: persons with Parkinson's disease; Pts: PwP; Ref: reference; SSRI: selective serotonin reuptake inhibitors; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; y:

years.*Mean (SD) unless otherwise stated; ** off state; ***months; [§]Data provided refers to the whole sample, including PwP who did not perform MRI scan. Significant between-groups differences (statistical threshold as reported in the original paper) are reported in bold type.

Cortical and subcortical volume studies. One study reported evidence of increased cortical volume in the inferior frontal gyrus bilaterally, and the right-side caudal anterior cingulate between the ICB+ vs. ICB- groups (Hlavatá et al., 2020). No other differences were detected at cortical level.

Two studies reported volume reduction in the left (Prasad et al., 2019) and right (Biundo et al., 2015) nucleus accumbens, whereas two other studies found no volumetric differences (Marín-Lahoz et al., 2020; Pellicano et al., 2015) between groups. Borderline reduction of right external globus pallidus volume was reported in one study (Ruitenberg et al., 2018). On the other hand, no between-groups volumetric differences were found in either the caudate nucleus, the globus pallidus, the putamen (Imperiale et al., 2018; Marín-Lahoz et al., 2020; Pellicano et al., 2015; Prasad et al., 2019), the thalamus (Imperiale et al., 2018; Marín-Lahoz et al., 2020; Prasad et al., 2019), the habenula (Markovic et al., 2017), the hippocampus (Imperiale et al., 2018; Marín-Lahoz et al., 2020; Pellicano et al., 2015; Prasad et al., 2019) or the amygdala (Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Pellicano et al., 2015; Prasad et al., 2019), although one study reported increase left amygdala volume in ICB+ (Biundo et al., 2015). Finally, one study reported volume reduction in the central and middle anterior (genu) corpus callosum of ICB+ vs. ICB- (Biundo et al., 2015).

Cortical thickness studies. Six of the ten studies examining Cth found abnormalities in ICB+ vs. ICB-, although the direction of thickness varied, while four studies reported no differences (Carriere et al., 2015; Hammes et al., 2019; Hlavatá et al., 2020; Marín-Lahoz et al., 2020).

Structures with cortical thinning included the left superior frontal and precentral gyri (Biundo et al., 2015; Imperiale et al., 2018), right postcentral gyrus (Tessitore et al., 2016), pars orbitalis (Biundo et al., 2015; Markovic et al., 2017), pars opercularis, left postcentral area, rostral middle frontal area, superior and inferior parietal areas, lingual and parahippocampal gyri, bilateral caudal middle frontal and supramarginal areas (Biundo et al., 2015), middle temporal gyrus and temporal pole (Prasad et al., 2019).

On the other hand, increased Cth was observed in the rostral anterior cingulate cortex and frontal pole (Pellicano et al., 2015), the left anterior cingulate cortex, left medial and lateral orbitofrontal cortex, left parahippocampal cortex, and left isthmus of the cingulate cortex (Tessitore et al., 2016).

Subcortical diffusion tensor imaging studies. Three studies examined white matter integrity using fractional anisotropy (FA), mean diffusivity (MD) (Canu et al., 2017; Imperiale et al., 2018; Yoo, Lee, et al., 2015), axial and radial diffusivity (RadD) (Canu et al., 2017; Imperiale et al., 2018), and one study investigated structural connectivity (Mosley et al., 2019).

Structural degeneration (i.e., decreased FA and increased MD and RadD) was reported in the left uncinate fasciculus and parahippocampal tract (i.e., both decreased FA and increased MD/RadD) (Imperiale et al., 2018), and in pedunculopontine tract on the left (Canu et al., 2017) and right sides (Imperiale et al., 2018) (i.e., increased RadD and MD). However, preserved white matter integrity (i.e., increased FA) was also reported in the anterior corpus callosum, partial left thalamic radiations, right dorsal and posterior cingula, right internal capsule (genu and posterior limbs), right superior temporo-occipital lobes, and right thalamic

radiations (Yoo, Lee, et al., 2015). The fibres of the corpus callosum were reported to be both more robust (i.e., increased FA) (Yoo, Lee, et al., 2015) and disrupted (i.e., increased RadD and MD) compared to ICB- (Canu et al., 2017; Imperiale et al., 2018).

A gambling task revealed that greater impulsivity was associated with lower structural connectivity between the left/right ventral striatum and the ventromedial prefrontal cortex in ICB+, with the opposite effect in ICB- (Mosley et al., 2019).

Key details of the 15 structural studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome are provided in Table 5.4.

Table 5. 4 Key details of the 15 structural studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs. ICB-
Cross-sectional								
Biundo et al. (2011)	VBM	ICB+: 33 ICB-: 24	MIDI; DSM-IV-TR criteria; clinical interview (PwP and carergiver)	HS: 11; CS: 9; GD: 1; punding: 2; ICB-M: 12	Sex, PD duration, UPDRS-III, total LEDD, DAED, BDI, MMSE	Age: ICB+<ICB-**	No differences	ICB+ = ICB-
Biundo et al. (2015)	Cth Subcortical volumes	ICB+: 58 ICB-: 52	QUIP-rs; MIDI; clinical interview (PwP and carergiver)	HS: 6; CS: 7; GD: 2; hoarding: 2; impulsive aggression: 1; M-ICB: 40	Sex, age, education, H&Y, UPDRS-III, DAED, MMSE, BDI-II	Age at PD onset: ICB+<ICB-; PD duration: ICB+>ICB-**; total LEDD: ICB+>ICB-**	CTh: left precentral and postcentral area, superior frontal and rostral middle frontal area, pars orbitalis, pars opercularis, superior and inferior parietal areas, lingual and parahippocampal gyrus, and bilaterally in the caudal middle frontal and supramarginal areas	ICB+ ↓
							Subcortical volumes: right NAc, and in the central and middle anterior corpus callosum	ICB+ ↓
							Left amygdala	ICB+ ↑

Table 5.4 (continued) Key details of the 15 structural studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs. ICB-
Cross-sectional								
Canu et al. (2017)	DTI	ICB+: 21 ICB-: 28	Clinical interview (PwP/caregiver) and semi-structured interview	Punding: 21	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, LEDD, MMSE, HAMA	HDRS: ICB+>ICB-**; Apathy scale: ICB+>ICB-**	Genu of corpus callosum adjusting for depression and apathy scores; left PPT adjusting for severity of depression only	ICB+ ↓
Carriere et al. (2015)	Cth	ICB+: 19 ICB-: 17	QUIP; semi-structured interview	HS: 14; GD: 7; BE: 7; CS: 5	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DAED, MMSE	NR	No differences	ICB+ = ICB-
Hammes et al. (2019)	Cth	ICB+: 18 ICB-: 44	QUIP-rs	GD: 3; HS: 11; CS:5; BE: 10; M-ICB: 7	NR	NR	CTh: no differences	ICB+ = ICB-
Hlavatà et al. (2020)	Cth	ICB+: 8 ICB-: 16	Clinical interview	GD: 5; HS: 2; CS: 1; BE: 3; HB: 1; punding: 1; hoarding: 1; pedantry: 1; excessive cleaning: 1	NR	NR	CTh: no differences Subcortical volumes: bilateral pars orbitalis, right caudal anterior cingulate	ICB+ = ICB- ICB+↑

Table 5.4 (continued) Key details of the 15 structural studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs. ICB-
Cross-sectional								
Imperiale et al. (2018)	Cth DTI	ICB+: 35 ICB-: 50	QUIP; clinical interview	GD: 4; HS: 4; CS: 1; BE: 3; punding: 15; DDS: 5; BE+ punding: 1; GD + punding: 1; DDS + punding: 1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DAED, MMSE	HDRS: ICB+>ICB-**; Apathy scale: ICB+>ICB-**	CTh: left superior frontal and precentral gyri DTI: GM: no differences WM: left parahippocampal tract and right PPT, genu of the corpus callosum, bilateral uncinate fasciculus	ICB+ ↓ ICB+ = ICB- ICB+↓
Marìn-Lahoz et al. (2020)	Cth Subcortical volumes	ICB+: 9 ICB-: 15	QUIP; QUIP-rs; clinical interview	HS: 2; BE: 3; HB: 3; BE + HB: 1	Sex, age, education, age at PD onset, PD duration, UPDRS-III, total LEDD, DAED	NR	CTh: no differences Subcortical volumes: no differences	ICB+ = ICB- ICB+ = ICB-
Markovic et al. (2017)	Cth Subcortical volumes	ICB+: 22 ICB-: 30	Interview including a semi-structured part (PwP and caregivers)	Punding: 17; Punding + BE: 2; Punding + GD: 1; Punding + DDS: 1; Punding + HS: 1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DAED	NR	CTh: right pars orbitalis of the inferior frontal gyrus Subcortical volumes investigated (habenula and amygdala): no differences	ICB+ ↓ ICB+ = ICB-

Table 5.4 (continued) Key details of the 15 structural studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs. ICB-
Cross-sectional								
Mosley et al. (2019)	DWI	ICB+: 17 ICB-: 40	QUIP-rs; semi-structed interview	GD: 10; HS: 9; BE: 1; CS: 3; DDS: 2; HB: 1	Age, PD duration, H&Y, total LEDD	NR	In a gambling task, increased structural connectivity between VS and vmPFC	ICB+↑
Pellicano et al. (2015)	Cth Subcortical volumes	ICB+: 18 ICB-: 18	QUIP; Semi-structured interview (DSM-IV-TR)	GD: 4; HS: 3; BE: 1; CS: 1; HS+CS: 2; GD+CS: 1; HS+BE: 1; GD+ DDS: 1; HS+GD+BE: 1; CS+BE+internet: 1; HS+BE+CS: 1; HS+GD+BE+CS: 1	Sex, age, age at PD onset, total LEDD, DAED, LD-LEDD, MMSE	PD duration: ICB+>ICB-**, UPDRS-III (OFF medication): ICB+>ICB-**; H&Y: ICB+>ICB-	CTh: rostral ACC and frontal pole Subcortical volumes: no differences	ICB+↑ ICB+ = ICB-
Prasad et al. (2019)	Cth Subcortical volumes	ICB+: 11 ICB-: 15	QUIP-rs	HS: 1; punding: 3; HB: 1; DDS: 2; HS+CS: 1; BE+HB: 1; GD+HB: 1; HS+BE+CS+DDS+punding: 1	Age, age at PD onset, disease duration, UPDRS-III (OFF), H&Y, total LEDD, LD-LEDD	DAED: ICB+>ICB-	Cth: right middle temporal gyrus and bilateral temporal pole Subcortical volumes: left nucleus accumbens	ICB+ ↓ ICB+ ↓

Table 5.4 (continued) Key details of the 15 structural studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs. ICB-
Cross-sectional								
Ruitenberg et al. (2018)	VBM	ICB+: 21 ICB-: 30	QUIP	GD: 1; HS: 9; CS: 7; BE: 11; others: 6; (9 were in combination)	Sex, age, age at PD onset, PD duration, UPDRS-III, total LEDD, MoCA, NART-R	NR	Right GPe (uncorrected threshold only)	ICB+ ↓
Tessitore et al. (2016)	VBM surface based Cth	ICB+: 15 ICB-: 15	MIDI	HS: 13; BE: 8; GD: 1	Sex, age, education, PD duration, H&Y, UPDRS-III, total LEDD, DAED, HAM-D, HADS, MMSE	—	VBM: no differences CTh: Left ACC, left medial frontal cortex, left lateral OFC, left parahippocampal cortex, and left isthmus of cingulate cortex Right postcentral gyrus	ICB+ = ICB- ICB+↑ ICB+ ↓
Yoo et al. (2015)	DTI	ICB+: 10 ICB-: 9	DSM-IV-TR	GD: 2; HS: 1; CS+BE: 4; CS+BE+HS: 1; GD+HS+BE:1; CS+BE+HS+GD:1	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DAED, GDS, MMSE	NR	Anterior corpus callosum, partial left thalamic radiations, right dorsal and posterior cingulum, right internal capsule (genu and posterior limbs), right superior temporo-occipital lobes, and right thalamic radiations	ICB+↑

Legend. ACC: anterior cingulate cortex; BDI: Beck depression inventory; BDI-II: Beck depression inventory II; BE: binge eating; CS: compulsive shopping; Cth: cortical thickness; DAED: dopamine agonists equivalent daily dose; DDS: dopamine dysregulation syndrome; DSM-IV-TR: Diagnostic and statistical manual of mental disorders – fourth edition text revision; DTI: diffusion tensor imaging; DWI: diffusion weighted imaging; GD: gambling disorder; GDS: geriatric depression scale; GM: grey matter; GPe: external portion of the globus pallidus; HADS: Hospital anxiety and depression scale; HAMA: Hamilton anxiety rating scale; HAM-D: Hamilton depression rating scale; HB: hobbyism; HDRS: Hamilton depression rating scale; HS: hypersexuality; H&Y: Hoehn & Yahr score; ICBs: impulsive compulsive behaviours; ICB+: PwP with ICBs; ICB-: PwP without ICBs; LD-LEDD: levodopa equivalent daily dosage levodopa only; M-ICB: multiple ICBs; MIDI: Minnesota Impulsive Disorders Interview; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment; MRI: magnetic resonance imaging; NAc: nucleus accumbens; NART-R: National adult reading test-revised; OFC: orbitofrontal cortex; PwP: persons with Parkinson's disease; PPT: pedunculopontine tract; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; ref.: reference; Total LEDD: levodopa equivalent daily dose total; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; VBM: voxel-based morphometry; vmPFC: ventromedial prefrontal cortex; VS: ventral striatum; WM: white matter. *comparison between ICB+ vs. ICB- ** variable differing between groups but included as covariate in the analyses.

Functional Studies

Drug naïve Persons with Parkinson's disease. Functional imaging connectivity in drug naïve PwP who will successively develop ICBs have been investigated in one longitudinal study only using rs-fMRI (Tessitore, De Micco, et al., 2017).

Demographic and clinical characteristics. Retrospective analysis of baseline data for the drug naïve PwP showed that ICB+ and ICB- groups at follow-up did not differ for age, PD duration, PD stage and motor symptoms severity. Demographic and clinical characteristics of the study are reported in Table 5.5.

Table 5. 5 Characteristics of the single study included in the systematic review: functional studies in drug naïve PwP.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	H&Y*	UPDRS-III (OFF)*	Antidepressant (N)
Tessitore, De Micco et al. (2017)	ICB+: 15 (5) ICB–: 15 (6)	ICB+: 57 (9.7) ICB–: 58.2 (7.3)	NR	ICB+: 1.4 (0.5) ICB–: 1.3 (0.5)	ICB+: 1.1 (0.3) ICB–: 1.2 (0.4)	ICB+: 15.7 (6) ICB–: 16.4 (6)	NR

Legend. H&Y: Hoehn & Yahr score; ICB+: PwP with ICBs; ICB-: PwP without ICBs; ICBs: impulsive-compulsive behaviours; NR: not reported; PD: Parkinson's disease; PwP: persons with Parkinson's disease; Pts: PwP; Ref: reference; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; y: years. *Mean (SD) unless otherwise stated.

Resting-state fMRI. At baseline, PwP who went on to develop ICBs showed increased connectivity in the left orbitofrontal cortex (salience network), decreased connectivity in the left supramarginal gyrus (central executive network), left precuneus and right middle temporal gyrus (default mode network) compared to PwP without ICBs at follow-up (Tessitore, De Micco, et al., 2017) (Figure 5.2).

Key details of the single functional study on drug naïve PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome are provided in Table 5.6.

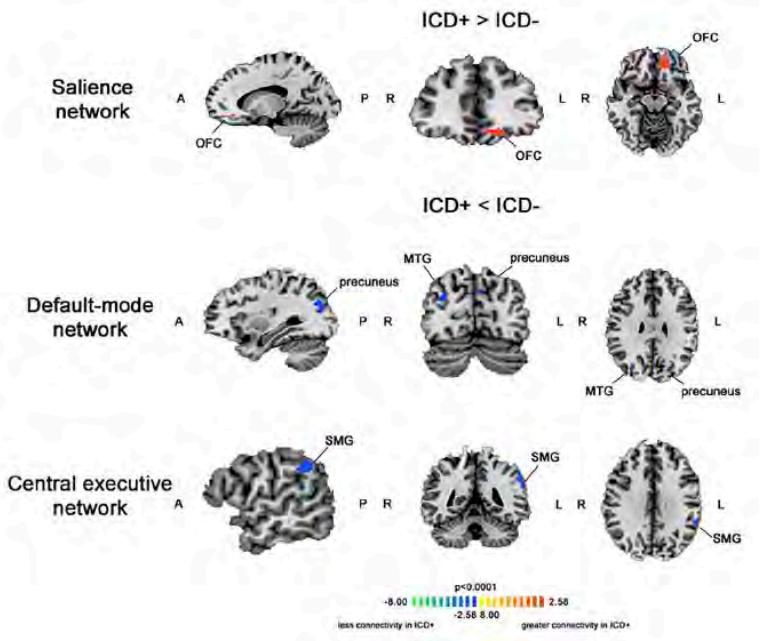


Figure 5. 2 Resting-state network connectivity change at baseline. Whole-brain significant connectivity differences between ICB+ and ICB- patients within central executive, default-mode, and salience networks. SN, salience network; CEN, central executive network; DMN, default mode network; OFC, orbitofrontal cortex; MTG, middle temporal gyrus; SMG, supramarginal gyrus; r, right; l, left; Reprinted under permission from Tessitore, De Micco et al., 2017, John Wiley and Sons and Copyright Clearance Center.

Table 5. 6 Key details of the single functional study on drug naïve PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Differences in brain region*	Findings: ICB+ vs. ICB-
Longitudinal								
Tessitore, De Micco et al. (2017)	rs-fMRI	ICB+: 15 ICB-: 15	QUIP-rs; clinical interview	HS: 6; BE: 5; GD:2; CS:2	Sex, age, education, PD duration, H&Y, UPDRS-III, Total LEDD, DAED, BDI-II, MMSE	NR	Increased connectivity in the left OFC within the SN; DMN coupling with the right CEN	ICB+↑
							Decreased connectivity in the left supramarginal gyrus within the right CEN; the left precuneus and right middle temporal gyrus within the DMN	ICB+ ↓

Legend. BDI-II: Beck depression inventory II; BE: binge eating; CEN: central executive network; CS: compulsive shopping; DAED: dopamine agonists equivalent daily dose; DMN: default-mode network; GD: gambling disorder; HS: hypersexuality; H&Y: Hoehn & Yahr score; ICBs: impulsive compulsive behaviours; ICB+: PwP with ICBs; ICB-: PwP without ICBs; MMSE: Mini-mental state examination; NR: not reported; OFC: orbitofrontal cortex; PwP: persons with Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; Ref.: reference; rs-fMRI: resting state functional magnetic resonance imaging; SN: salience network; Total LEDD: levodopa equivalent daily dose total; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score. *comparison between ICB+ vs. ICB-.

Dopaminergic replacement therapy-medicated Persons with Parkinson's disease. Seventeen cross-sectional functional imaging studies investigated ICBs in medicated PwP. Two studies reported measures of brain metabolism using resting state PET (Marín-Lahoz et al., 2020; Verger et al., 2018). Three reports explored cerebral blood flow measures, two of them using resting state SPECT "on" medication (Cilia et al., 2011, 2008), and one using arterial-spin-labelling "on" and "off" medication (Claassen et al., 2017). Five studies reported BOLD signal using task-based fMRI. PwP performance was examined on the temporal discounting task "on" and "off" medication (Girard et al., 2019), reward-related visual cues "off" (Frosini et al., 2010) and "on" medication (Loane et al., 2015; Politis et al., 2013) and the Iowa Gambling Task "on" medication only (Paz-Alonso et al., 2020). Further six studies investigated spontaneous low frequency BOLD fluctuations using rs-fMRI (Carriere et al., 2015; Imperiale et al., 2018; Markovic et al., 2017; Petersen et al., 2018; Ruitenberg et al., 2018; Tessitore, Santangelo, et al., 2017). Only a single study to date has examined changes in dynamic functional connectivity over time and this was conducted in "on" medicated PwP (Navalpotro-Gomez et al., 2020).

Demographic and clinical characteristics. ICB+ and ICB- were matched for age at evaluation (Carriere et al., 2015; Cilia et al., 2011, 2008; Claassen et al., 2017; Frosini et al., 2010; Girard et al., 2019; Imperiale et al., 2018; Loane et al., 2015; Marín-Lahoz et al., 2020; Markovic et al., 2017; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Petersen et al., 2018; Politis et al., 2013; Ruitenberg et al., 2018; Tessitore, Santangelo, et al., 2017; Verger et al., 2018), age at PD onset (Cilia et al., 2008; Imperiale et al., 2018; Markovic et al., 2017; Ruitenberg et al., 2018),

PD duration (Carriere et al., 2015; Cilia et al., 2011, 2008; Claassen et al., 2017; Frosini et al., 2010; Girard et al., 2019; Imperiale et al., 2018; Loane et al., 2015; Marín-Lahoz et al., 2020; Markovic et al., 2017; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Petersen et al., 2018; Politis et al., 2013; Ruitenberg et al., 2018; Tessitore, Santangelo, et al., 2017; Verger et al., 2018) and PD stage (Carriere et al., 2015; Cilia et al., 2011, 2008; Imperiale et al., 2018; Markovic et al., 2017; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Tessitore, Santangelo, et al., 2017; Verger et al., 2018), motor symptoms severity (Carriere et al., 2015; Cilia et al., 2011, 2008; Frosini et al., 2010; Girard et al., 2019; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Politis et al., 2013; Ruitenberg et al., 2018; Tessitore, Santangelo, et al., 2017; Verger et al., 2018), total LEDD (Carriere et al., 2015; Cilia et al., 2011, 2008; Claassen et al., 2017; Frosini et al., 2010; Girard et al., 2019; Imperiale et al., 2018; Loane et al., 2015; Marín-Lahoz et al., 2020; Markovic et al., 2017; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Petersen et al., 2018; Politis et al., 2013; Ruitenberg et al., 2018; Tessitore, Santangelo, et al., 2017; Verger et al., 2018), LD-LEDD (Girard et al., 2019; Loane et al., 2015), and DAED (Carriere et al., 2015; Cilia et al., 2011, 2008; Claassen et al., 2017; Frosini et al., 2010; Girard et al., 2019; Imperiale et al., 2018; Loane et al., 2015; Marín-Lahoz et al., 2020; Markovic et al., 2017; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Petersen et al., 2018; Tessitore, Santangelo, et al., 2017; Verger et al., 2018). In the remaining studies, ICB+ and ICB- groups were not matched for one or more clinical characteristics (see points i-ii), or clinical information was not reported (see point iii).

(i) Motor symptom severity was lower in ICB+ compared to ICB- "on" but not "off" medication (Claassen et al., 2017). Conversely, in a second study, ICB+ exhibited increased motor symptom severity both "on" and "off" medication compared to ICB- (Loane et al., 2015). Otherwise, the groups were matched for age, PD duration, total and DAED (Claassen et al., 2017; Loane et al., 2015).

(ii) One study reported higher DAED and lower LD-LEDD in ICB+ vs. ICB-, but the two groups were matched for age at evaluation, PD duration, motor symptoms severity, and total LEDD (Politis et al., 2013).

(iii) The following clinical information was not reported across all of the studies, combined: age at PD onset (Carriere et al., 2015; Cilia et al., 2011; Claassen et al., 2017; Frosini et al., 2010; Girard et al., 2019; Loane et al., 2015; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Petersen et al., 2018; Politis et al., 2013; Tessitore, Santangelo, et al., 2017; Verger et al., 2018), PD stage (Claassen et al., 2017; Frosini et al., 2010; Girard et al., 2019; Loane et al., 2015; Marín-Lahoz et al., 2020; Petersen et al., 2018; Politis et al., 2013; Ruitenberg et al., 2018), DAED (Ruitenberg et al., 2018) and LD-LEDD (Carriere et al., 2015; Cilia et al., 2011, 2008; Claassen et al., 2017; Frosini et al., 2010; Imperiale et al., 2018; Marín-Lahoz et al., 2020; Markovic et al., 2017; Navalpotro-Gomez et al., 2020; Paz-Alonso et al., 2020; Petersen et al., 2018; Ruitenberg et al., 2018; Tessitore, Santangelo, et al., 2017; Verger et al., 2018).

Demographic and clinical characteristics of the 17 studies are provided in Table 5.7.

Table 5. 7 Characteristics of the seventeen studies included in the systematic review: functional studies in DRT PwP.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	H&Y*	UPDRS-III*	Antidep (N)
Carriere et al. (2015)	ICB+:19 (15) ICB–: 17 (13)	ICB+:57.4 (8.9) ICB–: 57.4 (8)	NR	ICB+: 6.9 (3.8) ICB–: 7.2 (4.2)	ICB+:2.4 (0.6) ICB–: 2.3 (0.5)	ON: ICB+: 20.5 (7.7) ICB–: 19.6 (7.9) OFF: NR	ICB+: 1 ICB-: 2 (SSRI)
Cilia et al. (2008)	ICB+: 11 (10) ICB–: 40 (27)	ICB+: 57.4 (5.8) ICB–: 55 (7)	ICB+: 49.5 (4.7) ICB–: 46.4 (7.2)	ICB+: 8.4 (3.4) ICB–: 8.4 (5.1)	ICB+: 2.1 (0.6) ICB–: 2.3 (0.8)	ON: ICB+: 18.0 (11.0) ICB–: 19.1 (8.5) OFF: NR	No
Cilia et al. (2011)	ICB+: 15 (14) ICB–: 15 (14)	ICB+:59.2 (7.6) ICB–:58.6 (6.9)	NR	ICB+:8.7 (3.3) ICB–:9.1 (2.1)	ICB+:2.0 (0.6) ICB–:2.3 (0.7)	ON: ICB+: 16.9 (8.8) ICB–:18.3 (7.9) OFF: NR	No
Claassen et al. (2017)	ICB+:17 (10) ICB-: 17 (12)	ICB+:61.0 (7.1) ICB-:62.5 (10.4)	NR	ICB+:5.8 (4.5) ICB-:6.4 (3.8)	NR	**ON: ICB+:15.5 (7.1)** **ICB-:23.7 (10.9)** OFF ICB+:25.8 (11.1) ICB-:32.9 (12.2)	No
Frosini et al. (2010)	ICB+:7 ICB–: 7	ICB+: 57.5 (11.1) ICB–: 58.3 (8.6)	NR	ICB+:5.7 (2.0) ICB–: 6.8 (4.2)	NR	ON: ICB+: 15.5 (1.3) ICB–:18.0 (6.3) OFF: NR	NR
Girard et al. (2019)	ICB+: 13 (13) ICB-: 14 (14)	ICB+: 58.5 (8.3) ICB-: 57 (9.0)	NR	ICB+:7.5 (2.1) ICB-: 6.8 (2.6)	NR	ON: ICB+: 11.1 (5.1) ICB-: 12.6 (6.0) OFF: ICB+: 33.2 (11.2) ICB-: 28.4 (9.1)	NR

Table 5. 7 (continued) Characteristics of the seventeen studies included in the systematic review: functional studies in DRT PwP.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	H&Y*	UPDRS-III*	Antidep (N)
Imperiale et al. (2018)	ICB+: 35 (30) ICB–: 50 (36)	ICB+: 62.0 (10.4) ICB–:61.5 (8.9)	ICB+: 52.5 (10.4) ICB–: 52.5 (8.2)	ICB+: 9.5 (5.2) ICB–: 9.0 (6.1)	ICB+:2.7 (0.8) ICB–: 2.5 (0.7)	ON: ICB+: 47.2 (15.5) ICB–: 43.5 (12.4) OFF: NR	NR
Loane et al. (2015)	ICB+: 6 (5) ICB–: 12 (10)	ICB+: 56.8 (11.8) ICB–: 62.3 (9.7)	NR	ICB+: 10.7 (3.0) ICB–: 10.1 (6.4)	NR	**ON: ICB+: 28.8 (7.1)** **ICB–: 20.0 (5.5)** **OFF: ICB+:47.9 (10.6)** **ICB–: 34.9 (9.9)**	NR
Markovic et al. (2017)	ICB+: 22(19) ICB–: 30 (21)	ICB+: 63.1 (9.2) ICB–: 63.9 (6.6)	ICB+: 54.0 (9.8) ICB–:54.0 (7.8)	ICB+: 9.1 (5.4) ICB–: 9.9 (5.3)	ICB+: 2.5 (0.9) ICB–: 2.6 (0.5)	ON: ICB+: 43.1 (13.7) ICB–: 47.2 (8.0) OFF: NR	NR
Marìn-Lahoz et al. (2020)	ICB+: 9 (5) ICB–: 15 (8)	ICB+: 70.2 (8.4) ICB-: 70.8 (6.8)	NR	ICB+: 4.5 (2.5) ICB-: 6.1 (2.2)	NR	ON: ICB+: 29.0 (6.7) ICB-: 28.7 (9.6) OFF: NR	NR
Navalpotro-Gomez et al. (2020)	ICB+: 16 (14) ICB–: 20 (16)	ICB+: 61.25 (8.2) ICB-: 63.45 (8.1)	NR	ICB+:7.437 [4–10]§ ICB-: 6.68 [5–10]	ICB+: 2 [1.5–2.5]§ ICB-: 2 [1.5–3]	ON: ICB+: 20.35 (9.4) ICB-: 25.93 (7) OFF: NR	NR
Paz-Alonso et al. (2020)	ICB+: 18 (16) ICB-: 17 (15)	ICB+: 62.3 (7.6) ICB-: 61(8.7)	NR	ICB+: 8 [5.1–10]§ ICB-: 7 [4–10]	ICB+: 2 [1.5–2.5]§ ICB-: 2 [1.5–3]	ON: ICB+: 22.31 (6.6) ICB-: 25.90 (8.2) OFF: NR	NR

Table 5. 7 (continued) Characteristics of the seventeen studies included in the systematic review: functional studies in DRT PwP.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	H&Y*	UPDRS-III*	Antidep (N)
Petersen et al. (2018)	ICB+: 19 (12) ICB–: 18 (13)	ICB+: 61.0 (7.1) ICB–:62.7 (10.1)	NR	ICB+:6.2 (3.7) ICB–:6.1 (4.5)	NR	ON: NR OFF: NR	NR
Politis et al. (2013)	ICB+: 12 (11) ICB–: 12 (10)	ICB+:55.2 (9.2) ICB–:62.3 (9.7)	NR	ICB+:9.6 (5.2) ICB–:10.1 (6.4)	NR	ON: ICB+:23.1 (8.2) ICB–:20.0 (5.5) OFF: ICB+:40.2 (10.1) ICB–:34.9 (9.9)	NR
Ruitenberg et al. (2018)	ICB+: 21 (14) ICB–: 30 (19)	ICB+:60 (5) ICB–:62 (8)	ICB+: 55.9 (6.2) ICB–:58.1 (8.4)	ICB+: 57.3 (30.7)** ICB–:44.2 (37.7)**	NR	ON: NR OFF: ICB+: 26.0 (9.9) ICB–: 25.3 (9.5)	NR
Tessitore, Santangelo et al. (2017)	ICB+: 15 (13) ICB–: 15 (12)	ICB+:62.9 (8.6) ICB–:63.1 (8)	NR	ICB+: 5.3 (2.9) ICB–: 6.6 (3.9)	ICB+: 1.3 (0.5) ICB–: 1.4 (0.6)	ON: ICB+: 10.9 (4.5) ICB–: 12.1 (4.4) OFF: NR	NO
Verger et al. (2018)	ICB+: 18 (15) ICB–: 18 (10)	ICB+: 60.4 (7.3) ICB–:61.8 (6.4)	NR	ICB+: 10.9 (3.6) ICB–: 12.2 (2.9)	ICB+: 2.7 (0.8)*** ICB–: 2.7 (0.8)***	ON: ICB+: 5.3 (4.1) ICB–: 8.8 (6.2) OFF ICB+: 31.9 (12.0) ICB–: 30.8 (12.0)	NR

Table 5. 7 (continued). Characteristics of the seventeen studies included in the systematic review: functional studies in DRT PwP.

Ref	Total LEDD*	LD-LEDD*	DAED*
Carriere et al. (2015)	ICB+: 908 (492) ICB–: 817 (463)	NR	ICB+: 243 (114) ICB–: 336 (223)
Cilia et al. (2008)	ICB+: 811.8 (229.0) ICB–: 877.3 (289.3)	NR	ICB+: 289.1 (57.5) ICB–: 340.1 (157.2)
Cilia et al. (2011)	ICB+: 848.1 (253) ICB–:880 (245)	NR	ICB+: 296.1 (147.5) ICB–: 316.7 (115.6)
Claassen et al. (2017)	ICB+: 666.1 (429.9) ICB-: 600.6 (400.3)	NR	ICB+: 116.1 (76.0) ICB-:99.4 (64.2)
Frosini et al. (2010)	ICB+: 520 (219.1) ICB–:462 (228.7)	NR	ICB+: 408.3 (56.3) ICB–:325 (50)
Imperiale et al. (2018)	ICB+: 966.3 (438.7) ICB–: 800.8 (414.6)	NR	ICB+: 228.14 (164.0) ICB–: 255.53 (191.2)
Girard et al. (2019)	ICB+: 973.1 (422.6) ICB-: 1068.7 (398.8)	ICB+: 709.7 (361.3) ICB-: 779.8 (412.0)	ICB+: 282.1 (185.1) ICB-: 295.1 (161.3)
Loane et al. (2015)	ICB+: 975 (146) ICB–: 778 (278)	ICB+: 694 (423) ICB–: 646 (264)	ICB+: 281 (319) ICB–: 132 (143)
Markovic et al. (2017)	ICB+: 887.9 (348.3) ICB–: 934.8 (302.8)	NR	ICB+: 269.1 (141.2) ICB–: 315.7 (177.8)
Marìn-Lahoz et al. (2020)	ICB+: 634.2 (352.4) ICB-: 627.1 (205.5)	NR	ICB+: 175.3 (91.1) ICB-: 135.6 (118.3)

Table 5. 7 (continued) Characteristics of the seventeen studies included in the systematic review: functional studies in DRT PwP.

Ref	Total LEDD*	LD-LEDD*	DAED*
Navalpotro-Gomez et al. (2020)	ICB+: 913.6 (186.5) ICB-: 838.1 (213.2)	NR	ICB+: 295 (140.4) ICB-: 251 (151.2)
Paz-Alonso et al. (2020)	ICB+: 940.6 (94.9) ICB-: 841.4 (62.4)	NR	ICB+: 261.7 (69.5) ICB-: 211.8 (44.9)
Petersen et al. (2018)	ICB+: 639.1 (417.1) ICB–: 609.8 (390.3)	NR	ICB+: 117.6 (73.7) ICB–: 103.9 (65.1)
Politis et al. (2013)	ICB+:600 (327) ICB–:778 (278)	**ICB+:288 (326)** **ICB–:646 (264)**	**ICB+:311 (183)** **ICB–: 132 (143)**
Ruitenberg et al. (2018)	ICB+:561 (322) ICB–:486 (332)	NR	NR
Tessitore, Santangelo et al. (2017)	ICB+: 477.3 (222.9) ICB–: 532.1 (207.2)	NR	ICB+: 243.3 (82.1) ICB–: 243.3 (90.2)
Verger et al. (2018)	ICB+: 1124.1 (320.5) ICB–: 1145.9 (378.4)	NR	ICB+: 157.3 (130.0) ICB–: 205.4 (162.8)

Legend. Antidep: antidepressant; DAED: dopamine agonists equivalent daily dose (mg); DRT: drug replacement therapy; H&Y: Hoehn & Yahr score; ICB+: PwP with ICBs; ICB-: PwP without ICBs; ICBs: impulsive-compulsive behaviours; LD-LEDD: levodopa equivalent daily dosage levodopa only (mg); N: number of PwP; NR: not reported; PwP: persons with Parkinson's disease; Pts: PwP; Ref: reference; SSRI: selective serotonin reuptake inhibitors; Total LEDD: levodopa equivalent daily dose total (mg); UPDRS-III: unified Parkinson's disease rating scale part

III (motor subscale) score; y: years. *Mean (SD) unless otherwise stated; **months; *** off state; §data provided as mean and interquartile range.

Significant between-groups differences (statistical threshold as reported in the original paper) are reported in bold type.

Resting-state fMRI studies. ICB+ vs. ICB- comparison showed reduced connectivity between the basal ganglia nuclei and frontal cortical areas (Ruitenberg et al., 2018), between the habenula and left frontal and precentral cortices, and between right amygdala and hippocampus (Markovic et al., 2017) and in the DLPFC and inferior parietal cortex (Tessitore, Santangelo, et al., 2017), and between the left anterior putamen and the left inferior temporal and anterior cingulate gyrus, but no difference in connectivity in the ventral striatum (Carriere et al., 2015).

On the other hand, ICB+ compared to ICB- showed increased connectivity between the ventral striatum and limbic structures (Petersen et al., 2018), between the striatum and the habenula, the amygdala, the thalamus and bilaterally (Markovic et al., 2017), in the right ventral striatum and bilateral insula, and in the left middle temporal gyrus (Tessitore, Santangelo, et al., 2017).

In the single study that examined dynamic functional connectivity over time, ICB+ vs. ICB- were found to be engaged for longer in a brain configuration pattern characterized by strong 'within' network connections between superior temporal lobe, fronto-insular and cingulate cortices, at the expense of connectivity with other networks. The same study also reported increased local efficiency within the superior temporal lobe, fronto-insular and cingulate cortices (Navalpotro-Gomez et al., 2020).

Resting-state brain perfusion and brain metabolism. Two studies found increased metabolism in the right middle and inferior temporal gyri (Verger et al., 2018), and in the orbitofrontal cortex, amygdala, insula, posterior cingulate cortex, parahippocampus and supramarginal gyri (Marín-Lahoz et al., 2020) when comparing ICB+ to ICB-. Increased regional cerebral blood flow was also evident in

the orbitofrontal cortex, hippocampus, amygdala, insula, and the ventral pallidum in ICB+ PwP vs. ICB- ones (Cilia et al., 2008). However, “off” medication, there was no difference in regional cerebral blood flow in the striatum and frontal cortex, whilst “on” medication increased regional cerebral blood flow in these structures was reported in ICB+ vs. ICB- (Claassen et al., 2017) (Figure 5.3).

Connectivity was decreased between anterior cingulate cortex and the striatum (Cilia et al., 2011) and the left caudate and the right parahippocampus (Verger et al., 2018), but increased between the right middle, the inferior temporal gyri, the mesocorticolimbic system, and orbitofrontal regions (Verger et al., 2018).

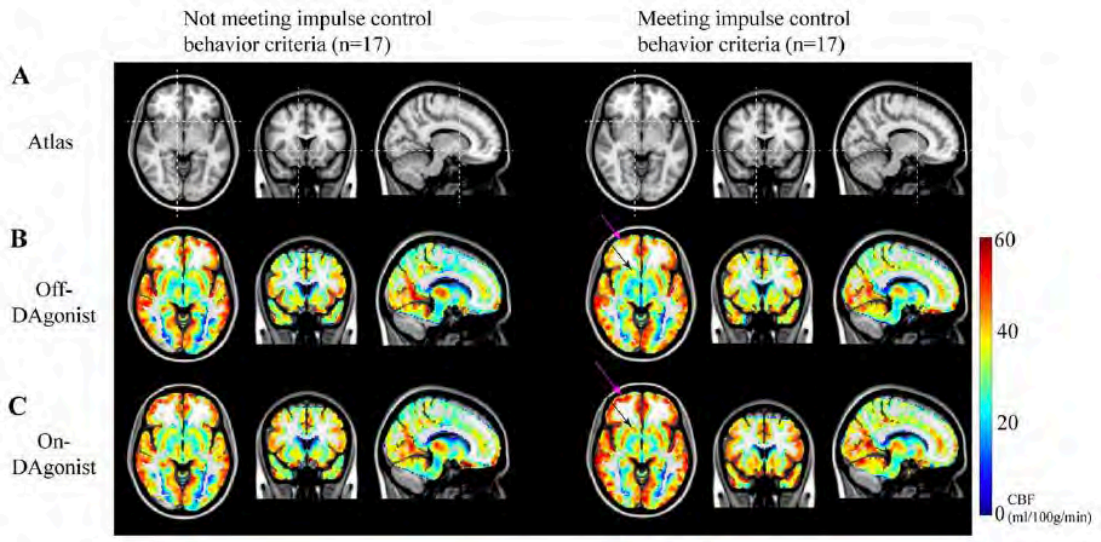


Figure 5. 3 CBF response to DA agonist. (A) Orthogonal representation of the 2-mm T1-weighted structural atlas, along with (B) quantitative CBF values in the off-DA agonist and (C) on-DA agonist states for ICB– (left) and ICB+ (right) patients. Limited CBF changes are observed in the ICB– group, yet increases in CBF in striatal (black arrow) and frontal (magenta arrow) regions are observed in the ICB+ patients. Reprinted under permission from Claassen et al., 2017, John Wiley and Sons and Copyright Clearance Center.

Task-based fMRI studies. Task-based fMRI studies consistently showed increased activation of reward-related areas; ICB+ PwP with gambling disorder showed increased BOLD signal in the anterior cingulate cortex, medial and superior frontal gyri, the precuneus, inferior parietal lobule, and ventral striatum after gambling-related visual cue exposure in comparison to ICB- ones (Frosini et al., 2010). A similar functional brain activation profile has been reported in PwP with hypersexuality after exposure to visual sexual cues (Girard et al., 2019; Politis et al., 2013). The BOLD signal was also reported to be increased in the ventral striatum of ICB+ PwP with dopamine dysregulation syndrome (DDS) after exposure to drug-related cues as compared to ICB- ones (Loane et al., 2015).

On a temporal discounting task, subjective value of the delayed reward was negatively correlated with activity in the ventromedial prefrontal cortex and ventral striatum in ICB+, with the opposite pattern in ICB- (Girard et al., 2019). ICB+ vs. ICB- showed increased BOLD signal in the right subthalamic nucleus, right inferior frontal gyrus, and right ventral striatum while performing the Iowa Gambling Task (Paz-Alonso et al., 2020) (Figure 5.4).

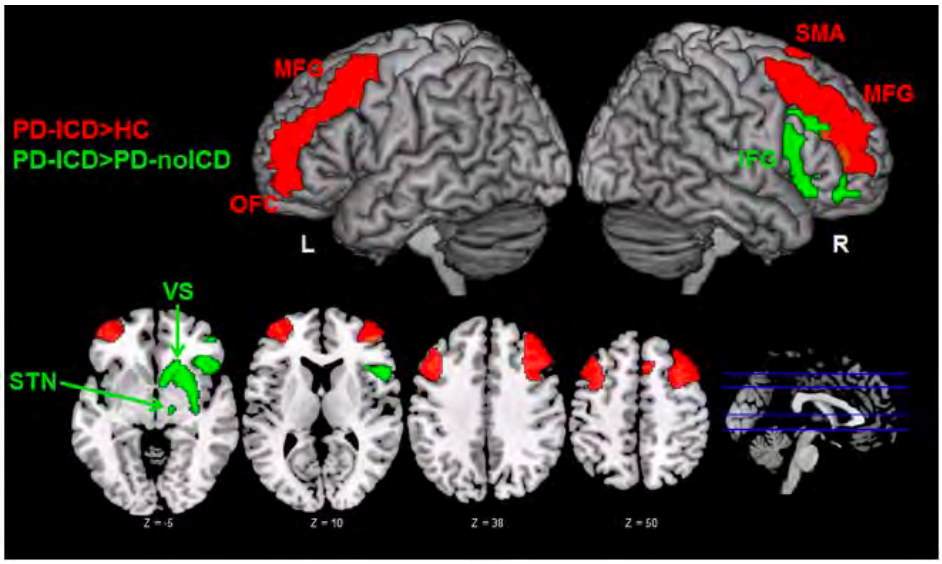


Figure 5. 4 Brain rendering and axial sections showing ROI analyses that revealed main-group effects in percent signal change. In red are regions with stronger activation for the ICB+ group compared with the HC group. Regions in green show higher activation for the ICB+ group compared wit the ICB- group. MFG, middle frontal gyrus; OFC, orbitofrontal cortex; SMA, supplementary motor area; IFG, inferior frontal gyrus; STN, subthalamic nucleus; VS, ventral striatum. Reprinted under permission from Paz-Alonso et al., 2020, John Wiley and Sons and Copyright Clearance Center.

Key details of the seventeen functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome are provided in Table 5.8.

Table 5. 8 Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Carriere et al. (2015)	rs-fMRI	ICB+: 19 ICB-: 17	QUIP; semi-structured interview	HS:14; GD:7; BE: 7; CS: 5	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DAED, MMSE	NR	PwP assessed after having received their usual antiparkinsonian medication	Decreased functional connectivity between left anterior putamen, left inferior temporal and anterior cingulate gyri	ICB+ ↓
Cilia et al. (2008)	SPECT	ICB+: 11 ICB-: 40	DSM-IV-TR; SOGS	GD: 4; GD+HS+BE:4; GD +HS+CS:1 ; GD +HS+CS+IA:1; GD +BE+HS+IA+CS:1	Sex, age, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DAED, GDS, MMSE	NR	PwP assessed in the morning during medication use	Increased brain perfusion: right OFC to insula, right hippocampus to parahippocampal gyrus, right amygdala, right ventral pallidum to NAc, left insula, right precuneus to cuneus and PCC, left precuneus to cuneus and PCC	ICB+↑

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Cilia et al. (2011)	SPECT	ICB+: 15 ICB-: 15	DSM-IV-TR; SOGS	NR	Sex, age, PD duration, H&Y, UPDRS-III, total LEDD, DAED, GDS, MMSE	NR	PwP assessed in the morning on-medication	Connectivity analysis: lack of covariance between the VLPFC and ACC, PCC; between the ACC and VS	ICB+ ↓
								Presence of covariance of ACC with insula, supplementary motor area, and cerebellum; VLPFC with ventral pallidum; medial prefrontal cortex with PCC; parahippocampal gyrus with insula	ICB+↑

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Claassen et al. (2017)	ASL (ON/OFF)	ICB+: 17 ICB-: 17	QUIP; semi-structured interview (PwP and spouse)	HB:11; HS: 10; CS: 4; BE:12	Sex, age, PD duration, UPDRS-III (OFF medication), total LEDD, DAED, AMNART, CESD-R, MoCA	UPDRS-III (ON medication): ICB+<ICB-;	Before MRI scan, PwP assessed by UPDRS III in the on-DA and off-Dopamine (LD + DA) state. Off condition: withdrawal for at least 36 hours for DA and 16 hours for LD. On condition: after taking prescribed DA medication, having withheld LD for at least 16 hours	OFF state: no differences ON state: CBF increase in VS and frontal cortex, (ICB-: no CBF increase)	ICB+=ICB- ICB+↑
Frosini et al. (2010)	Task-based fMRI (gambling-related visual cues and neutral stimuli)	ICB+: 7 ICB-: 7	DSM-IV-TR	GD+ HS:1; GD+BE:1; GD: 5	Age, PD duration, UPDRS-III, total LEDD, DAED, MMSE	NR	MRI scan performed after overnight drug washout (at least 12 hours)	Increased cue-related BOLD response bilaterally in the ACC, medial and superior frontal gyri and precuneus with right prevalence, right inferior parietal lobule, and left VS	ICB+↑

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Girard et al. (2019)	Task-based fMRI (temporal discounting ON/OFF)	ICB+: 13 ICB-: 14	Arduin scale; clinical interview	HS: 2; HS+CS: 1; HS+BE: 8; HS+HB: 9; HS+hyperactivity: 5	Age, PD duration, UPDRS-III (ON and OFF), total LEDD, LD-LEDD, DAED	NR	MRI scan performed both ON and OFF in counterbalanced order, one day apart. ON: 1h after a levodopa challenge (single supraliminar levodopa dose intake corresponding to 150% of the usual morning dose). OFF: after at least 12-h overnight antiparkinsonian drugs withdrawal	ON medication, when exposed to erotic picture after waiting for longer periods: increase activity in the anterior medial prefrontal/rostral ACC. ICB+ negative correlation between subjective value of the delayed reward and activity in the medial prefrontal cortex and VS (opposite pattern in ICB-).	ICB+↑
Imperiale et al. (2018)	rs-fMRI	ICB+: 35 ICB-: 50	QUIP; clinical interview	GD: 4; HS: 4; CS: 1; BE: 3; punding: 15; DDS: 5; BE+ punding: 1; GD + punding: 1; DDS+ punding: 1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DAED, MMSE	Depression (HDRS): ICB+>ICB-**; Apathy scale: ICB+>ICB-**	NR	Decreased functional connectivity of the right precentral gyrus, rolandic operculum and superior temporal gyrus within the sensorimotor network	ICB+ ↓

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Loane et al. (2015)	Task-based fMRI (rewarding cues and neutral stimuli, ON/OFF)	ICB+: 6 ICB-: 12	Clinical interview	All DDS with at least another ICB (GD; BE; HS; BE+ GD; BE+HS)	Sex, age, PD duration, total LEDD, LD-LEDD, DAED, MMSE	UPDRS-III (ON and OFF medication): ICB+>ICB-	Participants scanned in both OFF and ON medication condition after receiving LD 45 min prior to the scan. Motor performance was assessed with the UPDRS-III at baseline and immediately before scanning to ensure response to medication	Both ON and OFF medication (neural-cues): increased BOLD activity in the VS, ACC, BA 6, IFG and midbrain post drug-cues vs. neutral-cues exposure: increased BOLD activity in VS, ACC, BA 6, IFG and midbrain	ICB+↑
Markovic et al. (2017)	PET	ICB+: 9 ICB-: 15	QUIP; QUIP-rs; clinical interview	HS: 2; BE: 3; HB: 3; BE+HB: 1	Sex, age, education, age at PD onset, PD duration, UPDRS-III, total LEDD, DAED	NR	All acquisitions were performed in ON state	Glucose metabolism in PCC, bilateral supramarginal gyrus, right precuneus, bilateral fusiform gyrus, bilateral lingual, parahippocampal gyrus, left anterior insula, bilateral amygdala, bilateral uncus, bilateral inferior OFC, right BA10, left BA46, and left BA6	ICB+ ↑

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Marìn-Lahoz et al. (2020)	rs-fMRI	ICB+: 22 ICB-: 30	Interview including a semi-structured part (PwP and caregivers)	Punding:17; Punding + BE: 2; Punding + GD: 1; Punding + DDS: 1; Punding + HS:1	Sex, age, education, age at PD onset, PD duration, H&Y, UPDRS-III, total LEDD, DAED	NR	NR	Increased connectivity of the left habenula and the thalamus and striatum bilaterally and left posterior cingulum; between the right habenula and dorsal thalamus bilaterally; between the left amygdala and the thalamus bilaterally and left striatum; between the right amygdala and the left thalamus and caudate Decreased connectivity between the left habenula and the left frontal cortex; between the right habenula and the left posterior parietal regions; between the right amygdala and the right hippocampus	ICB+ ↑ ICB+ ↓

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Navalpotro-Gomez et al. (2020)	rs-fMRI	ICB+: 16 ICB-: 20	QUIP; QUIP-rs; clinical interview	HS: 3; BE: 2; CS: 1; HS+BE: 2; GD+BE: 1; CS+HB: 2; BE+ HB: 3; HS+CS+BE: 1; HS+CS+ punding+HB: 1	Sex, age, education, premorbid IQ, PD duration, UPDRS-III, H&Y, total LEDD, DAED	NR	PwP were studied under the effect of their usual dopaminergic medication.	Engaged for a longer time in a brain configuration patter characterized by enhanced within-network functional connectivity in temporal, frontoinsular, and cingulate cortices, key nodes of the SN	ICB+ ↑
Paz-Alonso et al. (2020)	Task-based fMRI (Iowa Gambling Task)	ICB+: 18 ICB-: 17	QUIP; QUIP-rs; clinical interview	HS: 3; BE: 3; HS+BE: 2; GD+BE: 1; CS+HB: 2; BE+ HB: 3; HS+CS+BE: 1; HS+CS+ punding+HB: 1; HS+CS+BE +punding: 1; CS+BE+HB :1	Sex, age, education, premorbid IQ, PD duration, UPDRS-III, H&Y, total LEDD, DAED	NR	All assessments and MRI scanning of PwP were done in the morning while they were still under the effect of their first regular dose of dopaminergic medication.	During IGT performance, hyper activation in right subthalamic nucleus, right IFG, right VS	ICB+ ↑

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Petersen et al. (2018)	rs-fMRI (ON/OFF)	ICB+: 19 ICB-: 18	QUIP; semi-structured interview (PwP and spouse)	HB:12; BE:13; HS:12; CS:4	Sex, age, PD duration, total LEDD, DA LEDD, CES-D	NR	PwP refrain from taking all dopaminergic medications prior to the off-dopamine therapy scan (16 h for LD, 36 h for DA) For the on-DA scan, PwP took their prescribed DA dosage (but not LD)	Increased connectivity between VS and the dorsal anterior cingulate gyrus, OFC, insula, putamen, globus pallidus, and thalamus. No main effect for drug.	ICB+ ↑
Politis et al. (2013)	Task-based fMRI (sexual cues, rewarding cues and neutral stimuli, ON/OFF)	ICB+: 12 ICB-: 12	Proposed operational diagnostic criteria	HS:4; HS+CS:2; HS+DDS: 2; HS+CS+BE:2; HS+GD +BE+CS:1 ; HS+DDS+ GD+BE:1	Sex, age, PD duration, UPDRS-III (ON and OFF medication), total LEDD, MMSE	LD LEDD: ICB+<ICB-; DA LEDD: ICB+>ICB-	PwP scanned in OFF medication condition and in ON medication condition after receiving an oral dose of LD 45 min prior to the scan starting. Motor performance was assessed with the UPDRS-III at baseline and immediately before scanning to ensure response to medication (defined as >25% improvements in UPDRS-III scores)	Sexual cues vs. neutral stimuli: Increased BOLD activity in the OFC, ACC, PCC, left amygdala, VS, hypothalamus, anterior prefrontal cortex, superior parietal lobule, lateral right inferior parietal lobule (in ON and OFF) Decreased BOLD activity in the insula and right claustrum (in the OFF scan only)	ICB+ ↑ ICB+ ↓

Table 5. 8 (continued) Key details of the 17 functional studies on DRT PwP including imaging technique, PwP numbers, ICBs type, matching/unmatching variables, and outcome.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Ruitenberg et al. (2018)	rs-fMRI	ICB+: 21 ICB-: 30	QUIP	GD: 1; HS:9; CS:7; BE:11; others:6; 9 multiple ICBs	Sex, age, age at PD onset, PD duration, UPDRS-III, total LEDD, MoCA, NART-R	NR	PwP were tested while their symptoms were being well controlled by DRT. UPDRS-III was used to assess motor symptoms	Increased connectivity between the left subthalamic nucleus and the left parietal operculum	ICB+ ↑
Tessitore, Santangelo et al. (2017)	rs-fMRI	ICB+: 15 ICB-: 15	MIDI	HS:13; BE:8; GD:1	Sex, age, education, PD duration, H&Y, UPDRS-III, total LEDD, DAED, HAM-D, HADS, MMSE	--	PwP were assessed in the morning during the ON medication state	Increased activity in bilateral insula and right ventral striatum (SN), and left middle temporal gyrus (DMN) Decreased activity in DLPFC and the inferior parietal cortices (CEN)	ICB+ ↑ ICB+ ↓

Table 5. 8 (continued) Characteristics of the seventeen studies included in the systematic review: functional studies in DRT PwP.

Ref.	Imaging technique	Subjects	ICBs diagnosis	ICBs type: N	Matched variables	Unmatched variables	Criteria for defining medication state	Brain region*	Findings: ICB+ vs. ICB-
Verger et al. (2018)	PET	ICB+: 18 ICB-: 18	MIDI; DSM-IV-TR; clinical interview	GD:4; HS: 2; CS:3 GD+HS:4; CS+ GD:3; CS+ HS:3; ICD+DDS: 3	Sex, age, PD duration, H&Y (OFF medication), UPDRS-III (ON and OFF medication), total LEDD, DAED, Mattis scale, BDI, LARS	NR	NR	Increased metabolism in right middle and inferior temporal gyri	ICB+ ↑
								Increased positive connectivity with right middle and inferior temporal gyri and right middle temporal gyrus, right middle and inferior frontal gyri, right middle and superior temporal gyri and parietal inferior lobule	ICB+ ↑
								Increased negative connectivity with right middle and inferior temporal gyri and left caudate and right parahippocampal gyrus	ICB+ ↑

Legend. ACC: anterior cingulate cortex; AMNART: American version of the national adult reading test; ASL: arterial spin labeling; BA: Brodmann Area; BDI: Beck Depression Inventory; BE: binge eating; BOLD: blood oxygen level dependent signal; CBF: cerebral blood flow; CEN: central executive network; CESD-R: Center for Epidemiologic Studies Depression Scale Revised; CS: compulsive shopping; DA: dopamine agonists; DAED: dopamine agonists equivalent daily dose; DDS: dopamine dysregulation syndrome; DSM-IV-TR: Diagnostic and

statistical manual of mental disorders – fourth edition text revision; DLPFC: dorsolateral prefrontal cortex; DMN: default mode network; DRT: drug replacement therapy; fMRI: functional magnetic resonance imaging; GD: gambling disorder; GDS: geriatric depression scale; HADS: Hospital anxiety and depression scale; HAM-D: Hamilton depression rating scale; HB: hobbyism; H&Y: Hoehn & Yahr score; HS: hypersexuality; IA: internet addiction; ICBs: impulsive compulsive behaviours; ICB+: PwP with ICBs; ICB-: PwP without ICBs; IFG: inferior frontal gyrus; LARS: Lille Apathy Rating Scale; LD-LEDD: levodopa equivalent daily dosage levodopa only; LD: levodopa; MIDI: Minnesota Impulsive Disorders Interview; MMSE: Mini-mental state examination; MoCA: Montreal cognitive assessment; MRI: magnetic resonance imaging; NAc: nucleus accumbens; NART-R: National adult reading test-revised; OFC: orbitofrontal cortex; PET: positron emission tomography; PCC: posterior cingulate cortex; PwP: persons with Parkinson's disease, ref.: reference; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale; rs-fMRI: resting state functional magnetic resonance imaging; SOGS: South Oaks gambling screen test; SN: salience network; SPECT: single photon emission computed tomography; Total LEDD: levodopa equivalent daily dose total; UPDRS-III: Unified Parkinson's disease rating scale part III (motor subscale) score; VLPFC: ventrolateral prefrontal cortex; vmPFC: ventromedial prefrontal cortex; VS: ventral striatum; *comparison between ICB+ vs. ICB-.

Discussion

The main objective for this systematic review was to report whether ICBs in PD are marked by abnormal brain structures and functional networks in areas related to incentive-driven decision-making, and whether brain changes predate ICBs onset.

The main findings from structural imaging studies were inconclusive. There was no consistent association between ICBs, both in medicated and drug naïve PwP, and changes in VBM, Cth, or white matter tracts in lateral prefrontal areas related to domain-specific and domain-general cognitive control (Badre & Nee, 2018), or in dorsomedial prefrontal cortex and subcortical structures implicated in motivation and salience response. On the other hand, results from functional imaging studies were more consistent, revealing four key findings.

The first key finding is that changes in resting-state networks activation were most consistently reported in the salience network, the central executive network (CEN) and the default mode network (DMN), both in medicated and drug naïve PwP. Medicated ICB+ showed reduced functional connectivity within the CEN and increased connectivity in the DMN and salience network (Tessitore, Santangelo, et al., 2017). The same results were reported in drug naïve PwP who later developed ICBs, except for the DMN that showed decreased connectivity compared to ICB-PwP (Tessitore, De Micco, et al., 2017). The DMN is active during internally-directed thoughts such as mind wondering, and it is suspended during cognitively-demanding tasks and goal-directed behaviours. It includes the ventromedial prefrontal cortex, posterior cingulate cortex, inferior parietal cortex and medial temporal lobe. The CEN is engaged when a cognitively demanding task or a goal-directed behaviour requiring attention is being performed, and is composed by the DLPFC and inferior parietal cortex (Tessitore, Santangelo, et al., 2017; Uddin,

Kelly, Biswal, Castellanos, & Milham, 2009). The salience network is activated by salient or rewarding stimuli (cognitive, emotional or homeostatic) therefore facilitating the DNM/CEN switching. It includes limbic-paralimbic structures, such as anterior insula, the anterior cingulate cortex, and the ventral striatum. In summary, resting-state networks findings highlight abnormal functional connectivity within regions involved in cognitive control (i.e., CEN) and in motivational processing (i.e., salience network) (Badre & Nee, 2018; Botvinick & Braver, 2015) which predate ICBs and remain stable once are fully developed. A limitation of the static functional connectivity studies is that connectivity is time-invariant. Dynamic functional connectivity takes into account the time-variant dynamic coupling that exists between nodes in a network (Menon & Krishnamurthy, 2019; Nomi et al., 2017). The study by Navalpotro-Gomez et al. (2020) is the only one to date to examine time-variant functional connectivity of ICBs in PD, and found that ICB+ were engaged across time in a brain configuration pattern characterized by lack of between-network connections at the expense of strong within-network connections in temporal, frontoinsular and cingulate cortices, all key nodes of the salience network. The increased temporal predominance of this state may be a consequence of, or lead to a reduction in the frequency of transitions between brain states, which is important for neural flexibility mediated through reconfiguration of general brain state organization (Nomi et al., 2017). The abnormally high connectivity within the salience network may lead ICB+ PwP to long and unregulated motivational states focused on or abnormally weighted towards reward-seeking behaviours. We may speculate that, along time, synaptic plasticity related to craving causes long-term potentiation in incentive-driven decision-making networks, as supported by evidence of ICBs development years after DRT initiation (Antonini et al., 2016). Once DRT

doses is decreased, ICBs may remit although it will reappear if PwP are exposed to the same dose.

The second key finding is that resting-state studies showed changes that mainly reflect an increase in brain metabolism (Marín-Lahoz et al., 2020; Verger et al., 2018) and cerebral blood flow (Cilia et al., 2008; Claassen et al., 2017) in brain areas belonging to the incentive-driven decision-making networks, such as the orbitofrontal cortex, amygdala, insula, ventral striatum, posterior cingulate cortex, parahippocampus and hippocampus, middle and inferior temporal, and supramarginal gyri. It has been suggested that the enhanced overdrive of the mesocorticolimbic system in response to DRT requires preserved metabolism to take action, and this may explain why ICB- PwP, who show lower metabolic preservation are less keen to develop ICBs under DRT (Marín-Lahoz et al., 2020).

The third key finding is that resting-state studies showed abnormal ventral striatal connectivity in ICB+. Ventral striatum show increased connectivity with limbic structures (e.g., habenula, amygdala, thalamus, insula) (Markovic et al., 2017; Petersen et al., 2018; Tessitore, Santangelo, et al., 2017), and decreased connectivity with the anterior cingulate cortex (Cilia et al., 2011). Furthermore, increased cerebral blood flow in the ventral striatum and frontal cortex is evident when “on” but not “off” medication (Claassen et al., 2017). Taken together these results not only evidence that ventral striatum is a brain area consistently associated with ICBs in PD but also that it is sensitive to the effect of DRT in ICB+ group only. Abnormal frontostriatal connectivity may disrupt integration of cognitive control and motivational inputs during incentive-driven decision-making.

The fourth key finding is that task-based fMRI studies showed increased rather than decreased BOLD signal during exposition to reward-related cues, and

during tasks measuring risk-taking and temporal discouting in the subthalamic nucleus, inferior frontal gyrus and ventral striatum, anterior and posterior cingulate cortex, ventromedial prefrontal cortex, and orbitofrontal cortex (Frosini et al., 2010; Girard et al., 2019; Loane et al., 2015; Paz-Alonso et al., 2020). The pattern of activation is generalized across ICBs type albeit each study focused on a specific and different ICBs.

Methodological considerations

Some limitations should be acknowledged.

First, in some studies ICBs were diagnosed using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease (QUIP) (Ricciardi et al., 2018; Ruitenberg et al., 2018; Zadeh et al., 2018), which is a validated screening tool with high sensitivity (94%) but low specificity (72%) to ICBs in PD, thereby possibly inflating the number of false positive subjects. Other studies used the Minnesota Impulsive Disorders Interview only (Tessitore et al., 2016; Tessitore, Santangelo, et al., 2017), without specifying how the ICBs not included in the interview (i.e. binge eating, punding/hobbyism, and dopamine dysregulation syndrome) were investigated. Although screening questionnaires are easily administrable and time-saving tools, ICBs should always be confirmed by a clinical interview based on diagnostic criteria. Caregiver should also be interviewed separately to confirm the diagnosis. Between-studies heterogeneity in procedures to ascertain ICBs may account for the discrepancy in their findings.

Second, most of the studies were constrained by small sample size, with the smallest including 7 ICB+ and 7 ICB- (Frosini et al., 2010), the largest including 58 ICB+ and 52 ICB- (Biundo et al., 2015), and none of them reporting power analysis

calculation. Underpowered studies may not detect a true effect and may reduce the likelihood for a significant result to reflect a true effect (Button et al., 2013). When economic resources are limited, larger samples can be obtained through collaborative research or using available shared databases (Poldrack, 2019).

Third, protocols of acquisitions and data analysis were not uniform across studies thereby limiting comparison. There is variability in scan duration, pre-processing and analysis, statistical threshold and methods to correct for multiple comparisons, with more liberal statistical thresholding procedure such as the false discovery rate, which in some cases may have inflated the false positive rate (Biundo et al., 2015; Canu et al., 2017; Cilia et al., 2008; Frosini et al., 2010; Loane et al., 2015; Markovic et al., 2017; Politis et al., 2013; Tessitore et al., 2016; Zadeh et al., 2018). Methodological differences can explain the lack of consistency in the results reported in this systematic review. For example, the inclusion of the ventral caudate and putamen in the ventral striatum seed region, rather than the nucleus accumbens alone (Carriere et al., 2015; Petersen et al., 2018). Replication studies using the same acquisition and analysis protocol are needed.

Fourth, a potential bias factor in resting-state studies is whether PwP are in "on" or "off" state. Most of the studies did not provide information to ensure that PwP were in a stable "on" state during MRI scan that may be long-lasting. Strategies that could be adopted include two resting-state sessions to increase reliability, exclude PwP with unpredictable "on-off" changes, or measure delta changes between motor symptoms score "on" vs. "off" medication.

Fifth, ICB+ and ICB- were not always fully matched for clinical variables that may predict or be associated with ICBs, thus these covariates might have contributed to neuroimaging findings. For example, in some studies ICB+ PwP had

higher levels of apathy and depression compared to ICB- ones (Canu et al., 2017; Imperiale et al., 2018; Markovic et al., 2017; Navalpotro-Gomez et al., 2020). The lack of consistency in the results may be due to between-studies differences in PD duration, co-presence of non-motor symptoms other than ICBs, or gender imbalance, since gender has been differently associated with specific ICB types (Weintraub et al., 2010). Disease-related gender-specific patterns of intrinsic brain connectivity, which may be differently affected by DRT, have been reported (De Micco et al., 2019).

Finally, the tasks used in the fMRI paradigm should reflect the ICB type investigated, otherwise their validity should be questioned. For example, in 1/5 task-based fMRI studies a gambling-related visual stimuli task has been used to also asses PwP with hypersexuality, binge-eating, compulsive shopping, hobbyism and punding (Paz-Alonso et al., 2020); however, a gambling task is not necessary a translatable marker of, for example, hypersexuality. Conversely, Girard et al. (2019) developed a temporal discounting task using sexual cues with PwP with HS. At the same time, other studies used visual drug-, gambling- and sexual-cues exposure with PwP all diagnosed with DDS (Loane et al., 2015), pathological gambling (Frosini et al., 2010) and hypersexuality (Politis et al., 2013), respectively. It is unknown whether different ICBs are supported by (at least in part) different brain structures as no study to date have investigate the brain correlates differences of single type ICBs. Therefore, it is important that the task used in the scanner resembles as much as possible the type of ICBs activity performed outside the scanner. Furthermore, once tasks are adapted without validations, they may lose some of their representativeness and generalisability. The link between surrogate research markers and clinical

behaviour should be cautiously interpreted until validated measures will be developed.

Limitations of the published reports and recommendations for future studies are provided in Table 5.9.

Table 5. 9 Limitations of the published reports and recommendations for future studies.

Limitations	Recommendations
	Sample selection
ICBs group allocation (diagnosis)	Use validated screening questionnaires followed by full diagnostic interview based on published or proposed criteria
Confounding variables (homogeneity of the sample)	PD groups should be matched for PD-related clinical variables (i.e., motor and non-motor symptoms)
Uncertain ON during rs-fMRI	Two resting state runs to increase reliability; PwP with unpredictable ON-OFF changes excluded; assessment of delta changes between UPDRS-III score ON vs. OFF compared to the UPDRS-III score immediately before MRI acquisition
	Paradigms
Validity	Use validated tasks in task-based fMRI studies. The tasks used should mirror the behaviour performed outside the scanner.
	Statistical Power
Low sample size	Information about power analysis should be provided; multicentre studies can increase recruitment rate and consequently power of the study
	Statistical analysis
Statistical threshold and methods to correct for multiple comparisons	Use more stringent thresholding procedures in order to reduce the false positive rate
	Results
Between studies comparisons	Provide results in Talairach or Montreal Neurological Institute coordinates, which can be meta-analysed using activation likelihood estimation approach

Legend. ICBs: impulsive compulsive behaviours; PD: Parkinson's disease; PwP: persons with Parkinson's disease; UPDRS-III: Unified Parkinson's disease rating scale part III (motor subscale) score; MRI: Magnetic Resonance Imaging; rs-fMRI: resting-state MRI.

Conclusions

Imaging studies have provided evidence of functional differences between ICB+ and ICB- in brain regions encompassing cognitive control and motivational processing networks, whose interactions support incentive driven decision-making.

In the last decade over 500 studies on ICBs in PD ranging from clinical to neuroimaging and genetic risk factors have been published (Rodríguez-Violante &

Antonini, 2019), however we still miss a firm understanding of ICBs neural signature. With a better understanding of ICBs underpinnings, pharmacological and/or non-pharmacological interventions targeting specific brain areas may be developed.

Key Findings

- In drug naïve PwP, no grey matter predictor of ICBs has been reported, whereas differences in functional connectivity within the salience, the default mode and the central executive networks predate ICBs development.
- Medicated ICB+ show increase metabolism and cerebral blood flow in orbitofrontal cortex, ventral striatum, amygdala, insula, posterior cingulate cortex, parahippocampus, inferior temporal and supramarginal gyri during resting-state.
- Medicated ICB+ show increased activity in ventral striatum, anterior and posterior cingulate cortices, ventromedial prefrontal and orbitofrontal cortices, subthalamic nucleus, and inferior frontal gyrus during reward-based task performance.
- Medicated ICB+ show reduced frontostriatal connectivity and increased mesolimbic connectivity.
- Brain changes involve motivation-cognitive control networks, which interactions regulate incentive-driven decision-making.

Study 6: Dopaminergic neurotransmission in persons with Parkinson's disease and Impulsive-compulsive behaviours: a systematic review and meta-analysis of PET/SPECT studies[11]

The study presented in this chapter has been published (Martini, Dal Lago, Edelstyn, Salgarello, et al., 2018), and is reproduced with permission of the copyright holder.

Abstract

Background: According to the dopaminergic overdose hypothesis, the dopamine replacement therapy (DRT) dose required to restore the dopaminergic levels in the motor dorsal striatum may overstimulate the relatively intact ventral striatum, which activity mediates reward-related behaviour, leading to impulsive-compulsive behaviours (ICBs). Brain positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies can provide a direct measurement of putative dopaminergic differences between persons with Parkinson's disease (PwP) with and without ICBs. The present study is the first systematic review and meta-analysis of PET or SPECT studies reporting striatal dopaminergic function in PwP with ICBs.

Methods: PubMed, Science Direct, EBSCO, and ISI Web of Science databases were searched (from inception to the 7-03-2018) for PET or SPECT studies reporting striatal dopaminergic function in PwP with ICBs vs. without ICBs. Studies including drug naïve PwP, exploring non-pharmacological procedures (e.g., deep brain stimulation), using brain blood perfusion or non-dopaminergic markers

[11] Martini, A., Dal Lago, D., Edelstyn, N.M.J., Salgarello, M., Lugoboni, F., Tamburin, S., (2018). Dopaminergic neurotransmission in patients with Parkinson's disease and Impulse Control Disorders: a systematic review and meta-analysis of PET and SPECT studies. *Frontiers in Neurology,* 9 (1018).

were excluded. Standardized mean difference (SDM) was used and random-effect models were applied. Separate meta-analyses were performed for dopamine transporter level (DAT), dopamine (DA) release, and DA receptors availability in the putamen, caudate, dorsal and ventral striatum.

Results: 238 studies were screened (title and abstract), of which 19 full-texts were assessed, and 9 were included (ICB+: 117 PwP; ICB-: 175 PwP). ICB+ showed a significant reduction of dopamine transporter binding in the putamen (SDM = −0.46; 95% CI: −0.80, −0.11; Z = 2.61; p = 0.009), caudate (SDM=−0.38; 95% CI: −0.73, −0.04; Z = 2.18; p = 0.03) and dorsal striatum (SDM= −0.45; 95% CI: −0.77, −0.13; Z = 2.76; p = 0.006), and increased dopamine release to reward-related stimuli/gambling tasks in the ventral striatum (SDM = −1.04; 95% CI: −1.73, −0.35; Z = 2.95; p = 0.003). Dopamine receptors availability did not differ between groups. Heterogeneity was low for dopamine transporter in the dorsal striatum (I^2 = 0%), putamen (I^2 = 0%) and caudate (I^2 = 0%), and pre-synaptic dopamine release in the dorsal (I^2 = 0%) and ventral striatum (I^2 = 0%); heterogeneity was high for dopamine transporter levels in the ventral striatum (I^2 = 80%), and for dopamine receptors availability in the ventral (I^2 = 89%) and dorsal (I^2 = 86%) striatum, putamen (I^2 = 93%), and caudate (I^2 = 71%).

Conclusions: ICB+ PwP show lower dopaminergic transporter levels in the dorsal striatum and increased dopamine release in the ventral striatum when engaged in reward-related stimuli/gambling tasks. This dopaminergic imbalance might represent a biological substrate for ICBs in PD. Adequately powered longitudinal studies with drug naïve PwP are needed to understand whether these changes may represent biomarkers of premorbid vulnerability to ICBs.

Introduction

ICBs are considered a complication of DA agonist treatment and, to a lesser extent, levodopa (Weintraub et al., 2010). This is supported by higher ICBs rates in medicated PwP compared to healthy controls (Erga et al., 2017; Perez-Lloret, Rey, Fabre, Ory, Spampinato, Brefel-Courbon, et al., 2012; Rodríguez-Violante et al., 2014; Valença et al., 2013) and drug naïve PwP (Antonini et al., 2011; Weintraub et al., 2013).

Studies in healthy volunteers show a modulatory effect of DA agonists on impulsivity; however, the direction of the effect is unclear, in that some studies report increased impulsivity while other ones show decreased impulsivity to DA agonists. For example, *d*-amphetamine decreases impulsive behaviour on the Stop task and in the Go/No-Go task (measured as Stop reaction time and number of false alarms), and decreases delay discounting (de Wit, Enggasser, & Richards, 2002). However, levodopa and DA agonist pramipexole increase impulsivity on delay discounting and gambling tasks (Pine, Shiner, Seymour, & Dolan, 2010; Riba, Krämer, Heldmann, Richter, & Münte, 2008). This implies that impulsivity is modulated by a complex interplay of DA activity across a network of systems, and DA agonists disrupt the balance between brain areas modulating impulsivity.

In the first stages of PD, ventral striatum activity is relatively more preserved than the dorsal striatum (Braak et al., 2004). Therefore, the dopaminergic treatment dose required to restore motor dorsal striatal dopaminergic levels may overstimulate the relatively intact ventral striatum (Voon, Mehta, et al., 2011). This hyperdopaminergic state may promote an abnormal activity in the connected cortico-striatal cognitive and limbic motivational pathways that mediate incentive-driven behaviour (Claassen et al., 2017). As a consequence, the control of goal-directed

behaviour is impaired, facilitating ICBs development. It should be noted that If the hypothesis of the ventral striatal overstimulation is correct, we may expect the presence of ICBs in every PwP treated with DRT, which is not the case. Therefore, the ventral striatal overstimulation may be one factor predisposing the development of ICBs in vulnerable individuals but not the only requirement for an ICB to be acted out. It cannot be excluded that compensatory mechanisms (e.g., behavioural, cognitive, neural) may be recruited in order to prevent an ICB from becoming clinically present (e.g., regular surveillance by carers, or being inpatient which means that PwP can adjust their motivation for acting or not the ICB).

If ICBs in PD are linked to the disruption of the equilibrium in DA activity across ventral and dorsal striatum, then PET and SPECT can provide a direct measurement of putative dopaminergic differences between PwP with and without ICBs. These nuclear medicine techniques use molecular imaging to assess biochemical, neurochemical, or pharmacological processes in the brain. For example, changes in neurotransmission can be detected using radiotracers with high affinity for DA receptors.

When a radiotracer is injected, it competes with DA for binding to free dopamine receptors. Thus, if DA is released endogenously, radiotracer binding can therefore be used as a marker for DA release (Badgaiyan, 2014). According to the binding affinity and the type of radiotracer, it is possible to investigate the nature of the dopaminergic dysfunction, whether linked to DA release, dopaminergic re-uptake in the presynaptic terminals, and $D_{2/3}$ post-synaptic receptors availability. The spatial resolution of current PET and SPECT machines allows separate assessment of the dorsal and ventral striatal regions, and their components (i.e., putamen, caudate).

A limitation of the PET and SPECT studies of ICBs in PD published so far is the small sample size, with the largest study including 21 PwP with ICBs and 68 without ICBs (Premi et al., 2016) and the smallest including 7 PwP with ICBs and 7 without ICBs (Steeves et al., 2009). Small sample sizes are not surprising, given the high cost of PET and SPECT exams. Moreover, variability in clinical and demographic characteristics, types of tracer, protocols of analysis and scanners makes the comparison between studies difficult.

A meta-analytic approach can overcome these limitations. Low powered studies can be combined and differences in striatal dopaminergic function between PwP with and without ICBs estimated with a higher reliability. This is the first systematic review and meta-analysis of striatal PET/SPECT studies on ICBs in PD.

Aim

The aim of this study was to investigate differences in striatal dopaminergic functioning of PwP with and without ICBs. To this aim, PET and SPECT based reports on dopamine transporter level, presynaptic dopamine release, and post-synaptic $D_{2/3}$ receptors availability in the ventral and dorsal striatum were systematically reviewed and meta-analysed.

Method

Study design, participants and comparators

A systematic review and meta-analysis were performed to identify striatal dopaminergic activity associated with ICBs in PD under DRT (ICB+). The comparator group was persons with PD but no history of ICBs (ICB-).

Search strategy

The PubMed, Science Direct, EBSCO, and ISI Web of Science databases were searched for peer-reviewed studies on PET or SPECT striatal dopaminergic function in PD-related ICBs, and published from database inception until the 7th of March 2018. The following search string was used: "((Parkinson's disease OR Parkinson) AND (impulse control disorders OR impulse control disorder OR impulsive compulsive behaviors OR impulsive compulsive behaviours OR impulsive compulsive behavior OR impulsive compulsive behaviour OR ICB OR ICB OR hypersexuality OR gambling OR buying OR shopping OR eating)) AND (Positron emission tomography OR PET OR Single Photon Emission Computed Tomography OR SPECT OR SPET OR DaTSCAN)". A total of 384 papers were identified. After the exclusion of duplicates, 238 papers went through title and abstract screening. Two authors (AM, DDL) independently screened titles and abstracts using Rayyan software (Ouzzani et al., 2016) and 17 papers were included in the full-text screening. The reference lists of these papers were manually searched for additional studies missed in the databases search, and two relevant papers were included at this stage. Two authors (AM, DDL) independently evaluated the 19 papers selected for full-text examination and disagreements were planned to be resolved via discussion with a third author (ST). However, there was 100% agreement between the two authors. Nine studies were included for quantitative analysis. The PRISMA diagram of the study is presented in Figure 5.5. List of studies excluded at the full-text screening stage with reasons for exclusions is provided in the Appendix AS.

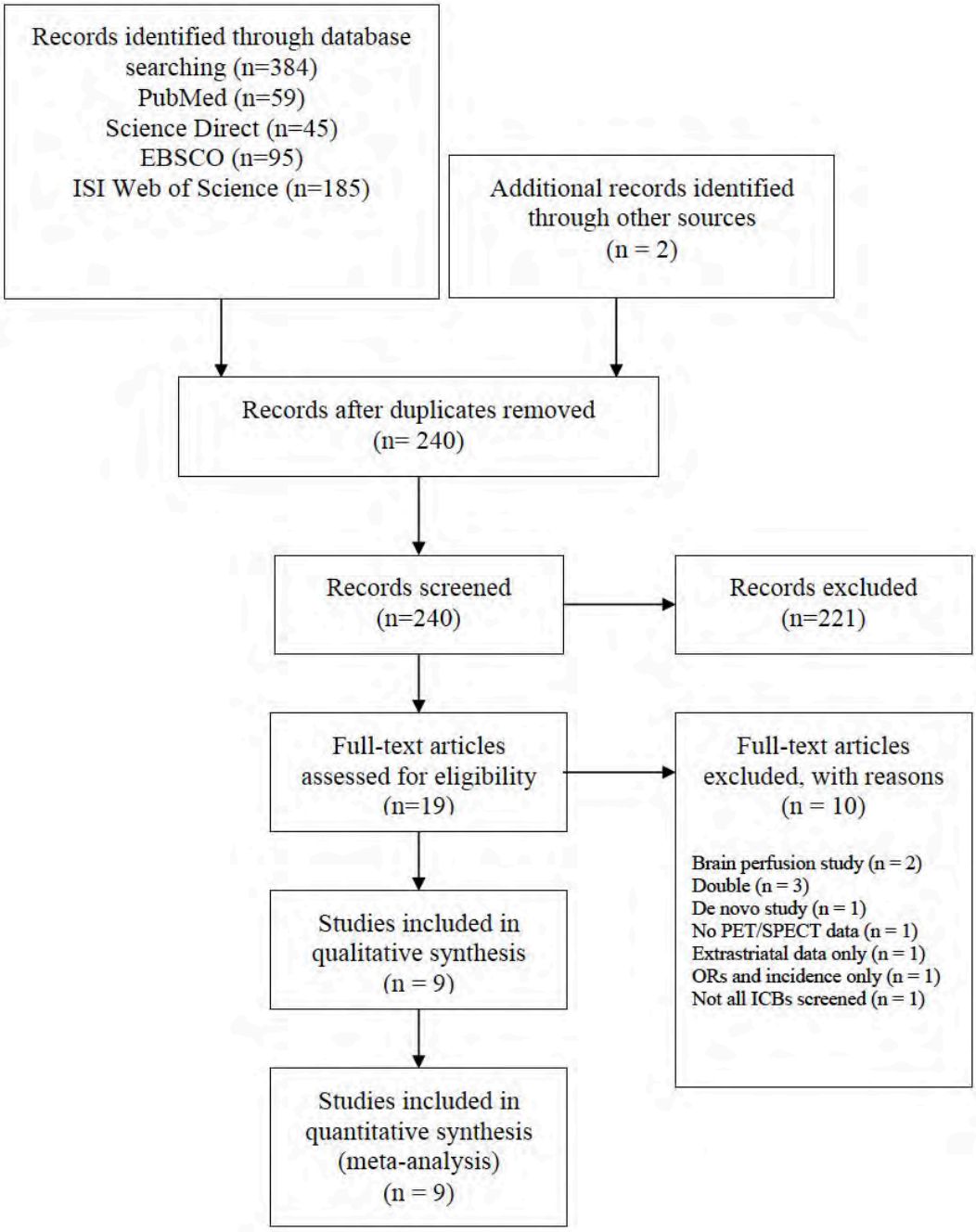


Figure 5. 5 PRISMA diagram of the study (www.prisma-statement.org). ICBs: impulsive-compulsive behaviours; ORs: odds ratios; PET: positron emission tomography; SPECT: single-photon emission computed tomography.

Selection criteria

Studies were included if they met the following inclusion criteria: i) PET or SPECT study; ii) PwP without ICBs (ICB-) compared with PwP with ICBs (ICB+); iii) data reported for at least one striatal region; iv) independence of the sample. Therefore, if a study sample was reported in multiple publications, only the study with the largest sample was included.

Studies were excluded if they were reviews, case studies, commentaries, letters, abstracts and dissertations, conference papers, and postal surveys. Contrary to Study 5, studies including drug naïve PwP were not included in the meta-analysis. There were only two PET/SPECT studies performed in drug naïve PwP (Smith et al., 2016; Vriend, Nordbeck, et al., 2014), with one of them not including separate means and SDs for ICB+ and ICB- groups (Smith et al., 2016), therefore precluding their inclusion in a separate meta-analysis of drug naïve PwP (i.e., at least two studies are needed). Drug naïve PwP represent a different sample than those treated with DRT, as the former have shorter PD duration, and are not chronically exposed to DRT. Therefore, dopaminergic systems may be affected and stimulated differently in medicated and non-medicated PwP. For this reason, including drug naïve and DRT PwP in the same analysis may have biased the findings. Studies in which PwP underwent deep brain stimulation (DBS) were also excluded, as ICBs may either improve or develop after DBS (Samuel et al., 2015). Finally, studies using measures of brain blood perfusion were excluded, as they do not explore striatal dopaminergic functioning. Similarly, studies using non-dopaminergic markers were excluded.

Data extraction

Corresponding authors of four studies (Cilia et al., 2010; Payer et al., 2015; Premi et al., 2016; Stark et al., 2018) were contacted for exact data. Data reported as median and range (Joutsa, Martikainen, Niemelä, et al., 2012) were converted to mean and SD (Hozo et al., 2005). When standard error was reported, it was converted to SD (Steeves et al., 2009; Wu et al., 2015). Two authors (AM, DDL) independently extracted the following demographic and clinical data: sample size, sex, age at evaluation, age at PD onset, PD duration, education (years), H&Y stage, UPDRS-III ON-medication, depression, antidepressant use, antipsychotic use, number of PwP under DA agonist treatment, DAED (mg), LD-LEDD (mg), total LEDD (mg), ICBs screening tool, and ICBs type. Methodological characteristics of the included studies were also extracted: imaging technique (i.e., PET or SPECT), type of tracer, reference region, imaging approach, radiotracer delivery method, drug delivered prior to scan, medication state (i.e., ON, OFF), withdrawal period.

The outcomes measures were the differences in the dopaminergic imaging parameters (e.g., binding potentials) between PwP with and without ICBs in striatal areas (i.e., ventral striatum, dorsal striatum, putamen, caudate).

Data analysis

Separate meta-analyses were performed for studies focusing on dopamine transporter (DAT) level, dopamine release (presynaptic), and dopamine receptors availability (postsynaptic) in the ventral striatum, dorsal striatum, putamen, and caudate. Data were analysed using ReviewManager v5.3 (The Nordic Cochrane Centre, 2014). Standardized mean difference (SMD) was used as effect size

measure, with values around 0.2, 0.5 and 0.8 considered as small, moderate and large, respectively (Cohen, 1977).

Heterogeneity between studies was calculated by the I^2 value with percentages around 25, 50, and 75 considered as low, moderate, and high, respectively (Higgins et al., 2003). As PwP samples may vary in their clinical (e.g., H&Y stage, UPDRS scores) and demographic characteristics (e.g., age, sex), random-effect models were applied.

Sensitivity analysis was performed by excluding studies clearly stating current antipsychotic or antidepressant use, as these drugs may affect dopamine receptor binding potential (Howes et al., 2012) or DAT uptake (Voon et al., 2014).

As the number of studies was low, we lacked the power for conducting moderator analysis (Sterne et al., 2011) or visual inspections of funnel plots for publication bias (Borenstein, 2009). A p-value of <0.05 was used as statistical significance threshold for all the analyses.

Results

Demographic and clinical characteristics of the 117 ICB+ and 175 ICB- PwP reported in the nine studies included in the meta-analysis are reported in Table 5.10. Methodological characteristics of the studies included are reported in Table 5.11.

There was heterogeneity on the procedure to assess ICBs across studies. ICBs were diagnosed either with a clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders fourth edition text revision (DSM-IV-TR) criteria (Cilia et al., 2010; Joutsa, Martikainen, Niemelä, et al., 2012; Lee et al., 2014; Payer et al., 2015; Stark et al., 2018; Voon et al., 2014), on the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) criteria (Wu et al.,

2015) or with the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease – rating scale (QUIP-rs) (Premi et al., 2016). In four studies, during the clinical interview the following tools were used: the South Oaks gambling screen (SOGS) (Cilia et al., 2010; Payer et al., 2015), the Gambling Symptom Assessment Scale (G-SAS) (Steeves et al., 2009), the QUIP-rs (Stark et al., 2018), and the Sexual Addiction Screening test (Payer et al., 2015). In the paper of Steeves et al. (2009), no specific information was provided on criteria for diagnosing ICBs apart from the use of SOGS for gambling disorder.

All PwP were under DRT. In seven studies there were no between-group differences in total LEDD or DAED (Cilia et al., 2010; Joutsa, Martikainen, Niemelä, et al., 2012; Lee et al., 2014; Stark et al., 2018; Steeves et al., 2009; Voon et al., 2014; Wu et al., 2015). One study reported a higher number of PwP under DA agonist, however total LEDD and DAED levels were comparable between ICB+ and ICB- groups (Premi et al., 2016). In one study ICB+ had higher LD-LEDD than ICB- (Payer et al., 2015).

Table 5. 10 Demographic and clinical characteristics of the studies included in the meta-analysis.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Edu (y)*	H&Y*	UPDRS-III (ON)*	Depression as exclusion criteria?	Antidep (N)
Cilia et al. (2010)	ICB+: 8 (7) ICB-: 21 (11)	ICB+: 60.7 (7.5) ICB-: 60.1 (9.4)	NR	ICB+: 6.25 (2) ICB-: 6.1 (2.4)	NR	ICB+: 2.1 (0.74) ICB-: 2 (0.53)	ICB+: 18.1 (9.3) ICB-: 20.2 (5.6)	NO (GDS available)	NO
Joutsa et al. (2012)	ICB+: 10 ICB-: 10	ICB+: 61.5 (45-7)¶ ICB-: 61.5 (53-7)¶	ICB+: 53 (40-64)¶ ICB-: 57 (47-63)¶	ICB+: 7 (3-9)¶ ICB-: 5 (1-8)¶	NR	All PwP were in stages 2 to 3	ICB+: 31 (24-41)¶ ICB-: 32 (19-49)¶	NO	NR
Lee et al. (2014)	ICB+: 11 (8) ICB-: 11 (6)	ICB+: 56.6 (8.7) ICB-: 58.5 (7.3)	ICB+: 46.4 (8.7) ICB-: 49.2 (7.3)	ICB+: 10.1 (6.9) ICB-: 9.4 (2.3)	NR	ICB+: 2.3 (0.4) ICB-: 2.1 (0.5)	ICB+: 14.2 (11.0) ICB-: 15.3 (7.6)	YES	NO
Payer et al. (2015)	ICB+: 11(9) ICB-: 21 (11)	ICB+: 58.9 (7.8) ICB-: 63.3 (8.7)	NR	ICB+: 12.1 (3.7) ICB-: 7.4 (4.5)	ICB+: 15.5 (2.7) ICB-: 15.1 (1.8)	NR	ICB+: 33.1 (10.2) ICB-: 28.1 (10.6)	YES	YES: ICB+: 1 ICB-: 0
Premi et al. (2016)	ICB+: 21 (16) ICB-: 63 (38)	ICB+: 65.8 (8.4) ICB-: 68.5 (11.0)	NR	ICB+: 1.9 (2.2) ICB-: 1.7 (2.4)	NR	ICB+: stage 1 (N =4); stage 1.5 (N = 3); stage 2 (N = 5); stage 2.5 (N = 5); stage 3 (N = 4) ICB-: stage 1 (N = 8); stage 1.5 (N = 13); stage 2 (N = 18); stage 2.5 (N = 17); stage 3 (N = 7)	ICB+: 16.5 (7.2) ICB-: 14.6 (7.7)	NO	YES: ICB+: 2 ICB-: 10

Table 5. 10 (continued) Demographic and clinical characteristics of the studies included in the meta-analysis.

Ref	Pts (males)	Age (y)*	PD onset (y)*	PD duration (y)*	Edu (y)*	H&Y*	UPDRS-III (ON)*	Depression as exclusion criteria?	Antidep (N)
Stark et al. (2018)	ICB+: 17 (11) ICB-: 18 (13)	ICB+: 60.9 (6.6) ICB-: 62.7 (10.1)	NR	ICB+: 5.7 (3.2) ICB-: 6.1 (4.5)	NR	NR	NR	YES	NR (unlikely considering the exclusion criteria)
Steeves et al. (2009)	ICB+: 7 (5) ICB-: 7 (6)	ICB+: 47-72§ ICB-: 51-74§	NR	ICB+: 7.4 (3.2) ICB-: 5.6 (2.5)	NR	ICB+: 2 (0.6) ICB-: 1.9 (0.7)	OFF medication: ICB+: 25.2 (4.5) ICB-: 20.2 (5.4)	NO	NR
Voon et al. (2014)	ICB+: 15 (9) ICB-: 15 (9)	ICB+: 55.1 (8.9) ICB-: 60.1 (8)	NR	ICB+: 7.5 (5.4) ICB-: 5.5 (5.2)	NR	ICB+: 3† ICB-: 3†	NR	NR	NR
Wu et al. (2015)	ICB+: 17 ICB-: 9	S-ICB: 62.3 (3.9)‖ M-ICB: 58.1 (2.8)‖ ICB-: 60.2 (3.2)‖	S-ICB: 51.7 (4)‖ M-ICB: 43.8 (3.4)‖ ICB-: 50.3 (3.4)‖	S-ICB: 10.6 (2)‖ M-ICB: 14.3 (11.2)‖ ICB-: 9.9 (2.1)‖	NR	NR	OFF medication: S-ICB: 42.1 (3.8)‖ M-ICB: 41 (3.5)‖ ICB-: 32.8 (3)‖	NO (but BDI scores available)	NR

Table 5.10 (continued). Demographic and clinical characteristics of the studies included in the meta-analysis.

Ref	Antipsy use (N)	Drugs that may affect PET binding exclusion criterion	PwP under DA treatment (N/Total)	LEDD (mg)			Dementia excluded	ICB	
				Total LEDD*	LD-LEDD*	DAED*		Diagnosis**	Type: N
Cilia et al. (2010)	NO	YES	NR	ICB+: 831.2(293.6) ICB-: 852.3 (301.1)	NR	ICB+: 240.6 (118) ICB-: 251.6 (121)	YES (MMSE<24)	Clinical interview (DSM-IV-TR criteria); SOGS	2 GD; 5 GD+HS; 3 GD+BE; 2 GD+CS
Joutsa et al. (2012)	NR	NO but none used nicotine or had current substance-use disorder	ICB+: 9/10 ICB-:9/10	ICB+: 635 (250-876)¶ ICB-: 826 (210-1127)¶	NR	ICB+: 171.5 (0-280)¶ ICB-: 200 (0-320)¶	NO	Structured Clinical Interview for DSM-IV Axis I Disorders	4 GD; 1 GD+subclinical HS; 1 HS; 2 HS+subclinical BE; 1 HS+subclinical CS; 1 BE
Lee et al. (2014)	NO	YES	NR	ICB+: 914.4 (338.7) ICB-: 925.2 (458.4)	NR	ICB+: 217.9 (175.3) ICB-: 153.2 (110.7)	YES (MMSE<24)	Clinical interview (DSM-IV-TR criteria); modified MIDI	1 HS; 2 GD; 3 CS+BE; 1 CS+HS+BE; 1 CS+HS+BE+GD; 2 CS+BE+punding; 1 HS+BE+GD
Payer et al. (2015)	NR (unlikely considering the exclusion criteria)	YES. Current treatment with DA was exclusionary	ICB+: 0/11 ICB-: 0/21	NR	ICB+: 813.6 (318.5) ICB-: 426.2 (144.6)	NR	YES (MMSE<26)	clinical interview according to proposed criteria; SOGS; DSM-IV-based gambling questionnaire; sexual addiction screening test	10 GD; 3 HS; 1 CS. Only 5 PwP meeting ICB criteria at the time of the study

Table 5. 10 (continued) Demographic and clinical characteristics of the studies included in the meta-analysis.

Ref	Antipsy use (N)	Drugs that may affect PET binding exclusion criterion	PwP under DA treatment (N/Total)	LEDD (mg)			Dementia excluded	ICB	
				Total LEDD*	LD-LEDD*	DAED*		Diagnosis**	Type: N
Premi et al. (2016)	NR	Antidepressant therapy, if present, was suspended three weeks before the assessment	ICB+: 19/21 ICB-: 30/63	ICB+: 594.2 (388.6) ICB-: 359.1 (280.1)	NR	ICB+: 282.1 (227.9) ICB-: 174.4 (97.2)	NO but MMSE scores reported	QUIP-rs	12 BE; 7 GD; 6 HS; 2 punding; 33 DDS + other ICBs; 1 DDS
Stark et al. (2018)	NR (unlikely considering the exclusion criteria)	PwP excluded if they were prescribed psychoactive drugs that could alter dopamine receptor availability	ICB+: 17/17 ICB-: 18/18	ICB+: 673.8 (440) ICB-: 693.9 (406.3)	NR	ICB+: 103.9 (65.1) ICB-: 135.4 (76.4)	YES (MoCA<22)	Clinical interview (DSM-IV-TR criteria); QUIP-rs;	11 HS; 11 BE; 4 CS; 12 hobbyism
Steeves et al. (2009)	NR	NR	ICB+: 7/7 ICB-: 7/7	ICB+: 856 (407) ICB-: 756 (400)	NR	ICB+: 138 (172) ICB-: 167 (113)	YES	G-SAS	7 GD

Table 5. 10 (continued) Demographic and clinical characteristics of the studies included in the meta-analysis.

Ref	Antipsy use (N)	Drugs that may affect PET binding exclusion criterion	PwP under DA treatment (N/Total)	LEDD (mg)			Dementia excluded	ICB	
				Total LEDD*	LD-LEDD*	DAED*		Diagnosis**	Type: N
Voon et al. (2014)	NR	PwP were required to stop any drug that would bind to the DAT seven days prior to the scan	ICB+: 13/15 ICB-: 10/15	ICB+: 785.8 (402.7) ICB-: 852.1 (520.4)	NR	ICB+: 325.8 (156.1) ICB-: 384.3 (212.8)	NR	clinical interview	4 HS; 5 CS; 3 GD; 6 punding
Wu et al. (2015)	NR	NR	NR	S-ICB: 782.3 (83.4)‖ M-ICB: 724 (99)‖ ICB-: 831.9 (119.2)‖	S-ICB: 538 (83.4)‖ M-ICB: 268.5 (84.9)‖ ICB-: 666.3 (129)‖	S-ICB: 244.3 (51.4)‖ M-ICB: 244 (55.4)‖ ICB-: 165.6 (48.8)‖	YES (MMSE<24)	semi-structured interview	4 HS; 3 GD; 1 CS+three ICBs; 2 CS+two ICBs; 7 CS +one ICB;

Legend. Antipsy: antipsychotic use; Antidep: antidepressant use; BDI: Beck depression inventory; BE: binge eating; CS: compulsive shopping; DA: dopamine; DAED: dopamine agonist levodopa equivalent daily dose; DAT: dopamine transporter; DDS: Dopamine dysregulation syndrome; DSM-IV: diagnostic and statistical manual of mental disorders, fourth edition; DSM-IV-TR: diagnostic and statistical manual of mental disorders, fourth edition, text revision; Edu: education; G-SAS: Gambling symptom assessment scale; GDS: Geriatric depression scale; H&Y: Hoehn & Yahr score; HS: hypersexuality; ICB: impulsive-compulsive behaviour; PwP: persons with Parkinson's disease; ICB+: PwP

with ICBs; ICB-: PwP without ICBs; total LEDD: levodopa equivalent daily dosage (mg) total; LD-LEDD: LEDD for levodopa only; M-ICB: multiple ICBs; MIDI: Minnesota impulsive disorder interview; MMSE: mini mental state examination; MoCA: Montreal cognitive assessment; N: number of PwP; NR: not reported. PD: Parkinson's disease; GD: gambling disorder; Pts: PwP; QUIP-rs: Questionnaire for impulsive-compulsive disorders in Parkinson's disease rating scale; Ref: reference number; S-ICB: single ICB; SOGS: South Oaks gambling screen; UPDRS-III: unified Parkinson's disease rating scale part III (motor subscale) score; y: years. [*]Mean (SD) unless otherwise stated. [¶]Median (range). [§]Range. [†]Median. [‖]Mean (SEM). [**]Questionnaire or method use to screen and/or diagnose ICBs.

Table 5. 11 Methodological characteristics of the studies included in the meta-analysis.

Ref	Imaging tech	Type of tracer	Reference region	Imaging approach	Radiotracer delivery	Drug delivered prior scan	ON/ OFF	Withdrawal period
Cilia et al. (2010)	SPECT	[123I]FP-CIT	Occipital cortex	Single scan	Intravenous injection	Thyroid blockade (oral Lugol solution 10–15 mg) 30-40 min before the injection	OFF	Overnight withdrawal of dopaminergic medications
Joutsa et al. (2012)	PET	[18F]fluorodopa	Occipital cortex	Single scan	Bolus injection	Carbidopa 150 mg 1h before the scan	OFF	At least 12 h drug discontinuation (>24 h for slow-release medications)
Lee et al. (2014)	PET	[18F]FP-CIT	Cerebellum	Single scan	Bolus injection	NO	OFF	At least 12 h withdrawal of all PD medications
Payer et al. (2015)	PET	[11C]-(+)-PHNO	Cerebellum	Single scan	Bolus injection	NO	OFF	At least 8 h withdrawal of levodopa (current DA use was an exclusion criteria)
Premi et al. (2016)	SPECT	[123I]FP-CIT	Occipital lobe	Single scan	Intravenous injection	$KClO_4$ 800 mg 30 min before the injection	NR	NR
Stark et al. (2018)	PET	[18F]fallypride	Cerebellum	3 emissions scans	Bolus injection	NO	OFF	Washout was at least 40 h for DA and 16 h for levodopa
Steeves et al. (2009)	PET	[11C]raclopride	Cerebellum	2 scans in 2 separate days within 2 weeks (randomized): baseline and gambling task	Ten mCi injections	NO	OFF	12-18 h overnight withdrawal of PD medications
Voon et al. (2014)	SPECT	[123I]FP-CIT	Occipital lobe	Single scan	Intravenous injection	Thyroid blockade (oral potassium iodate) 24h prior to the study	ON	NO
Wu et al. (2015)	PET	[11C]raclopride	Cerebellum	2 scans in 2 separate days: neutral and reward-related stimuli	Bolus injection	NO	OFF	12 h withdrawal of PD medications

Legend. Imaging tech: imaging technique; DA, dopamine agonist; mCi, millicurie; PD, Parkinson's disease; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

One study divided the ICB+ group in single and multiple ICBs subgroups (Wu et al., 2015). As the comparison between single and multiple ICBs was not relevant for this meta-analysis, means and SDs of the subgroups were merged by calculating the pooled means and SDs.

Six studies provided results in the left/right (Cilia et al., 2010; Joutsa, Martikainen, Niemelä, et al., 2012; Lee et al., 2014; Premi et al., 2016; Voon et al., 2014; Wu et al., 2015) and/or anterior/posterior striatal sub-regions (Joutsa, Martikainen, Niemelä, et al., 2012); data from these studies were merged by calculating the pooled means and SDs.

Seven studies provided means and SDs for putamen and caudate separately (Joutsa, Martikainen, Niemelä, et al., 2012; Lee et al., 2014; Payer et al., 2015; Premi et al., 2016; Stark et al., 2018; Voon et al., 2014; Wu et al., 2015). For these studies, putamen and caudate measures were merged to generate a measure of the whole dorsal striatum, according to Howes et al. (2012). To this aim, the means of the dopaminergic index in the putamen and caudate were weighed by their volumes to reflect the larger contribution of the putamen compared to the caudate, and then averaged (Howes et al., 2012). Since none of the studies reported the putamen and caudate anatomical volumes, those used by Howes et al. (2012) and derived from healthy adults (n=34, mean age=32.5 years, SD=8.8 years; mean, SD mm^3 volume: putamen=8805, 994; caudate=5562, 865) were used. SD was calculated accounting for the dependency of measures, by assuming a between-measures correlation of r=0.5 in the striatal sub-regions. To test whether the whole dorsal striatum measure might have concealed differences in its sub-regions, analyses were repeated considering the putamen and caudate separately.

According to the radiotracer and the imaging approach used, studies were categorized as investigating i) DAT level (Cilia et al., 2010; Joutsa, Martikainen, Niemelä, et al., 2012; Lee et al., 2014; Premi et al., 2016; Voon et al., 2014), ii) dopamine release (Steeves et al., 2009; Wu et al., 2015), and iii) dopamine receptors availability (Payer et al., 2015; Stark et al., 2018; Steeves et al., 2009; Wu et al., 2015). Information about radiotracers used in the studies included in the meta-analysis is reported in Table 5.12.

Table 5. 12 Radiotracers used in studies included in the meta-analysis.

Type of tracer	Study	Function and characteristics	Radiotracer delivery method
[123I]FP-CIT	Cilia et al. (2010); Premi et al. (2016); Voon et al. (2014)	SPECT radiotracer with high affinity for DAT (Booij et al., 1997) and serotonin transporter (Booij et al., 2007)	Intravenous injection
[18F]FP-CIT	Lee et al. (2014)	SPECT radiotracer with high affinity for DAT with high signal-to-noise ratio and kinetics (Wang et al., 2006)	Bolus injection
[18F]fluorodopa	Joutsa et al. (2012)	PET radiotracer for both presynaptic dopamine metabolism (synthesis) (de Vries, Luurtsema, Brussermann, Elsinga, & Vaalburg, 1999) and striatal dopamine uptake	Bolus injection
[11C]raclopride	Steeves et al. (2009); Wu et al. (2015)	PET selective D2/D3 antagonist sensitive to changes in endogenous dopamine levels; it can be used to assess both basal levels of receptor availability and changes in availability caused by alterations in striatal dopamine concentration (Yoder, Kareken, & Morris, 2008)	Bolus injection
[11C]-(+)-PHNO	Payer et al. (2015)	PET ligand with high affinity and selectivity for D_3 receptors (Narendran et al., 2006)	Bolus injection
[18F]fallypride	Stark et al. (2018)	PET ligand with high affinity to $D_{2/3}$ receptors in striatal and extrastriatal regions (Mukherjee et al., 2002)	Bolus injection

Legend. DAT, dopamine transporter; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

In the DAT level subgroup, three studies (Cilia et al., 2010; Premi et al., 2016; Voon et al., 2014) used [^{123}I]FP-CIT, a SPECT radiotracer with high affinity for DAT and modest affinity for the serotonin transporter (Joling et al., 2017); one study (Lee et al., 2014) used the [^{18}F]FP-CIT radiotracer, which has also cross-affinity to serotonin transporter but a better contrast than [^{123}I]FP-CIT (Lee et al., 2018); and one study (Joutsa, Martikainen, Niemelä, et al., 2012) used [18F]fluorodopa, which is a marker of both dopaminergic re-uptake and dopamine synthesis (Kaasinen et al., 2001).

The pre-synaptic dopamine release subgroup included two studies (Steeves et al., 2009; Wu et al., 2015) using [11C]raclopride, which is a competitive $D_{2/3}$ antagonist sensitive to changes in endogenous dopamine levels (Yoder et al., 2008). Both studies (Steeves et al., 2009; Wu et al., 2015) used a two PET sessions design, with one baseline scan (i.e., control task (Steeves et al., 2009), neutral cues visual exposure (Wu et al., 2015)) and one scan during the experimental condition (i.e., gambling task (Steeves et al., 2009), reward cues visual exposure (Wu et al., 2015)). The binding potential in baseline condition is a measure of basal level of receptor availability. Conversely, the change in binding potential between baseline and experimental conditions is an indirect measure of alteration in striatal dopamine concentration due to pre-synaptic dopaminergic release. A decrease in binding potential in comparison to baseline is associated with increase in dopamine, while an increase in binding potential in comparison to baseline is associated with a dopamine decrease (Yoder et al., 2008). Therefore, for the pre-synaptic dopamine release studies (Steeves et al., 2009; Wu et al., 2015), the outcome was the percentage [11C]raclopride binding potential reduction when comparing the experimental and baseline conditions.

Finally, the post-synaptic dopamine receptors availability subgroup included one study (Payer et al., 2015) with [11C]-(+)-PHNO, a D_3-preferring $D_{2/3}$ receptor ligand, and one study (Stark et al., 2018) with [18F]fallypride, which is one of the high affinity $D_{2/3}$ receptor ligands that allow quantification of both striatal and extrastriatal binding. Two studies (Steeves et al., 2009; Wu et al., 2015) with [11C]raclopride were also included in the post-synaptic dopamine receptors availability analysis; for these studies the outcome was the value reported for the baseline conditions.

A total of 292 subjects were included in the meta-analysis, 117 were PwP with ICBs (age range: 45–72 years; PD duration: 1.9–14.3 years; H&Y: 2–3; UPDRS-III score ON medication: 14.2–41) and 175 were PwP without ICBs (age: 51–74 years; PD duration: 1–9.9 years; H&Y stage: 1.9–3; UPDRS-III score ON medication: 14.6–49) (Table 5.10).

Four meta-analyses were performed for the DAT levels in the ventral striatum, dorsal striatum, putamen, and caudate. Two meta-analyses were performed for the pre-synaptic dopamine release in the ventral and dorsal striatum; the putamen and caudate were not explored for this outcome because only one study provided separate values for these two structures (Wu et al., 2015). Four meta-analyses were performed for the post-synaptic dopamine receptors availability in the ventral striatum, dorsal striatum, putamen, and caudate. Results of the meta-analyses are provided in Table 5.13.

Table 5. 13 Results of the meta-analysis.

			Random-effect model results				Heterogeneity		
Outcome	**K**	**N**	**SMD**	**[95% CI]**	**Z**	***p***	X^2	***p***	I^2
Dopamine transporter level – ventral striatum	3	71	-0.91	[-2.10, 0.27]	1.51	0.13	10.14	*0.006*	80%
Dopamine transporter level – dorsal striatum	5	184	-0.45	[-0.77, -0.13]	2.76	*0.006*	1.99	0.74	0%
Dopamine transporter level – putamen	4	155	-0.46	[-0.80, -0.11]	2.61	*0.009*	1.43	0.70	0%
Dopamine transporter level – caudate	4	155	-0.38	[-0.73, -0.04]	2.18	*0.03*	1.79	0.62	0%
Dopamine release – ventral striatum	2	40	-1.04	[-1.73, -0.35]	2.95	*0.003*	0.22	0.64	0%
Dopamine release – dorsal striatum	2	40	-0.36	[-1.01, 0.28]	1.10	0.27	0.42	0.52	0%
Receptors availability – ventral striatum	4	107	-1.29	[-2.68, 0.10]	1.82	0.07	26.71	*<0.00001*	89%
Receptors availability – dorsal striatum	4	107	-0.69	[-1.86, 0.48]	1.16	0.25	21.90	*<0.00001*	86%
Receptors availability – putamen	3	93	-1.06	[-2.94, 0.81]	1.11	0.26	28.99	*<0.00001*	93%
Receptors availability – caudate	3	93	-0.59	[-1.40, 0.23]	1.41	0.16	6.86	*0.03*	71%

Legend. K*:* number of studies; N: number of participants; SMD: standardized mean difference; CI: confidence interval. *p* values below the significance level ($p<0.05$) are reported in italics.

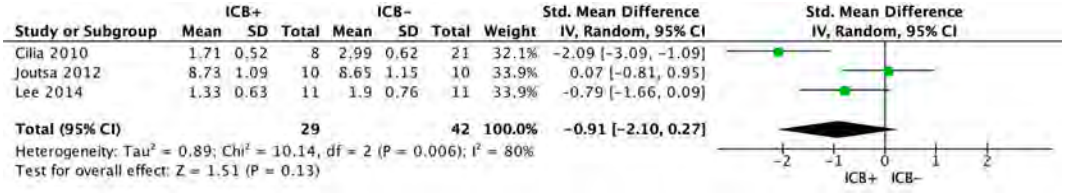
Dopamine Transporter Levels

Compared to the ICB- group, tracer binding in the ICB+ group was significantly reduced in the dorsal striatum (SDM=-0.45; 95% CI: -0.77, -0.13; Z= 2.76; *p*=0.006) but not in the ventral striatum (SDM=-0.91; 95% CI: -2.10, 0.27; Z= 1.51; *p*=0.13). When dorsal striatum sub-regions were analysed separately, both putamen (SDM=-0.46; 95% CI: -0.80, -0.11; Z= 2.61; *p*=0.009) and caudate (SDM=-0.38; 95% CI: -0.73, -0.04; Z= 2.18; *p*=0.03) tracer bindings were significantly reduced in the ICB+ vs. ICB- (Table 5.13). Forest plots for dopamine transporter levels are provided in Figure 5.6.

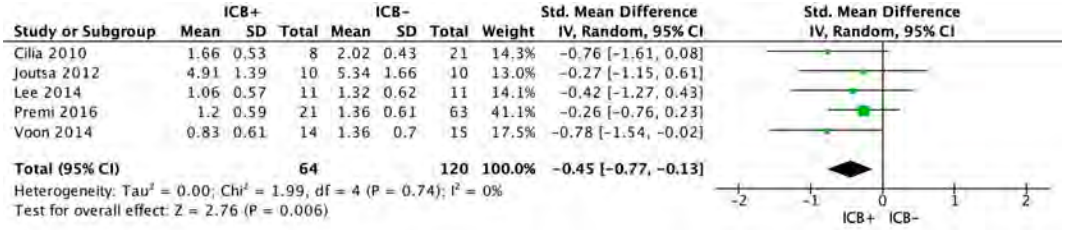
Heterogeneity was low for the dorsal striatum (χ^2=1.99, p=0.74, I^2=0%), putamen (χ^2=1.43, p=0.70, I^2=0%), and caudate (χ^2=1.79, p=0.62, I^2=0%). However, heterogeneity in the ventral striatum was high (χ^2=10.14, p=0.006, I^2=80%; Table 5.13 and Figure 5.6).

Sensitivity analysis was performed by excluding Premi et al. (2016), which enrolled 12 PwP under anti-depressant treatment that was suspended three weeks before assessment. Exclusion of Premi et al. (2016) did not change overall effect size for dorsal striatum (SDM=-0.58; 95% CI: -0.99, -0.16; Z= 2.73; *p*=0.006), putamen (SDM=-0.54; 95% CI: -1.02, -0.06; Z= 2.23; *p*=0.03), and caudate (SDM=-0.54; 95% CI: -1.02, -0.07; Z= 2.24; *p*=0.03), and heterogeneity (dorsal striatum: χ^2=1.07, p=0.78, I^2=0%; putamen: χ^2=1.19, p=0.55, I^2=0%; caudate: χ^2=0.87, p=0.65, I^2=0%).

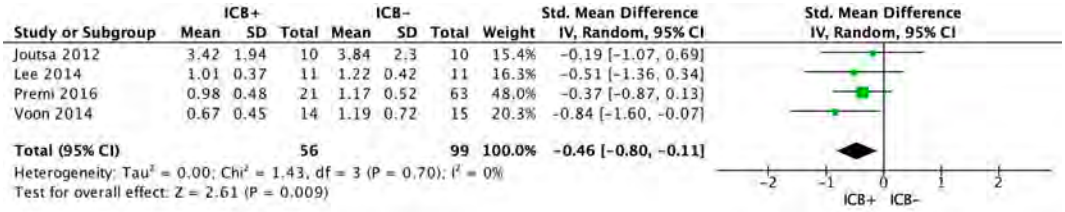
A. Dopamine transporter levels ventral striatum



B. Dopamine transporter levels dorsal striatum



C. Dopamine transporter levels putamen



D. Dopamine transporter levels caudate

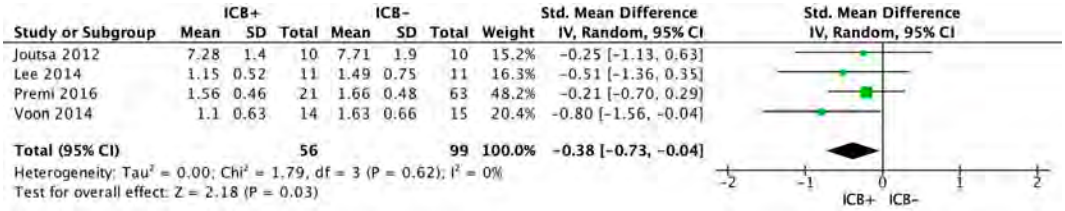


Figure 5. 6 Forest plots for dopamine transporter levels. Here are reported forest plots for dopamine transporter levels in the ventral striatum (A), dorsal striatum (B), putamen (C), and caudate (D). Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate lower dopamine transporter levels in PwP

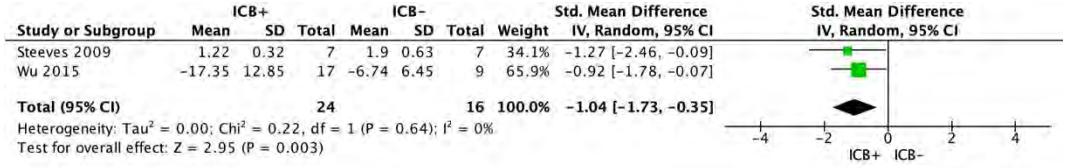
with ICBs (ICB+) in comparison to those without ICBs (ICB–). ICBs, impulsive-compulsive behaviour; PwP, persons with Parkinson's disease.

Pre-Synaptic Dopamine Release

ICB+ group, compared to the ICB- group, showed reduced binding in response to reward-related stimuli/gambling task in the ventral (SDM=-1.04; 95% CI: -1.73, -0.35; Z= 2.95; *p*=0.003), but not in the dorsal striatum (SDM=-0.36; 95% CI: -1.01, 0.28; Z= 1.10; *p*=0.27; Table 5.13). Forest plots for dopamine release are provided in Figure 5.7.

Heterogeneity was low for both ventral (χ^2=0.22, p=0.64, I^2=0%) and dorsal (χ^2=0.42, p=0.52, I^2=0%) striatal regions (Table 5.13 and Figure 5.7).

A. Dopamine release ventral striatum



B. Dopamine release dorsal striatum

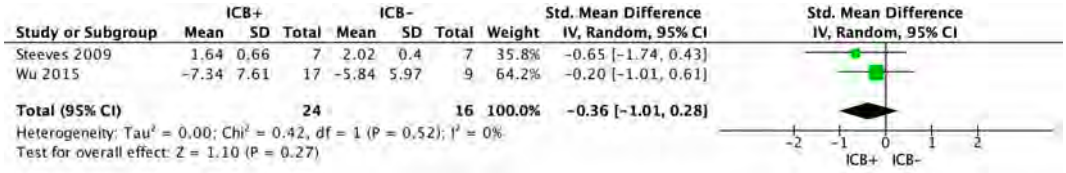


Figure 5. 7 Forest plots for dopamine release. Here are reported forest plots for dopamine release in the ventral striatum (A), and in dorsal striatum (B). Standardized mean difference represents Hedges's g effect size. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate lower dopamine release in PwP with ICBs (ICB+) in comparison to those without ICBs (ICB–). ICBs, impulsive-compulsive behaviour; PwP, persons with Parkinson's disease.

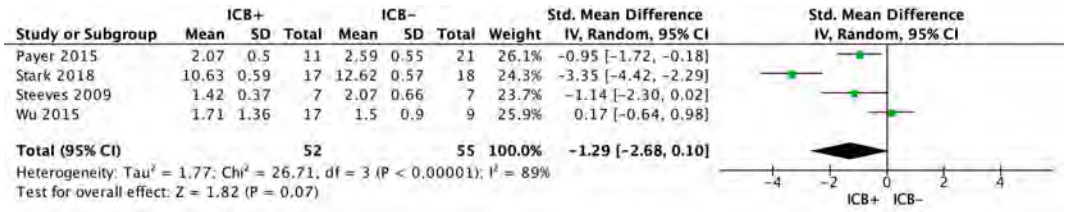
Post-Synaptic Dopamine Receptors Availability

Post-synaptic dopamine receptor bindings potentials did not differ between ICB+ and ICB- groups in the ventral striatum (SDM=-1.29; 95% CI: -2.68, 0.10; Z= 1.82; *p*=0.07), dorsal striatum (SDM=-0.69; 95% CI: -1.86, 0.48; Z= 1.16; *p*=0.25), putamen (SDM=-1.06; 95% CI: -2.94, 0.81; Z= 1.11; *p*=0.26), and caudate (SDM=-0.59; 95% CI: -1.40, 0.23; Z= 1.41; *p*=0.16; Table 5.13). Forest plots for post-synaptic receptors availability are provided in Figure 5.8.

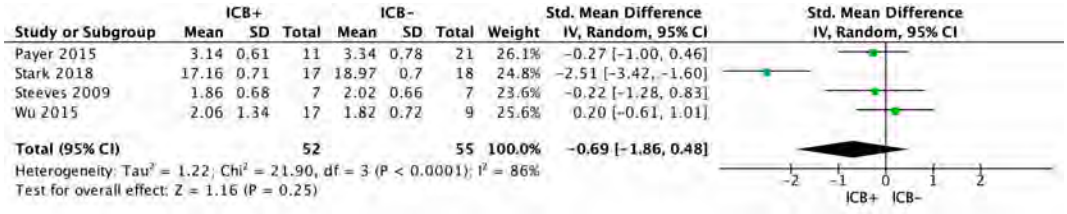
Heterogeneity was high in the ventral striatum (χ^2=26.71, p<0.00001, I^2=89%), dorsal striatum (χ^2=21.90, p<0.0001, I^2=86%), putamen (χ^2=28.99, p<0.00001, I^2=93%), and caudate (χ^2=6.86, p=0.03, I^2=71%; Table 5.13 and Figure 5.8).

Sensitivity analysis was performed by excluding Payer et al. (2015), which enrolled one PwP taking antidepressant. Exclusion of Payer et al. (2015) did not change the overall effect size for the ventral striatum (SDM=-1.42; 95% CI: -3.54, 0.69; Z= 1.32; *p*=0.19), dorsal striatum (SDM=-0.84; 95% CI: -2.55, 0.86; Z= 0.97; *p*=0.33), putamen (SDM=-1.54; 95% CI: -4.87, 1.80; Z= 0.90; *p*=0.37), and caudate (SDM=-0.56; 95% CI: -1.99, 0.87; Z= 0.77; *p*=0.44), and heterogeneity (ventral striatum: χ^2=26.58, p<0.00001, I^2=92%; dorsal striatum: χ^2=20.53, p<0.0001, I^2=90%; putamen: χ^2=25.42, p<0.00001, I^2=96%; caudate: χ^2=6.86, p=0.009, I^2=85%).

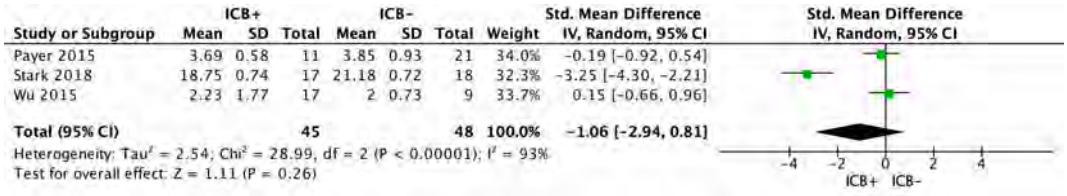
A. Receptors availability ventral striatum



B. Receptors availability dorsal striatum



C. Receptors availability putamen



D. Receptors availability caudate

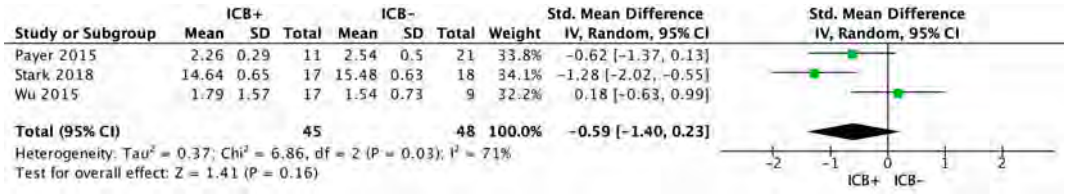


Figure 5. 8 Forest plots for post-synaptic receptors availability. Here are reported forest plots for post-synaptic receptors availability in the ventral striatum (A), dorsal striatum (B), putamen (C), and caudate (D). Standardized mean difference represents Hedges. The size of the square indicates the weight of the study. The horizontal line represents the 95% confidence interval. The diamond represents the pooled effect size. Negative effect sizes indicate lower receptors availability in PwP with ICBs (ICB+) in comparison to those without ICBs (ICB–). ICBs, impulsive-compulsive behaviour; PwP, persons with Parkinson's disease.

Discussion

This is the first systematic review and meta-analysis on PET/SPECT dopaminergic striatal correlates of ICBs in PD. The aim was to investigate if striatal dopaminergic function differs in PwP with and without ICBs. To this aim, studies on DAT levels, presynaptic dopamine release, and post-synaptic $D_{2/3}$ receptors availability in the ventral and dorsal striatum were reviewed and analysed. ICB+ were found to be associated with (i) lower DAT levels in the dorsal striatum and in its subdivisions (i.e., putamen, caudate) and (ii) reduced binding (i.e., increased dopamine release) in the ventral striatum in response to reward-related stimuli or gambling task, but (iii) no relationship between ICB+ and striatal post-synaptic receptors availability in either the dorsal or ventral striatum.

Dopamine Transporter Levels

ICB+ group showed lower dorsal striatum DAT binding than the ICB- one. In the striatum, DAT is localized in axon varicosities and terminals that contain synaptic vesicles, as well as in non-synaptic region where it regulates and terminates extracellular dopamine activity (Voon et al., 2014). Therefore, reduced DAT might reflect more pronounced dorsal striatal dopaminergic terminal loss, functional DAT downregulation, or genetically determined lower membrane expression on otherwise normal neurons (Cilia et al., 2010).

The hypothesis of more severe degeneration of nigrostriatal projections in ICB+ PwP is supported by a recent meta-analysis of case-control studies showing that the risk of ICBs in PwP increases with disease duration and being medicated for PD (Molde et al., 2018), two factors that are directly correlated with the amount of nigrostriatal loss. Moderator analysis for these two factors was not possible, because

of the small number of studies included in the meta-analysis.

The lower DAT binding in ICB+ may also reflect medication-related DAT downregulation, but DAT regulation by DRT was found to be modest (Guttman et al., 2001; Voon et al., 2014). It is unlikely that lower DAT binding is a compensatory effect of medication, as longitudinal studies on drug naïve PwP show that dorsal striatal DAT levels precede DRT initiation and ICBs onset (Smith et al., 2016; Vriend, Nordbeck, et al., 2014). SPECT findings are further supported by a genetic study showing an association between ICBs in PD and a variant of the dopamine transporter gene, i.e., 9-repeat allele of the SLC6A3 (Cilia et al., 2016); this variant results in lower presynaptic DAT expression, reduced synaptic clearance, and increased DA availability in the synaptic space (Forbes et al., 2009).
It should be noted that dorsal striatum binding was reduced in ICB+ vs. ICB- despite comparable UPDRS-III motor scores. This could be due to the low precision of drawing regions of interest and activity that may be improved in the future.

Pre-Synaptic Dopamine Release

ICB+ group showed reduced binding potential in ventral but not dorsal striatum when exposed to reward-related cues or when engaged in a gambling task. Participants to a gambling task are required to actively choose options associated either with reward or penalty and process related feedback. Conversely, in reward-related cues paradigms, participants passively view neutral or reward-related stimuli (e.g., food, erotic pictures, gambling or shopping related activities) without any active choice. Albeit being different, these tasks share neurobiological underpinnings. In pathological gamblers, reductions of ventral striatal and ventromedial prefrontal cortex activity have been documented in a gambling task (Reuter et al., 2005) and reward-related reactivity has been shown to also

involve the dorsal lateral prefrontal cortex network (Crockford, Goodyear, Edwards, Quickfall, & El-Guebaly, 2005) that is functionally connected to the ventral striatum.

[11C]raclopride is sensitive to competition from endogenously released dopamine to a stimulus, therefore decreased binding potential found in ICB+ vs. ICB- groups in response to gambling tasks or rewarding stimuli reflects increased dopamine release. These findings are in keeping with functional imaging studies of behavioural and pharmacological addiction in the general population, whereby monetary and sexual stimuli elicit the same patterns of striatal activation as recreational drugs (Steeves et al., 2009; Volkow, Fowler, Wang, Baler, & Telang, 2009). Increased dopamine release during a gambling task has been reported in pathological gamblers (Linnet, Møller, Peterson, Gjedde, & Doudet, 2011; Linnet, Peterson, Doudet, Gjedde, & Møller, 2010) and it correlates both with gambling severity (Joutsa, Johansson, et al., 2012) and increased excitement levels despite lower performances (Linnet et al., 2011). This may be the consequence of conditioned response to the reward-related or gambling cues, although increased dopaminergic release has been observed also for unconditioned stimuli (Wu et al., 2015).Whether the increased dopamine release in the ventral striatum exists in the premorbid phase therefore representing a vulnerability factor or it is the consequence of repeated exposure to gambling or rewarding-related stimulus (de Wit & Stewart, 1981; Singer, Scott-Railton, & Vezina, 2012), to DRT (Laruelle et al., 1995), or a combination of these factors (Steeves et al., 2009) is unknown. Only preclinical models and prospective studies can address this point. These findings have important implications, since the exposure to any reward-related cue (e.g., through advertisement) may have the potential to increase abnormal dopamine release in vulnerable PwP (O'Sullivan, Wu, et al., 2011), as supported by a study showing

increased dopamine release in single ICB PwP to reward-cues not related to their ICB (e.g., gamblers to food-related cues) (Wu et al., 2015).

There are two other neuropharmacological mechanisms that should be considered. First, in PwP treated with dopamine agonists the activation of D_2-like presynaptic autoreceptors in the mesolimbic system reduces phasic dopamine release in the nucleus accumbens (Pes et al., 2017; Pizzagalli et al., 2008; Riba et al., 2008). Therefore, reward responsiveness is blunted and risk propensity enhanced in order to normalize mesolimbic efflux (Pes et al., 2017). Second, reward detection capacity depends on phasic dopaminergic cell firing. Phasic dopamine dips encode prediction errors therefore providing outcome-related feedback which signal the need of behavioural adjustments as reward contingencies change (Stopper & Floresco, 2015). In rats, a low dose of monoamine-depleting agent reserpine administered together with pramipexole, exacerbated pramipexole effects on disadvantageous decision-making without changing pramipexole-induced decrease in the phasic dopamine release. This suggests that the effect of dopamine agonist on ICBs may not be caused by changes in phasic dopamine release in the nucleus accumbens (Pes et al., 2017). Moreover, dopamine agonists tonically bind to D_2 receptors irrespective of phasic changes in firing (Frank et al., 2004).

Post-Synaptic Dopamine Receptors Availability

No changes in $D_{2/3}$ receptors availability between ICB+ and ICB- PwP were found. This finding is, to some extent, surprising for a number of considerations. Animal PD models showed increased D_3 expression after repeated administration of DRT (Payer et al., 2015). A PET study found relationships between higher D_3 levels, dopamine release in the ventral striatum, and ICBs severity in people without PD

(Boileau et al., 2014). Preclinical rats models of PD shows that ICB-like behaviours can be triggered by pramipexole (Holtz, Tedford, Persons, Grasso, & Napier, 2016; Rokosik & Napier, 2012) and ropinirole (Cocker, Tremblay, Kaur, & Winstanley, 2017; Tremblay et al., 2017), which mainly target $D_{2/3}$ receptors. Polymorphisms of $D_{2/3}$ receptors genes are associated with addictive behaviours in PD (Lee et al., 2009), and in the general population (Leeman & Potenza, 2013). D_3 receptor antagonists may block reward seeking in animal models (Khaled et al., 2010; Vorel et al., 2002; Xi & Gardner, 2007).

Different lines of reasoning may explain this apparently paradoxical finding. Heterogeneity was high for this outcome in the meta-analysis, and this may reflect differences in the radiotracers used by the studies included. However, random effect model does not assume homogeneity of the effect and findings should have been robust to heterogeneity. $D_{2/3}$ receptors localize both to pre-synaptic mesolimbic terminal auto-receptors and post-synaptic indirect-pathway medium spiny neurons (Stark et al., 2018). Therefore, binding of radiotracers may reflect a mix of pre- and post-synaptic changes (Payer et al., 2015). Moreover, $D_{2/3}$ receptors changes have not been universally observed across the spectrum of maladaptive reward-seeking behaviour, where reductions are notably absent in primary gambling addiction (Nutt, Lingford-Hughes, Erritzoe, & Stokes, 2015; Stark et al., 2018). In individuals with substance dependence there is lower $D_{2/3}$ receptors availability than healthy controls (Volkow et al., 2001), but no differences have been reported in pathological gamblers (Linnet et al., 2011, 2010).

Limitations

The main limitation of the present meta-analysis is the small number of studies included, and consequently the low statistical power, which impede any definite conclusions on the mechanisms underlying ICBs in PD. The small number of studies hampered a moderator analysis, which would have added information on the variables potentially contributing to the results. Therefore, more studies with large numbers of PwP are needed. They should have a longitudinal design with de novo drug naïve PwP, to clarify the causative relations between striatal dopaminergic changes and ICBs, and whether they are pre-morbid vulnerability traits, or a consequence of DRT. Current cross-sectional studies may only document associative links. Future studies should incorporate a healthy control group (Cilia et al., 2010; Lee et al., 2014; Payer et al., 2015), as some dopaminergic changes might be age-related and not directly linked to PD or ICBs (Raz et al., 2003).

PET/SPECT studies on extrastriatal regions, which interact with the striatum in the control of motivated and addictive behaviour (Joutsa, Martikainen, Niemelä, et al., 2012; Lee et al., 2014), are still scarce, and focus on a range of different structures, impeding a meta-analysis. The role of extrastriatal dopaminergic changes should be assessed. At the time of the literature search, five studies reported data on extrastriatal regions, including the orbitofrontal (Joutsa, Martikainen, Niemelä, et al., 2012), medial orbitofrontal (Payer et al., 2015), ventromedial prefrontal (Lee et al., 2014), and left anterior cingulate cortex (Ray et al., 2012), the amygdala (Lee et al., 2014), substantia nigra (Payer et al., 2015), globus pallidus (Payer et al., 2015; Stark et al., 2018), ventral pallidus (Payer et al., 2015), thalamus (Stark et al., 2018), and the midbrain (Ray et al., 2012; Stark et al., 2018). Exploring these areas would be important; for example, abnormal functioning of $D_{2/3}$ midbrain receptors might

results in increased dopamine release (Buckholtz et al., 2010).Since the dopamine system may not be the only player in ICBs development, multi-modal imaging studies should explore the contribution of serotoninergic systems to ICBs in PD (Cilia et al., 2016; Lee et al., 2012; Premi et al., 2016).

Finally, ICBs in PD was found to be associated with cognitive, and affective and motivational factors (Study 2) (Martini, Dal Lago, Edelstyn, Grange, et al., 2018). The potential confounding role of these clinical variables should be considered in future PET/SPECT studies.

Conclusions

The meta-analysis showed specific patterns of dopaminergic dysfunction in the dorsal and ventral striatum in PwP with ICBs. These changes, which, to some extent, differ from those with PD but no ICBs, may reflect either a pre-existing neural trait vulnerability for impulsivity or the expression of a maladaptive synaptic plasticity under non-physiological dopaminergic stimulation (Premi et al., 2016).

Key Findings

- ICB+ have lower DAT levels in the dorsal striatum and in its subdivisions (i.e., putamen, caudate) than ICB-;
- ICB+, compared to ICB-, show increased dopamine release to reward-related stimuli or gambling task in the ventral striatum;
- ICB+ and ICB- have similar striatal post-synaptic receptors availability in both the dorsal and ventral striatum.

Interim Conclusion

In this chapter, brain imaging correlates have been investigated with two studies. The first study is a systematic review of structural and functional brain imaging studies (Study 5). The systematic review shows that structural changes are not consistently evident in PwP with ICBs. Conversely, functional brain imaging studies showed (i) brain changes in resting state networks related to cognitive control and motivation (i.e., CEN and salience network) that precede ICBs onset and remain stable once ICBs are developed. Resting-state studies also show (ii) increase metabolism and cerebral blood flow in brain areas supporting incentive-driven decision-making (i.e., orbitofrontal cortex, amygdala, insula, ventral striatum, posterior cingulate cortex, parahippocampus and hippocampus, middle and inferior temporal, and supramarginal gyri) as well as (iii) abnormal frontostriatal and mesolimbic connectivity. Task-based functional imaging studies evidenced (iv) increase BOLD signal during rewarding stimulus exposition or incentive-driven decision-making task in in brain areas involved in incentive-driven decision-making (i.e., subthalamic nucleus, inferior frontal gyrus and ventral striatum, anterior and posterior cingulate cortex, ventromedial prefrontal cortex, and orbitofrontal cortex).

The systematic review did not include neuropharmacological PET or SPECT studies as they provide neuropharmacological instead of anatomical data. In order to provide information about neuropharmacological striatal PET or SPECT ICBs correlates, a systematic review and meta-analysis has been performed (Study 6). This second study shows (i) lower DAT levels in the dorsal striatum and in its subdivisions (i.e., putamen and caudate), and (ii) increase DA release to reward-related stimuli or gambling task in PwP with vs. without ICBs. Conversely, (iii)

striatal post-synaptic receptors availability, both in ventral and dorsal striatum, does not differ between groups.

Taken together, activity in the network conveying motivational signal appear to be enhanced in PwP with ICBs, both during resting state (as evidenced by rs-fMRI and perfusions studies) and task performance (as evidenced by task-based fMRI and PET studies). Functional imaging studies further evidence frontostriatal disruption. Finally, SPECT studies shows reduced dorsal striatum DAT binding in PwP with ICBs, which may be explained by nigrostriatal terminal loss, functional downregulation, or genetically determined lower membrane expression on otherwise normal neurons. A still open question is how changes in the ventral striatal synaptic transmission influence cortical changes. Future studies should include multiple brain measure to assess in the same cohort of individuals both striatal synaptic transmission and cortical changes. Furthermore, functional connectivity does not imply specific directional effects, therefore, whether the proposed changes in the multiple cortical areas identified by functional brain imaging studies are directly responsible for promoting ICBs to occur (or less able to prevent ICBs from occurring) is unknown. For example, when connectivity between brain areas is reported to be increased or reduced, this does not necessarily mean that those brain areas work better or worse, but simply that brain activity is differently modulated between groups. A future challenge of brain imaging studies concerns the ability to make diagnostic predictions based on imaging markers. A closely related question concerns the extent in which a brain imaging marker predict the performance on a criterion related to everyday life e.g., return to work/social life or being financially independently without requiring partner's surveillance. Now that cortical networks have been identified, future studies should investigate which brain changes predict

performance in daily life. Furthermore, a future area of research concern whether non-invasive brain stimulation (e.g., transcranial magnetic stimulation) targeting the cortical brain areas identified could improve in vulnerable individuals the ability to refrain from acting the ICBs.

Chapter 6 General Discussion

This final chapter of this thesis begins with a summary of the main findings. Then, methodological strengths will be acknowledged and biases within the methodology used will be assessed. Finally, clinical implications and future areas of research that may arise from this thesis' findings will be discussed.

The psychological and neural correlates of Impulsive-compulsive behaviours in Parkinson's disease

The overarching aim of this thesis was to identify psychological (cognitive, affective and motivational) and neural correlates of impulsive-compulsive behaviours (ICBs) in already diagnosed cases, as a first step toward a future longitudinal investigation of newly diagnosed cases of persons with Parkinson's disease (PwP) as they start dopamine replacement therapy (DRT).

Identifying reliable correlates of ICBs has important clinical implications as (i) findings may inform psychological intervention and the development of potentially effective drug treatments, and (ii) they may also have a transdiagnostical application to ICBs that develop in other non-PD populations such as restless leg syndrome, fibromyalgia, and addiction. Correlates of ICBs in PD also have scientific relevance as the PD population provides a mean for testing cognitive and neural models of incentive-driven decision-making developed in healthy populations.

In the current thesis, psychological and neural correlates of ICBs have been investigated across three behavioural, one neurophysiological and two brain imaging studies. In line with the Research Domain (RDoC) framework promoted by the National Institute of Mental Health (Insel et al., 2010), multiple units of assessment

approach has been used (see section “thesis framework”, page 13). The underlying premise is that, for a feature to be a reliable marker of ICBs, it should be evident across multiple levels of analyses. This is important because literature on psychological and neural correlates of ICBs in PD is undermined by inconsistency in studies’ findings. The main findings of the studies of this thesis are illustrated in Figure 6.1. The left-hand panel of Figure 6.1 has already been illustrated in Chapter 1 (see Figure 1.1, page 15) and here it has been completed with the right-hand side with the main findings.

On the basis of the studies of this thesis, the overarching aim was not completely met, nor the controversy in the literature has been completely resolved. However, this thesis makes a significant original contribution to the body of knowledge by providing evidence that supports some mechanisms compared to others as underpinnings of ICBs in PD.

Cognitive correlates have been investigated with two behavioural empirical studies, one systematic review and meta-analysis, and one neurophysiological investigation (Studies 1, 3, 2 and 4, respectively; Chapters 3 and 4). Evidence from this thesis weakens the claims of one hypothesis about the cognitive processes involved in ICBs in PD, which is abnormal negative feedback processing (Frank et al., 2004; Sinha et al., 2013; van Eimeren et al., 2009), as two units of assessments (behavioural and neurophysiology) suggest comparable negative feedback processing in PwP with and without ICBs. Alternative hypothesis —supported by neuroimaging data of this thesis — is about enhanced sensitivity toward positive feedback or reward (Frank et al., 2004; Sinha et al., 2013; Voon, Pessiglione, et al., 2010). Finally, cognitive control seems to be affected in PwP with ICBs as showed by behavioural and brain imaging data, although data do not allow to identify what is

the specific task-related cognitive process of cognitive control implicated in ICBs in PD, as the findings of the behavioural studies are not consistent.

Affective and motivational correlates have been investigated with two behavioural empirical studies and one systematic review and meta-analysis (Studies 1, 3 and 2, respectively; Chapter 3). Evidence from this thesis suggests that depression might be a reliable correlate of ICBs in PD. Conversely, apathy seems not to be associated with ICBs in PD. Whether anxiety and impulsivity are correlates of ICBs in PD remain unresolved as there are disagreements in the findings of the three studies.

Neural correlates of ICBs have been investigated through one systematic review and one systematic review and meta-analysis (Studies 5 and 6; Chapter 5). Evidence suggests that functional brain changes in PwP with ICBs encompass mesolimbic brain areas involved in the reward processing as well as prefrontal brain areas involved in the top-down cognitive control. Finally, lower dopaminergic transporter (DAT) levels in the dorsal striatum during resting-state and increase dopamine release in the ventral striatum during gambling task or reward-based stimuli exposure seem to characterize ICBs in PD. Quantitative analysis of the structural and functional brain changes (except for dopaminergic neurotransmission, which has been investigated in Study 6) was not possible due to the small number and heterogeneity of the studies included.

Taken together, the studies of this thesis support the following hypotheses about the mechanisms involved in ICBs in PD: i) spared negative feedback processing, ii) possibly enhanced sensitivity toward reward; iii) reduced cognitive control, iv) increased depression and spared apathy, v) functional brain changes in prefrontal and mesolimbic areas of the brain supporting cognitive control and

motivation vi) reduced DAT binding in the dorsal striatum. These hypotheses should be further tested in a homogeneous clinical population and, if subsequent evidence strengthens this thesis findings, then data may have strong implications for clinical purposes. Correlates of this thesis will be included in a longitudinal study and, based on the results of this thesis, predictions will be made.

Consistency of findings across multiple units of assessments are illustrated in Table 6.1. Each of the main findings have been discussed below, together with recommendations for future investigations.

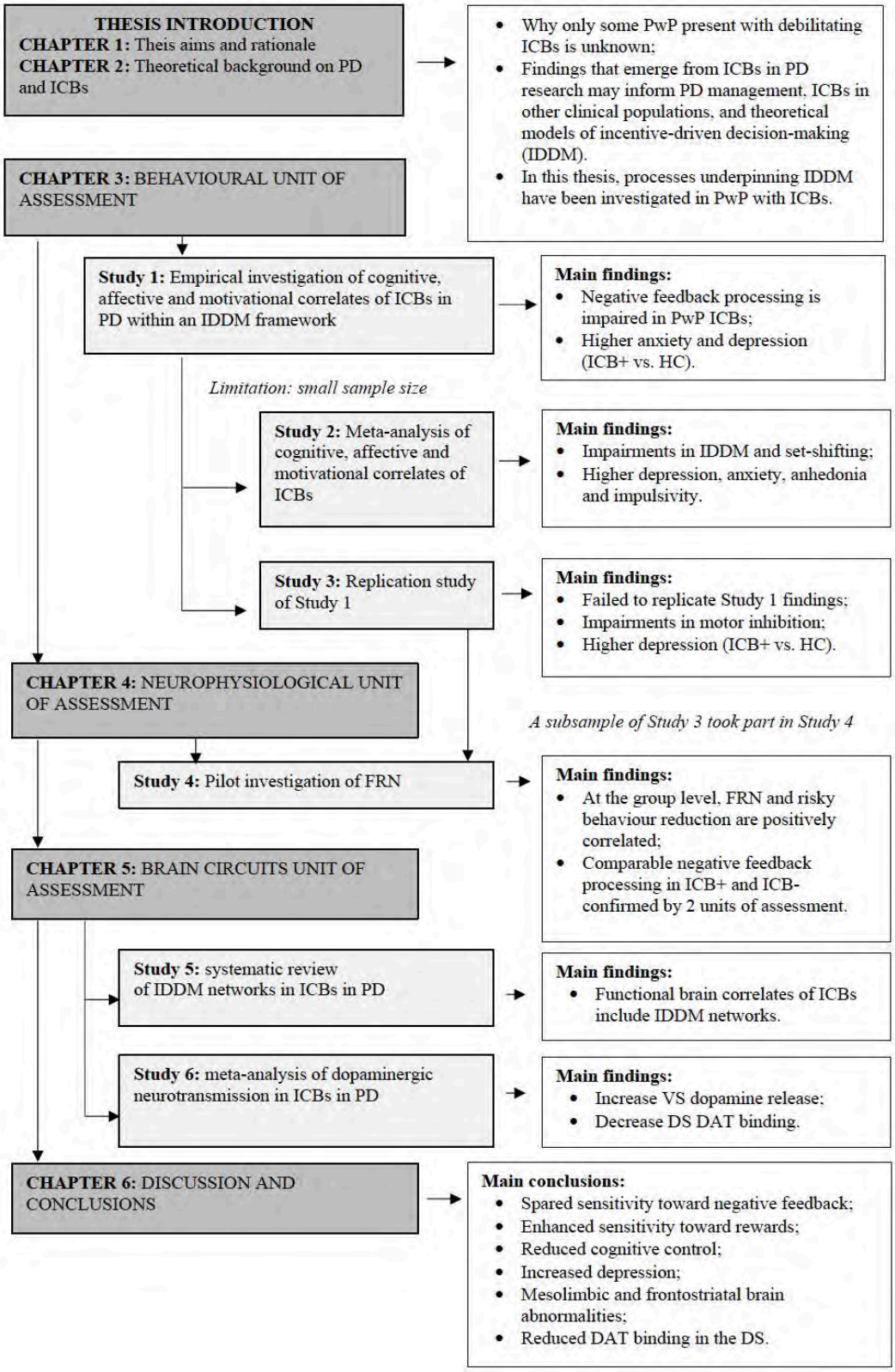


Figure 6. 1 Summary of the thesis' main findings. PD: Parkinson's disease; ICBs: impulsive-compulsive behaviours; IDDM: incentive-driven decision-making; FRN: feedback-related negativity; DS: dorsal striatum; VS: ventral striatum; HC: healthy

controls; ICB+: persons with PD and ICBs; ICB-: persons with PD but no ICBs; DAT: dopaminergic transporter.

Table 6. 1 Consistency of findings across multiple units of assessments.

ICBs correlates	**Behavioural**	**Neurophysiological**	**Brain Circuit**	**Reliable (between or within assessments levels)**
Negative feedback processing	-	-	Not investigated	Probably not associated
Enhanced sensitivity toward positive feedback	+-	Not investigated	+	Unclear
Cognitive control	+	Not investigated	+	Possible
Depression	+	Not investigated	Not investigated	Possible
Decrease DAT binding in DS	Not investigated	Not investigated	+	Possible

Legend. ICBs: impulsive-compulsive behaviours; DAT: dopamine transporter; DS: dorsal striatum; +: associated; -: not associated; +-: unclear.

Cognitive correlates

Negative Feedback Processing During Incentive-driven decision-making. Evidence of this thesis weakens the claim of one hypothesis about the mechanisms supporting ICBs in PD, which is abnormal negative feedback processing (Frank et al., 2004; Sinha et al., 2013; van Eimeren et al., 2009).

The behaviour of individuals with addiction is characterised by perseverating in activities that, in the longer-term, lead to negative and often devastating consequences, such as financial debts, relationship breakdown, impairments in work and social life, and legal problems (American Psychiatric Association, 2013). The serious situations in which PwP with debilitating ICBs are often involved suggested an inability to adequately estimate negative consequences of reward-seeking behaviours. Optimal incentive-driven decision-making reflects the ability to choose the most advantageous behavioural option over a range of alternatives, considering both positive and negative consequences. Once the behaviour is acted, adequate processing of negative and positive feedback is crucial for the comparison of the real outcomes of the behaviours with the predicted ones. Such comparison plays a role in learning and it is important for decisions that should be taken in the future (Sinha et al., 2013). The processing of rewards and punishments is mediated by dopamine (Frank et al., 2004), and chronic tonic stimulation by DRT could prevent pauses in the dopaminergic signalling, thereby interfering with the detection of negative prediction errors, which could decrease sensitivity to negative outcomes (Bodi et al., 2009; Frank et al., 2004; van Eimeren et al., 2009; Voon et al., 2017). As ICBs may arise after DRT initiation, it has been hypothesised that dopaminergic medication, in predisposed individuals, may disrupt negative feedback processing resulting in an underestimation of adverse consequences of reward-seeking behaviours.

However, findings of this thesis do not support this hypothesis. In the first study, both PwP without ICBs and healthy controls, but not PwP with ICBs, decreased their risky behaviour after a negative feedback in the Balloon Analogue Risk Task (BART); albeit promising, this data has not been replicated in the larger study, which failed to find between groups differences (Study 3). The lack of between group differences cannot be attributed to the lack of sensitivity of the behavioural assessment, as this data has been confirmed by a second unit of assessment (Study 4). In particular, the amplitude of the 'feedback-related negativity event-related potential' (FRN), which occurs 200-300 msec after negative feedback, correlated with risky behaviour after negative feedback although no differences between PwP with and without ICBs were found. Therefore, two units of assessments converge to suggest that negative feedback impairments do not account for ICBs in PD. However, these findings should be cautiously interpreted for two reasons. First, in Study 3 the effect of negative feedback was significant only when education was not included as covariate in the model. Second, in Study 4 the sample size is too small for between-groups comparison. However, being Study 4 the first investigation of FRN in PwP with ICBs, this thesis sets up a scenario from which predictions about negative feedback processing in ICBs in PD can be drawn. Previously, research was theory-based, but now there is a prediction (i.e., spared negative feedback processing) that it is empirically informed.

Literature on ICBs in PD provides inconsistent findings on impairments in negative feedback processing. For example, Piray et al. (2014) showed that, in 16 PwP with ICBs vs. 15 PwP without ICBs, learning is better for reward and worse for punishment. However, there is also evidence of decreased learning from negative feedback and increased learning from positive feedback in the "off" compared with

"on" dopaminergic medication in 18 ICB+, with the opposite pattern in the 12 ICB- (Djamshidian et al., 2010), which is the opposite of what it could be predicted based on Frank et al. (2004). Using the BART, Claassen et al. (2011) showed that both PwP with and without ICBs (ICB+: 22; ICB-: 19) decrease their risky behaviour after losses, suggesting preserved sensitivity toward negative feedback. Differences in paradigms used for assessing negative feedback processing may account for variability of studies' findings, with some tasks being more sensitive than others. It is possible that the BART, which has been used in this thesis, is not the best task for assessing negative feedback processing. The hypothesis of impaired negative feedback processing could be ruled out if more rigorous studies, using several paradigms, converge in supporting preliminary findings of this thesis.

This thesis makes a significant original contribution to the body of knowledge by adding evidence that support the hypothesis that negative feedback processing is not a mechanism of ICBs in PD. This hypothesis needs to be further replicated with subsequent data in a homogeneous clinical population. In future investigations, Bayesian model could be used as it reallocates credibility across the different possible causes of a behaviour based on the evidence gathered, subsequently updating from prior to posterior as more data are collected (Etz, Gronau, Dablander, Edelsbrunner, & Baribault, 2018).

Alternative plausible factor that may contribute to ICBs in PD is enhanced sensitivity toward positive feedback, and detailed information is provided below.

Enhanced Sensitivity Toward Reward. Alternative plausible factor that may contribute to ICBs in PD and that should be further investigated is enhanced sensitivity toward positive feedback. Consumption of reward — being food, sex or

receiving money or buying new items — produces a hedonic state, important for consolidating cues that predict availability of rewards in the future or actions that facilitate rewards achievement (Wise & Kiyatkin, 2011). Based on prior experience, our brain is able to store and estimate the value of certain actions, which is crucial for selecting advantageous options over a range of alternatives (Sinha et al., 2013).

This thesis points to the possibility that enhanced sensitivity toward rewards is a mechanism supporting ICBs in PD. This is evident from the systematic review of brain imaging studies (Study 5) which shows resting-state enhanced activity in the salience network (which includes limbic-paralimbic structures, such as anterior insula, the anterior cingulate cortex, and the ventral striatum, that are activated by salient or rewarding stimuli) of PwP with ICBs (Navalpotro-Gomez et al., 2020; Tessitore, Santangelo, et al., 2017). Interestingly, this alteration is also evident before ICBs onset thereby suggesting a premorbid vulnerability trait (Tessitore, De Micco, et al., 2017). Furthermore, PwP with ICBs show enhanced brain metabolism (Marín-Lahoz et al., 2020; Verger et al., 2018) and cerebral blood flow (Cilia et al., 2008; Claassen et al., 2017) in brain areas implicated in reward processing such as orbitofrontal cortex, amygdala, insula, ventral striatum. In task-based fMRI studies, the same areas exhibit increase Blood Oxygenation Level Dependent (BOLD) signal during exposition to reward-related cues or during performances of tasks assessing risk-taking behaviour and temporal discounting (Frosini et al., 2010; Loane et al., 2015; Paz-Alonso et al., 2020; Politis et al., 2013). The systematic review and meta-analysis of PET/SPECT striatal studies further supports the notion of enhanced sensitivity toward rewards by showing increased dopamine release in the ventral striatum of PwP with vs. without ICBs during gambling task and/or exposure to reward-related stimuli (Study 6).

The main risk factor for ICBs development in PD is DRT use (Molde et al., 2018; Weintraub et al., 2010), although a clear dose-response relationship has to be established yet (Biundo et al., 2017; Corvol et al., 2018; Erga et al., 2017; Hurt et al., 2014; Isaias et al., 2008; Perez-Lloret, Rey, Fabre, Ory, Spampinato, Brefel-Courbon, et al., 2012; Valença et al., 2013; Vela et al., 2016). Dopamine mediates the way in which our brain stores and estimates the value of certain actions (Frank et al., 2004; Pignatelli & Bonci, 2015). The role of dopamine in reward processing is supported by evidence of impairments in reward learning in drug naïve PwP, which is remediated after dopamine (DA) agonist administration (Bodi et al., 2009). In vulnerable individuals, sensitivity toward reward may be enhanced by DRT facilitating reward-seeking behaviours that, along time, become addictions.

The findings of this thesis are in line with the broad addiction literature in PD and non-PD populations. Several studies show that dysfunctional reward processing might contribute to the onset of the addictive behaviours in humans. For example, impulsive individuals tend to prefer smaller immediate rewards over larger but temporally delayed rewards (Amlung et al., 2019), and this also extends to ICBs in PD (Housden et al., 2010; Voon, Sohr, et al., 2011), although there are also data showing comparable performances (Joutsa et al., 2015). Furthermore, DA agonist enhanced learning from reward in 14 PwP with ICBs compared to 14 PwP without ICBs, which was associated with higher ventral striatal activity (Voon, Pessiglione, et al., 2010). A recent study showed heightened sensitivity to monetary rewards cues both “on” and “off” DRT (as indexed by pupillary dilatation) in 23 PwP with ICBs, whilst in 26 PwP without ICBs reward sensitivity was reduced when “off” DRT (Drew et al., 2020); interestingly, pupil reward sensitivity was predictive of future ICBs development in PwP without ICBs.

Despite promising, the hypothesis of enhanced reward sensitivity should be corroborated by larger studies with homogeneous clinical samples, and using multiple levels of assessment. The behavioural data of this thesis do not support a clear association between ICBs and reward sensitivity as between-groups differences in reward-based measures were found in the systematic review and meta-analysis (Study 2, Chapter 3; temporal discounting task, Iowa Gambling Task, risk taking and probabilistic reward tasks), but not in the empirical studies (Studies 1 and 3, Chapter 3; temporal discounting task, Iowa Gambling Task, and the BART). In this thesis, neurophysiological data are missing as the BART version used prevents any analyses of event-related potential underlying reward valuation and magnitude (i.e., P300). Future studies should assess reward sensitivity in a single cohort of PwP with and without ICBs using multiple units of assessments approach (see section "future research", page 443).

Reduced Cognitive Control. Evidence of this thesis supports the notion that cognitive control may be implicated in ICBs in PD; however, what are the specific cognitive processes involved remains unclear.

Cognitive control reflects the ability to effectively and adaptively identify, manipulate and process relevant information in order to direct behaviour towards one's internal goals and suppress automatic pre-potent responses when necessary (Badre, 2011). Cognitive control processes are therefore implicated in the option generation and selection, and action inhibition or initiation stages of incentive-driven decision-making (Sinha et al., 2013) (see Figure 3.1, page 86). Cognitive control, and the neural systems that support it, are componential (Badre, 2011).

The behavioural studies of this thesis found that PwP with ICBs show worse performance compared to PwP without ICBs in two components of cognitive control — namely, set-shifting and inhibition —, although there is no consistency across studies. In other words, the systematic review and meta-analysis shows impaired set-shifting ability (as assessed by TMT-B) and spared inhibitory control (as assessed by Go/No-Go, Stop Signal task, and Stroop tasks) in PwP with ICBs vs. without ICBs (Study 2); the opposite was found in the second empirical study (i.e., impaired performances in the Go/No-Go task but comparable performance in the TMT-B) (Study 3).

Based on lesion mapping studies, set-shifting and inhibitions relies on prefrontal cortex regions such as rostral anterior cingulate cortex (ACC) and left dorsolateral prefrontal cortex (DLPFC), respectively (Gläscher et al., 2012). This is in line with cognitive neuroscience studies that show that cognitive control relies on prefrontal cortex functioning based on rostro-caudal hierarchical organization (Azuar et al., 2014; Badre & Nee, 2018). In particular, rostral parts of the lateral prefrontal cortex get gradually more involved when cognitive control demands become increasingly abstract and the apex of this hierarchy resides in the mid-DLPFC (Badre & Nee, 2018; Nee & D'Esposito, 2016).

The systematic review of structural and functional correlates of ICBs in PD provides evidence that neural correlates of ICBs encompass brain structures important for cognitive control. For example, resting-state imaging studies show reduced functional connectivity in the central executive network (composed by the DLPFC and inferior parietal cortices) in PwP with ICBs, which is also evident in drug naïve PwP who later develop ICBs (Tessitore, De Micco, et al., 2017;

Tessitore, Santangelo, et al., 2017); the central executive network is usually engaged during cognitively demanding tasks or goal-directed behaviours.

According to cognitive neuroscience research, cognitive control interacts with motivation during incentive-driven decision-making, therefore impacting on the extent to which goal directed behaviours are regulated, or not as in the case of ICBs [for a review see (Yee & Braver, 2018)]. Indeed, studies included in the systematic review show reduced frontostriatal connectivity in ICB+ vs. ICB- (Carriere et al., 2015; Cilia et al., 2011; Girard et al., 2019; Markovic et al., 2017; Mosley et al., 2019; Ruitenberg et al., 2018). For example, greater impulsivity in a gambling task has been associated with lower structural connectivity between the ventral striatum and the ventromedial prefrontal cortex in ICB+, with the opposite effect in ICB- (Mosley et al., 2019). Decreased connectivity between ventral striatum and the lateral orbitofrontal cortex and the ACC has been observed (Cilia et al., 2011) suggesting a dysfunctional inhibitory fronto-striatal network. This dysfunctional frontostriatal connectivity may disrupt integration of cognitive control and motivational inputs during incentive-driven decision-making. Indeed, impaired top-down inhibitory control is a feature of addiction in general population, that leads to impaired salience attribution to drug-cues, decreases sensitivity to non-drug reinforcers, and decrease inhibition of maladaptive behaviours (Goldstein & Volkow, 2011). It should be noted that the cross-sectional design of the studies included in the thesis impede any interpretation about the direction of the effect, therefore two not mutually exclusive hypothesis could be drawn. The first is that reduced cognitive control predate ICBs onset, thereby promoting the initiation of ICBs-related behaviours. In other words, when cognitive control functions deficiently, it can affect impulse control abilities leaving PwP unable to manage

urges that, over time, lead to financial, personal, and family problems that affect quality of life (Esteban-Peñalba, Paz-Alonso, Navalpotro-Gómez, & Rodríguez-Oroz, 2021). Alternatively, reduced cognitive control may be a consequence of chronic exposure to risky behaviours involving rewards which may trigger adaptive changes in the fronto-striatal reward system. For example, some PwP may experience their ICBs as stressful events (Delaney, Simpson, et al., 2012), and stress can impair performance on cognitive control tasks by increasing release of catecholamine in the prefrontal cortex (Cools, 2016). Finally, it cannot be excluded that cognitive control and ICBs presence might co-occur as epiphenomena of shared neural correlates (i.e., DLPFC) (Botvinick & Braver, 2015; Martini et al., 2020; Yee & Braver, 2018). Taken together, evidence from behavioural (Studies 2 and 3) and brain imaging level of assessments (Study 5) suggest that cognitive control may be a feature of ICBs in PD. Considering the lack of consistency in the behavioural findings, any interpretation about the specific cognitive control processes involved in ICBs in PD should be cautiously done and further investigation is required.

Affective correlates

Increased depression. This thesis provides evidence that, within the affective and motivational factors investigated, depression seems to be a reliable marker of ICBs in PD. Using the same paradigm (i.e., Hospital Anxiety and Depression scale), in two empirical studies (Studies 1 and 3; Chapter 3) higher depression levels in PwP with ICBs compared to healthy controls were observed. Moreover, in the systematic review and meta-analysis of cognitive, affective and motivational correlates of ICBs in PD (Study 2; Chapter 3), higher depression levels were reported in PwP with ICBs compared to PwP without ICBs. It should be noted

that in Study 4 no differences in depression levels between PwP with and without ICBs have been found, probably due to the small sample size and reduced statistical power.

Increased depression levels in PwP with ICBs is in line with previous reports showing co-occurrence of ICBs and depression in PD (Callesen et al., 2014; Gallagher et al., 2007; Joutsa, Martikainen, Vahlberg, Voon, et al., 2012; Pontone et al., 2006; Voon, Sohr, et al., 2011), although this data has not been consistently reported (Bentivoglio et al., 2013; Biundo et al., 2011, 2015; Cilia et al., 2008; Claassen et al., 2015; Mack et al., 2013; Piray et al., 2014; Tessitore et al., 2016; Vitale et al., 2011). Reasons for inconsistency may range from variability in demographic and clinical characteristics of the studies' sample to paradigms used to assess depression. For example, risk factors for depression in PD include longer disease duration, motor fluctuations, female sex, disability, higher doses of levodopa, and younger age (Marinus et al., 2018); if samples are not well matched for these clinical characteristics, this could create a bias in the findings. Moreover, many symptoms of depression (e.g., fatigue, weight loss, psychomotor retardation) overlap with symptoms of PD or the side-effects of medication making diagnosis of depression problematic (Marinus et al., 2018); therefore, depression scales with limited motor symptoms assessment may be more sensitive to detect depression in PD (Schrag et al., 2007).

Random-effect model meta-analysis can overcome these limitations. This is because it allows to estimate the effects in the population by combining effect sizes from a variety of studies which may differ in their demographic and clinical characteristics or in the paradigms used for assessing the variable of interest (Field & Gillet, 2010). Using this approach, this thesis contributes to the body of knowledge

by showing an association between ICBs in PD and depression. Clear understanding of this association is limited by the use of DA agonists (in particular pramipexole) which may be a potential confounder, as DA agonists are one of the main risk factors for ICBs (Weintraub et al., 2010), but mood may also improve when they are administered (Barone et al., 2010). This thesis supports the notion that depression may be a correlate of ICBs, despite of the use of DA agonists or other DRT type. Indeed, the meta-analysis showed no effect of DA agonist or levodopa dose on the association between depression and ICBs.

The cross-sectional design of the studies included in the thesis impede any interpretation about the direction of the effect; in other words, depression could be a direct consequence of ICBs, being a psychological reaction to the negative consequences of ICBs, which can range from lower quality of life and higher caregiver burden (Erga et al., 2020; Leroi, Harbishettar, et al., 2012; Phu et al., 2014) to severe compromising of social, affective and working areas of functioning (American Psychiatric Association, 2013). Alternatively, ICBs may be a way to cope with a condition as PD, which can cause, among others, social isolation and work retirement. While engaged in their ICBs, PwP could avoid negative thoughts and negative emotions, thus using the behaviour as an emotion-focused coping strategy through emotional avoidance (Delaney, Simpson, et al., 2012). In support of the latter, longitudinal investigations found depression to predate ICBs onset and further increase the risk of developing them (Marín-lahoz et al., 2019; Vriend, Nordbeck, et al., 2014). Finally, it cannot be ruled out that, as mesocorticolimbic dysfunction may be involved both in depression and ICBs, they might co-occur as epiphenomena of shared neural correlates (Vriend, Pattij, et al., 2014). Lesion locations associated with depression are highly heterogeneous, but they can be mapped in a connected

brain circuit centred on the left DLPFC (Padmanabhan et al., 2019). The same region is implicated in ICBs in PD, as supported by structural and functional brain imaging data of the systematic review (Study 5; Chapter 5).

Other affective and motivational correlates. This thesis adds evidence to support the notion that apathy may not be implicated in ICBs in PD. This is supported by comparable apathetic levels between PwP with and without ICBs in all behavioural studies. Apathy and impulsivity are considered as the opposite sides of a dopaminergic continuum, associated with hypodopaminergic and hyperdopaminergic states, respectively (Sinha et al., 2013). This is supported by evidence that DA agonist pramipexole improves apathy (Leentjens et al., 2009) but also increases impulsivity in PD (Weintraub et al., 2010). Conversely, anhedonia seems to be associated with ICBs in PD, as supported by the results of the systematic review and meta-analysis (Study 2). Higher anhedonic levels may be explained by decreased ability to experience pleasure when not engaged in ICBs. This hypothesis is supported by evidence of anhedonic states during withdrawal syndrome in individuals with alcohol or drug addiction (Hatzigiakoumis et al., 2011). If this is true, we might expect this feature to be present only once ICBs have been developed and not in the premorbid stages. However, the systematic review includes only two studies investigating anhedonia, therefore interpretations about the role of anhedonia in ICBs in PD should be cautiously done.

Whether anxiety (Study 1: ICB+ > HC; Study 2: ICB+ > ICB-; Study 3: no difference) and impulsivity (Study 1: no difference; Study 2: ICB+ > ICB-; Study 3: trend toward ICB+ > ICB-) may be correlates of ICBs in PD remain unresolved;

findings of this thesis further perpetuate the ambiguity that exists in the literature since data are not consistent across studies.

Neural correlates

Evidence from the brain imaging studies included in this thesis suggest that brain areas part of the cognitive control and motivational networks supporting incentive-driven decision-making may potentially be neural correlates of ICBs in PD.

In particular, having an ICB is associated with enhanced brain activity in the network conveying motivational signal, which includes orbitofrontal cortex, amygdala, insula, ventral striatum, posterior cingulate cortex, parahippocampus and hippocampus, middle and inferior temporal, and supramarginal gyri, both during resting-state (as evidenced by rs-fMRI and perfusions studies; Study 5, Chapter 5) and task-based studies (as evidenced by task-based fMRI and PET studies; Studies 5-6, Chapter 5). Interestingly, enhanced activity in the salience network — which includes limbic-paralimbic structures, such as anterior insula, ACC, and the ventral striatum — precedes ICBs onset (Tessitore, De Micco, et al., 2017). Furthermore, frontostriatal disruption seems to be implicated in the ICBs in PD, possibly disrupting the integration of cognitive control and motivational inputs during incentive-driven decision-making (Cilia et al., 2011; Mosley et al., 2019; Ruitenberg et al., 2018).

PwP with ICBs also show reduced DAT binding in dorsal striatum, which may be explained by nigrostriatal terminal loss, functional downregulation, or genetically determined lower membrane expression (Study 6). However, it is unlikely that reduced DAT binding is related to functional downregulation due to

DRT, as reduced dorsal striatum DAT binding predate DRT initiation (Smith et al., 2016; Vriend, Nordbeck, et al., 2014). Conversely, higher nigrostriatal degeneration is supported by evidence of increased risk of ICBs in PwP with longer disease duration and under DRT (Molde et al., 2018), two factors which are directly correlated with the amount of nigrostriatal loss. Genetically determined lower membrane expression is supported by higher risk of ICBs in PwP carrying a variant of a gene (i.e., 9-repeat allele of the SLC6A3) which has been associated with lower presynaptic DAT expression, reduced synaptic clearance, and increased DA availability in the synaptic space (Cilia et al., 2016). However, these findings should be further investigated.

Contrary to functional brain imaging, findings from structural imaging are inconclusive. Reasons for inconsistency include small sample size and reduced statistical power, variability in the protocol of acquisition (e.g., scan duration) and data analysis (e.g., pre-processing and analysis, statistical threshold and methods to correct for multiple comparisons), as well as differences in clinical and demographic characteristics of the studies sample (e.g., disease duration, age at PD onset). Due to the small number of studies investigating either functional or structural brain changes (structural only: N = 12; functional only: N = 12; structural and functional: N = 6; see Figure 5.1, page 309) no separate meta-analyses have been done in this thesis; according to the current recommendations, at least 20 studies are needed in order to achieve sufficient statistical power for moderate effects in the Activation Likelihood Estimation coordinate-based neuroimaging meta-analysis (which is possible for whole brain voxel-based, but not for ROI-based studies, therefore further reducing the number of studies that could have been included) (Eickhoff et al., 2016).

Summary

Taken together findings suggest that ICBs in PD may be characterized by reduced dorsal striatum DAT binding, increased brain activity in the mesolimbic reward system and disrupted frontostriatal top-down inhibitory control. The latter is also supported by impaired behavioural performances in cognitive control tasks (i.e., set-shifting and inhibition). Depression seems to be associated with ICBs in PD, potentially as response to the negative consequence of ICBs as negative feedback processing seems to be spared in PwP with ICBs. Subsequent studies are needed to further strengthen or weaken predictions based on the evidence provided by this thesis.

Strengths and Limitations

The main strength of this programme of research is the use of different units of assessments for investigating PwP presenting debilitating ICBs (Insel et al., 2010). Specifically, the units of assessments used include behaviour (Studies 1, 2, and 3; Chapter 3), neurophysiology (Study 4; Chapter 4) and brain circuits (Studies 4 and 5; Chapter 5). The use of multiple units of assessments allows to investigate the same phenomenon from different points of views, looking for convergence. For any feature to be a reliable marker of ICBs, it should be evident across multiple units of analyses. This is the first attempt to shed light on the underpinnings of ICBs using a framework that promotes reliability of studies' findings.

The second main strength of this programme of research concerns the conservative approach used for the allocation of PwP in the ICB+ group. In the empirical studies, ICBs were diagnosed by using a clinical interview based on

published diagnostic criteria. Compared to other clinical tools often used in the clinical and research settings such as the Questionnaire for impulsive-compulsive disorders in Parkinson's disease (QUIP) and the Questionnaire for impulsive-compulsive disorders in Parkinson's disease rating scale (QUIP-rs), only PwP with clinically significant and debilitating ICBs were diagnosed as having ICBs. The QUIP and the QUIP-rs, despite being easy administrable and time saving tools, are constrained by high rate of false positives (Weintraub et al., 2009, 2012) that may not be confirmed, or evaluated as subclinical cases, in a subsequent thorough evaluation. Subclinical ICBs symptoms are considered as a disorder only when their presence interferes with PwP daily life or become harmful for the person (American Psychiatric Association, 2013). Therefore, recruitment of subclinical ICBs could induce interference in the outcomes (Filip et al., 2018). For example, top-down inhibitory control could be spared in PwP who are able to refrain from continuing to gamble after their first bet compared to PwP who continue to gamble for chasing losses. To further confirm ICBs diagnosis, in Study 3 the caregiver was independently interviewed for ICBs presence. This is important because PwP may lack awareness of their ICBs, or be motivated to conceal them due to feeling of guiltiness or shame (Baumann-Vogel et al., 2015).

The third strength of this thesis is the feasibility of the design adopted in the empirical studies. This is supported by the low withdrawal rate (1 PwP in Study 1, none PwP in Studies 3 and 4), therefore excluding attrition bias (i.e., systematic differences between groups in withdrawal from a study).

There are also some limitations that should be taken into account when drawing conclusions from this programme of research.

The main limitation, which is evident across all studies, is the reduced statistical power. When the sample size is small, the statistical power is reduced. The statistical power is the probability that the null hypothesis will be correctly rejected when the null hypothesis is false. Therefore, low statistical power reduces the likelihood of detecting a true effect. At the same time, low statistical power increases the risk that a statistically significant result reflects a spurious finding (i.e., low positive predictive value) (Button et al., 2013). Low statistical power is an endemic problem in neuroscience research [for a review see (Button et al., 2013)] and this also applies to literature on ICBs in PD as evidenced by this thesis. For example, the largest study included in the meta-analysis of cognitive, affective and motivational correlates of ICBs in PD included 58 ICB+ (Biundo et al., 2015) and the smaller included 7 ICB+ (Rossi et al., 2010). The largest study included in the systematic review of structural and functional brain imaging studies of PwP with ICBs included 58 ICB+ (Biundo et al., 2015) and the smaller included 6 ICB+ (Loane et al., 2015). The largest study included in the meta-analysis of striatal PET/SPECT studies of ICBs in PD included 21 ICB+ (Premi et al., 2016) and the smallest 7 (Steeves et al., 2009). In this thesis, the issue of reduced statistical power has been faced using several approaches. First, meta-analyses have been conducted (e.g., for cognitive, affective, motivational factors in Study 2, and for PET/SPECT studies in Study 6) and random-effect models — that weighed effect sizes by their variance, which is higher in smaller studies (Field & Gillet, 2010) — were applied. Second, to ascertain reliability of Study 1 findings, they were replicated in a larger study (Study 3); replication studies are not so common in the psychological research and once performed their replicability is very low [for an example see (Open Science Collaboration, 2015)]. Third, aside of p-values — which depend on both sample size

(the larger is the sample, the lower is the p-value) and effect sizes — , effect sizes have been provided; effect sizes are independent of sample size (Sullivan & Feinn, 2012). Finally, in order to increase recruitment rate, multicentre design was implemented in Study 3. Since small sample size could increase both Type I and Type II errors, any interpretation of the studies' findings as well as generalization to the larger PwP population should be carefully done.

The second limitation concerns the variability in demographic and clinical characteristics of the studies' sample. For example, in Study 1 there were no differences in PwP with and without ICBs, but in Study 3 PwP with ICBs had younger age at PD onset, longer disease duration, and higher DRT levels. Differences between studies emerged despite using the same inclusion and exclusion criteria. This makes the conclusions about replicability of Study 1 problematic, as findings may differ due to baseline differences in the studies' sample (namely, selection bias). Recruitments of unmatched samples is frequent in the ICBs in PD literature. This is supported by the systematic review of brain imaging studies (Study 5) which included 11/30 studies where PwP with and without ICBs groups were not matched for demographic and clinical characteristics that may impact studies' findings, such as DRT levels, age at PD onset, PD duration, PD stage, severity of motor functioning (see Tables 5.2, 5.4, 5.6, 5.8, Chapter 5). In the meta-analyses, the issue of homogeneity of the samples was approached by using random-effect models, which consider both within and between study variances (Field & Gillet, 2010). Future studies should recruit a larger number of PwP in order to match cases and controls for avoiding baseline differences in the studies sample.

The third limitation is the presence of PwP with short disease duration and consequently short DRT initiation. Longitudinal studies evidence that ICBs can

appear also after 5 years of DRT initiation (Corvol et al., 2018), therefore PwP allocated to the ICB- group with PD duration < 5 years may have not developed a debilitating ICB yet, but they may will do it in the future. This may be problematic because these individuals may present pre-morbid vulnerability changes potentially creating a bias in the findings and possibly leading to null results.

The fourth limitation is the use of blinding procedure in one study only (Study 1). Unblinding of assessors may increase the risk of performance bias, as previous knowledge of group allocation may affect tools administration and scoring. Due to the feasibility of the study procedure, blinding was not possible in the second empirical study (Study 3) as the research visits assessor was also involved in the screening session. In this study, contrary to predictions findings are unlikely to be affected by performance bias, whilst positive findings (i.e., higher false alarms in the Go/No-Go task) are unlikely to be affected either as they concern computerized task with responses automatically recorded and instructions visually presented in the computer screen. Finally, questionnaires were filled independently by participants. Blinding procedures are very uncommon in the ICBs in PD literature, as supported by evidence in Study 2 of only 2/25 studies indicating assessor blinding procedures.

Clinical implications

Negative feedback processing. The findings of this thesis suggest that PwP with ICBs are able to process negative feedback and consequently adjust their goal-oriented behaviour. If subsequent evidence strengths these findings in a larger and homogeneous clinical population with PD duration longer than >5 years (see section "strengths and limitations", page 434), then this data may have strong implications for clinical practice.

If individuals with ICBs are able to adequately process negative feedback, they are aware of the consequences of what they do, but still cannot restrain from pursuing in their behaviour. This in turn may have a negative impact on their mental state, potentially leading to increased levels of distress, which are evident in higher levels of depression and anxiety in PwP with ICBs, as reported in this thesis. Therefore, when clinicians are facing PwP with ICBs, they should pay attention to their mental health.

If awareness of negative consequences of ICBs results in increased depression and anxiety, we may expect to find a positive correlation between negative feedback (i.e., discrepancy score in the BART) and any affective measure (i.e., depression and anxiety). However, the behavioural studies of this thesis fail to find any association between measures. This finding is in line with previous evidence of depression levels correlating with memory but not executive dysfunction (including impulsivity) in PwP with ICBs (Mack et al., 2013). The lack of association between affective measures and negative feedback processing may be due to the nature of the affective questionnaires used, which may not be suitable for directly investigating the emotional effect of negative feedback processing. Future studies should investigate the relationship between awareness of the negative consequences of behaviour and emotion using specifically validated tools. Furthermore, it should be also noted that being aware of the negative consequences of a behaviour is not the same as recognizing the behaviour as problematic, and this topic warrants further investigation.

Prevalence rates of ICBs based on PwP self-reports are lower than the ones reported by their caregivers (Baumann-Vogel et al., 2015; Lim et al., 2011), suggesting two mutually exclusive hypotheses: (i) lack of awareness of ICBs, or (ii)

feelings of guilt and shame that may prevent PwP to disclose the behaviours or deny its presence. Findings of this thesis support the latter hypothesis, as PwP were found able to process negative feedback and change their behaviour accordingly. This is also in line with a qualitative study showing that for some PwP their ICBs represent a coping mechanisms for facing PD impact on their lives (Delaney, Simpson, et al., 2012), and with a study showing that PwP with ICBs are aware of their executive dysfunction, including impulsivity (Mack et al., 2013) In summary, this thesis opens up an important clinical question (i.e., the relationship between negative feedback processing, awareness and emotional impact in ICBs in PD) for which research is needed to explore further.

Cognitive control. The findings of this thesis suggest that PwP with ICBs may show reduced cognitive control. Specifically, the behavioural studies of this thesis found that PwP with ICBs show worse performance compared to PwP without ICBs in two components of cognitive control — namely, set-shifting and inhibition —, although there is no consistency across studies. Furthermore, the systematic review of structural and functional correlates of ICBs in PD provides evidence that one of the neural correlates of ICBs involves prefrontal cortex brain areas (mainly, DLPFC) important for cognitive control. If further evidence collected will confirm those findings, then psychological interventions targeting those dimensions may be developed.

ICBs and impulsive responding may result from failures in the top-down prefrontal cortex systems to regulate behaviours at the level of the striatum (Dalley, Everitt, & Robbins, 2011). The top-down cognitive control allows the suppression of goal-irrelevant stimuli and behavioural responses which may not ideal for goal-

oriented behaviours. If ICBs are, at least in part, the result of a disruption of the top-down cognitive control processes, this could explain why in some cases they remain unexpressed until PwP are strictly monitored by the carer and emerge when this external inhibitory control ends. In this scenario, it is even more important to provide carers with detailed information (e.g., implementing parent-training sessions) about ICBs in order to improve surveillance.

The top-down model could be considered when developing and implementing non-pharmacological interventions. This is important because, within all factors involved in ICBs in PD, cognitive changes may be considered potentially modifiable as there are readily available therapies. For example, cognitive control training using paper and pencil tasks or computerized programs have been found to improve cognitive control in older adults and clinical populations (Amer, Campbell, & Hasher, 2016; Anguera et al., 2013; Edwards, Barch, & Braver, 2010). Alternatively, psychological interventions for addictive behaviours [e.g., Relapse Prevention model (Hendershot, Witkiewitz, George, & Marlatt, 2011)] may focus on coping strategies for handling high risk situations therefore preventing relapses in individuals with reduced cognitive control that are at risk of performing ICBs behaviours. Within psychological interventions, cognitive behavioural therapy (CBT) has been found to be effective in reducing ICBs in PD. For example, a recent randomized controlled trial of 12 sessions of CBT compared to a waiting list control condition found improvement at the 6-months follow-up in global symptom severity in the CBT intervention group vs the control condition (Okai et al., 2013). The intervention consisted in sessions including psychoeducation on ICBs but also on executive dysfunction (which include cognitive control), motivational interviewing to identify where the patient was in terms of the cycle of change, monitoring of

behaviour, problem solving and pleasant activity scheduling. Future studies may develop CBT trainings tailored to the specific cognitive control impairments reported in PwP with ICBs, which may increase effectiveness of treatments. The National Institute for Health and Care Excellence (NICE) guidelines recommend CBT for PwP with ICBs as management strategy, above all when the approach of discontinuing or tampering DA agonists is not successful (National Institute for Health and Care Excellence, 2017; Rogers et al., 2017), However, there are only two studies investigating CBT in PwP with ICBs and larger trials are warrant.

Depression. The findings of this thesis suggest that depression may be a consistent feature of ICBs in PD. If further evidence supports this finding (the studies of this thesis may have not provided adequate power for affective measures), depression should be routinely assessed in clinical practice. Its presence could inform clinicians about the likelihood that an ICB could co-occur or may be developed in the future, therefore optimizing medical decisions (e.g., type of medications to be prescribed, closed follow-up for early detection of ICBs onset). In order to do that, clinicians may use tools that include low number of motor items which may be confounded for motor features of PD; in this regard, the Hospital Anxiety and Depression Scale (HADS) is a not time-consuming tool that has been recommended for screening depression in PD since the low number of somatic items included (Schrag et al., 2007).

Association between ICBs and depression paves the way for future studies on non-pharmacological treatments of ICBs. The two conditions share some neural correlates, in particular the DLPFC (Padmanabhan et al., 2019; Tessitore, De Micco, et al., 2017; Tessitore, Santangelo, et al., 2017), as well as ACC, orbitofrontal cortex,

thalamus, amygdala and hippocampus (Martini et al., 2020; Wen, Chan, Tan, & Tan, 2016). Non-invasive brain stimulation of the left DLPFC using high frequency transcranial magnetic stimulation (HF-rTMS) for treating major depression has been proven to be effective in general population (level A recommendation) and probably effective in PD (level PD recommendation) (Lefaucheur et al., 2020). Whether the HF-rTMS of the DLPFC could be useful to also improve ICBs warrants further investigation, as there are no such studies in PwP with ICBs.

Future Research

The present research generates five main questions that would be of a particular interest for further investigation. Each of them is considered in turn.

Enhanced sensitivity toward positive feedback. The present research was unable to inform whether sensitivity toward positive feedback is enhanced in PwP with ICBs. As explained above, positive feedback processing is crucial for incentive-driven decision-making (Sinha et al., 2013) and it has been shown to be modulated by dopamine (Bodi et al., 2009; Frank et al., 2004). If individuals are oversensitive toward positive feedback, their motivation toward pursuing rewards is enhanced and cognitive control mechanisms may not be strong enough for inhibiting strong drives associated with behaviours that in the longer terms may be associated with negative consequences. Increased reward sensitivity is supported by evidence of increased dopamine release during gambling task or reward-based stimuli exposure (Study 6) as well as by increased brain activity in areas implicated in reward processing (Study 5). Behavioural data of this thesis do not clearly support an association between enhanced sensitivity toward reward and ICBs in PD (e.g., PwP with and without

ICBs differences in temporal discounting in Study 2, but not in Studies 1 and 3). Neurophysiological investigation of reward processing was not possible in this thesis, as the paradigm used prevents analyses on the positive feedback trials (see page 273; Chapter 4). Future studies may include multiple levels of assessments for evaluating sensitivity toward reward in a single cohort of PwP with and without ICBs, thereby controlling for differences in PD population, screening and assessment measures. In order to do that, a modified version of the IGT which allows separate ERP analyses (i.e., FRN and P300) for positive and negative feedback could be used (Mapelli et al., 2014), as well as fMRI analyses on resting-state and task-based conditions (Frosini et al., 2010; Loane et al., 2015; Politis et al., 2013; Tessitore, Santangelo, et al., 2017).

An intriguing question is whether enhanced sensitivity toward reward, if present, is maintained when ICBs are remitted. If so, this could support the notion that, along time, synaptic plasticity related to craving causes long-term potentiation in the reward system. Once DRT dose is decreased, ICBs remit although they will appear if PwP are exposed to the same dose. No study on reward sensitivity in remitters vs. active ICBs and non-ICBs has been published yet.

Longitudinal investigation of ICBs in PD. The present work adds evidence that support several hypotheses about the cognitive and affective correlates of ICBs in PD, which are (i) cognitive control, and (ii) depression. Furthermore, potential neural correlates of ICBs have also been identified, which are (i) lower DAT binding in dorsal striatum, (ii) increased brain activity of areas belonging to the incentive-driven decision-making networks (i.e., ventral striatum, orbitofrontal cortex, ventromedial prefrontal cortex, anterior and posterior cingulate cortex, amygdala,

insula, parahippocampus and hippocampus, middle and inferior temporal, and supramarginal gyri), and (iii) frontostriatal disconnection as well as decreased activity of the central executive network (DLPFC and inferior parietal cortices) during resting-state. Therefore, the studies of this thesis that could be expanded to answer the prediction question of which PwP may develop clinically significant ICBs are the behavioural (depression and cognitive control) and brain imaging ones.

In particular, these ICBs correlates will be included in a longitudinal study and, based on the results of this thesis, predictions will be done. Longitudinal study can ascertain whether changes, if present, predate ICBs onset and DRT initiation.

Cross-sectional studies only evidence whether there is reciprocal relationship between ICBs and the investigated factors (i.e., the two things go together); conversely, longitudinal studies can indicate whether ICBs correlates are expression of risk factors (premorbid vulnerability) or represent changes associated with constantly being engaged in the behaviour (episode-related factors). Understanding of the role of correlates of ICBs has important implications. Once they appear, ICBs are usually treated by reducing the DRT dose or switching to another DRT type (National Institute for Health and Care Excellence, 2017); however, this approach is not always effective (see page 8, Chapter 1) and a shift toward a preventive approach should be pursued. In order to encourage this change, factors associated with ICBs should be divided in vulnerability (i.e., factors abnormal before ICBs development) and episode-related (i.e., abnormal during the ICB, but not when the ICBs is remitted). This partition has two synergic implications. On one hand, (i) once episode-related factors are identified, new therapeutic strategies (novel agents and non-pharmacological treatments) could be developed targeting specific impairments. On the other hand, (ii) once vulnerability factors are identified, new tools could be

developed for assessing ICBs risk in drug naïve PwP; patients with high risk of ICBs could be carefully monitored and, if subclinical changes emerge, they may be offered with psychological therapies. PwP with subclinical ICBs are those individuals who show some index features on ICBs surrogate measures, but in whom there is no clinical impact of the ICBs. Even if the symptoms may not meet the criteria for being considered clinically significant, any behavioural change from baseline should not be underestimated. Clinicians should monitor closely these individuals (possibly with frequent follow-up visits) to ascertain the behaviours do not increase in their severity. Moreover, it is important to provide the carer with detailed information about ICBs in order to improve surveillance. For example, it is important to provide information about what ICBs are, what could be the consequences, and the fact that behaviours could be concealed. The carer should be aware that it is important to inform immediately the clinician if any behavioural change has been noted. Counselling about ICBs should be done at any follow-up visit, above all when changing DRT.

Replication studies are needed. This thesis raises a concern related to the broad psychological literature (Open Science Collaboration, 2015), and more specifically ICBs in PD, which is the reproducibility of studies' findings with new data. When the first study of this thesis has been replicated, findings were not aligned with the original research.

Replicability of Study 1 was tested as this study was limited by small sample size, albeit the number of the participants included was in line with the broad ICBs in PD literature. This finding questions the reliability of many other studies on ICBs in PD, which may also be undermined by sample size issues. However, in the ICBs

in PD literature, there are no studies specifically designed for investigating replicability of the findings. Furthermore, the systematic review of the structural and functional brain imaging studies evidences variability in the study design, protocol of acquisition and data analysis, which could have accounted for discrepancy in studies' findings. Future studies should replicate previous imaging studies using the same design, protocol of acquisition and data analysis. One of the reasons for the paucity of reproducibility studies in the literature is because the incentives for individual scientists and publication practices prioritizes novelty over replication (Nosek, Spies, & Motyl, 2012). However, a discipline is unlikely to develop if it is based on false positive or false negative results. Failure in replicating does not undermine the reason for conducting the original study in the first place; if the initial hypotheses were always correct, then there would not be a reason for conducting research. Therefore, a balance between resourcing and publishing innovation and verification is aimed (Open Science Collaboration, 2015).

Transdiagnostic approach. Future studies should include a non-PD clinical group with ICBs to test whether spared sensitivity toward negative feedback, reduced cognitive control, increased depression, reduced DAT binding, and abnormal activity in the mesolimbic and frontostriatal areas are also evident in other non-PD clinical populations with ICBs. Low doses of DA agonist and levodopa are effective in the treatment of restless legs syndrome, and dopamine agonists are also used off-label in the treatment of fibromyalgia, with the risk, in both conditions, of developing ICBs (Cornelius et al., 2010; Holman, 2009; Voon, Schoerling, et al., 2011).

According to a transdiagnostic approach underlying the RDoC framework (Insel et al., 2010), reward-seeking exists on a continuum that spans the full range of normal human behaviour, with varying degrees of dysfunction cutting across traditional diagnostic boundaries. Therefore, findings on ICBs in PD may have relevance also for ICBs in restless legs syndrome and fibromyalgia. Previous studies on ICBs in restless syndrome show that they are associated with higher DA agonists doses, younger age at restless legs syndrome onset, history of experimental drug use, female gender, and family history of gambling disorder (Voon, Schoerling, et al., 2011). In fibromyalgia, cases of ICBs have been reported but no analysis has been done to identify correlates of ICBs (Holman, 2009). Future studies should investigate whether ICBs in PD and in non-PD conditions share some psychological and neural mechanisms.

Other levels of assessments should be integrated. Finally, findings should be supported by other units of assessments such as genetic. Previous candidate gene studies found specific polymorphisms in ICBs in PD (Abidin et al., 2015; Cilia et al., 2016; Cormier-Dequaire et al., 2018; Erga et al., 2018; Kraemmer et al., 2016; Krishnamoorthy et al., 2016; Lee et al., 2012, 2009); however, the current state of the field emphasizes the need of more robust evidence of association between behavioural changes and genetic background. Such power could result from adequately powered genome wide association studies, instead of candidate gene approaches. Genome wide association studies involve exploring the entire human genome in a hypothesis-free manner with the purpose of discovering patterns in the entire human genome rather than investigating pre-specified relationships. Candidate genes studies can be done after genome wide association studies, in order to confirm

and extend findings. As genome wide association studies require big sample size, they may require multicentre collaborative research or the use of existing databases. Findings from genetic studies have important implications as they may inform the development of screening tools for identifying PwP at risk of ICBs before DRT initiation and/or the development of new therapeutic agents.

Conclusions

This thesis has extended the understanding of the psychological (cognitive, affective and motivational) and neural mechanisms underlying ICBs in PD. In order to do that, several units of assessments have been investigated: behavioural, neurophysiological and brain circuits. It was proposed that one or more processes supporting incentive-driven decision-making would be affected in PwP with ICBs (Sinha et al., 2013). Using two units of assessments — behavioural and neurophysiology —findings show that negative feedback processing may be spared in PwP with ICBs. Alternative explanation, which is supported by brain imaging findings and warrants further investigation, is that sensitivity toward reward is enhanced in ICBs in PD. Changes in brain areas supporting cognitive control have been found, as well as impairments in cognitive processes related to cognitive control, namely set-shifting and inhibition. Taken together, results suggest that cognitive control mechanisms may not be strong enough for inhibiting strong drives associated with behaviours that in the longer-term result in negative consequences. ICBs in PD are associated with higher levels of depression, but not apathy; these findings, despite being evaluated with a single unit of assessment (i.e., behavioural, self-report questionnaires) have been consistently found across the studies of this thesis. Finally, ICBs in PD are associated with reduced DAT binding in the dorsal

striatum. These findings have important clinical implications for identifying PwP likely to have ICBs, for developing psychological interventions, and for investigating ICBs arising as DRT side-effects in other non-PD populations. Moreover, they may increase our understanding of incentive-driven decision-making.

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Appendices

Appendix A: Study 1 Ethical approval letter *NRES Committee Midlands - Edgbaston*

NHS
Health Research Authority

West Midlands - Edgbaston Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

21 November 2017

Dr Darren Clement
University Hospitals of North Midlands NHS Trust
Department of Research and Development, Courtyard Annexe, C Block
Royal Stoke University Hospital
Newcastle Road, Stoke-on-Trent
ST4 6QG

Dear Dr Clement

Study title:	**Prevention is Better than Cure: A Proof of Concept Study Investigating Vulnerability Factors for Impulse Control Behaviour in Patients with Parkinson's Disease.**
REC reference:	**14/WM/1097**
Protocol number:	**PD-ICB**
Amendment number:	**SA5**
Amendment date:	**23 October 2017**
IRAS project ID:	**150548**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		12 October 2017
Notice of Substantial Amendment (non-CTIMP)	SA5	23 October 2017
Other [Case Report Form - Clean]	5.0	12 October 2017
Other [Case Report Form - Tracked]	5.0	12 October 2017
Research protocol or project proposal [Clean]	6.0	12 October 2017
Research protocol or project proposal [Tracked]	6.0	12 October 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/WM/1097:	**Please quote this number on all correspondence**

Yours sincerely

pp. S. O'Neil

Mr Paul Hamilton
Chair

E-mail: NRESCommittee.WestMidlands-Edgbaston@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Darren Clement, University Hospital of North Staffordshire Trust Research and Development Department*
Dr Simon Ellis, University Hospital of North Staffordshire

West Midlands - Edgbaston Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 13 November 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Chris Foy	Medical Statistician	Yes	
Mr Paul Hamilton	Parish Administrator	Yes	Chair

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Joanne O'Neil	REC Assistant

Appendix B: Study 1 Ethical approval letter Keele University Ethical Review Panel

Keele University

Ref: ERP1206

5th November 2015

Alice Martini
School of Psychology
Dorothy Hodgkin Building
Keele University

Dear Alice,

Re: Prevention is better than cure: A proof of concept study investigating vulnerability factors for impulse control behaviour in patients with Parkinsons disease

Thank you for submitting your application to amend study. I am pleased to inform you that your application has been approved by the Ethical Review Panel.

The following documents have been reviewed and approved by the panel as follows:

Document	Version	Date
Health Participant Consent Form	1.1	20/10/2015
Health Participant Information Sheet	2.1	20/10/2015

If the fieldwork goes beyond the **31st January 2016** you must notify the Ethical Review Panel via the ERP administrator at uso.erps@keele.ac.uk stating **ERP1** in the subject line of the e-mail.

If there are any other amendments to your study you must submit an 'application to amend study' form to the ERP administrator stating **ERP1** in the subject line of the e-mail. This form is available via http://www.keele.ac.uk/researchsupport/researchethics/

If you have any queries, please do not hesitate to contact me via the ERP administrator on uso.erps@keele.ac.uk stating **ERP1** in the subject line of the e-mail.

Yours sincerely

C H Bonsman
PP

Dr Jackie Waterfield
Chair – Ethical Review Panel

CC RI Manager

Directorate of Engagement & Partnerships
T: +44(0)1782 734467

Keele University, Staffordshire ST5 5BG, UK
www.keele.ac.uk +44 (0)1782 732000

Appendix C: Study 1 persons with Parkinson's disease participants study pack consisting of a letter of invitation, information sheet, reminder letter

Letter of Invitation

University Hospital of North Staffordshire NHS Trust

Neurology Research Team
First Floor, B Block,
Newcastle Road
ST4 6QG
Tel: 01782 675393

Dear <Insert participant's name>,

You are being invited to consider taking part in a pilot study organised jointly by the University Hospital of North Staffordshire and School of Psychology, Keele University. The study is investigating the development of certain types of behaviours called "Impulse Control Behaviours" which may be linked to certain types of medication given to people with Parkinson's.

The enclosed *Information Sheet* outlines the study and what your participation in it will entail.

You are free to decide whether you would like to participate.

If you are interested in finding out more about the study, please complete the response slip below and return it to the Neurology Research Nurse in the stamped addressed envelope within the next two weeks.

If you are unable or do not wish to take part, you can either return the opt-in slip having ticked the second option, or you don't need to get back in touch with us all. However, we will be sending out one reminder letter in 2 weeks to everyone who hasn't returned the response slip – just in case the original letter and study documentation has been lost.

If you don't want to receive this reminder pack, please also return the response slip.

Best wishes,

Dr Simon Ellis Miss Alice Martini Prof Nicky Edelstyn Prof Tony Fryer Mr Tom Shepherd

Letter of Invitation v1 (11/07/2014)

Keele University

University Hospital of North Staffordshire NHS Trust

Neurology Research Team
First Floor, B Block,
Newcastle Road
ST4 6QG
Tel: 01782 675393

Response slip

□ I am interested in taking part.

□ I am not interested in taking part.

Name: ....

Print Signature Date

Telephone number: .....

Email address: .....

University Hospitals of North Midlands NHS
NHS Trust

Neurology Research Team
First Floor, B Block,
Newcastle Road
ST4 6QG
Tel: 01782 675393

Patient-Participant Information Sheet (Parkinson's)

Title of Project: Prevention is Better than Cure: A Proof of Concept Study Investigating Vulnerability Factors for Impulse Control Behaviour in Patients with Parkinson's.

Investigators: Dr Simon Ellis, Miss Alice Martini, Professor Nicky Edelstyn, Professor Tony Fryer and Mr Tom Shepherd.

Invitation: You are being invited to consider taking part in a small study investigating "Impulse Control Behaviours" in People with Parkinson's. The study is being organised jointly by Dr Simon Ellis, Consultant Neurologist, The University Hospital of North Staffordshire, and researchers in the School of Psychology, Keele University.

Before you decide, it is important for you to understand why this research is being done and what it will involve. Please take time to read this leaflet carefully and discuss it with your carers, friends and relatives if you wish. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part.

What is the study about?

The movement difficulties in Parkinson's are usually effectively managed with dopamine replacement medications. However these medications can, in up to 40% of people with Parkinson's, cause impulse control behaviour.

Impulse control behaviours (ICBs) are uncontrollable urges, which are usually harmful either to the person with Parkinson's and/or to those around them. Examples include addiction to alcohol or drugs, compulsive eating, compulsive gambling, compulsive shopping, compulsive hair pulling and repetitive behaviours that serve no purpose such as assembling and disassembling objects. ICBs may also extend to dopamine replacement medication where people take more medication than is prescribed. ICBs cause significant distress to the individual with Parkinson's, their partner/care-giver, wider families and social networks, and, in addition, may have serious social and legal consequences.

Exactly why some people with Parkinson's develop an ICB and others do not is unclear. Factors that may play a role include a genetic predisposition causing high levels of a brain chemical called dopamine and also behaviour traits such as risk-taking and impulsivity. In order for us to find out if having an ICB means some mental processes, personality traits and/or genes are different we need to compare 2 groups of people with Parkinson's: those who have an ICB and those who do not.

Why have I been invited to take part?

You are invited to take part because you have a diagnosis of Parkinson's. You may also have an ICB, but not necessarily. Either way, if you do have an ICB or not, we would like you to consider taking part. The assessment of ICBs will take place with Dr Simon Ellis, Consultant Neurologist, in a screening visit.

We are looking for people ages between 35-85 years, and have mild or moderate Parkinson's. There are a number of other "exclusion" criteria which will determine if you are eligible to take part, so if any of the following applies to you we are sorry but we can't include you in this study:

- Those not fluent in English;
- Severe Parkinson's (indicated by a score of 4 or 5 on the Hoehn and Yahr disease severity rating scale, assessed at the screening visit);
- Family history of Parkinson's disease;
- Diagnosed with another neurological illness (other than Parkinson's) such as Alzheimer's, Multiple Sclerosis, epilepsy;
- Unable to provide informed consent due to cognitive decline (determined at the screening visit);
- History of learning difficulty including dyslexia;
- Physical inability to take part in research, such as upper limb amputations, crippling degenerative arthritis;
- Cancer;
- Major psychotic phenomenology including hallucinations or lack of awareness of dyskinesias (to be determined at screening visit);
- Incapacitating dyskinesias on a stable dose of l-dopa;
- Participants taking any of the following drugs:
    - Centrally acting anticholinergics;
    - Atypical antipsychotics.

Do I have to take part?

You are free to decide if you wish to take part or not. If you do decide to take part you will be asked to sign a consent form and be given a copy.

We would also like to contact you about possible participation in future research studies. If you do not wish to receive this information then please tick "NO" on point 8 on the consent form.

You are free to withdraw from this study at any time and without giving reason. You can do this simply by leaving a message on the Neurology Research Nurse's answer phone located in the Neurology Research office (Tel: **01782 675393**). This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future.

However we would like to use any data we have collected from you up until this point. The data we collect will be anonymized and there is no way anyone will be able to link

the data with you as individual. Issues around how we keep data about you confidential and anonymous are outlined further on in this leaflet.

What will happen if I take part?

You will be invited to attend 3 appointments. The first will be a screening visit with Dr Ellis and the Neurology Research Nurse in the Guy Hilton Research Centre. He will review eligibility to take part, answer any questions about the study and if you're happy to proceed into the study, he will take consent. You will firstly be asked if we could measure your height and weight (vital signs) you will then be asked to give a small blood sample (1 ml, less than a teaspoon) so we can look at your dopamine gene. Your blood sample will be stored in a freezer and tested at the hospital and then disposed of in accordance to hospital procedures. Your sample will not be used in any other research. Dr Ellis will also complete a number of questionnaires with you concerning your current and past medical history and in particular Parkinson's. At the end of the screening visit, you will be given some questionnaires to complete at home before the first research visit at Keele. Please bring the completed questionnaires (and your reading glasses if you use them) to the research visit. Some of the questions could be upsetting, if you find some of the questions upsetting, then there is no need to answer them. However, please bring all of the questionnaires (completed or only partially completed) with you to the first research visit. Both research visits at Keele will take place with Miss Alice Martini, Research Assistant, Mr Tom Shepherd and Prof Nicky Edelstyn in the Neuropsychology Research Lab, School of Psychology, Keele University. Here you will be asked to complete questionnaires and a number of assessments of memory, attention and decision-making.

We would like to arrange for these 3 visits to take place within a 14 days period and for the two research visits at Keele take place on consecutive days. The screening visit will last about 60-90 minutes and the two research visits will last about 90-120 minutes. Travel expenses will be paid for each visit, and we will also provide as much tea, coffee, cakes etc. as required!

It's very important that during both research visits that you don't mention anything about your Parkinson's history – especially if you have experienced an impulse control behaviour.

There is a lot of information here! So, please do not hesitate to ask questions either by phoning us before your decide to take part, or at any point during the screening and research visits.

What do I have to do?

If you wish to find out more about the study please return the response slip (attached to the covering letter) in the stamped addressed envelope. We will send you a reminder letter just in case you're interested but have lost the response slip. We won't send anymore reminders.

If you don't want to take part in this study, you can either return the response slip telling us so or do nothing. However, we will be sending out reminder letters to everyone we haven't heard from.

What are the benefits of taking part?

There are no tangible benefits arising from this study for the participants, anyway there is evidence to suggest that some volunteers gain psychological benefit from participating in research such as increases in self-esteem and the knowledge that they are helping others.

However, we want to reduce the number of people affected by Impulse control behaviours. To do this, clinicians need to be provided with the tools for identifying people at risk of impulse control behaviour, so they can provide advice to patients about impulse control behaviours and consider them when making treatment choices. This study is the first step towards achieving this.

What if something goes wrong?

We don't expect any problems to arise in this study. If you are harmed by agreeing to take part in this research, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of the study, you may address this to Professor Michael Murray at School of Psychology, Keele University, ST5 5BG or 01782733311, alternatively you can phone the Patient Advice and Liaison Service (PALS) at the University Hospital of North Staffordshire on 01782 676450 or 676455.

Will my taking part be kept confidential?

All of the research data that we collect during the study will be kept strictly confidential unless you make known to us information relating to a criminal offence, or that could result in harm to yourself or others. In such cases we would be obliged to report this to the appropriate authorities.

Your blood sample will not contain identifiable information, but will be labelled with your participant ID. It will not be possible to identify you from your blood sample.

Any information which has your name, address and any other identifying information will be kept in a locked filing cabinet in the School of Psychology. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name.

How will the results of the study be communicated?

At the end of the study, we will send you a letter to thank you for participating. In this letter you will also be informed whether the study was successful and if further work will follow. However, findings from this study will be submitted as part of a PhD for Ms Martini, and also

written up for publications in scientific and medical journals, and presented at conferences. However, the data collected will be anonymised before any submissions or presentations.

Who is organizing the research?

Dr Simon Ellis, Consultant Neurologist, University Hospital of North Staffordshire; Miss Alice Martini, Research Assistant, School of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University; Professor Tony Fryer, Institute for Science and Technology in Medicine, Keele University and Mr Tom Shepherd, PhD student, School of Psychology, Keele University have organised the study.

Contact for further information Please contact the Neurology Research Office for further information if required, on 01782 **675393.**

Reminder Letter

Keele University

University Hospital of North Staffordshire NHS Trust

Neurology Research Team
First Floor, B Block,
Newcastle Road
ST4 6QG
Tel: 01782 675393

Dear <Insert participant's name>,

Two weeks ago we sent you information about a study we are conducting in North Staffordshire, which is investigating the Impulse Control Behaviours in Parkinson's.

We haven't heard from you and are therefore sending this reminder letter along with the same study documentation just in case you are interested but haven't got round to letting us know.

This is the only reminder letter we'll be sending, so if we don't hear from you we understand that you don't want to take part.

Best wishes,

Dr Simon Ellis Miss Alice Martini Prof Nicky Edelstyn Prof Tony Fryer Mr Tom Shepherd

Reminder Letter v1 (11/07/2014)

Keele University

University Hospital of North Staffordshire NHS Trust

Neurology Research Team
First Floor, B Block,
Newcastle Road
ST4 6QG
Tel: 01782 675393

Response slip

I am interested in taking part.

Name: ....

Print Signature Date

Telephone number:.....

Email address.....

Reminder Letter v1 (11/07/2014)

Appendix D: Study 1 persons with Parkinson's disease participants consent form

University Hospital of North Staffordshire NHS Trust

Neurology Research Team
First Floor, B Block,
Newcastle Road
ST4 6QG
Tel: 01782 675393

CONSENT FORM (Parkinson's)

Title of Project: *Prevention is Better than Cure*: A Proof of Concept Study Investigating Impulse Control Disorder Vulnerability Factors in People with Parkinson's.

Investigators: Dr Simon Ellis, Miss Alice Martini, Professor Nicky Edelstyn, Professor Tony Fryer and Mr Tom Shepherd

Please initial the box

1	I confirm that I have read and understand the information sheet (version 6.0) dated 12th October 2015 for the above study and have had the opportunity to ask questions.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that data collected about me during this study will be anonymised before it is submitted for publication in scientific and medical journals, and presented at conferences.	☐
4	I understand that sections of any of my medical notes may be looked at by authorized individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
5	I agree to take part in this study.	☐
6	If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analyses.	☐
7	I agree to give a sample of blood for research.	☐
		YES **NO**
8	I agree to be contacted about possible participation in future research projects.	☐ ☐

----------	----------	----------
Research Participant Name	Signature	Date
----------	----------	----------
Researcher Name	Signature	Date

Consent Form (Parkinson's) v4.2 (12/10/15)
1 for patient participant, 1 for hospital record, 1 for site file.

Appendix E: Impulsive-compulsive behaviours diagnostic interview

Keele University

University Hospitals of North Midlands NHS
NHS Trust

Study code:_____

Prevention is Better than Cure: A Proof of Concept Study Investigating Vulnerability Factors for Impulse Control Behaviour in Patients with Parkinson's Disease.

Impulse Control Behaviours Screening Interview

☐ ICB history ☐ no ICB history

INDEX

PATOLOGICAL GAMBLING

A. SYMPTOMS
Since diagnosed with PD:

	YES	NO
Have you had the need to gamble with increasing amounts of money in order to be thrilled?		
When you tried to cut down or stop gambling, have you experienced a feeling of restlessness or have you started to be irritable?		
Have you repeated unsuccessful efforts to control, cut back, or stop gambling?		
Have you been often preoccupied with gambling (e.g., having persistent thoughts of reliving past gambling experiences, handicapping or planning the next venture, thinking of ways to get money with which to gamble)?		
Have you often gambled when feeling distressed (e.g., helpless, guilty, anxious, depressed)?		
After losing money gambling, have you often returned another day to get even ("chasing" one's losses)?		
Have you lied to hide the extent of involvement with gambling?		
Have you experienced a strong desire for gambling?		
Have you relied on others to provide money to relieve desperate financial situations caused by gambling?		
(4 or more YES answers are required)		

B. GENERAL FUNCTIONING	YES	NO
Have you put at risk or lost a significant relationship, job, or educational or career opportunity because of gambling?		
Has the gambling become excessively time consuming?		
(1 or more YES answer is required)		

C. DURATION	YES	NO
Has the need to gamble persisted for at least 1 month?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
FOR THE CLINICIAN: Is the gambling behaviour better explained by a manic episode?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:.....
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BINGE EATING DISORDER

A. SYMPTOMS
Since diagnosed with PD:

	YES	NO
Have you ever eat in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than what most people would eat in a similar period of time under similar circumstances?		
Have you experienced a sense of lack of control over eating during this episode (e.g., a feeling that you cannot stop eating or control what or how much you are eating)?		
(BOTH YES answers are required for define a Binge Eating Episode)		

During these episodes have you ever experienced:	YES	NO
Eating much more rapidly than normal?		
Eating until feeling uncomfortably full?		
Eating large amounts of food when not feeling physically hungry?		
Eating alone because of feeling embarrassed by how much are you eating?		
Feeling disgusted with yourself, depressed, or very guilty afterward?		
(THREE or more YES answers are required)		

B. GENERAL FUNCTION	YES	NO
Has the lack of control over eating caused you marked distress?		
(answer YES is required)		

C. DURATION	YES	NO
Has the lack of control over eating been occurring, on average, at least once a week for 3 months?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
FOR THE CLINICIAN: Is the binge eating associated with the recurrent use of inappropriate compensatory behaviour as in bulimia nervosa and does occur exclusively during the course of bulimia nervosa or anorexia nervosa?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:.....
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DOPAMINE DYSREGULATION SINDROME

A. SYMPTOMS
Since diagnosed with PD:

	YES	NO
FOR THE CLINICIAN: Does the patient-participant have documented levodopa responsiveness?		
Have you needed to increase doses of your Parkinson's medication in excess of those normally required to relieve Parkinsonian symptoms and signs?		
When you tried to reduce the level of your Parkinson's medication, did you experience changes in mood like dysphoria, depression, irritability, and anxiety?		
Have you repeated unsuccessful efforts to control, cut back, or stop to increase dose of your medication?		
Have you been often preoccupied with your Parkinson's medication doses (e.g., having persistent thoughts of reliving past increased dose of medication experiences, handicapping or planning the next dose, thinking of way to take increased dose of medication)?		
Have you lied to hide the extent of involvement with the need to increase your Parkinson's medication?		
Have you needed to increase your Parkinson's medication even in the presence of excessive and significant dyskinesias despite being 'ON'?		
Have you experienced a strong desire for medication?		
Have you had worse mood or feeling unmotivated at a lower dosage?		
Have you hoard or hide your Parkinson's medications to increase the overall dosage?		
FOR THE CLINICIAN: Does the patient develop hypomanic, manic, or cyclothymic affective syndrome in relation to Dopamine replacement therapy?		
(5 or more YES answers are required)		

B. GENERAL FUNCTIONING	YES	NO
Has the need to increase doses of your Parkinson's medication caused you difficulties in social or occupational functioning such as fights, violent behaviour, loss of friends, absence from work, loss of job, legal difficulties, arguments or difficulties with family?		
(answer YES is required)		

C. DURATION	YES	NO
Has the need to increase doses of your Parkinson's medication persisted for at least 1 month?		
(answer YES is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:.....
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COMPULSIVE SHOPPING

A. SYMPTOMS:
Since diagnosed with PD:

	YES	NO
Have you had experienced excessive preoccupation with buying or shopping that is manifested as thoughts or behaviour that are irresistible, intrusive, and/or senseless?		
Does it result in frequent buying of more than can be afforded, items that are not needed, or longer periods of time than intended?		
Have you had the need to buy or shopping in order to be thrilled?		
When you tried to cut down or stop buying, have you experienced a feeling of restlessness or have you started to be irritable?		
Have you repeated unsuccessful efforts to control, cut back, or stop to buy or to shop?		
Have you often shopped when feeling distressed (e.g., helpless, guilty, anxious, depressed)?		
Have you lied to hide the extent of involvement with shopping?		
Have you relied on others to provide money to relieve desperate financial situation caused by shopping?		
(4 or more YES answer are required)		

B. GENERAL FUNCTIONING	YES	NO
Have you put at risk or lost a significant relationship, job, or educational or career opportunity because of shopping?		
Has the shopping thoughts or behaviours become excessively time consuming?		
(1 or more YES answer is required)		

C. DURATION	YES	NO
Has the need to shop persisted for at least 1 month?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
FOR THE CLINICIAN: Does the behaviour occur exclusively during periods of hypomania or mania?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:.....

HYPERSEXUALITY		
A. SYMPTOMS: **Since diagnosed with PD:**	**YES**	**NO**
Have you had the need to carry out sexual behaviours that are excessive or are an atypical of your habitual behaviour?		
When you tried to cut down or stop atypical sexual thoughts or behaviours, have you experienced a feeling of restlessness or have you started to be irritable?		
Have you repeated unsuccessful effort to control, cut back, or stop to have atypical sexual thoughts or behaviours?		
Have you been often preoccupied with sexual thoughts or behaviours (e.g., having persistent thoughts of reliving past sexual experiences, handicapping or planning the next venture)?		
Have you often experienced sexual thoughts or behaviours when feeling distressed (e.g., helpless, guilty, anxious, depressed)?		
Have you lied to hide the extent of involvement with excessive sexual thoughts or behaviours?		
Have you had inappropriately or excessively requesting sex from spouse or partner?		
Have you had habitual promiscuity?		
Have you had compulsive masturbation?		
Have you done calls to telephone sex lines or viewing of pornography?		
Have you had sexual fantasies, feelings, or activities involving a non human object, a non consenting partner or pain or humiliation of oneself or one's partner?		
Has the sexual thought or behaviour caused you marked distress?		
(4 or more YES answers are required)		

B. GENERAL FUNCTIONING	YES	NO
Have you put at risk or lost a significant relationship, job, or educational or career opportunity because of excessive sexual thought or behaviours?		
Has the sexual thoughts or behaviours became excessively time consuming?		
(1 or more YES answer is required)		

C. DURATION	YES	NO
Has the behaviour persisted for at least 1 month?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
Does the behaviour occur exclusively during periods of hypomania or mania?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		
Comments:.....		

OTHER EXCESSIVE BEHAVIOUR
Insert name:_____

A. SYMPTOMS:
Since diagnosed with PD:

	YES	NO
Have you spent too much time on specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)?		
Have you had the need to carry out specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.) in order to be thrilled?		
When you tried to cut down or stop such activity, have you experienced a feeling of restlessness or have you started to be irritable?		
Have you repeated unsuccessful efforts to control, cut back, or stop such activity?		
Have you been often preoccupied with such activity (e.g., having persistent thoughts of reliving past experience associated with the activity, handicapping or planning the next venture, thinking a way to carry out the next venture activity)?		
Have you often carry out such activity when feeling distressed (e.g., helpless, guilty, anxious, depressed)?		
Have you lied to hide the extent of involvement with such activity?		
Have you experienced a strong desire for such activity?		
Have you relied on others to provide money to relieve desperate financial situations caused by such activity?		
(4 or more YES answers are required)		

B. GENERAL FUNCTIONING	YES	NO
Have you put a risk or lost a significant relationship, job, or educational career opportunity because of such activity?		

Have the thoughts or behaviours about such activity become excessively time consuming?		
(1 or more YES answer is required)		

C. DURATION	YES	NO
Has the behaviour persisted for at least 1 month?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
Does the behaviour occur exclusively during periods of hypomania or mania?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:
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OTHER EXCESSIVE BEHAVIOUR
Insert name:_____

A. SYMPTOMS:
Since diagnosed with PD:

	YES	NO
Have you spent too much time on specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)?		
Have you had the need to carry out specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.) in order to be thrilled?		
When you tried to cut down or stop such activity, have you experienced a feeling of restlessness or have you started to be irritable?		
Have you repeated unsuccessful efforts to control, cut back, or stop such activity?		
Have you been often preoccupied with such activity (e.g., having persistent thoughts of reliving past experience associated with the activity, handicapping or planning the next venture, thinking a way to carry out the next venture activity)?		
Have you often carry out such activity when feeling distressed (e.g., helpless, guilty, anxious, depressed)?		
Have you lied to hide the extent of involvement with such activity?		
Have you experienced a strong desire for such activity?		
Have you relied on others to provide money to relieve desperate financial situations caused by such activity?		
(4 or more YES answers are required)		

B. GENERAL FUNCTIONING	YES	NO
Have you put a risk or lost a significant relationship, job, or educational career opportunity because of such activity?		

Have the thoughts or behaviours about such activity become excessively time consuming?		
(1 or more YES answer is required)		

C. DURATION	YES	NO
Has the behaviour persisted for at least 1 month?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
Does the behaviour occur exclusively during periods of hypomania or mania?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:
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OTHER EXCESSIVE BEHAVIOUR
Insert name:_____

A. SYMPTOMS:
Since diagnosed with PD:

	YES	NO
Have you spent too much time on specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)?		
Have you had the need to carry out specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.) in order to be thrilled?		
When you tried to cut down or stop such activity, have you experienced a feeling of restlessness or have you started to be irritable?		
Have you repeated unsuccessful efforts to control, cut back, or stop such activity?		
Have you been often preoccupied with such activity (e.g., having persistent thoughts of reliving past experience associated with the activity, handicapping or planning the next venture, thinking a way to carry out the next venture activity)?		
Have you often carry out such activity when feeling distressed (e.g., helpless, guilty, anxious, depressed)?		
Have you lied to hide the extent of involvement with such activity?		
Have you experienced a strong desire for such activity?		
Have you relied on others to provide money to relieve desperate financial situations caused by such activity?		
(4 or more YES answers are required)		

B. GENERAL FUNCTIONING	YES	NO
Have you put a risk or lost a significant relationship, job, or educational career opportunity because of such activity?		

Have the thoughts or behaviours about such activity become excessively time consuming?		
(1 or more YES answer is required)		

C. DURATION	YES	NO
Has the behaviour persisted for at least 1 month?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
Does the behaviour occur exclusively during periods of hypomania or mania?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:
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OTHER EXCESSIVE BEHAVIOUR
Insert name:_____

A. SYMPTOMS:
Since diagnosed with PD:

	YES	NO
Have you spent too much time on specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.)?		
Have you had the need to carry out specific tasks, hobbies or other organized activities (such as writing, painting, gardening, repairing or dismantling things, collecting, computer use, working on projects, etc.) in order to be thrilled?		
When you tried to cut down or stop such activity, have you experienced a feeling of restlessness or have you started to be irritable?		
Have you repeated unsuccessful efforts to control, cut back, or stop such activity?		
Have you been often preoccupied with such activity (e.g., having persistent thoughts of reliving past experience associated with the activity, handicapping or planning the next venture, thinking a way to carry out the next venture activity)?		
Have you often carry out such activity when feeling distressed (e.g., helpless, guilty, anxious, depressed)?		
Have you lied to hide the extent of involvement with such activity?		
Have you experienced a strong desire for such activity?		
Have you relied on others to provide money to relieve desperate financial situations caused by such activity?		
(4 or more YES answers are required)		

B. GENERAL FUNCTIONING	YES	NO
Have you put a risk or lost a significant relationship, job, or educational career opportunity because of such activity?		

Have the thoughts or behaviours about such activity become excessively time consuming?		
(1 or more YES answer is required)		

C. DURATION	YES	NO
Has the behaviour persisted for at least 1 month?		
(answer YES is required)		

D. DIFFERENTIAL DIAGNOSIS	YES	NO
Does the behaviour occur exclusively during periods of hypomania or mania?		
(answer NO is required)		

EPISODE(s)	DATE (year)	DURATION
1st episode		
2nd episode		
3rd episode		
4th episode		
5th episode		
6th episode		
7th episode		
8th episode		
9th episode		
10th episode		
11th episode		

Comments:
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Appendix F: Study 1 healthy controls study pack consisting of a letter of invitation, information sheet, and response letter

Letter of Invitation

School of Psychology
Keele University
Keele, Staffordshire
ST5 5BG

Title of Project: Prevention is Better than Cure: A Proof of Concept Study Investigating Vulnerability Factors for Impulse Control Behaviour in Patients with Parkinson's.

Dear <Insert participant's name>,

You are being contacted because your name is on our database and you are being invited to consider taking part in a pilot study organised jointly by the University Hospital of North Staffordshire and School of Psychology, Keele University. The study is investigating the development of certain types of behaviours called "Impulse Control Behaviours" which may be linked to certain types of medication given to people with Parkinson's.

The enclosed *Information Sheet* outlines the study and what your participation in it will entail.

You are free to decide whether you would like to participate.

If you are interested in finding out more about the study, please complete the response slip below and return it to Prof Nicky Edelstyn in the stamped addressed envelope within the next two weeks.

If you are unable or do not wish to take part, you can either return the response slip having ticked the second option, or you don't need to get back in touch with us all. However, we will be sending out one reminder letter in 2 weeks to everyone who hasn't returned the response slip – just in case the original letter and study documentation has been lost.

If you don't want to receive this reminder pack, please also return the response slip.

Best wishes,

Dr Simon Ellis Miss Alice Martini Prof Nicky Edelstyn Prof Tony Fryer Mr Tom Shepherd

Letter of Invitation v1.1 (18/08/2014)

School of Psychology
Keele University
Keele, Staffordshire
ST5 5BG

Response slip

□ I am interested in taking part.

□ I am not interested in taking part.

Name: ....

Print Signature Date

Telephone number: .....

Email address: .....

Information sheet

School of Psychology
Keele University
Keele, Staffordshire
ST5 5BG

Healthy Participant Information Sheet

Title of Project: Prevention is Better than Cure: A Proof of Concept Study Investigating Vulnerability Factors for Impulse Control Behaviour in Patients with Parkinson's.

Investigators: Miss Alice Martini, Professor Nicky Edelstyn, Professor Tony Fryer, Mr Tom Shepherd and Dr Simon Ellis.

Invitation

You are being invited to consider taking part in a small study investigating "Impulse Control Behaviours" in People with Parkinson's. The study is being organised jointly by Miss Alice Martini and Prof Nicky Edelstyn, researchers in the School of Psychology, Keele University and clinicians in the University Hospital of North Staffordshire.

Before you decide, it is important for you to understand why this research is being done and what it will involve. Please take time to read this leaflet carefully and discuss it with relatives and friends if you wish. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part.

What is the study about?

The movement difficulties experienced by people with Parkinson's are usually effectively managed with dopamine replacement medications. However these medications can, in up to 40% of people with Parkinson's, cause impulse control behaviours.

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Keele, Staffordshire
ST5 5BG

Impulse control behaviours (ICBs) are uncontrollable urges, which are usually harmful either to the person with Parkinson's and/or to those around them. Examples include addiction to alcohol or drugs, compulsive eating, compulsive gambling, compulsive shopping, compulsive hair pulling and repetitive behaviours that serve no purpose such as assembling and disassembling objects. ICBs may also extend to dopamine replacement medication where people take more medication than is prescribed. ICB cause significant distress to the individual with Parkinson's, their partner/care-giver, wider families and social networks, and, in addition, may have serious social and legal consequences.

Exactly why some people with Parkinson's develop ICB and others do not is unclear. Factors that may play a role include a genetic predisposition causing high levels of a brain chemical called dopamine and also behaviour traits such as risk-taking and impulsivity.

In order for us to find out if having an ICB means some mental processes, personality traits and/or genes are contributory factors, we need to compare 2 groups of people with Parkinson's: those who have an ICB and those who do not.

We also need to compare these Parkinson's' groups with healthy individuals who do not have Parkinson's or an ICB (or any other neurological condition).

We would like you to consider being a member of our healthy participant group.

Why have I been chosen?

If you are aged between 35 – 85, and can answer "NO" to all of the following criteria we would like you to consider being a member of our healthy participant group:

- English is a second language;
- Diagnosed with Parkinson's;
- Family history of Parkinson's;
- Diagnosed with any neurological condition such as Alzheimer's, Multiple Sclerosis, epilepsy;

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ST5 5BG

- Attending a memory clinic;
- Unable to provide informed consent due to cognitive decline;
- History of learning difficulty including dyslexia;
- Physical inability to take part in research, such as upper limb amputations, crippling degenerative arthritis;
- Cancer;
- Psychiatric history including schizophrenia, depressive illness;
- Family history of schizophrenia, depressive illness;
- Major psychotic phenomenology including hallucinations and delusions;
- Hypotension;
- History of alcohol or drug abuse;
- History of ICB (such as gambling, compulsive shopping, compulsive eating);
- Participants taking any of the following drugs:
  - anticholinergics;
  - antipsychotics (typical or atypical);
  - antidepressants.

Do I have to take part?

You are free to decide if you wish to take part or not. If you do decide to take part you will be asked to sign two consent forms, one is for you to keep and the other is for our records.

We would also like to contact you about possible participation in future research studies. If you do not wish to receive this information then please **do not** tick point 6 on the consent form.

You are free to withdraw from this study at any time and without giving reason. However we would like to use any data we have collected from you up until this point. The data we collect will be anonymized and there is no way anyone will be able to link the data with you as individual. Issues around how we keep data about you confidential and anonymous are outlined further on in this leaflet.

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Keele Universit
Keele, Staffordshir
ST5 5B(

What will happen to me if I take part?

You will be invited to attend 2 appointments that will take place with Miss Alice Martini, Research Assistant and Prof Nicky Edelstyn in the Neuropsychology Research Lab, School of Psychology, Keele University. Here you will be asked to complete questionnaires and a number of assessments of memory, attention and decision-making. At the end of the first research visit you will be given some questionnaires to complete at home before the second research visit at Keele. You will need about 30 minutes to complete all the home questionnaires. Please bring the completed questionnaires (and your reading glasses if you use them) to the research visit.

Each of two research visits will last about 90-120 minutes and will follow each other on two consecutive days and, if possible, at the same time of the day.

Travel and parking expenses will be reimbursed (0.45p/mile).

What do I have to do?

If you wish to find out more about the study please return the response slip (attached to the covering letter) in the stamped addressed envelope. We will send you a reminder letter just in case you're interested but have lost the response slip. We won't send anymore reminders.

If you don't want to take part in this study, you can either return the response slip telling us so or do nothing. However, we will be sending out reminder letters to everyone we haven't heard from.

School of Psychol
Keele Univers
Keele, Staffordsh
ST5 5

What might be the benefits of taking part?

There are no tangible benefits arising from this study for the participants, anyway there is evidence to suggest that some volunteers gain psychological benefit from participating in research such as increases in self-esteem and the knowledge that they are helping others.

However, we want to reduce the number of people affected by Impulse Control Behaviours. To do this, clinicians need to be provided with the tools for identifying people at risk of impulse control behaviour, so they can provide advice to patients about impulse control behaviours and consider them when making treatment choices. This study is the first step towards achieving this.

Will my taking part in this study be kept confidential?

All personal data that we collect during the study will be kept strictly confidential. Any information which has your name, address and any other identifying information will be kept in a locked filing cabinet in the School of Psychology. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name.

Contact for Further Information

For study related questions/queries please contact member and research team Ms Alice Martini (e mail: a.martini@keele.ac.uk) or Professor Nicky Edelstyn (e mail: n.edelstyn@keele.ac.uk or phone number: 01782 734318) and for independent advice please contact Ms Nicola Leighton (e mail: uso.erps@keele.ac.uk or phone number: 01782 733306).

Reminder letter

School of Psychology
Keele University,
Keele, Staffordshire
ST5 5BG

Title of Project: Prevention is Better than Cure: A Proof of Concept Study Investigating Vulnerability Factors for Impulse Control Behaviour in Patients with Parkinson's.

Dear <Insert participant's name>,

Two weeks ago we sent you information about a study we are conducting in North Staffordshire, which is investigating the Impulse Control Behaviours in Parkinson's.

We haven't heard from you and are therefore sending this reminder letter along with the same study documentation just in case you are interested but haven't got round to letting us know.

This is the only reminder letter we'll be sending, so if we don't hear from you we understand that you don't want to take part.

Best wishes,

Dr Simon Ellis Miss Alice Martini Prof Nicky Edelstyn Prof Tony Fryer Mr Tom Shepherd

School of Psychology
Keele University,
Keele, Staffordshire
ST5 5BG

Response slip

- ☐ I am interested in taking part.
- ☐ I am not interested in taking part.

Name: ....

Print Signature Date

Telephone number:.....

Email address.....

Appendix G: Study 1 healthy controls consent form

School of Psychology
Keele University
Keele, Staffordshire
ST5 5BG

HEALTHY PARTICIPANT CONSENT FORM

Title of Project: Prevention is Better than Cure: A Proof of Concept Study Investigating Vulnerability Factors for Impulse Control Behaviour in Patients with Parkinson's.

Name of Researcher: Dr Simon Ellis, Miss Alice Martini, Professor Nicky Edelstyn, Professor Tony Fryer and Mr Tom Shepherd.

		Please initial the box
1	I confirm that I have read and understand the information sheet dated 20th October 2015 for the above study and have had the opportunity to ask questions.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3	I understand that the data collected during the study will be analysed and used in the final report and follow up publications. However, I have been made aware that the data will anonymised.	☐
4	I agree to take part in this study.	☐
5	If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analyses.	☐
6	I agree to be contacted about possible participation in future research projects.	☐

Name participant .....

Signature of participant.....

Name person taking consent.....

Signature of person taking consent.....

Consent form v1.1 (20/10/2015)
1 for participant, 1 for researcher.

Appendix H: modified Hoehn and Yahr Scale

Stage	Hoehn and Yahr Scale	Modified Hoehn and Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only
1.5	-	Unilateral and axial involvement
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
2.5	-	Mild bilateral disease with recovery on pull test
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided	Wheelchair bound or bedridden unless aided

Appendix I: Unified Parkinson's disease Rating Scale

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:
ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see". Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's Disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on Levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

	SCORE
3.3 RIGIDITY Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity. 0: Normal: No rigidity. 1: Slight: Rigidity only detected with activation maneuver. 2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved. 3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort. 4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.	☐ Neck ☐ RUE ☐ LUE ☐ RLE ☐ LLE
3.4 FINGER TAPPING Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/ her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down; then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problem. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum up to two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13. 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from arms of chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13. 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13 0: Normal: No problems: Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

	SCORE
3.16 KINETIC TREMOR OF THE HANDS Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L
3.17 REST TREMOR AMPLITUDE Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating. Extremity ratings 0: Normal: No tremor. 1: Slight: ≤ 1 cm in maximal amplitude. 2: Mild: > 1 cm but < 3 cm in maximal amplitude. 3: Moderate: 3 - 10 cm in maximal amplitude. 4: Severe: > 10 cm in maximal amplitude. Lip/Jaw ratings 0: Normal: No tremor. 1: Slight: ≤ 1 cm in maximal amplitude. 2: Mild: > 1 cm but ≤ 2 cm in maximal amplitude. 3: Moderate: > 2 cm but ≤ 3 cm in maximal amplitude. 4: Severe: > 3 cm in maximal amplitude.	☐ RUE ☐ LUE ☐ RLE ☐ LLE ☐ Lip/Jaw

3.18 CONSTANCY OF REST TREMOR

SCORE

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0: Normal:	No tremor.
1: Slight:	Tremor at rest is present ≤ 25% of the entire examination period.
2: Mild:	Tremor at rest is present 26-50% of the entire examination period.
3: Moderate:	Tremor at rest is present 51-75% of the entire examination period.
4: Severe:	Tremor at rest is present > 75% of the entire examination period.

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and dyskinesias. For "OFF dystonia", the total "Off" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching". It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture".

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects".

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A. DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]: Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculations).

0: Normal:	No dyskinesias.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours with Dyskinesia: _____
3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS

SCORE

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.
1: Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
2: Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
3: Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.
4: Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.

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B. MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6.

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are general awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function ____ (use this number for your calculations).

0: Normal:	No OFF time.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions. 1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer. *Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable (≤ 25%).	☐

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient [and caregiver]: In one of the questions I asked earlier, you said you generally have ____ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0: Normal:	No dystonia OR NO OFF TIME.
1: Slight:	≤ 25% of time in OFF state.
2: Mild:	26-50% of time in OFF state.
3: Moderate:	51-75% of time in OFF state.
4: Severe:	> 75% of time in OFF state.

1. Total Hours Off: _____
2. Total Off Hours w/Dystonia: _____
3. % Off Dystonia = ((2/1)*100): _____

Appendix J: Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS)

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	CHANCE OF DOZING (0-3)
Sitting and reading	
Watching television	
Sitting inactive in a public place (e.g. a theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	
TOTAL SCORE	

Appendix K: Mini-Mental State Examination

Folstein Mini-Mental State Exam		
I. **ORIENTATION** (Ask the following questions; correct = ☑)	**Record Each Answer:**	(Maximum Score = 10)
What is today's date?	Date (eg, May 21)	1 ☐
What is today's year?	Year	1 ☐
What is the month?	Month	1 ☐
What day is today?	Day (eg, Monday)	1 ☐
Can you also tell me what season it is?	Season	1 ☐
Can you also tell me the name of this hospital/clinic?	Hospital/Clinic	1 ☐
What floor are we on?	Floor	1 ☐
What city are we in?	City	1 ☐
What county are we in?	County	1 ☐
What state are we in?	State	1 ☐
II. IMMEDIATE RECALL	(correct = ☑)	(Maximum Score = 3)
Ask the subject if you may test his/her memory. Say "ball, "flag," "tree" clearly and slowly, about on second for each. Then ask the subject to repeat them. Check the box at right for each correct response. The first repetition determines the score. If he/she does not repeat all three correctly, keep saying them up to six tries until he/she can repeat them	Ball	1 ☐
	Flag	1 ☐
	Tree	1 ☐
		NUMBER OF TRIALS: _____
III. **ATTENTION AND CALCULATION**		
A. Counting Backwards Test	(Record each response, correct = ☑)	(Maximum Score = 5)
Ask the subject to begin with 100 and count backwards by 7. Record each response. Check one box at right for each correct response. Any response 7 or less than the previous response is a correct response. The score is the number of correct subtractions. For example, 93, 86, 80, 72, 65 is a score of 4; 93, 86, 78 70, 62, is 2; 92, 87, 78, 70, 65 is 0.	93	1 ☐
	86	1 ☐
	79	1 ☐
	72	1 ☐
	65	1 ☐
B. Spelling Backwards Test		
Ask the subject to spell the word "WORLD" backwards. Record each response. Use the instructions to determine which are correct responses, and check one box at right fore each correct response.	D	1 ☐
	L	1 ☐
	R	1 ☐
C. Final Score	O	1 ☐
Compare the scores of the Counting Backwards and Spelling Backwards tests. Write the greater of the two socres in the box labeled FINAL SCORE at right, and use it in deriving the **TOTAL SCORE**.	W	1 ☐
		FINAL SCORE_____ (Max of 5 or Greater of the two Scores)

IV. **RECALL**	(correct = ☑)	(Maximum Score = 3)
Ask the subject to recall the three words you previously asked him/her to remember. Check the Box at right for each correct response.	Ball	1 ☐
	Flag	1 ☐
	Tree	1 ☐
V. Language	(correct = ☑)	(Maximum Score = 9)
Naming	Watch	1 ☐
Show the subject a wrist watch and ask him/her what it is. Repeat for a pencil.	Pencil	1 ☐
Repetition		
Ask the subject to repeat "No, ifs, ands, or buts."	Repetition	1 ☐
Three -Stage Command		
Establish the subject's dominant hand. Give the subject a sheet of blank paper and say, "Take the paper in your right/left hand, fold it in half and put it on the floor."	Takes paper in hand	1 ☐
	Folds paper in half	1 ☐
	Puts paper on floor	1 ☐
Reading		
Hold up the card that reads, "Close your eyes." So the subject can see it clearly. Ask him/her to read it and do what it says. Check the box at right only if he/she actually closes his/her eyes.	Closes eyes	1 ☐
Writing		
Give the subject a sheet of blank paper and ask him/her to write a sentence. It is to be written sponataneously. If the sentence contains a subject and a verb, and is sensible, check the box at right. Correct grammar and punctuation are not necessary.	Writes sentence	1 ☐
Copying		
Show the subject the drawing of the intersecting pentagons. Ask him/her to draw the pentagons (about one inch each side) on the paper provided. If ten angles are present and two intersect, check the box at right. Ignore tremor and rotation.	Copies pentagons	1 ☐

Appendix L: Cambridge Cognitive Examination (CAMCOG)

Section B Cognitive examination – CAMCOG

Before commencing, make sure you have the following items:

Booklet	**Pencil**	**Wristwatch (with a second hand for timing)**
Blank sheet of paper (A4)	**Envelope**	**Coins: two coins of different value**

Ensure that calendars and clocks are not available to assist subjects in answering questions about date and time.

This section contains all 19 items of the Mini-Mental State Examination of Folstein et al. (1975). Some, but not all of these items are used in scoring the more comprehensive Cambridge Cognitive Examination (CAMCOG). A list of the items comprising each of these examinations is set out on pp. 65–66

It is important that you speak slowly and clearly. If the subject appears not to have heard or understood, repeat the question (unless the item specifically prohibits repetition).

Do not give correct answer if a wrong answer or no answer is given.

Make a note of any unusual responses including extra memory items recalled.

Coding: This section differs from other sections of the CAMDEX in that subjects who don't know, refuse to answer or give a silly answer are given a score of 0 (not 8), which is equivalent to giving an incorrect answer. Where a score of 9 or 99 is recorded, indicate why the question was not asked.

I am going to ask you some questions now which have to do with your memory and concentration. Some of them may seem rather easy, others may be difficult, but we need to ask everyone the same questions.

Orientation

Time

139. What day of the week is it?	Incorrect	**0**	
	Correct	**1**	**9**

What is the date today?

140. Date	Incorrect	**0**	
	Correct	**1**	**9**
141. Month	Incorrect	**0**	
	Correct	**1**	**9**
142. Year	Incorrect	**0**	
	Correct	**1**	**9**
143. What is the season?	Incorrect	**0**	
	Correct	**1**	**9**

Allow flexibility when season changes, e.g. for northern hemisphere:
March = winter/spring: June = spring/summer
September = summer/autumn: December = autumn/winter

Place

144. Can you tell me where we are now? For instance, what county (state) are we in?	Incorrect Correct	0 1	 9
145. What is the name of this town (city)?	Incorrect Correct	0 1	 9
146. What are two main streets nearby (or near your home)?	Incorrect Correct	0 1	 9
147. What floor of the building are we on?	Incorrect Correct	0 1	 9
148. What is the name of this place? *(or* What is this address? *if subject tested at home)*	Incorrect Correct	0 1	 9

If tested at home, the address must include enough information for mail to arrive

Language

Comprehension: Motor response

If the subject does not complete the full sequence then the whole instruction may be repeated, without change in tone or tempo, to ensure that it has been heard and understood. Prompting and coaching stage by stage are not allowed

I am going to ask you to carry out some actions, so please listen carefully

149. Please nod your head.	Incorrect Correct	0 1	 9
150. Touch your right ear with your left hand.	Incorrect Correct	0 1	 9
151. Before looking at the ceiling please look at the floor.	Incorrect Correct	0 1	 9
152. Tap each shoulder twice with two fingers keeping your eyes shut.	Incorrect Correct	0 1	 9

Comprehension: Verbal response

I am going to ask you some questions and would like you to answer 'yes' or 'no'

153. Is this place a hotel?	Incorrect Correct ('no')	0 1	 9
154. Are villages larger than towns?	Incorrect Correct ('no')	0 1	 9
155. Was there wireless/radio in this country before television was invented?	Incorrect Correct ('yes')	0 1	 9

Expression: Naming

In questions 156 and 157 accurate naming is needed. Descriptions of function or approximate answers are not acceptable. Acceptable answers may depend on local usage. Some items may have more than one correct name, as has been indicated. Errors include description of function (e.g. 'used for telling the time' for watch) and approximate answers (e.g. 'weighing machine' for scales; 'bag' or 'carrier' for suitcase; 'light' for lamp).

In the case of approximate answers, you should say 'Can you think of another word for it?'

Tick each item correctly named in questions 156 and 157 and enter number correct under Total

156. ***Show pencil***
What is this called? — Pencil ___
Show wristwatch
What is this called? — Wristwatch ___
Total |__| **9**

157. I am going to show you some objects.
Please tell me the name of each one.
Show 'Pictures for naming' in booklet.
Shoe, sandal ___
Typewriter ___
Scales ___
Suitcase, Portmanteau ___
Barometer. ___
Table lamp, lamp ___
Total |__| **9**

Expression: Fluency

158. Name as many different animals as you can think of. You will have one minute to do this.

Only if subject asks for clarification, explain that animals include birds, fish, insects, humans, etc. If subject gets stuck, encourage him/her with 'Can you think of any more?' Record number correct in one minute (repetitions not to be counted but age and sexual variants should be counted e.g. calf, cow, bull)

List all items

Number correct |__|__|

Note: Recode: For CAMCOG score
0 = **0**
1–4 = **1**
5–9 = **2**
10–14 = **3**
15–19 = **4**
20–24 = **5**
25+ = **6**
|__| **9**

Expression: Definitions

For questions 159–162, acceptable answers may depend on local usage

159. What do you do with a hammer?
Incorrect **0**
Any correct use **1** **9**

Hit is not enough. Some other detail should be given without prompting.

160. Where do people usually go to buy medicine?
Shop (if unable to specify) **0**
Chemist, pharmacy **1** **9**

In questions 161–162 a general (abstract) definition scores 2 and a specific or limited definition scores 1. Examples are given beside each score

161. What is a bridge?
Incorrect **0**
Cross the bridge **1**
Goes across a river etc **2** **9**

162. What is an opinion?	Incorrect	0	
	A good opinion of someone	1	
	A person's ideas about something; what you think	2	9

Expression: Repetition

Only one presentation is allowed so it is essential that you read the phrase clearly and slowly, enunciating all the S's.

163. I am going to say something and I would like you to repeat it after me: 'No ifs, ands or buts'.	Incorrect	0	
	Correct	1	9
Code 1 only if entire phrase is correct			

Memory

Recall

164. Can you tell me what were the objects in the coloured pictures I showed you a little while ago?	Shoe, sandal	—	
	Typewriter	—	
	Scales	—	
	Suitcase	—	
	Barometer	—	
	Table lamp, lamp	—	
Either descriptions or names are acceptable. Tick each item correctly recalled and enter number correct under Total	**Total**	|__|	9
If subject previously gave an incorrect name in question 157 but recalls it at this stage, score as correct			

Recognition

Show: 'Pictures for recognition' in booklet

Tick each item correctly recognised and enter number correct under Total

165. Which of these did I show you before?	Shoe, sandal	—	
	Typewriter	—	
	Scales	—	
	Suitcase	—	
	Barometer	—	
	Table lamp, lamp	—	
	Total	|__|	9

Retrieval of remote information

Note: Questions 166–171 should be asked if the subject was born before 1940. Questions 166a–171a should be asked if the subject was born after 1940.

Now I am going to ask you some questions about the past

166. When did the First World War begin? **(Within 1 year)**	Incorrect	0	
	1914 (in Europe)	1	9
167. When did the Second World War begin? **(Within 1 year)**	Incorrect	0	
	1939 (in Europe)	1	9
168. Who was the leader of the Germans in the Second World War?	Incorrect	0	
	Hitler	1	9

169. Who was the leader of the Russians in the Second World War?	Incorrect	0	
	Stalin	1	9
170. What was Mae West famous for? *Any appropriate verbal or non-verbal answer which indicates memory*	Incorrect	0	
	Entertainer, Film Star, Life jacket	1	9
171. Who was the famous flyer whose son was kidnapped? *Close approximations to the name are acceptable*	Incorrect	0	
	Lindbergh	1	9
Questions 166a–171a to be asked if subject was born after 1940			
166a. Who was the US President who was shot in Texas?	Incorrect	0	
	John F. Kennedy	1	9
167a. What is Yoko Ono famous for?	Incorrect	0	
	Wife of Beatle, John Lennon	1	9
168a. Who was the first man to set foot on the moon?	Incorrect	0	
	Neil Armstrong	1	9
169a. What was Edmund Hilary famous for?	Incorrect	0	
	First to reach summit of Mt Everest	1	9
170a. Who was the first woman Prime Minister of India?	Incorrect	0	
	Indira Ghandhi	1	9
171a. Who was the famous cinema actress who married Prince Rainier of Monaco? *Close approximations to the name are acceptable*	Incorrect	0	
	Grace Kelly	1	9
Retrieval of recent information			
172. What is the name of the present King or Queen?	Incorrect	0	
	Correct	1	9
173. Who is likely to be the next King or Queen?	Incorrect	0	
	Correct	1	9
174. What is the name of the Prime Minister? *For one month after an election, if the name of the former PM is given, ask 'Is he/she still Prime Minister?'*	Incorrect	0	
	Correct	1	9
175. What has been in the news in the past week or two? *If a general answer is given, e.g. 'war' ask for details*	Incorrect	0	
	Correct	1	9

Registration

I am going to name three objects. After I have finished saying all three, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

176.	*Name the following three objects taking one second to say each: apple, table, penny.* *Tick which are correct on the first attempt and enter number correct under total.*	Apple Table Penny **Total**	— — — |_|_|	**9**
177.	*If any errors or omissions are made on the first attempt, repeat all the names until subject learns all three (maximum of five repeats). Record number of repeats (record 0 if all correct on first attempt)*	Number of repeats	|_|_|	**9**

Attention/concentration

178.	Now I would like you to count backwards from 20.	Two or more errors One error Correct	**0** **1** **2**	**9**
179.	Now I would like you to take 7 away from 100. Now take 7 away from the number you get. Now keep subtracting 7 until I tell you to stop.	93 86 79 72 65 **Total**	— — — — — |_|_|	**9**

Record answers. Score 1 point each time the difference is 7, even if a previous answer was incorrect. Maximum score = 5 points

Memory: Recall

180.	What were the three objects I asked you to repeat a little while ago?	Apple Table Penny **Total**	— — — |_|_|	**9**

Tick each item answered correctly and enter number correct under Total

Language: Reading comprehension

Show 'Reading comprehension' in booklet.
I would like you to read this and do what it says
It is not necessary for the subject to read aloud. If subject reads instruction but fails to carry out action, say 'now do what it says'

If failure appears to be due to illiteracy, enquire whether subject learned to read. If illiterate code 7

181.	Close your eyes.	Incorrect Correct Illiterate	**0** **1** **7**	**9**

182. If you are older than 50 put your hands behind your head.	Incorrect Correct Illiterate	0 1 7		9

Praxis

Copying and Drawing

The subject should draw and write on the sheet of paper provided, see p. 56
Make sure the subject has finished before moving on to the next picture, e.g. by saying 'have you finished that one'?

183. Copy this design (pentagon). *Each pentagon should have 5 sides and 5 clear corners and the overlap should form a diamond*	Incorrect Correct	0 1		9
184. Copy this design (spiral). *Three connected loops are required in the correct orientation.*	Incorrect Correct	0 1		9
185. Copy this design (3D house). *Requires windows, door and chimney in correct position and in 3-dimensional representation*	Incorrect Correct	0 1		9
186. Draw a large clock face and put all the numbers in. *When the subject has done this say,* 'Now set the hands to 10 past 11 (11.10)'. *Tick each component correctly completed and enter number under Total*	Circle (or square) All numbers in correct position Correct time **Total**	— — — [ ]		9

Writing: Spontaneous

187. Write a complete sentence on this sheet of paper. *Indicate bottom of drawing sheet. Ask the subject what he/she has written and transcribe it onto the drawing sheet. Spelling and grammar are not important, but the sentence must have a subject (real or implied) and a verb. 'Help!' or 'Go away' are acceptable.*	Incorrect Correct Illiterate	0 1 7		9

Praxis: Ideational

Read the following statement and then hand a sheet of paper to the subject. Make a point of handing to the subject's midline. No repetition of this question is allowed. Speak clearly and slowly having first made sure you have the subject's full attention.

188. I am going to give you a piece of paper. When I do, take the paper in your *right* hand. Fold the paper in half with both hands, and put the paper down on your lap. *Do not repeat instructions or coach* *Score a move as correct only if it takes place in the correct sequence.* *Tick each correct move and enter number correct under Total*	Right hand Folds On lap **Total**	— — — [ ]		9

Hand an envelope to the subject.

189. Put the paper in the envelope and seal the envelope.	Incorrect Correct	0 1		9

Writing to dictation

190. Write this name and address on the envelope:
Mr. John Brown
42 West Street, Bedford

Incorrect	0	
Poor but acceptable	1	
Correct	2	
Illiterate	7	9

Spelling and neatness are not important. Criterion is whether letter is likely to reach exact destination, e.g. 'Jon Brwn' is acceptable; '24' and 'Burford' are incorrect

Then say: Please try to remember this name and address as I shall be asking you about them later on

If the subject is unable to write, code 7 and say the address slowly, twice, and ask him/her to remember it

Praxis: Ideomotor

In questions 191–193 a correct MIME is needed. If the subject uses fingers to represent scissors or brush, say e.g. 'Pretend you are holding a toothbrush.' Score 1 if the subject makes a brushing movement but not as though holding a toothbrush

191. Show me how you wave goodbye.

Incorrect	0	
Correct	1	9

192. Show me how you would cut with scissors.

Incorrect	0	
Partially correct	1	
Correct	2	9

193. Show me how you would brush your teeth with a toothbrush.

Incorrect	0	
Partially correct	1	
Correct	2	9

Calculation

Mental calculation is required. Paper and pencil are not allowed.

Show the subject two different commonly used coins or notes of different value.

194. How much money does this make?

Incorrect	0	
Correct	1	9

Record amount and response

195. If somebody went shopping and was given 15 pence as change from £1, how much did they spend?

Incorrect	0	
Correct	1	9

Record response

Memory: Recall

196. What was the name and address you wrote on the envelope a short time ago?

Tick each item answered correctly and enter number correct under Total

John	__	
Brown	__	
42	__	
West Street	__	
Bedford	__	
Total	|__|	9

Executive function

Abstract thinking

These questions investigate the capacity to work out the general relationships between objects. Fully correct answers score 2, partially correct answers score 1.

Examples are given beside each score. If the subject says 'They are not alike', say 'They are alike in some way. Can you tell me in which way they are alike?'

I am going to name two things and I would like you to tell me in what way they are alike. For example, a dog and a monkey are alike because they are both animals.

197. In what way are an apple and a banana alike?

Record answer

For this question only, if score is less than 2 say 'They are also alike because they are both fruit.'

Round, have calories	0	
Food, grow, have peel	1	
Fruit	2	9

198. In what way are a shirt and a dress alike?

Record answer

Have buttons	0	
To wear, made of cloth, keep you warm	1	
Clothing or garments	2	9

199. In what way are a table and a chair alike?

Record answer

Wooden, have 4 legs	0	
Household objects, used for meals	1	
Furniture	2	9

200. In what way are a plant and an animal alike?

Record answer

Useful to man, carry germs	0	
Grow, need food, natural	1	
Living things	2	9

Ideational Fluency

200a. I am going to give you the name of a common object and I would like you to tell me as many uses for it as you can. For example, if the object was a SHEET OF PAPER it could be used to write on, to make a fan or it could be used to make a paper plane. The uses don't have to be serious – they can be ridiculous or humorous as well – so let your imagination have a free rein. The important thing is to try and think of as many uses as you possibly can in the time given. Try to make the uses as different from each other as possible.
Begin when I say the object and continue until I tell you to stop.
How many different uses can you think of for a BOTTLE?

Start timing and continue for 90 seconds, then say STOP.

Record all responses.

A correct response is any possible use of a single bottle, pieces of a bottle or numerous bottles, e.g. for strong liquid, as a weapon, as an instrument, smashed into pieces and used for art work, for juggling. Correct responses must specify a use; 'to smash', 'to stand on' are incorrect.

Number correct	|_|_|	9
Note: Recode: >8 = 8 Enter 0–8 as above	|_|	9

A response is considered a perseveration if it is repeated verbatim or if the same idea is repeated with different examples, e.g. to store water, beer, cordial, orange juice, wine.

Number of perseverations	|_|_|_|	9

Visual reasoning

200b. ***Show 'Visual reasoning test' in booklet***

Show first item

Here are four boxes. Three of them have an object inside and this one is empty. Which of these objects below should go in the empty box? *Encourage subject to point to the correct response*

If subject makes an error on any of the first two items, point to the correct response and explain why it is correct.

Item 1:
The top row has a big yellow circle with a big blue circle beside it, so the bottom row needs a big blue circle.

Item 2:
The top row is blue; it has a little square beside the big circle. The bottom row is yellow, so it needs a little yellow square beside the yellow circle.

Do not make any further corrections.

If subject made an error, record which item (A to F) was chosen.

C	—	
A	—	
E	—	
D	—	
F	—	
B	—	
Total	|___|	**9**

Perception: Visual

Famous people

Show 'Recognition of famous people' in booklet

201. Who is this?

Score as correct if picture is recognised
Correct name is not required, but record any answer which does not correspond exactly to the examples given

Queen	—	
Pope, Archbishop, Bishop	—	
Total	|___|	**9**

Object constancy

Show 'Recognition of objects' in booklet

202. These are pictures of objects taken from unusual angles.
Can you tell me what they are?

Criterion is whether the object is recognised, not that it is named correctly, therefore descriptions of function are acceptable.
Tick each item answered correctly and enter number correct under Total

Spectacles	—	
Shoe	—	
Purse, suitcase	—	
Cup and saucer	—	
Telephone	—	
Pipe	—	
Total	|___|	**9**

Recognition of person/function

Indicate any two people available, e.g cleaner, doctor, nurse, patient, relative
If none available, score 9

203. Can you tell me who this is, or what he/she does?	Incorrect Correct	**0** **1**	**9**

Passage of time

204. Without looking at your watch, can you tell me what the time is now (to the nearest hour)?	Incorrect Correct	**0** **1**	**9**
205. Without looking at your watch, can you tell me how long you think we have been talking together?	Time in minutes	|_|_|_|	**999**
206. ***Record finishing time of interview with subject.***		|_|_|_|	
Actual duration of interview (minutes) *Check against starting time recorded at beginning of Section A.*	Time in minutes	|_|_|_|	**999**

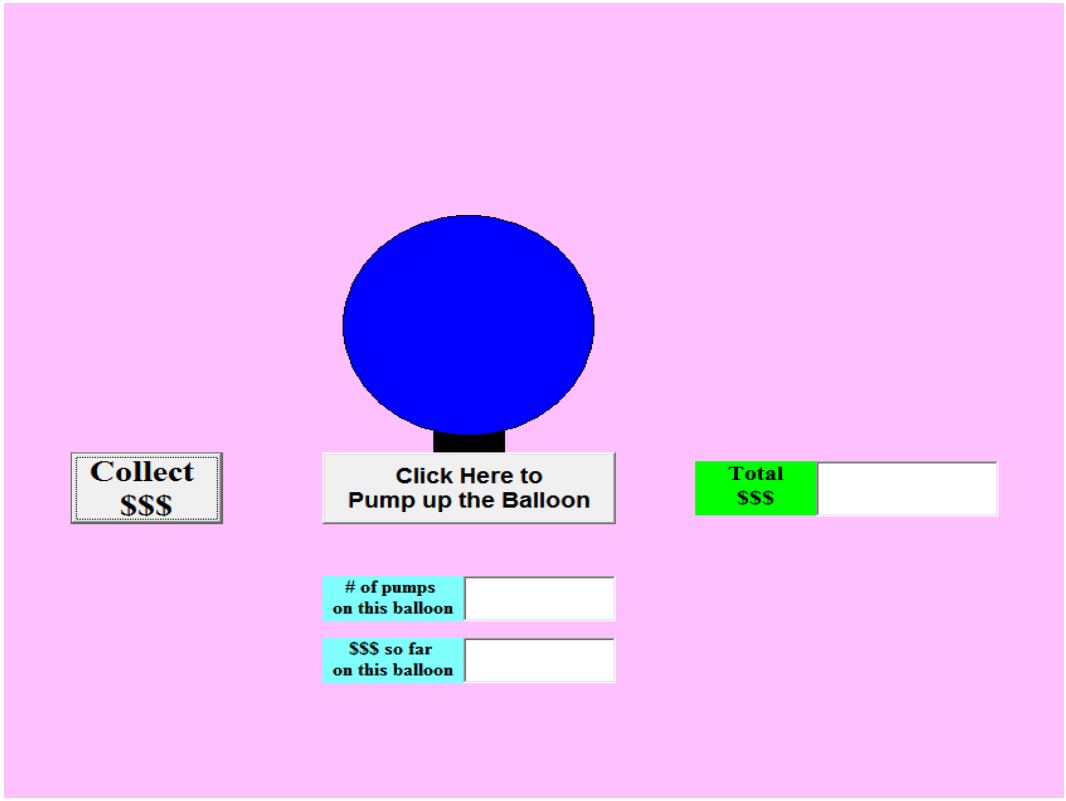
Appendix M: Wechsler Test of Adult Reading

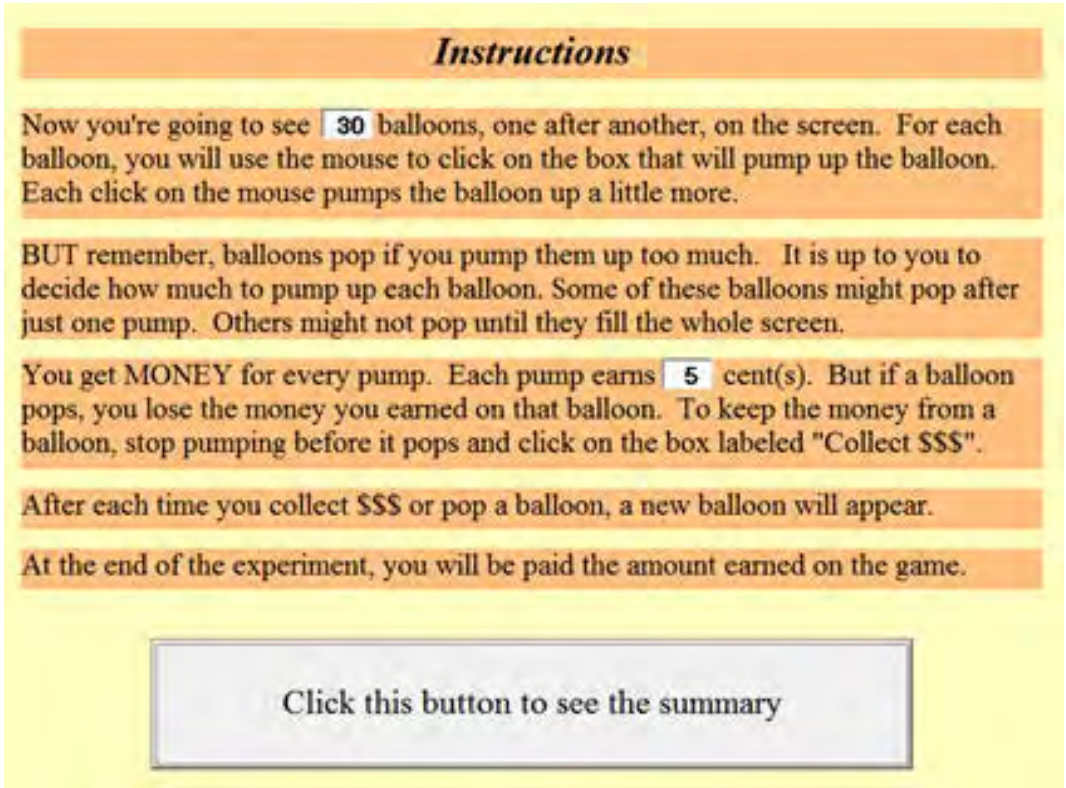
WTAR Word List - UK pronunciation guide

Say, **I will show you some words that I will ask you to pronounce.** Place the WTAR Word Card in front of the examinee. As you point to the card, say, **Beginning with the first word on the list, pronounce each word aloud. Start with this word** (point to item 1), **and go down this column, one after the other, without skipping any. When you finish this column, go to the next column** (point to the second column). **Pronounce each word even if you are unsure. Do you understand?** When you are sure that the examinee understands the task, say, **Ready? Begin.**

	Item	Pronunciation	Score (0, 1)		Item	Pronunciation	Score (0, 1)
1.	again	ah-GEHN ah-GAIN *or* uh-GEHN or uh-GAIN		26.	conscientious	con-shee-EN-shss	
2.	address	ah-DRESS *or* uh-DRESS		27.	homily	HOM-ih-lay *or* HOM-ih-lee	
3.	cough	kawf *or* kof		28.	malady	MAL-uh-day *or* MAL-uh-dee	
4.	preview	PREE-vyue		29.	subtle	SUH-tl	
5.	although	awl-THO		30.	fecund	FE-cund *or* FEE-cund	
6.	most	mohst		31.	palatable	PAL-ah-tuh-bul *or* PAL-uh-tuh-bul	
7.	excitement	eck-SITE-munt *or* ik-SITE-munt		32.	menagerie	meh-NA-juh-ree	
8.	know	noh *or* no		33.	obfuscate	OB-fuh-skate	
9.	plumb	plum		34.	liaison	lee-AY-zon *or* lee-AY-zn	
10	decorate	DEK-oh-rate *or* DEK-uh-rate		35.	exigency	eks-IH-jen-say *or* eks-IH-jen-see	
11.	fierce	fee-us *or* feerss		36.	xenophobia	zen-oh-FO-bee-uh	
12.	knead	need		37.	ogre	OH-gur	
13.	aisle	iyle		38.	scurrilous	SKUR-ih-lus *or* SKUR-uh-lus	
14.	vengeance	VEN-jnss		39.	ethereal	ih-THEE-ree-ul *or* ih-THEER-ee-ul	
15.	prestigious	pre-STIJ-us *or* pre-STEEJ-us		40.	paradigm	PAH-rah-dime	
16.	wreathe	reeTH *or* REEEth		41.	perspicuity	per-spuh-KYEW-uh-tee	
17.	gnat	nat		42.	plethora	PLETH-oh-rah *or* PLETH-eh-rah	
18.	amphitheatre	AM-fih-thee-uh-ter		43.	lugubrious	loo-GOOB-ree-uss *or* loo-GOO-bree-uss	
19.	lieu	loo *or* l(y)oo		44.	treatise	TREE-tiz *or* TREET-iz	
20.	grotesque	gro-TESK		45.	dilettante	DILL-ih-tan-tay *or* DILL-uh-tahnt	
21.	iridescent	ihr-ih-DESS-unt *or* ihr-uh-DESS-unt		46.	vertiginous	ver-TIDJ-in-iss	
22.	ballet	BA-lay *or* ba-LAY *or* bal-ay		47.	ubiquitous	you-BIC-wuh-tiss *or* you-BIC-wuh-tus	
23.	equestrian	eh-KWESS-tree-un *or* ih- KWESS-tree-un		48.	hyperbole	hy-PER-bul-lay *or* hy-PUR-bul-lay	
24.	porpoise	PAW-pss *or* POR-poyz (Scots)		49.	insouciant	in-SOO-see-yunt	
25.	aesthetic	ess-THET-ik *or* ees-THET-ik		50.	hegemony	heh-GEM-o-nee *or* heh-JEM-o-nee *or* HEH-geh-mon-ee	
						WTAR Raw Score	
						WTAR Standard Score	

Appendix N: Balloon Analogue Risk Task



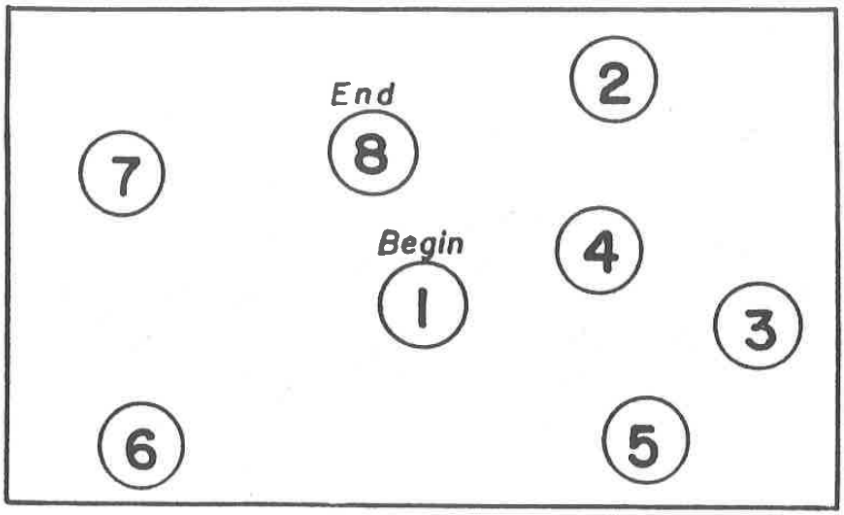


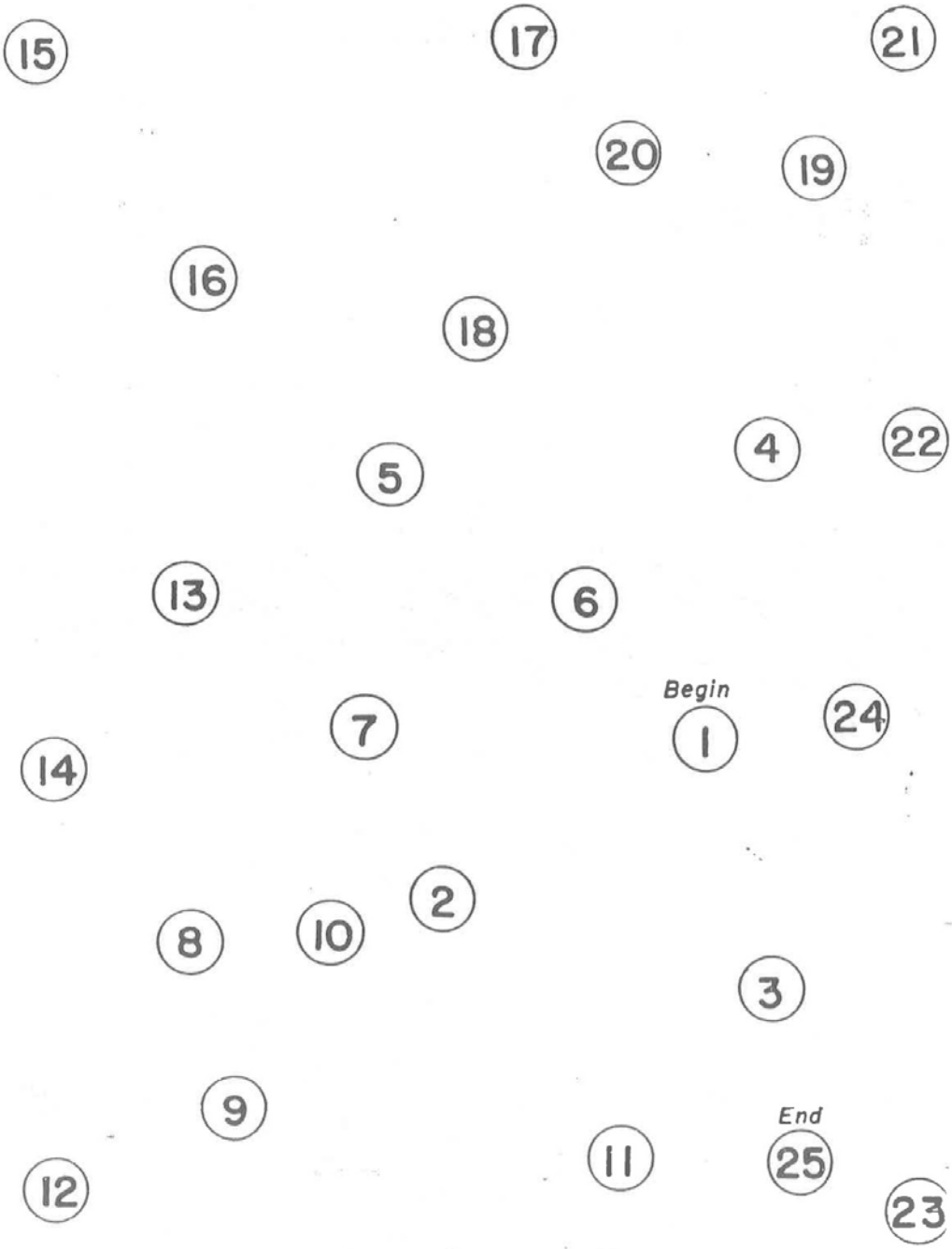
Appendix O: Trail Making Test Part A and B

TRAIL MAKING

Part A

SAMPLE

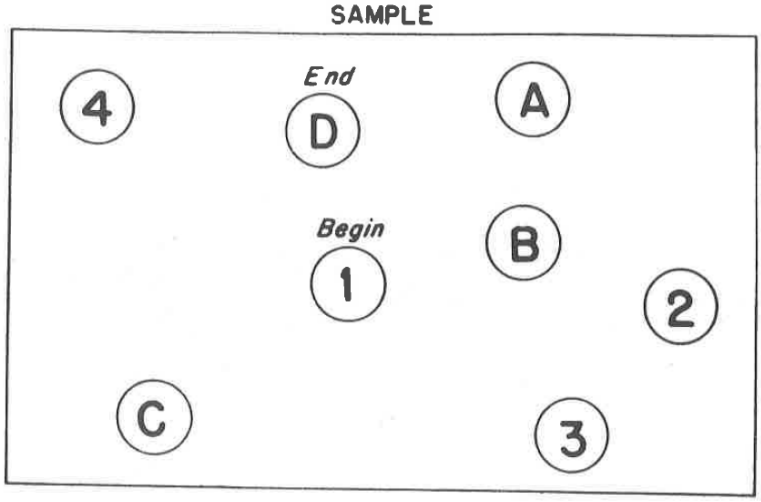


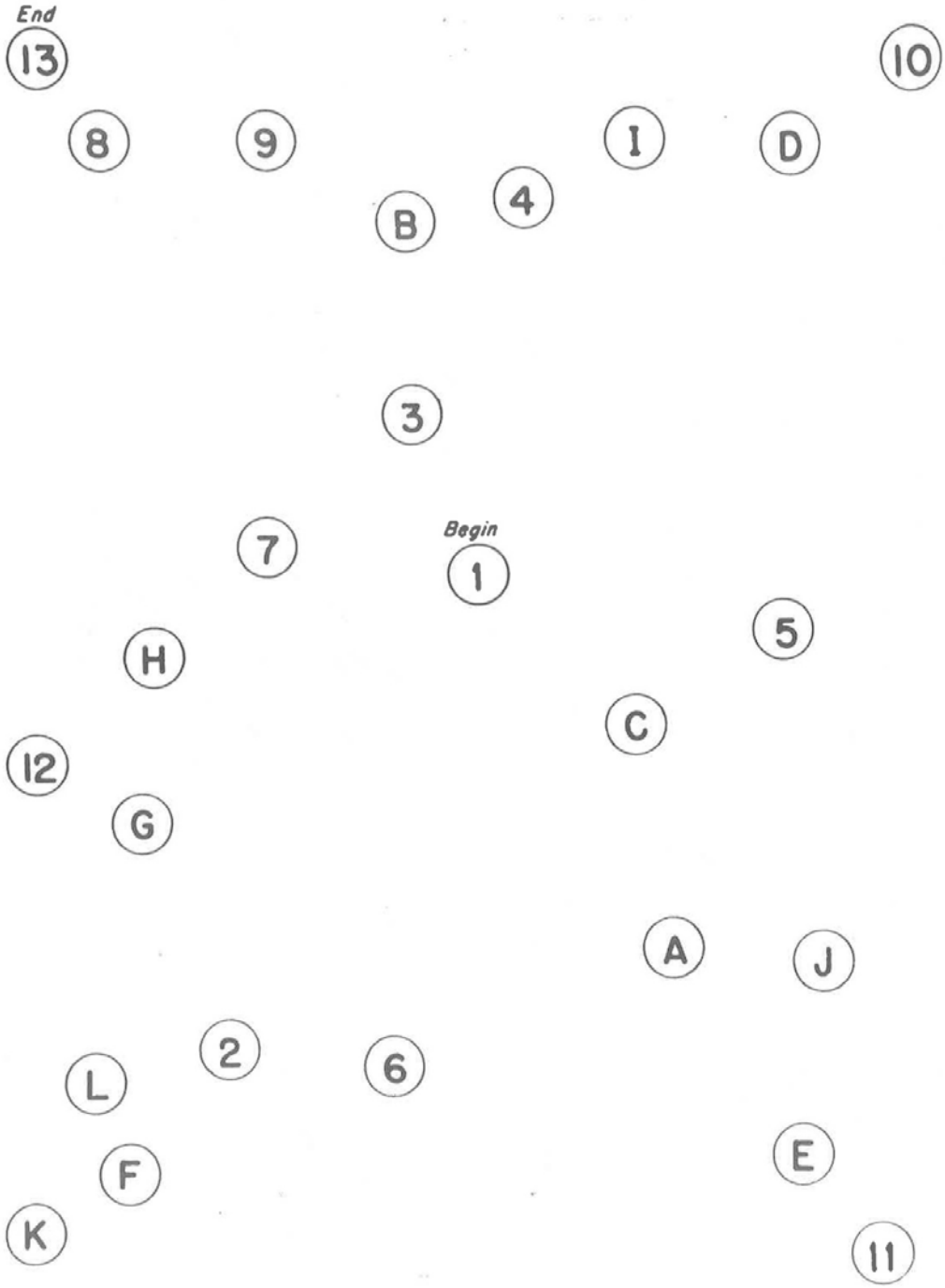

15
17
21
20
19
16
18
4
22
5
13
6
Begin
7
1
24
14
2
8
10
3
9
End
11
25
12
23

TRAIL MAKING

Part B

SAMPLE




End
13
10
8
9
I
D
4
B
3
7
Begin
1
5
H
C
12
G
A
J
2
6
L
E
F
K
11

Trail Making Test Parts A and B instructions

TRAIL MAKING

A sample: **"On this page** (point) **are some numbers. Begin at number 1** (point to 1) **and draw a line from 1 to 2** (point to 2), **2 to 3** (point to 3), **3 to 4** (point to 4), **and so on, in order, until you reach the end** (point to the circle marked "end"). **Draw the lines as fast as you can. Ready? Begin".** If the ppant made a mistake on the sample, point out the error and explain it. If it is clear that the ppant intended to touch a circle do not count it as an omission. If correct, say: **"Good, let's try the next one."**

A main test: **"On this page are numbers from 1 to 25. Begin at number 1** (point to 1) **and draw a line from 1 to 2** (point to 2), **2 to 3** (point to 3), **3 to 4** (point to 4), **and so on, in order, until you reach the end** (point to the circle marked "end"). **Remember, work as fast as you can. Ready? Begin.**" If the ppant makes an error, call their attention to it immediately and have them carry on from that point, do not stop timing. Upon completion say: **"That's fine".**

Record time to completion.

B sample: **"On this page are some numbers and letters. Begin at number 1** (point to 1) **and draw a line from 1 to A** (point to A), **A to 2** (point to 2), **2 to B** (point to B), **B to 3** (point to 3), **3 to C** (point to C), **and so on, in order, until you reach the end** (point to the circle marked "end"). **Remember, first you have a number** (point to 1) **and then a letter** (point to A), **then a number** (point to 2),**then a letter** (point to B), **and so on. Draw the lines as fast as you can. Ready? Begin.** If the ppant made a mistake on the sample, point out the error and explain it. If it is clear that the ppant intended to touch a circle do not count it as an omission. If correct, say: **"Good, let's try the next one.**"

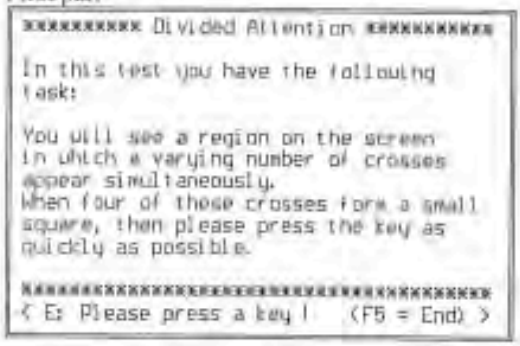
B main test: **"On this page are both numbers and letters. Do this the same way. Begin at number 1** (point to 1) **and draw a line from 1 to A** (point to A), **A to 2** (point to 2), **2 to B** (point to B), **B to 3** (point to 3), **3 to C** (point to C), **and so on, in order, until you reach the end (point). Remember, first you have a number** (point to 1) **and then a letter** (point to A), **then a number** (point to 2),**then a letter** (point to B), **and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready? Begin.** If the ppant makes an error, call their attention to it immediately and have them carry on from that point, do not stop timing. Upon completion say: **"That's fine".**

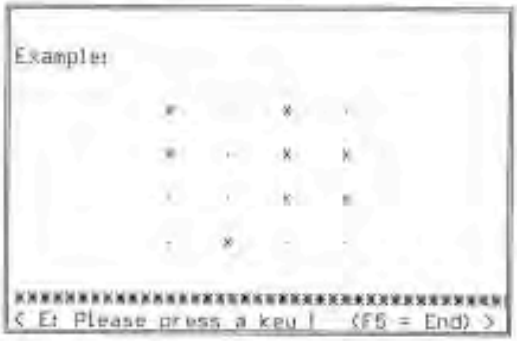
Record time to completion.

Appendix P: Divided Attention task

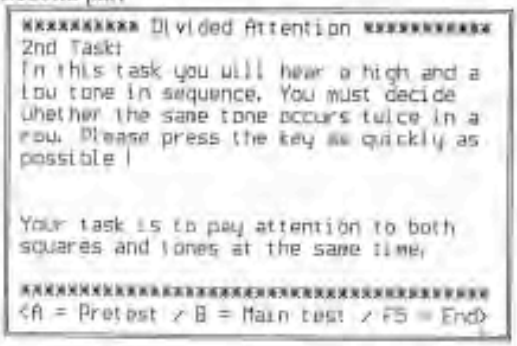
Instructions:

First part



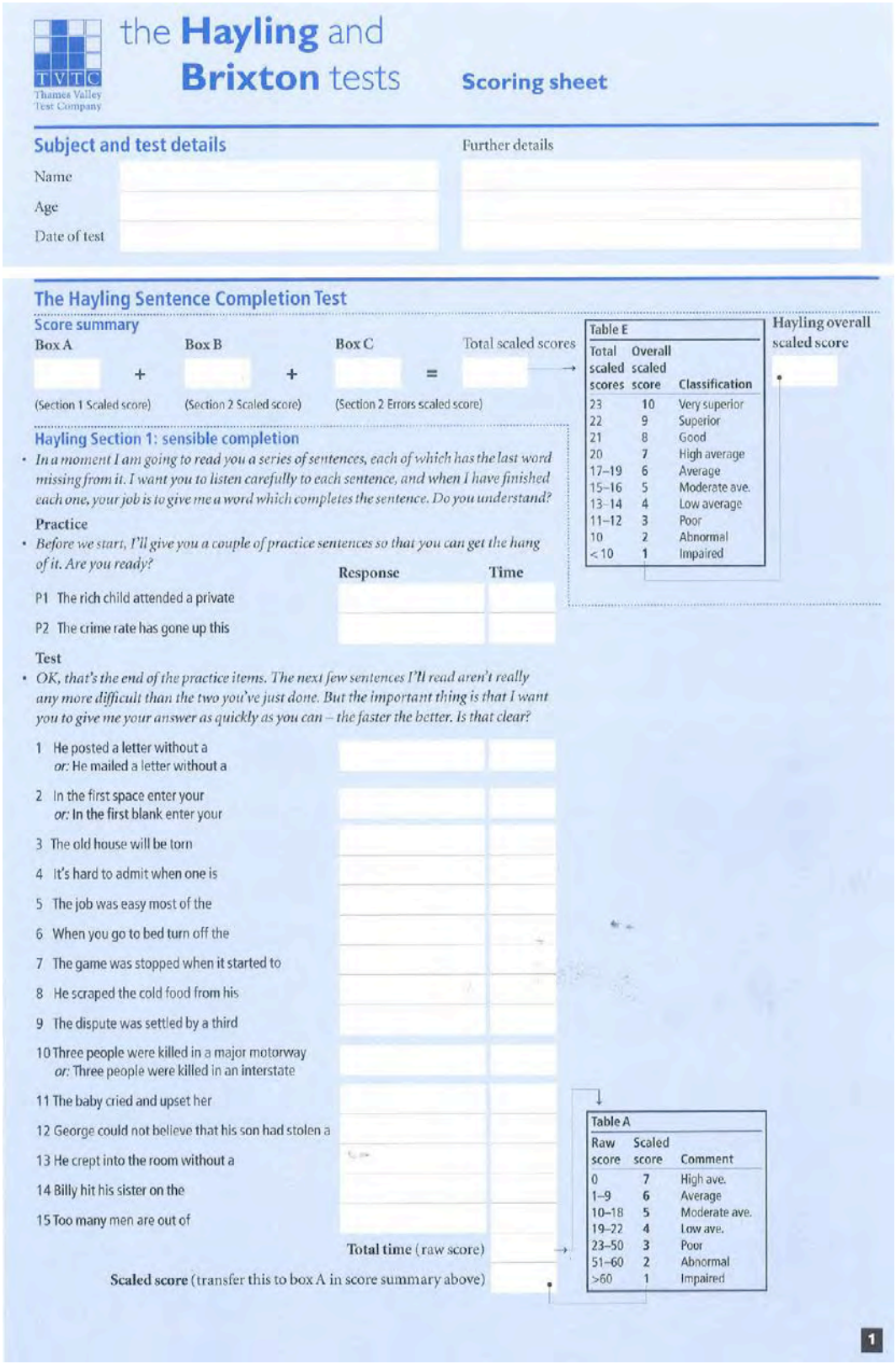


Second part



Results: The trial number, type of task (visual, auditory), the number of correct and incorrect responses, and the reaction times for correct responses are given. In addition, the number of correct and incorrect responses (missed signals, false positives), outliers, as well as median values, means and standard deviations are presented. A graphical presentation is optionally given of the median reaction times for the visual and auditory tasks.

Appendix Q: Hayling Sentence Completion Task



TVTC Thames Valley Test Company

the Hayling and Brixton tests — Scoring sheet

Subject and test details

Name

Age

Date of test

Further details

The Hayling Sentence Completion Test

Score summary

Box A		Box B		Box C		Total scaled scores	Hayling overall scaled score
	+		+		=	→	
(Section 1 Scaled score)		(Section 2 Scaled score)		(Section 2 Errors scaled score)			

Table E		
Total scaled scores	Overall scaled score	Classification
23	10	Very superior
22	9	Superior
21	8	Good
20	7	High average
17–19	6	Average
15–16	5	Moderate ave.
13–14	4	Low average
11–12	3	Poor
10	2	Abnormal
< 10	1	Impaired

Hayling Section 1: sensible completion

- *In a moment I am going to read you a series of sentences, each of which has the last word missing from it. I want you to listen carefully to each sentence, and when I have finished each one, your job is to give me a word which completes the sentence. Do you understand?*

Practice

- *Before we start, I'll give you a couple of practice sentences so that you can get the hang of it. Are you ready?*

	Response	Time
P1 The rich child attended a private		
P2 The crime rate has gone up this		

Test

- *OK, that's the end of the practice items. The next few sentences I'll read aren't really any more difficult than the two you've just done. But the important thing is that I want you to give me your answer as quickly as you can – the faster the better. Is that clear?*

1 He posted a letter without a *or:* He mailed a letter without a		
2 In the first space enter your *or:* In the first blank enter your		
3 The old house will be torn		
4 It's hard to admit when one is		
5 The job was easy most of the		
6 When you go to bed turn off the		
7 The game was stopped when it started to		
8 He scraped the cold food from his		
9 The dispute was settled by a third		
10 Three people were killed in a major motorway *or:* Three people were killed in an interstate		
11 The baby cried and upset her		
12 George could not believe that his son had stolen a		
13 He crept into the room without a		
14 Billy hit his sister on the		
15 Too many men are out of		
Total time (raw score)		→
Scaled score (transfer this to box A in score summary above)		•

Table A		
Raw score	Scaled score	Comment
0	7	High ave.
1–9	6	Average
10–18	5	Moderate ave.
19–22	4	Low ave.
23–50	3	Poor
51–60	2	Abnormal
>60	1	Impaired

1

Hayling Section 2: unconnected completion

- *Now we are going to move on to the second section of the test. In this section I will read you a set of sentences with the last word missing just like the ones you have already done, but this time I want you to give me a word which does not fit at the end of the sentence – I want the word you give me to be completely unconnected to the sentence in every way. Do you understand?'*

Practice

- *Before we start, I'll give you a couple of practice sentences so that you can get the hang of what is required'.*

	Response	Time
P1 London is a very busy		
P2 Her new shoes were the wrong		

- If the subject makes an error refer to instructions in Manual (page 8).

Test

- *'OK, that's the end of the practice items. Remember that the words you give me must be unconnected to the sentence, and that it is important for you to give me your answer as quickly as you can. Are you ready?'*

	Response	Time	Correct (unconnected)	Category A error (connected)	A score	Category B error (somewhat connected)	B score
1 The captain wanted to stay with the sinking			☐	☐		☐	
2 They went as far as they			☐	☐		☐	
3 Most cats see very well at			☐	☐		☐	
4 Jean was glad the affair was			☐	☐		☐	
5 The whole town came to hear the mayor			☐	☐		☐	
6 Most sharks attack very close to			☐	☐		☐	
7 None of the books made any			☐	☐		☐	
8 The dough was put in the hot			☐	☐		☐	
9 She called the husband at his			☐	☐		☐	
10 All the guests had a very good			☐	☐		☐	
11 He bought them in the sweet *or:* He bought them in the candy			☐	☐		☐	
12 His leaving home amazed all his			☐	☐		☐	
13 At last the time for action had			☐	☐		☐	
14 The dog chased our cat up the			☐	☐		☐	
15 At night they often took a short			☐	☐		☐	

Total Category A errors	A score	Total Category B errors	B score
1	3	1	1
2	6	2	2
3	10	3	3
4	14	4	4
5	18	5	9
6	24	6	14
7	30	7	19
8	36	8	24
9	42	9	29
10	48	10	34
11	54	>10	50
12	60		
13	66		
14	72		
15	78		

Total time (raw score) ←

Scaled score (transfer this to box B in score summary on page 1) •

Total Cat. A errors → **A score** | Total Cat. B errors → **B score** | **Converted score** (A score + B score)

Table B		
Raw score	Scaled score	Comment
0	8	Good
1–2	7	High average
3–50	6	Average
51–60	5	Moderate ave.
61–100	4	Low average
101–120	3	Poor
121–130	2	Abnormal
>130	1	Impaired

Table C		
Converted score	Scaled score	Comment
0	8	Good
1–3	7	High average
4–9	6	Average
10–12	5	Moderate ave.
13–14	4	Low average
15–17	3	Poor
18–29	2	Abnormal
≥ 30	1	Impaired

Hayling 2 errors scaled score (transfer this to box C in score summary on page 1)

2

Appendix R: Kirby Monetary Choice Questionnaire

For each of the next 27 choices, please indicate which reward you would prefer: the smaller reward today, or the larger reward in the specified number of days. Please, underlie your answer, as showed in the two examples below.

0. Would you prefer £1 today, or £2 in 15 days?

00. Would you prefer £3 today, or £4 in 20 days?

1. Would you prefer £36 today, or £37 in 117 days?

2. Would you prefer £37 today, or £50 in 61 days?

3. Would you prefer £13 today, or £17 in 53 days?

4. Would you prefer £21 today, or £57 in 7 days?

5. Would you prefer £9 today, or £17 in 19 days?

6. Would you prefer £31 today, or £33 in 160 days?

7. Would you prefer £10 today, or £23 in 13 days?

8. Would you prefer £17 today, or £40 in 14 days?

9. Would you prefer £52 today, or £54 in 162 days?

10. Would you prefer £27 today, or £37 in 62 days?

11. Would you prefer £7 today, or £20 in 7 days?

12. Would you prefer £45 today, or £50 in 119 days?

13. Would you prefer £22 today, or £23 in 186 days?

14. Would you prefer £18 today, or £33 in 21 days?

15. Would you prefer £46 today, or £57 in 91 days?

16. Would you prefer £33 today, or £40 in 89 days?

17. Would you prefer £54 today, or £57 in 157 days?

18. Would you prefer £16 today, or £23 in 29 days?

19. Would you prefer £22 today, or £54 in 14 days?

20. Would you prefer £19 today, or £20 in 179 days?

21. Would you prefer £22 today, or £33 in 30 days?

22. Would you prefer £17 today, or £20 in 80 days?

23. Would you prefer £27 today, or £50 in 20 days?

24. Would you prefer £36 today, or £40 in 111 days?

25. Would you prefer £36 today, or £54 in 30 days?

26. Would you prefer £15 today, or £17 in 136 days?

27. Would you prefer £13 today, or £37 in 7 days?

Appendix S: Go/No-Go

2.2.7. Go/No-go Test

The Go/No-go test has been designed to assess the specific ability of subjects to suppress undesired responses, an ability which is especially disturbed following prefrontal lobe lesions. Luria (1966) refers to a "disturbed voluntary motor control" in patients with frontal lobe damage. Drewe (1975a,b) could, in part, replicate the findings of Luria (1966), whereas Verfaillie and Heilman (1987) only found an impairment in patients with right frontal lobe damage. Heubeck (1989) found deficits in the Go/No-go test in patients with fronto-lateral but not fronto-medial lesions. Heubeck (1989) could not substantiate a significant right-left sided difference. Some patients with temporal lobe lesions also showed in impairment on this task.

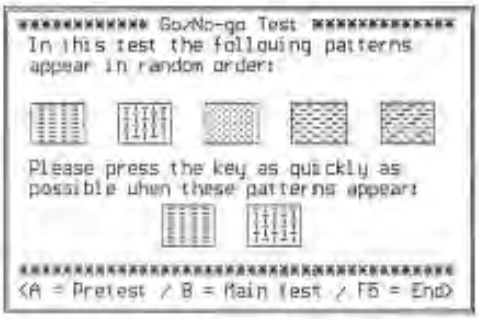
After analyzing a substantial amount of patient data, Fimm (1988) concluded that a specific factor, which he refers to as "response-selection performance", is impaired in these patients.

The present test should assess a subject's ability to suppress unwanted responses to irrelevant stimuli, as well as determining the choice reaction time under conditions of stimulus selection (compare the simple reaction time task given in the Alertness Test, Section 2.2.1).

In the Go/No-go test, two different versions with different stimulus material are provided. In the first version, reaction times and errors are recorded in a simple Go/No-go test with two stimuli (+ and x ; 2 stimuli, 1 critical stimulus). In the second version, 5 stimuli are given (boxes filled with different textures), of which 2 are defined as the critical stimuli (5 stimuli, 2 critical stimuli). In the first version, the number of trials is set to 40, whereas, in the second version, 50 trials are given (20 trials for each critical stimulus).

After starting the test, the experimenter is prompted with the following display:

Instruction: (second version with 5 stimuli)



Results: The number of correct responses and errors (missed critical stimuli and false positives) are given, along with median reaction times, means, standard deviations, and outliers.

Appendix T: Brixton Spatial Anticipation Test

TVTC
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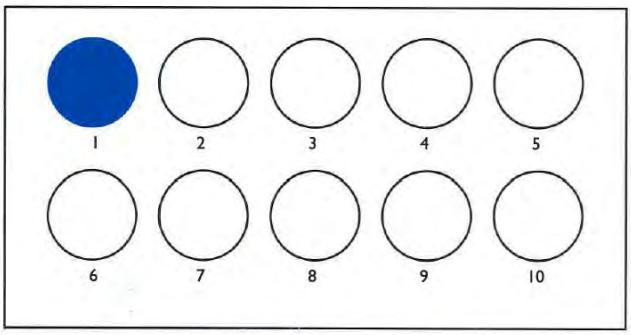

the **Brixton** test

Appendix U: Logical Memory

2. Logical Memory I *(continued)*

	Score 0 or 1		
Story A	**Story Unit**	**Thematic Unit**	**Scoring Criteria**
Anna			*Anna* or variant of the name
Thompson			*Thompson* is required
of South			*South* (in any context)
London,			*London* (in any context)
			indication of a main character who is female
employed			indication that she held a job
as a cook			*cook* or some form of the word is required
in a school			*school* is required
canteen,			*canteen* is required
			indication that main character is employed or is working
reported			indication that a formal statement was made to someone in authority (in any context)
at the police			*police* (in any context)
station			*station* (in any context) or a word or phrase denoting a police station
that she had been held up			indication that she had been held up (i.e., gunpoint or knife)
on the High Street			*the High Street* (in any context)
the night before			indication that the hold-up occurred the previous night
and robbed			indication that a robbery took place
of fifty-six pounds,			indication that an amount of money greater than £49 but less than £60 was taken from her
			indication that main character reported that she was robbed
She had four			*four* is required together with an indication that the children were hers
small children,			*children* or a synonym is required
			indication that main character had children
the rent was due,			a phrase indicating that the rent was due
and they had not eaten			indication that her children or the family were without food
for two days.			*two days* is required, or a phrase meaning about two days
			indication that characters were in need or required assistance
The police,			a word or phrase signifying one or more members of the police (in any context)
touched by the woman's story,			indication that her story evoked sympathy
			indication that the police felt sympathy for the woman
made up a collection			a phrase indicating that money was collected
for her.			indication that the money collected was for her or her children
			indication that the police directly responded to her need

Story A Recall Unit Score Range = 0 to 25 | | Story A Thematic Unit Score Range = 0 to 7

Story B–1st Recall

2. Logical Memory I *(continued)*

At 6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. A weather report interrupted the programme to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old films.

	Score 0 or 1		
Story B — 1st Recall	**Story Unit**	**Thematic Unit**	**Scoring Criteria**
At 6:00			*6:00* is required
on Monday			*Monday* is required
evening,			*evening* (in any context)
Joe			*Joe* or variant of the name
Grant			*Grant* is required
of Liverpool			*Liverpool* is required
			indication of a main character who is male
was watching television			indication that he was watching/listening to the television
as he dressed			indication that he was getting dressed
to go out.			indication that he was going out
			indication that the character was preparing to leave
A weather report			indication that there was an announcement about weather
interrupted the programme			indication of a break in the regularly scheduled programme
			indication of a weather announcement
to warn that thunderstorms			indication that there was a warning about a storm
would move into the area			indication that the storm was coming
			indication of a storm moving into the area
within the next 2 to 3 hours			a phrase meaning about 2 or 3 hours
and remain until morning.			indication that the storm would stay until morning
			indication of storm duration
The announcer said			indication that someone was reporting about a storm
the storm could bring hail			indication that hail was possible
and up to 4 inches			*4 inches* is required
of rain			*rain* is required
and cause the temperature to drop			indication that the temperature would drop or decrease
by 15 degrees.			a relative decrease of 15 degrees is required
			indication of storm's activity
Joe decided to stay home.			indication that he decided to stay home
			indication that the character decided to stay in
He took off his coat			indication that he took off outer clothing
and sat down			indication that he was sitting down
to watch old films.			indication of viewing films is required
			indication that the character decided to watch a film or TV

Story B — 1st Recall Unit Score Range = 0 to 25 | Story B — 1st Recall Thematic Unit Score Range = 0 to 8

1st Recall Total Score Calculation

Story A Recall Unit Score Range = 0 to 25 + Story B — 1st Recall Unit Score Range = 0 to 25 = 1st Recall Total Score Range = 0 to 50

Story B–2nd Recall

2. Logical Memory I *(continued)*

At 6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. A weather report interrupted the programme to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old films.

	Score 0 or 1		
Story B — 2nd Recall	**Story Unit**	**Thematic Unit**	**Scoring Criteria**
At 6:00			*6:00* is required
on Monday			*Monday* is required
evening,			*evening* (in any context)
Joe			*Joe* or variant of the name
Grant			*Grant* is required
of Liverpool			*Liverpool* is required
			indication of a main character who is male
was watching television			indication that he was watching/listening to the television
as he dressed			indication that he was getting dressed
to go out.			indication that he was going out
			indication that the character was preparing to leave
A weather report			indication that there was an announcement about weather
interrupted the programme			indication of a break in the regularly scheduled programme
			indication of a weather announcement
to warn that thunderstorms			indication that there was a warning about a storm
would move into the area			indication that the storm was coming
			indication of a storm moving into the area
within the next 2 to 3 hours			a phrase meaning about 2 or 3 hours
and remain until morning.			indication that the storm would stay until morning
			indication of storm duration
The announcer said			indication that someone was reporting about a storm
the storm could bring hail			indication that hail was possible
and up to 4 inches			*4 inches* is required
of rain			*rain* is required
and cause the temperature to drop			indication that the temperature would drop or decrease
by 15 degrees.			a relative decrease of 15 degrees is required
			indication of storm's activity
Joe decided to stay home.			indication that he decided to stay home
			indication that the character decided to stay in
He took off his coat			indication that he took off outer clothing
and sat down			indication that he was sitting down
to watch old films.			indication of viewing films is required
			indication that the character decided to watch a film or TV

Story B—2nd Recall Unit Score Range = 0 to 25 [ ][ ]

Story B— 2nd Recall Thematic Unit Score Range = 0 to 8

Recall Total Score Range = 0 to 75 [ ][ ]

Thematic Total Score Range = 0 to 23

(Sum Recall Unit Scores for Story A, Story B-1st, Story B-2nd)

(Sum Thematic Unit Scores for Story A, Story B-1st, Story B-2nd)

Learning Slope Calculation

[ ] – [ ] = [ ]

Story B—2nd Recall Unit Score Range = 0 to 25

Story B—1st Recall Unit Score Range = 0 to 25

Learning Slope Range = -25 to + 25

12. Logical Memory II

ADMINISTER 25–35 MINUTES AFTER LOGICAL MEMORY I.

Recall

RECORDING:
Place a tick (✔) next to each story unit recalled verbatim. Write non-verbatim responses next to the story unit.

SCORING RULE:
0–1 pt. for each story or thematic unit

Reminder Given? ❑ Yes ❑ No

	Score 0 or 1		
Story A	**Story Unit**	**Thematic Unit**	**Scoring Criteria**
Anna			*Anna* or variant of the name
Thompson			*Thompson* is required
of South			*South* (in any context)
London,			*London* (in any context)
			indication of a main character who is female
employed			indication that she held a job
as a cook			*cook* or some form of the word is required
in a school			*school* is required
canteen,			*canteen* is required
			indication that main character is employed or is working
reported			indication that a formal statement was made to someone in authority (in any context)
at the police			*police* (in any context)
station			*station* (in any context) or a word or phrase denoting a police station
that she had been held up			indication that she had been held up (i.e., gunpoint or knife)
on the High Street			*the High Street* (in any context)
the night before			indication that the hold-up occurred the previous night
and robbed			indication that a robbery took place
of fifty-six pounds.			indication that an amount of money greater than £49 but less than £60 was taken from her
			indication that main character reported that she was robbed
She had four			*four* is required together with an indication that the children were hers
small children,			*children* or a synonym is required
			indication that main character had children
the rent was due,			a phrase indicating that the rent was due
and they had not eaten			indication that her children or the family were without food
for two days.			*two days* is required, or a phrase meaning about two days
			indication that characters were in need or required assistance
The police,			a word or phrase signifying one or more members of the police (in any context)
touched by the woman's story,			indication that her story evoked sympathy
			indication that the police felt sympathy for the woman
made up a collection			a phrase indicating that money was collected
for her,			indication that the money collected was for her or her children
			indication that the police directly responded to her need
Story A Recall Unit Score Range = 0 to 25			Story A Thematic Unit Score Range = 0 to 7

12. Logical Memory II *(continued)*

Reminder Given? ❑ Yes ❑ No

	Score 0 or 1		
Story B	**Story Unit**	**Thematic Unit**	**Scoring Criteria**
At 6:00			*6:00* is required
on Monday			*Monday* is required
evening,			*evening* (in any context)
Joe			*Joe* or variant of the name
Grant			*Grant* is required
of Liverpool			*Liverpool* is required
			indication of a main character who is male
was watching television			indication that he was watching/listening to the television
as he dressed			indication that he was getting dressed
to go out.			indication that he was going out
			indication that the character was preparing to leave
A weather report			indication that there was an announcement about weather
interrupted the programme			indication of a break in the regularly scheduled programme
			indication of a weather announcement
to warn that thunderstorms			indication that there was a warning about a storm
would move into the area			indication that the storm was coming
			indication of a storm moving into the area
within the next 2 to 3 hours			a phrase meaning about 2 or 3 hours
and remain until morning.			indication that the storm would stay until morning
			indication of storm duration
The announcer said			indication that someone was reporting about a storm
the storm could bring hail			indication that hail was possible
and up to 4 inches			*4 inches* is required
of rain			*rain* is required
and cause the temperature to drop			indication that the temperature would drop or decrease
by 15 degrees.			a relative decrease of 15 degrees is required
			indication of storm's activity
Joe decided to stay home.			indication that he decided to stay home
			indication that the character decided to stay in
He took off his coat			indication that he took off outer clothing
and sat down			indication that he was sitting down
to watch old films.			indication of viewing films is required
			indication that the character decided to watch a film or TV

Story B Recall Unit Score
Range = 0 to 25

Story B Thematic Unit Score
Range = 0 to 8

Recall Total Score
Range = 0 to 50
(Sum Recall Unit Scores for Story A & Story B)

Thematic Total Score
Range = 0 to 15
(Sum Thematic Unit Scores for Story A & Story B)

12. Logical Memory II *(continued)*

Recognition

RECORDING:
Circle Y or N.

SCORING RULE:
0–1 pt. for each item

Item	Circle Y or N	Score 0 or 1
Story A		
1. Was the woman's name Anna Thompson?	**Y** N	
2. Was the story setting in South London?	**Y** N	
3. Was the woman a cook?	**Y** N	
4. Did she work in a canteen?	**Y** N	
5. Did she have four children?	**Y** N	
6. Were the children teenagers?	Y **N**	
7. Did the robbery take place on the High Street?	**Y** N	
8. Did the woman report being robbed two nights before?	Y **N**	
9. Did she report the robbery at the Police Station?	**Y** N	
10. Was the woman robbed of 75 pounds?	Y **N**	
11. Did the family go without food for four days?	Y **N**	
12. Was the rent due?	**Y** N	
13. Did the police catch the thief?	Y **N**	
14. Did the police feel sorry for the woman?	**Y** N	
15. Did the police make up a collection?	**Y** N	
Story B		
16. Was the man's name Joe Green?	Y **N**	
17. Was it Sunday evening?	Y **N**	
18. Was it 6:00?	**Y** N	
19. Was the story setting in Liverpool?	**Y** N	
20. Was Joe dressing to go out?	**Y** N	
21. Was Joe watching television?	**Y** N	
22. Was the programme interrupted?	**Y** N	
23. Was the storm expected to move into the area on Tuesday?	Y **N**	
24. Was the storm expected to stay in the area through the night?	**Y** N	
25. Was the temperature predicted to drop 30 degrees?	Y **N**	
26. Did the announcer predict 10 inches of rain?	Y **N**	
27. Did the announcer warn of possible flooding?	Y **N**	
28. Did the announcer warn that it could hail?	**Y** N	
29. Did Joe decide to stay home?	**Y** N	
30. Did Joe sit down to watch a sports programme?	Y **N**	

Recognition Total Score
Range = 0 to 30 ☐

Percent Retention Calculation

☐ ÷ ☐ x 100 = ☐ Percent Retention Range = 0 to 100%

Logical Memory II Recall Total Score Range = 0 to 50

Logical Memory I Story A Recall Unit Score + Story B-2nd Recall Unit Score Range = 0 to 50

2. Logical Memory I

Say **I am going to read a short story to you. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through, I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Are you ready?**

Read Story A.

Anna Thompson of South London, employed as a cook in a school canteen, reported at the police station that she had been held up on the High Street the night before and robbed of fifty-six pounds. She had four small children, the rent was due, and they had not eaten for two days. The police, touched by the woman's story, made up a collection for her.

After reading the story, say **Tell me everything you can remember about this story. Start at the beginning.**

After the examinee has recalled as much of Story A as he or she can, and you have recorded the examinee's response, proceed to Story B.

Logical Memory I — Story A

Say **Now I am going to read another short story to you. As with the first story, try to remember it just the way I read it. Ready?**

Read Story B.

At 6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. A weather report interrupted the programme to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old films.

Then say **Tell me everything you can remember about this story. Start at the beginning.**

After the examinee has recalled as much of Story B as he or she can, and you have recorded the examinee's response, say **I am going to read the same story to you again. Listen carefully and try to remember it just the way I read it, as close to the same words as you can. When I am through, tell me everything you can remember. Ready?**

Reread Story B.

At 6:00 on Monday evening, Joe Grant of Liverpool was watching television as he dressed to go out. A weather report interrupted the programme to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old films.

Then say **Tell me everything that you can remember about this story. Start at the beginning.**

After the examinee has recalled as much of Story B as he or she can, and you have recorded the examinee's response, say **I want you to remember as much of these stories as you can because I will ask you to tell me the stories again later.**

12. Logical Memory II

Recall

Say **Do you remember the stories I read to you a little while ago? I want you to tell me the stories again. Tell me everything that you can remember about the first story. Start at the beginning.**

If the examinee does not recall any Story A units, say **The story was about a woman who was robbed.**

Do not give any further help other than general encouragement. Note on the Record Form whether the reminder was given.

When the examinee has recalled as much of Story A as he or she can, say **Now tell me everything that you can remember about the second story. Start at the beginning.**

If the examinee does not recall any Story B units, say **The story was about a weather report.**

Do not give any further help other than general encouragement. Note on the Record Form whether this reminder was given.

When the examinee has recalled as much of Story B as he or she can, and you have recorded the examinee's response, proceed to Recognition.

Recognition

Say **I am going to ask you some questions about the first story. If you are not sure of the answers, give your best guess.**

Read the Recognition questions for Story A from the Record Form and record the examinee's responses.

Then say **Now I will ask you some questions about the second story. If you are not sure of the answers, give your best guess.**

Read the Recognition questions for Story B from the Record Form and record the examinee's responses.

Appendix V: Barratt Impulsiveness Questionnaire

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

	① Rarely/Never	② Occasionally	③ Often	④ Almost Always/Always
1	I plan tasks carefully.			① ② ③ ④
2	I do things without thinking.			① ② ③ ④
3	I make-up my mind quickly.			① ② ③ ④
4	I am happy-go-lucky.			① ② ③ ④
5	I don't "pay attention."			① ② ③ ④
6	I have "racing" thoughts.			① ② ③ ④
7	I plan trips well ahead of time.			① ② ③ ④
8	I am self controlled.			① ② ③ ④
9	I concentrate easily.			① ② ③ ④
10	I save regularly.			① ② ③ ④
11	I "squirm" at plays or lectures.			① ② ③ ④
12	I am a careful thinker.			① ② ③ ④
13	I plan for job security.			① ② ③ ④
14	I say things without thinking.			① ② ③ ④
15	I like to think about complex problems.			① ② ③ ④
16	I change jobs.			① ② ③ ④
17	I act "on impulse."			① ② ③ ④
18	I get easily bored when solving thought problems.			① ② ③ ④
19	I act on the spur of the moment.			① ② ③ ④
20	I am a steady thinker.			① ② ③ ④
21	I change residences.			① ② ③ ④
22	I buy things on impulse.			① ② ③ ④
23	I can only think about one thing at a time.			① ② ③ ④
24	I change hobbies.			① ② ③ ④
25	I spend or charge more than I earn.			① ② ③ ④
26	I often have extraneous thoughts when thinking.			① ② ③ ④
27	I am more interested in the present than the future.			① ② ③ ④
28	I am restless at the theater or lectures.			① ② ③ ④
29	I like puzzles.			① ② ③ ④
30	I am future oriented.			① ② ③ ④

Appendix W: Starkstein Apathy Scale

1. Are you interested in learning new things?	Not at all	slightly	some	a lot
2. Does anything interest you?	Not at all	slightly	some	a lot
3. Are you concern about your condition?	Not at all	slightly	some	a lot
4. Do you put much effort into things?	Not at all	slightly	some	a lot
5. Are you always looking for something to do?	Not at all	slightly	some	a lot
6. Do you have plans and goals for the future?	Not at all	slightly	some	a lot
7. Do you have motivation?	Not at all	slightly	some	a lot
8. Do you have the energy for daily activities?	Not at all	slightly	some	a lot
9. Does someone have to tell you what to do each day?	Not at all	slightly	some	a lot
10. Are you indifferent to things?	Not at all	slightly	some	a lot
11. Are you unconcerned with many things?	Not at all	slightly	some	a lot
12. Do you need to be pushed to get started on things?	Not at all	slightly	some	a lot
13. Are you neither happy nor sad, just in between?	Not at all	slightly	some	a lot
14. Do you consider yourself apathetic?	Not at all	slightly	some	a lot

Appendix X: Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale

(A)	**1.**	**I feel tense or 'wound up':**
3	1.	Most of the time
2	2.	A lot of the time
1	3.	From time to time
0	4.	Not at all
(D)	**2.**	**I still enjoy the things I used to enjoy:**
0	1.	Definitely as much
1	2.	Not quite so much
2	3.	Only a little
3	4.	Hardly at all
(A)	**3.**	**I get a sort of frightened feeling as if something awful is about to happen:**
3	1.	Very definitely and quite badly
2	2.	Yes, but not too badly
1	3.	A little, but it doesn't worry me
0	4.	Not at all
(D)	**4.**	**I can laugh and see the funny side of things:**
0	1.	As much as I always could
1	2.	Not quite so much now
2	3.	Definitely not so much now
3	4.	Not at all
(A)	**5.**	**Worrying thoughts go through my mind:**
3	1.	A great deal of the time
2	2.	A lot of the time
1	3.	From time to time but not too often
0	4.	Only occasionally
(D)	**6.**	**I feel cheerful:**
3	1.	Not at all
2	2.	Not often
1	3.	Sometimes
0	4.	Most of the time
(A)	**7.**	**I can sit at ease and feel relaxed:**
0	1.	Definitely
1	2.	Usually
2	3.	Not often
3	4.	Not at all

(D) **8. I feel as if I am slowed down:**

3 1. Nearly all the time
2 2. Very often
1 3. Sometimes
0 4. Not at all

(A) **9. I get a sort of frightened feeling like 'butterflies' in the stomach:**

0 1. Not at all
1 2. Occasionally
2 3. Quite often
3 4. Very often

(D) **10. I have lost interest in my appearance:**

3 1. Definitely
2 2. I don't take as much care as I should
1 3. I may not take as much care
0 4. I take just as much care as ever

(A) **11. I feel restless as if I have to be on the move:**

3 1. Very much indeed
2 2. Quite a lot
1 3. Not very much
0 4. Not at all

(D) **12. I look forward with enjoyment to things:**

0 1. As much as I ever did
1 2. Rather less than I used to
2 3. Definitely less than I used to
3 4. Hardly at all

(A) **13. I get sudden feelings of panic:**

3 1. Very often indeed
2 2. Quite often
1 3. Not very often
0 4. Not at all

(D) **14. I can enjoy a good book or radio or TV programme:**

0 1. Often
1 2. Sometimes
2 3. Not often
3 4. Very seldom

Appendix Y: Study 2 List of studies excluded at the full-text screening stage and reason(s) for their exclusions

Authors (year)	Reason(s) for exclusion
Auyeung et al[1]	No suitable outcome measure (only hallucination and previous history of depression and anxiety explored)
Averbeck et al[2]	No criteria for ICB diagnosis reported; participants included in multiple studies/double.
Balasubramani et al[3]	No suitable outcome measure (experimental task); no criteria for ICB diagnosis reported
Callesen et al[4]	Postal survey (QUIP) only (i.e., no clinical interview to confirm/exclude ICB)
Cerasa et al[5]	Patients screened only for PG (i.e., control group might include patients with other types of ICB)
Claaseen et al[6]	No exact data available
Crockford et al[7]	Patients screened only for PG (i.e., control group might include patients with other types of ICB)
Djamshidian et al[8]	No suitable outcome measure (experimental task)
Djamashidian et al[9]	No suitable outcome measure (experimental task)
Djamshidian et al[10]	No suitable outcome measure (salivary cortisol dosage); participants included in multiple studies/double
Djamshidian et al[11]	No suitable outcome measure (experimental task)
Djamshidian et al[12]	Three participants in the ICB+ group had substance abuse
Djamshidian et al[13]	No suitable outcome measure (experimental task)
Evans et al[14]	No ICB- control group (no comparison ICB+ vs. ICB-)
Farnikova et al[15]	No suitable outcome measure (MMPI)
Garlovsky et al[16]	No PD-no ICB control group (patients divided into high vs. low QUIP score without defining a cut-off value); three PD patients treated with DBS
Gee et al[17]	No ICB- control group
Gescheidt et al[18]	Dementia not excluded
Goerlich-Dobre et al[19]	No ICB+ vs. ICB- comparison
Hurt et al[20]	Dementia not excluded
Joutsa et al[21]	Postal survey (QUIP, SOGS) only (i.e., no clinical interview to confirm/exclude ICB)
Joutsa et al[22]	Postal survey (QUIP) only (i.e., no clinical interview to confirm/exclude ICB)
Joutsa et al[23]	No suitable outcome measure (PET imaging study)
Klos et al [24]	Case series including PD and MSA patients; no cognitive, affective or behavioural measure reported
Kim et al[25]	Study on treatment (DBS) effect on ICB (data on ICB before DBS assessed retrospectively)
Leplow et al[26]	No suitable outcome measure (experimental task)
Leroi et al[27]	Participants included in multiple studies/double
Leroi et al[28]	Dementia not excluded; no information on ICB preceding PD onset in the control group

Authors (year)	Reason(s) for exclusion
Lim et al[29]	Patients with PD-dementia were included; QUIP only (i.e., no clinical interview to confirm/exclude ICB)
Mamikonyan et al[30]	Patients with ICB history included in the ICB- control group; no cognitive, affective or behavioural measure reported
Olley et al[31]	Patients with ICB history included in the ICB- control group
Pellicano et al[32]	No suitable outcome measure (neuroimaging study)
Phu et al[33]	No suitable outcome measure (quality of life)
Politis et al[34]	No suitable outcome measure (neuroimaging study)
Pontone et al[35]	No suitable outcome measure (neuropsychiatric inventory that offers a composite behavioural score)
Rao et al[36]	Dementia not excluded; no suitable outcome measure (neuroimaging study)
Ray et al[37]	Unclear whether patients with ICB history, other than PG, were included in the ICB- control group; one patient treated with DBS; no suitable outcome measure (neuroimaging study)
Sachdeva et al[38]	Patients with alcohol history included in the study
Saez-Francas et al[39]	Nearly a third of the sample were de novo drug naïve PD patients
Santangelo et al[40]	Control group included 2 PD patients with hypersexuality and 1 PD patient with compulsive shopping
Siri et al[41]	Dementia not excluded (two patients in the control group with clinical signs of dementia); patients grouped in active PG vs. ICB- control group (i.e., patients with ICB other than PG likely not included)
Siri et al[42]	Dementia not excluded
Steeves et al[43]	Unclear whether patients with ICB history, other than PG, were included in the ICB- control group; no suitable outcome measure (PET imaging study)
Van Eimeren et al[44]	Unclear whether patients with ICB history, other than PG, were included in the ICB- control group; no suitable outcome measure (PET imaging study)
Voon et al[46]	Patients with personal or immediate family history of alcohol abuse were included
Voon et al[47]	Patients with substance abuse disorders were included; participants included in multiple studies/double
Voon et al[48]	Patients with substance abuse disorders were included; participants included in multiple studies/double; no suitable outcome measure (experimental task and neuroimaging study)
Voon et al[49]	Dementia not excluded
Voon et al[50]	Patients with substance abuse disorder were included; participants included in multiple studies/double; no suitable outcome measure (experimental task and neuroimaging study)
Vriend et al[51]	All patients were drug-naïve at baseline; dementia not excluded at follow-up
Weintraub et al[52]	Dementia not excluded; no suitable outcome measure (no cognitive, affective or behavioural data were recorded)

Authors (year)	Reason(s) for exclusion
Wylie et al[53]	No exact data available
Yoo et al[54]	Patients screened only for punding (i.e., control group might include patients with other types of ICB)
Yoo et al[55]	No suitable outcome measure (neuroimaging study)

Legend. DBS: deep brain stimulation; ICB: impulsive-compulsive behaviour; MSA: multiple system atrophy; PD: Parkinson's disease; PG: pathological gambling; QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; SOGS: South Oaks Gambling Screen.

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Appendix Z: Study 3 Independent Peer Review approval letter

13th June 2017

Keele University

Dear Dr. Stefano Tamburin,

Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorders; a multicentre cross-sectional investigation of an Italian Parkinson's disease cohort

As you know the above project was initially awarded a grade 2 but following assessment of your response to the issues raised the project now has received final approval from the Independent Peer Review Committee and can be submitted for NHS ethical approval and HRA approval

I am attaching a letter addressed along with the original peer review comments which you can enclose with your NSMI application and/or NHS REC/HRA application as appropriate.

Management approval

You should arrange for all relevant NHS care organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant care organisation before commencing any research procedures. Where a substantive contract is not held with the care organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Clinical trial of a medicinal product

Please remember that, if your project is a clinical trial of a medicinal product, MHRA approval is required. You must submit a request for a clinical trial authorisation under the Medicines for Human Use (Clinical Trials) Regulations 2004. Further details can be found at
http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con2022633.pdf

If you have any queries, please do not hesitate to contact Nicola Leighton 01782 733306.

Yours sincerely

N Leighton

pp Professor Nicky Edelstyn
Chair – Independent Peer Review Committee

Enc

Appendix AA: Study 3 Keele University Ethical Review Panel approval

Keele University FNS Psychology Faculty Research Ethics Committee
psychology.ethics@keele.ac.uk

13.08.19

Dear Alica Martini,

Project Title:	Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorders: a multicentre investigation of an Italian Parkinson's disease cohort (PROACTIVE-PD)
REC Project Reference:	PS-190068
Type of Application	Amendment

Keele University's Psychology Research Ethics Committee (PSY-FREC) reviewed the above amendment.

Favourable Ethical opinion
The members of the Committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Yours sincerely,

Joseph Brooks
Chair / Lead Reviewer

Appendix AB: Study 3 University Hospital of Verona Ethical Review Panel approval - *Ethical Review Panel of Verona and Rovigo Territory*

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA VERONA

(D.Lgs. n. 517/1999 - Art. 3 L.R.Veneto n. 18/2009)

Sede Legale: P.le A. Stefani, 1 - 37126 Verona - P.IVA/Codice Fiscale 03901420236

Deliberazione del Direttore Generale

N. 401 del 25/05/2018

OGGETTO: AUTORIZZAZIONE ALLA CONDUZIONE DELLO STUDIO NO PROFIT 1456CESC, APPROVATO NELLA SEDUTA DEL COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DEL 18/04/2018. APPROVAZIONE DELLA CONVENZIONE ECONOMICA.

TRASMESSA PER L'ESECUZIONE:
(UOS) UNITA` RICERCA CLINICA - BT

PER CONOSCENZA:
DIREZIONE AZIENDALE DIREZIONE AMMINISTRATIVA
DIREZIONE AZIENDALE DIREZIONE SANITARIA
DIREZIONE AZIENDALE DIREZIONE GENERALE
(UOC) CONTABILITA` E BILANCIO

ESECUTIVA ai sensi di Legge dal 25/05/2018	**PUBBLICATA**, a norma di Legge, a decorrere dal 29/05/2018	**TRASMESSA** al Collegio Sindacale il 29/05/2018
Il Direttore (UOC) Affari Generali	Il Direttore (UOC) Affari Generali	Il Direttore (UOC) Affari Generali
F.to Spallino	F.to Spallino	F.to Spallino

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA - VERONA

(D.Lgs. n. 517/1999 - Art. 3 L.R.Veneto n. 18/2009)

DELIBERAZIONE DEL DIRETTORE GENERALE NR. 401 **DEL** 25 MAG. 2018

OGGETTO: AUTORIZZAZIONE ALLA CONDUZIONE DELLO STUDIO NO PROFIT 1456CESC, APPROVATO NELLA SEDUTA DEL COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DEL 18/04/2018. APPROVAZIONE DELLA CONVENZIONE ECONOMICA.

Il sottoscritto Direttore Generale,

Premesso:

- che in ottemperanza alle disposizioni dettate al riguardo dal decreto legge n.158 13.09.2012 convertito, con modificazioni, nella legge n.189 dell'8.11.2012 e dal Decreto Ministeriale dell'08.02.2013 e che, a seguito e in conformità delle disposizioni di cui sopra con deliberazione n.689 del 26.09.2013, l'Azienda Ospedaliera Universitaria Integrata Verona (AOUI) ha provveduto a prendere atto e recepire, per quanto di competenza, le determinazioni della DGRV n. 1066 del 28.06.2013 in materia di Comitati Etici per le Sperimentazioni Cliniche istituendo il Comitato Etico per la Sperimentazione Clinica (CESC) delle Province di Verona e Rovigo;

Rilevata l'opportunità di provvedere alla periodica formale autorizzazione alla conduzione degli studi no profit condotti presso l'AOUI Verona.

Atteso che da parte del Dott. Tamburin Stefano, in servizio presso l'UOC di Neurologia B, con nota prot. n. 39351del 14/08/2017, è stato richiesto di sottoporre all'approvazione del CESC delle Province di Verona e Rovigo l'attuazione dello studio così identificato:

Prog. CESC	1456CESC
Titolo	Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorders: a multicentre cross-sectional investigation of an Italian Parkinson's disease cohort (PROACTIVE-PD)
Sigla	PROACTIVE-PD
Codice EudraCT	Non applicabile
Struttura interessata	Neurologia B
Sperimentatore principale	Dott. Tamburin Stefano
Direttore UOC/	Prof. Monaco Salvatore

Responsabile USD	
Parere Unico	Non applicabile
Valutazione CESC	18/04/2018 (prot. n. 25371 del 26/04/2018)
Conferma di approvazione definitiva	Non applicabile
Polizza assicurativa (compagnia, contraente, n. di polizza, periodo di copertura)	Non applicabile
Comodato d'uso	Non applicabile

Precisato quanto segue per la conduzione operativa dello studio sopra indicato:

Pazienti previsti per lo studio	102
Durata dello studio	12 mesi
Quota paziente	Non applicabile
Altro contributo	Non applicabile
Altri costi rimborsabili	Non applicabile
Fondo di copertura	Non applicabile

Preso atto che è stata esaminata tutta la documentazione pertinente allo studio in esame, richiamata nel sopraesposto prospetto, agli atti della Segreteria del CESC il quale ha:
- valutato tutti gli aspetti inerenti la validità scientifica e l'utilità della ricerca, il protocollo e il disegno sperimentale, la correttezza etica, la dichiarazione dello sperimentatore principale, Dott. Tamburin Stefano, per lo studio progr.CE 1456CESC, relativa al conflitto di interessi, l'idoneità delle strutture coinvolte e le eventuali compensazioni finanziarie/modulo di fattibilità;
- considerate con particolare attenzione tutte le condizioni di copertura per i pazienti che partecipano allo studio clinico, dalle modalità di arruolamento alle forme di acquisizione del consenso ed all'eventuale indennizzo;
- approvato lo studio no profit sopra richiamato avendo riscontrato che tutti gli aspetti dello stesso sono pienamente corrispondenti alle indicazioni normative in materia di sperimentazioni cliniche.

Visto il D.M. 17.12.2004, riferimento normativo trattandosi di studio no profit;

Sulla base di quanto fin qui illustrato si propone di autorizzare l'effettuazione dello studio in argomento.

Considerato che con deliberazione di questa Azienda n. 756/2014 è stata approvata la delega ai Direttori delle Unità Operative Complesse tecnico-amministrative e ai Responsabili degli uffici amministrativi e tecnici dell'Azienda Ospedaliera Universitaria Integrata – Verona, nell'ambito delle materie di rispettiva competenza, così come compiutamente definite nel vigente Atto Aziendale, la funzione di firma delle convenzioni, dei contratti e degli altri atti aventi natura negoziale i cui schemi siano approvati mediante provvedimenti deliberativi del Direttore Generale;

Su proposta del Responsabile dell'Unità Ricerca Clinica;

Acquisito agli atti il parere favorevole espresso dal Direttore Amministrativo e dal Direttore Sanitario per quanto di rispettiva competenza;

DELIBERA

per i motivi esposti in premessa che si intendono integralmente richiamati:

1. di autorizzare la conduzione presso l'Azienda Ospedaliera Universitaria Integrata Verona dello studio No profit 1456CESC valutato nella seduta del 18/04/2018, la cui documentazione è conservata agli atti della Segreteria del CESC;
2. di approvare il testo di convenzione allegato al presente provvedimento quale parte integrante e sostanziale dello stesso, all'uopo predisposto per disciplinare gli aspetti normativi ed economici dei rapporti tra l'Azienda Ospedaliera Universitaria Integrata Verona e le parti contraenti;
3. di dare atto che la convenzione di cui al precedente punto 2 decorrerà dalla data di sottoscrizione e fino al momento di conclusione dello studio presso l'AOUI, salvo proroga o anticipato scioglimento per mutuo consenso scritto o per recesso di una delle parti;
4. di dare atto che la convenzione di cui al precedente punto 2 avrà validità ed efficacia dall'acquisizione del parere favorevole alla sperimentazione clinica rilasciata dall'Autorità Competente (Agenzia Italiana del Farmaco) nelle modalità previste dalla legislazione vigente e che pertanto lo studio non potrà essere avviato fino alla ricezione del parere favorevole/silenzio assenso della suddetta autorità;
5. di dare atto che è stata stipulata a cura e a totale carico del Promotore idonea polizza assicurativa per lo studio prog.CE 1456CESC di cui al precedente punto 1;
6. di dare atto che nessun costo riferito allo studio in argomento è a carico del Servizio Sanitario Nazionale (SSN) né dei soggetti arruolati nello studio;

7. di dare atto che si allega al presente provvedimento, quale sua parte integrante e sostanziale, la dichiarazione relativa al conflitto di interesse, redatta su modello standard del Comitato Etico per la Sperimentazione Clinica delle province di Verona e Rovigo, resa dallo Sperimentatore Principale, Dott. Tamburin Stefano, per lo studio progr.CE 1456CESC;
8. di dare atto che eventuali costi aggiuntivi troveranno la copertura come da modulo di fattibilità agli atti presso la Segreteria del CESC.

Verona, 25 MAG. 2018

IL DIRETTORE GENERALE
Dott. Francesco Cobello

CLINICAL STUDY AGREEMENT	ACCORDO PER STUDIO CLINICO
This AGREEMENT is made on the Effective Date BETWEEN:	Questo ACCORDO è stipulato alla Data Effettiva sottoscrizione TRA:
(1) UNIVERSITY OF KEELE, a university established by the University of Keele Act 1962 (10 &11 Eliz. 2 Ch Xv) and the granting of a Royal Charter in 1962, of Keele, Staffordshire ST5 5BG, UK ("Coordinating Sponsor"); and	1) UNIVERSITY OF KEELE, università fondata mediante l' 'University of Keele Act 1962 (10 &11 Eliz. 2 Ch Xv)' ed il benestare della Royal Charter nel 1962, con sede in Keele Staffordshire ST5 5BG, UK ("Sponsor Coordinatore"); e
(2) AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA VERONA (AOUI Verona) with legal head offices in Verona, Piazzale Aristide Stefani 01, 37126, Italy, Fiscal Code and VAT n 03901420236, represented by the General Manager Dr Francesco Cobello who authorized Dr.ssa Giulia Bisoffi, Head of the "Unità Ricerca Clinica",to stipulate the present agreement, with resolution n. 756 of the 5th of December 2014 ("National Coordinating Centre")	2) AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA VERONA (AOUI Verona) con sede legale a Verona, Piazzale Aristide Stefani 01, 37126, Italia, Codice Fiscale e P. IVA n 03901420236, in persona della Dott.ssa Giulia Bisoffi, Responsabile dell'Unità Ricerca Clinica, giusta delega alla presente stipulazione del legale rappresentante *pro tempore* Direttore Generale Dott. Francesco Cobello, disposta con deliberazione n. 756 del 5 Dicembre 2014 ("Centro di Coordinamento Nazionale)
each a "Party" and together, "the Parties".	D'ora in avanti, indicati individualmente "Parte" e collettivamente "le Parti".
WHEREAS	PREMESSO CHE
A. Both Parties wish to jointly undertake a clinical study entitled: "Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorders: a multicentre cross-sectional investigation of an Italian Parkinson's disease cohort (PROACTIVE-PD) (the "Study"), in Italy" (the "Country").	A. Entrambe le parti desiderano congiuntamente prendere parte ad uno studio clinico intitolato "Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorders: a multicentre cross-sectional investigation of an Italian Parkinson's disease cohort (PROACTIVE-PD) (d'ora in avanti lo "Studio"), in Italia" (d'ora in avanti il "Paese").
B. The Study is to be conducted pursuant to the Protocol.	B. Lo studio verrà condotto secondo il Protocollo.
C. The Protocol has been developed by and is the responsibility of the Coordinating Sponsor in cooperation with a number of other institutions and organisations.	C. Il protocollo è stato sviluppato da ed è responsabilità dello Sponsor Coordinatore, in cooperazione con altre istituzioni ed organizzazioni.
D. The Coordinating Sponsor delegates certain sponsor responsibilities in relation to this Study to the extent set out in this Agreement.	D. Lo Sponsor Coordinatore delega alcune proprie responsabilità relative al presente Studio nei limiti stabiliti dal presente accordo.
E. The National Coordinating Centre will take on certain delegated sponsor responsibilities for the Study within the Country and the Coordinating Sponsor will remain responsible for	E. Il Centro di Coordinamento Nazionale assumerà alcune della responsabilità delegate dello sponsor per lo Studio all'interno del Paese, mentre lo Sponsor Coordinatore rimarrà responsabile per lo Studio nel

the Study in the UK.	Regno Unito.
F. The Parties agree to delegate sponsor responsibilities as set out below and in Schedule 1.	F. Le Parti acconsentono a delegare le responsabilità dello sponsor come di seguito indicato e come altresì stabilito nell'Allegato 1.
G. The Study is non-profit according to Italian D.M. 17.12.2004	G. Lo Studio è qualificabile come attività no-profit secondo la normativa italiana posta dal D.M. 17.12.2004.
In consideration of the mutual promises set out in this agreement, the Parties agree as follows:	In considerazione delle premesse consensuali stabilite in questo accordo, le Parti si accordano come segue:
1. DEFINITIONS	1. DEFINIZIONI
1.1. The following expressions shall have the following meanings in this Agreement including its recitals, unless the context requires otherwise:	1.1. Le seguenti espressioni dovranno avere i seguenti significati all'interno dell'accordo, incluse le premesse, a meno che il contesto non richieda altrimenti:
"Agreement" means this agreement and its Schedule and any variations made from time to time pursuant to clause 13.2;	Per "Accordo" si intende il presente accordo e l'Allegato allo stesso, nonché ogni variazione dovesse intervenire sugli stessi in applicazione della clausola 13.2;
"Confidential Information" means any and all information, data and material of any nature belonging to either Party which either Party may receive or obtain in connection with this Agreement which is personal data or sensitive personal data (as defined under "Data Protection Requirements") which relates to any patient or Study subject or his or her treatment or medical history, or other information, the release of which is likely to prejudice the commercial interests of either Party, or which is a trade secret;	Per "Informazioni Confidenziali" si intende qualsiasi informazione, dato o materiale di qualsiasi natura che appartenga a qualunque Parte, che entrambe le parti potrebbero ricevere od ottenere in relazione a questo accordo, siano essi dati personali o sensibili (secondo la definizione di cui alla sezione "Requisiti di protezione dei dati"), che sia collegato a qualsiasi paziente o soggetto dello Studio o al suo trattamento o alla sua storia medica, o qualsiasi altra informazione la cui divulgazione possa astrattamente pregiudicare gli interessi commerciali di entrambe le parti, o sia tutelata quale segreto commericiale.
"Data Protection Requirements" means the Data Protection Act 1998 or the equivalent in Country, Directive 95/46/EC of the European Parliament or any national or European legislation and/or regulations implementing them or made in pursuance of them;	Per "Requisiti di protezione dei dati" si intendono i requisiti di cui al Data Protection Act 1998 o fissati dall'equivalente normativo del Paese, della direttiva 95/46/EC del Parlamento Europeo o di qualsiasi legge e/o regolamentazione nazionale o europea che vi abbia dato attuazione o sia stata posta in applicazione delle stesse;
"Effective Date" means the date of last signature;	Per "Data effettiva" si intende la data dell'ultima sottoscrizione del presente Accordo;
"National Coordinating Investigator" means Dr Stefano Tamburin being the individual who shall take on the role of chief investigator for the Study	Per "Sperimentatore Coordinatore Nazionale" si

in the Country; "Protocol" means the protocol for the Study as approved by the relevant ethics committee setting out the objectives, design methodology, statistical considerations and organisation of the Study attached as Schedule 2 and as may be amended and supplemented from time to time; "Site" means a site in the Country selected by the National Coordinating Centre where the Study will be undertaken; "Site Principal Investigator" means the individual taking responsibility for the conduct of the Study at an individual Site in the Country. For the avoidance of doubt in the case where the National Coordinating Centre is the only Site in the Country this person may be the same individual as the National Coordinating Investigator; "Study" means the clinical study entitled 'Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorders: a multicentre cross-sectional investigation of an Italian Parkinson's disease cohort (PROACTIVE-PD); and "Sub-Contractor" means any third party engaged by the National Coordinating Centre to carry out duties in relation to this Agreement which may but does not exclusively include any Sites. 2. RESEARCH GOVERNANCE The Study shall be conducted by the Parties: 2.1 acting in all aspects in accordance with their respective roles and responsibilities as described in this Agreement; 2.2 in accordance with the Protocol and any subsequent amendments to the Protocol; 2.3 in compliance with any laws, regulations and codes of practice applicable to the performance of the Study including but not limited to: 2.3.1 The Declaration of Helsinki (1996), entitled "Ethical Principles for Medical Research Involving Human Subjects";	intende il Dott. Stefano Tamburin il quale sarà colui che assumerà il ruolo di ricercatore capo per lo studio nel Paese; Per "Protocollo" si intende il protocollo dello studio come approvato dai comitati etici rilevanti che stabilisce gli obiettivi, il disegno sperimentale, le considerazioni statistiche e l'organizzazione dello studio allegato come all'allegato 2 ed ogni sua eventuale modifica; Per "Sito" si intende un luogo nel paese selezionato del centro di coordinamento nazionale dove lo studio verrà condotto; Per "Ricercatore principale in loco" si intende la persona che assume la responsabilità di condurre lo Studio in un luogo unico nel Paese. Per evitare dubbi, nel caso in cui il centro di coordinazione nazionale sia l'unico sito nel Paese, tale persona può essere lo stesso soggetto che funge da Sperimentatore Coordinatore Nazionale; Per "Studio" si intende lo studio clinico intitolato 'Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorders: a multicentre cross-sectional investigation of an Italian Parkinson's disease cohort (PROACTIVE-PD); e Per "Sub-appaltatore" si intende un soggetto terzo incaricato dal centro di coordinamento nazionale per espletare gli obblighi relativi a questo accordo, che dovessero, ma non in modo esclusivo, interessare qualsiasi sito. 2. AMMINISTRAZIONE DELLE RICERCA Lo studio dovrà essere condotto dalle Parti: 2.1. agendo in tutti gli aspetti in accordo con i loro rispettivi ruoli e responsabilità come descritto in questo accordo; 2.2 in accordo con il protocollo ed ogni successiva modifica del protocollo; 2.3 in conformità con ogni legge, regolamentazione e prassi applicabili all'esecuzione dello Studio incluse ma non limitatamente a:

2.3.2 The Directive 2001/20/EC of the European Parliament and any local enactment thereof; 2.3.3 In accordance with relevant Data Protection Requirements; 2.3.4 The Freedom of Information Act 2000 and any equivalent local legislation in the host country of the Coordinating Sponsor; and 2.3.5 Good Clinical Practice as encompassed by relevant legislation ("GCP"). 2.4 All references in clause 2.3 above shall be deemed to include references to any statute, subordinate legislation, or declaration which amends, extends, consolidates or replaces the legislation referenced in clause 2.3 3. CONDUCT OF THE STUDY 3.1 The Parties agree to allocate and perform the responsibilities of sponsor for the Study in the Country according to Schedule 1. Delegation of responsibilities to the National Coordinating Centre is limited to sponsor obligations, which arise in the context of the performance of the Study in the Country and for the avoidance of doubt the National Coordinating Centre shall have no responsibility for any part of the Study undertaken outside the Country. 3.2 Both Parties reserve the right to audit each other for the purpose of ensuring compliance with all legal requirements of their respective roles under this Agreement. 3.3 Obligations of the Coordinating Sponsor 3.3.1 In addition to the obligations and responsibilities set out in Schedule 1 the Coordinating Sponsor is responsible for: 3.3.1.1 Provision of English versions of essential study documentation (e.g. Protocol, Case Report Form, Patient Information Sheets etc) to facilitate the conduct of the study by the National Coordinating Centre; and 3.3.1.2 Generating a final Study report. The Coordinating Sponsor shall provide the National Coordinating Centre with a copy of the Study report summary not later than 1 year after the Study database is frozen. 3.4 Obligations of the National Coordinating Centre	2.3.1. La Dichiarazione di Helsinki (1996), intitolata "Principi Etici per la Ricerca Medica inerente i Soggetti Umani"; 2.3.2 La Direttiva 2001/20/CE del Parlamento Europeo e ogni attuazione locale di esso; 2.3.3 In accordo ai Requisiti di protezione dei dati pertinenti; 2.3.4 Il Freedom of Information Act 2000 ed ogni legislazione equivalente all'interno del Paese ospitante dello Sponsor Coordinatore; e 2.3.5 Pratiche di Buona Ricerca come previste nella legislazione rilevante ("GCP"). 2.4 Tutti i riferimenti contenuti nella clausola 2.3 sopra dovranno essere considerati nell'includere riferimenti a qualsiasi statuto, legislazione subordinata, o dichiarazione che modifichi, estenda, consolidi o sostituisca la legislazione riposta in clausola 2.3 3. MESSA IN ATTO DELLO STUDIO 3.1 Le parti concordano ad assegnare ed eseguire le responsabilità dello Sponsor per lo studio nel Paese in accordo all'allegato 1. La delegazione delle responsabilità al Centro di coordinamento nazionale è limitata ai doveri dello sponsor, che emergano nel contesto dell'esecuzione dello studio nel Paese e per evitare ogni dubbio il Centro di Coordinamento Nazionale non dovrà avere responsabilità per qualsiasi parte dello studio intrapresa fuori dal Paese. 3.2 Entrambe le Parti si riservono il diritto di sottoporsi a vicenda ad audit al fine di assicurare il rispetto dei requisiti legali dei loro rispettivi ruoli all'interno di questo Accordo. 3.3 Obblighi dello Sponsor Coordinatore 3.3.1 In aggiunta agli obblighi e responsabilità delineate in allegato 1, lo Sponsor Coordinatore è responsabile di: 3.3.1.1 Provvedere a fornire una versione in inglese di tutta la documentazione fondamentale dello studio (e.g., Protocollo, Case Report Form, Foglio informativo del paziente, ecc.) per facilitare l'esecuzione dello studio da parte del Centro di Coordinamento Nazionale; e 3.3.1.2 Redigere una relazione finale dello studio. Lo sponsor coordinatore dovrà fornire al Centro di Coordinamento Nazionale una copia del riassunto del resoconto dello studio non più tardi di 1 anno dalla chiusura del database dello studio.

3.4.1 The National Coordinating Centre shall fulfil the allocated responsibilities detailed in Schedule 1 and ensure compliance with all statutory provisions relevant to the Study in the Country. 3.4.2 The National Coordinating Centre shall be responsible for the review and acceptance of the Protocol and any amendments to the Protocol for use in the Country but not elsewhere and will authorise the Protocol for use in the Country. 3.4.3 The National Coordinating Centre shall be responsible for the preparation and establishment of contracts with Sites where necessary. 3.4.4 The National Coordinating Centre will on request provide all documents (if applicable as copy) necessary for the international master file to the Coordinating Sponsor. 3.4.5 If additional Sites are recruited in addition to the National Coordinating Centre then the National Coordinating Centre will ensure the appointment of a named Site Principal Investigator at each site. The National Coordinating Centre will ensure that the Site Principal Investigator and his or her team are appropriately qualified, trained and skilled to perform the clinical procedures required by the Study. 3.4.6 The National Coordinating Centre shall ensure the Site carries out its activities in accordance with this agreement and in particular clause 2 that are hereby allocated to the National Coordinating Centre but that will be performed by the Site. 4. COSTS Except as otherwise provided, the National Coordinating Centre shall be responsible for all costs and expenses incurred in respect of activity relating to the Study in the Country 5. STUDY DATA 5.1 All case report forms and other data (including without limitation, written, printed, graphic, video and audio material, and information contained in any computer database or computer readable form) created or developed during the course of the Study at Authorized Institution (the "Data") shall be the property of the Coordinating Sponsor, whom may utilize the Data in any way it deems appropriate, subject to	3.4 Obblighi del Centro di Coordinamento Nazionale 3.4.1 Il Centro di Coordinamento Nazionale deve ottemperare a tutte le obbligazioni elencate nell'allegato 1 ed assicurare l'adesione a tutte le disposizioni imperative di legge a cui va soggetto lo Studio nel Paese. 3.4.2 Il Centro di Coordinamento Nazionale deve essere responsabile per la revisione ed accettazione del protocollo e di ogni modifica del Protocollo per l'utilizzo nel Paese ma non altrove ed autorizzerà l'uso del Protocollo all'interno del Paese. 3.4.3 Il Centro di Coordinamento Nazionale dovrà occuparsi della preparazione ed avviamento dei contratti con i siti ove necessario. 3.4.4 Il Centro di Coordinamento Nazionale provvederà su richiesta a fornire tutta la documentazione (se valida anche in copia) necessaria per il master file internazionale allo Sponsor Coordinatore. 3.4.5 Se siti aggiuntivi dovessero essere reclutati in aggiunta al Centro di Coordinamento Nazionale, allora il Centro di Coordinamento Nazionale assicurerà la nomina di uno Sperimentatore Principale in ogni sito. Il Centro di Coordinamento Nazionale assicurerà che lo Sperimentatore Principale del sito e il suo team siano adeguatamente qualificati, formati ed abbiano le abilità necessarie ad eseguire le procedure cliniche richieste dallo studio. 3.4.6 Il Centro di Coordinamento Nazionale dovrà assicurarsi che il Sito conduca le sue attività, che sono assegnate al Centro di Coordinamento Nazionale ma che verranno eseguite dal Sito, in conformità con questo accordo ed in particolare con la clausola 2. 4. COSTI Ad eccezione di quanto altrimenti assegnato, il Centro di Coordinamento Nazionale dovrà essere responsabile per tutti i costi e le spese sostenute rispetto alle attività connesse allo Studio nel Paese. 5. DATI DELLO STUDIO 5.1 Tutti i case report form e gli altri dati (inclusi senza limitazioni, materiale scritto, stampato, materiale grafico, audio e video, e le informazioni contenute in ogni database del computer o in forme leggibili tramite computer) creati o sviluppati durante

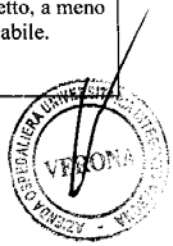
and in accordance with applicable Laws and Regulations and the terms of this Agreement. The Coordinating Sponsor shall have unrestricted access to all Data relevant to the Study, except for personally identifiable data under the terms and conditions of this Agreement. The Data will be centrally managed and analysed by the Coordinating Sponsor.	il corso dello Studio presso l'ente autorizzato (i "dati") saranno proprietà dello Sponsor Coordinatore, il quale potrà utilizzare i dati in ogni modo ritenga appropriato, in conformità con le leggi e le regolamentazioni ed i termini di questo accordo. Lo Sponsor Coordinatore dovrà avere accesso illimitato a tutti i dati rilevanti per lo studio, ad eccezione di dati da cui siano ricavabili informazioni personali secondo i termini e le condizioni di questo accordo. I dati verranno gestiti centralmente e analizzati dallo Sponsor Coordinatore.
5.2 The National Coordinating Centre will ensure the Sites are responsible for the collection of patient data in compliance with the Protocol, relevant legislation and GCP and for the continual completion of the Case Report Forms (CRFs). The National Coordinating Centre warrants that all Study staff members assign to the National Coordinating Centre all right, title and interest in and to the Data, in order that the National Coordinating Centre may fully assign the rights to the Coordinating Sponsor as provided above.	5.2 Il Centro di Coordinamento Nazionale assicurerà che i Siti siano responsabili dell'acquisizione dei dati del paziente in conformità con il Protocollo, la legislazione rilevante e il GCP, e del completamento del Case Report Form (CRFs). Il Centro di Coordinamento Nazionale assicura che tutti i membri dello staff dello Studio assegnino al Centro di Coordinamento Nazionale tutti i diritti, titoli ed interessi rispetto ai dati, in modo che il Centro di Coordinamento Nazionale possa pienamente affidare I diritti allo Sponsor Coordinatore come illustrato sotto.
6. PUBLICATION 6.1 The National Coordinating Centre agrees that the first publication of the results of the Study shall be made as a joint multicentre publication according to the Protocol under the lead of the Coordinating Sponsor. The National Coordinating Centre will oblige all investigators and other personnel involved in the Study to comply with the provisions of this paragraph.	6. PUBBLICAZIONI 6.1 Il Centro di Coordinamento Nazionale acconsente che la prima pubblicazione dei risultati dello Studio debba essere fatta come una pubblicazione collettiva multicentrica in accordo al protocollo sotto la guida dello Sponsor Coordinatore. Il Centro di Coordinamento Nazionale obbligherà gli sperimentatori e l'ulteriore personale coinvolto nello Studio ad attenersi alle disposizioni di questo paragrafo.
6.2 If there is no multi-site publication within eighteen (18) months after the Study has been completed or terminated at all Sites and all data have been received by the Coordinating Sponsor, the National Coordinating Centre and any Sub-Contractors shall have the right to publish results from the Study, subject to the following notice requirements:	6.2 Se non vi saranno pubblicazioni multi-sito entro diciotto (18) mesi dal completamento o termine dello Studio in tutti i siti e da quando i dati sono stati ricevuti dello Sponsor Coordinatore, il Centro di Coordinamento Nazionale e ogni sub-contraente avrà il diritto di pubblicare i risultati dallo Studio, soggetto ai seguenti requisiti di notifica:
6.2.1 The National Coordinating Centre shall be permitted to publish the results of the Study in accordance with normal academic practice. The National Coordinating Centre shall send the Coordinating Sponsor a draft of all intended publications in advance of publication, for the Coordinating Sponsor to review for the possible inclusion of any of its Confidential Information. The Coordinating Sponsor shall have 30 days, after the receipt of the draft to request in writing	6.2.1 Al Centro di Coordinamento Nazionale dovrà essere permesso di pubblicare i risultati dello Studio secondo le usuali pratiche accademiche. Il Centro di Coordinamento Nazionale dovrà mandare allo Sponsor Coordinatore una bozza di tutte le pubblicazioni previste in anticipo, per permettere allo

the delay or amendment of such proposed publication on the grounds that there is subject matter to prevent publication of any Confidential Information of the Coordinating Sponsor failing which, without comment after the expiry of this period, the National Coordinating Centre will be free to publish. 6.2.2 A copy of all publications and publicity communications related to the Study shall be sent to National Coordinating Centre for information. 6.2.3 The contributions of either Party shall be credited in all publications and communications related to the Study and authorship determined in accordance with the Vancouver Protocol. 7. RIGHTS TO THE STUDY RESULTS 7.1 All study-related documents and data (including without limitation written, printed, graphic, video and audio material and information contained in any computer database or computer readable form) created or developed during the course of the study shall be the property of the Coordinating Sponsor, who may utilise these documents / data in any way it seems appropriate, subject to and in accordance with applicable state, federal and European privacy laws and the terms of this agreement. 7.2 The Coordinating Sponsor shall have unrestricted access to all data relevant to the Study and will be able to use that data for any purpose, except for commercial exploitation and for profit purposes. In the event there is a legal requirement that prevents this then the National Coordinating Centre should notify the Coordinating Sponsor prior to Site initiation. The National Coordinating Sponsor will only be able to use the data for internal research, development and clinical purposes but shall not be able to commercially exploit the data or any analysis thereof. 7.3 The existing inventions and technologies of the Coordinating Sponsor or the National Coordinating Centre, Sites, National Coordinating Investigator or any Sub-Contractors of the National Coordinating Centre are their separate property and are not affected by this Agreement. Any developments to existing inventions and technologies that are not detailed as part of the Protocol but which may be developed during the	Sponsor Coordinatore di revisionare le possibili inclusioni di ogni sua Informazione Confidenziale. Lo Sponsor Coordinatore avrà 30 giorni, dopo il ricevimento della bozza, per richiedere per via scritta una proroga o modifica di tale proposta pubblicazione ove ci fossero argomenti di discussione per impedire la pubblicazione di qualsiasi Informazione Confidenziale dello Sponsor Coordinatore in mancanza, senza commenti dopo la scadenza di tale periodo, il Centro di Coordinamento Nazionale sarà libero di pubblicare. 6.2.2 Una copia di tutte le pubblicazioni e comunicazioni pubblicitarie legate allo Studio dovrà essere mandata al Centro di Coordinamento Nazionale per informazione. 6.2.3. Il contributo di entrambe le Parti dovrà essere menzionato in tutte le pubblicazioni e comunicazioni collegate allo Studio e l'autorizzazione determinata in accordo con il Protocollo di Vancouver. 7. DIRITTI SUI RISULTATI DELLO STUDIO 7.1 Tutti i documenti e dati legati allo studio (inclusi senza limitazione materiale scritto, stampato, materiale grafico, audio e video, e le informazioni contenute in ogni database del computer o in forme leggibili tramite computer) creati o sviluppati durante il corso dello studio saranno di proprietà dello Sponsor Coordinatore, che potrà utilizzare tali documenti/dati secondo con le leggi sulla privacy statali, federali e Europee applicabili, ed i termini di questo accordo. 7.2 Lo Sponsor Coordinatore dovrà avere accesso illimitato a tutti i dati rilevanti dello Studio e potrà utilizzare quei dati per qualsiasi proposito, eccetto che per utilizzo commerciale e per propositi di profitto. Nel caso in cui vi siano dei requisiti legali che impediscano di far ciò, allora il Centro di Coordinamento Nazionale dovrà notificarlo allo Sponsor Coordinatore prima dell'inizio presso il sito. Il Centro di Coordinamento Nazionale sarà in grado solo di usare i dati per fini interni alla ricerca, allo sviluppo e ai fini clinici, ma non potrà sfruttare commercialmente i dati o qualsiasi analisi di questi. 7.3 Le invenzioni e tecnologie esistenti dello Sponsor Coordinatore o del Centro di Coordinamento Nazionale, dei Siti, dello Sperimentatore Nazionale di Coordinamento, o qualsiasi Sub-contraente del Centro di Coordinamento Nazionale sono di loro proprietà e tali diritti non sono interessati da questo

Study will be owned by the owner of the pre-developed background.	accordo. Qualsiasi sviluppo di invenzioni esistenti e tecnologie che non siano descritte come parte del protocollo ma che potrebbero essere sviluppate durante lo studio diverranno proprietà del proprietario del presviluppato background.
7.4 The entire right, title and interest in and to any inventions, discoveries or other intellectual property rights that are conceived or developed from the Study, including all improvements or modifications which are anticipated by the Protocol or rely on, use, or incorporate any Confidential Information of the Coordinating Sponsor, shall be the exclusive property of the Coordinating Sponsor.	7.4 L'intero diritto, titolo ed interesse nel e in tutte le invenzioni, scoperte o altri diritti di proprietà intellettuale che siano concepite o sviluppate dallo studio, incluso tutti i miglioramenti o modifiche che siano anticipate dal Protocollo o che dipendano da, usino, o incorporino qualsiasi Informazione Confidenziale, dovranno essere proprietà esclusiva dello Sponsor Coordinatore.
7.5 The National Coordinating Centre shall promptly report in writing to the Coordinating Sponsor each invention or discovery and shall use reasonable endeavours to procure that the National Coordinating Investigator and all Sites assign to the Coordinating Sponsor all of the rights, title and interest, if any, in and to each such invention or discovery.	7.5 Il Centro di Coordinamento Nazionale dovrà prontamente riportare in forma scritta allo Sponsor Coordinatore ogni invenzione o scoperta e dovrà usare ragionevoli sforzi per ottenere che il Centro di Coordinamento Nazionale e tutti i Siti assegnino allo Sponsor Coordinatore tutti i diritti, titoli e interesse, se presenti, di ogni invenzione o scoperta.
7.6 The Parties shall execute such documents as are necessary to give effect to these provisions.	7.6 Le parti dovranno predisporre tale documentazione come è necessario per dare effetto a tali misure.
7.7 The Coordinating Sponsor hereby grants to the National Coordinating Centre and any Sites a fully paid up, non-exclusive, non-sub-licensable right to use the Study Results for internal non-commercial research, clinical and teaching purposes.	7.7 Con la presente lo Sponsor Coordinatore garantisce al Centro di Coordinamento Nazionale e ad ogni sito un diritto interamente pagato, non esclusivo, non sub-licenziabile, ad utilizzare i risultati dello studio per scopi di ricerca interna non commerciali, clinici e di insegnamento.
8. TERM AND TERMINATION OF THE AGREEMENT 8.1 This Agreement shall commence on the Effective Date and shall continue in force until the Study has been completed by the National Coordinating Centre as defined by the Protocol unless terminated earlier pursuant to this clause 8.3.	8. TERMINI E DURATA DELL'ACCORDO 8.1 Questo accordo dovrà cominciare alla Data Effettiva e dovrà continuare fino a quando lo studio non sarà stato completato dal Centro di Coordinamento Nazionale come definito nel Protocollo, a meno che non venga concluso prima come previsto dalla clausola 8.3.
8.2 Either Party may give notice to the other to suspend the Study on the grounds of concerns over patient safety and to allow for investigation of such concerns provided that if either Party then considers that it is not possible to address those concerns adequately to protect patient safety then it may give notice to terminate this Agreement under clause 8.3 below.	8.2 Ciascuna Parte può notificare all'altra la sospensione dello studio per motivi di sicurezza del paziente e per permettere di indagare su tali problematiche, fermo restando che, se entrambe le parti considerano che non sia possibile affrontare adeguatamente tali problematiche per proteggere la

8.3 This Agreement may be terminated by either Party giving written notice to the other party in the following circumstances:	sicurezza del paziente, allora si potrà rendere nota la chiusura di questo accordo come previsto alla successiva clausola 8.3.
8.3.1 on provision of 30 days' notice to the other Party and the other Party may agree to such termination but only where such termination would not be to the detriment of patient care or health; or 8.3.2 it is considered necessary in the interests of protecting patient safety; or 8.3.3 the other Party is in material breach of this Agreement and (if such breach is capable of remedy) the breach has not been remedied within 30 days after receipt of written notice specifying the breach and requiring its remedy, or 8.3.4 the other Party becomes insolvent or has an order made or a resolution passed for its winding up (except voluntarily for the purpose of solvent amalgamation or reconstruction, or if an administrator, administrative receiver to receiver is appointed over the whole or any part of its assets or if it makes any arrangement with its creditors; or 8.3.5 If the National Coordinating Investigator is no longer able (for whatever reason) to act as the National Coordinating Investigator and no mutually acceptable replacement can be found within 30 days.	8.3 Questo accordo può essere risolto da entrambe le parti mediante comunicazione scritta all'altra parte nelle seguenti circostanze: 8.3.1 con notifica con preavviso di 30 giorni all'altra Parte e dall'altra Parte accettata sulla risoluzione del contratto ma solo ove da tale cessazione non possa derivare danno alla cura o salute del paziente; o 8.3.2 sia considerato necessario nell'interesse di salvaguardare la sicurezza del paziente; o 8.3.3 l'altra Parte abbia agito in sostanziale violazione di questo accordo e (se tale violazione è passibile di rimedio) la violazione non sia stata rimossa entro 30 giorni dalla ricevuta di notifica scritta specificante la violazione e richiedente la sua cessazione, o 8.3.4 l'altra Parte divenga insolvente o abbia ricevuto un ordine o una decisione di liquidazione (ad eccezione di volontaria liquidazione finalizzata all'effettuazione di una fusione o riorganizzazione *in bonis*, o se un amministratore o un liquidatore sia incaricato di stipulare un accordo con i creditori riguardante l'intero capitale sociale o parte di esso; o 8.3.5 Se lo sperimentatore del Centro di Coordinamento Nazionale non sia più in grado (per qualsivoglia ragione) di agire in qualità di sperimentatore del Centro di Coordinamento Nazionale e un suo sostituto mutualmente accettabile non sia disponibile entro 30 giorni.
8.4 As soon as reasonably practicable after the date of termination of this Agreement, the National Coordinating Centre will submit to the Coordinating Sponsor all patient data sets up to the date of termination and ensure all regulatory obligations in the Country with regard to termination and study closure are met.	8.4 Non appena sia ragionevolmente possibile, dopo la data del termine di questo accordo, il Centro di Coordinamento Nazionale invierà allo Sponsor Coordinatore tutti i dati del paziente fino alla data del termine dello Studio e assicurerà che tutti gli obblighi nel Paese con riferimento al termine e alla chiusura dello studio siano soddisfatti.
8.5 Immediately upon notice of termination being given by either party, the National Coordinating Investigator shall stop enrolling patients into the Study and shall cease conducting procedures on patients already enrolled in the Study as directed by the Coordinating Sponsor, to the extent medically permissible.	8.5 Immediatamente dopo che la notizia del termine dello Studio verrà data ad entrambe le parti, lo sperimentatore Coordinatore Nazionale dovrà smettere di reclutare pazienti per lo Studio e dovrà cessare di condurre le procedure sui pazienti già reclutati nello studio come diretto dallo Sponsor Coordinatore, fino a quanto medicalmente
8.6 Except as otherwise specifically provided herein, termination of this Agreement shall not relieve any Party from any obligation under this Agreement that accrued or arose from facts and	

circumstances in existence prior thereto.	permissibile.
8.7 In addition, the provisions of this Agreement that by their nature contemplate continuing obligations shall survive expiration or termination of this Agreement.	8.6 Ad eccezione di quanto specificatamente disposto di seguito, il temine di questo accordo non solleverà nessuna Parte da qualsiasi responsabilità relativa a questo accordo che maturi o nasca da fatti e circostanze ad esso precedenti.
9. PRIVACY AND DATA PROTECTION 9.1 The Parties agree that each will comply with their respective obligations as required under applicable privacy and data protection laws.	8.7 In aggiunta, le disposizioni di questo accordo che per loro natura contemplino il perpetuarsi di obbligazioni dovranno valere oltre la scadenza o termine di questo accordo.
9.2 The National Coordinating Centre and National Coordinating Investigator will ensure that each Site will obtain the consent of each data subject to the use, processing, holding and transfer of their data to countries other than their own, that may not have the same level of data protection as their own country. 9.3 For any personal information received from either the Study patients or the Site, the Coordinating Sponsor will be the data controller as the Study is within the EU.	9. PRIVACY E PROTEZIONE DEI DATI 9.1 Le Parti acconsentono che ognuna adempia ai propri rispettivi doveri come richiesto dalle leggi applicabili sulla privacy e sulla protezione dei dati. 9.2 Il Centro di Coordinamento Nazionale e lo sperimentatore Coordinatore Nazionale assicureranno che ciascun sito ottenga il consenso per utilizzare, elaborare, trattenere qualsiasi dato del soggetto e trasferire tali dati in altri paesi rispetto a quelli di provenienza, che potrebbero non avere lo stesso livello di protezione dei dati come quello del proprio paese. 9.3. Per ogni informazione personale ricevuta o dai pazienti dello studio o dal sito, lo Sponsor Coordinatore sarà il controllore dei dati dato che lo studio è svolto entro l'Unione Europea.
9.4 The National Coordinating Centre shall provide the personal details including but not limited to name, of the National Coordinating Investigator and all Site Principal Investigators and shall obtain the consent of all such persons for the Coordinating Sponsor and third parties involved in the Study to use the personal data for any purpose permitted by law. 10. CONFIDENTIALITY 10.1 Any and all information related to the Study shall be Confidential Information and neither of the Parties shall during this Agreement and for a period of five (5) years after termination of this Agreement, without the prior written permission of the disclosing Party, disclose the same to any third party other than as required to perform the Study hereunder, except if required by applicable law.	9.4 Il Centro di Coordinamento Nazionale deve fornire i dettagli personali, incluso, ma non limitatamente al, il nome dello Sperimentatore Coordinatore Nazionale e tutti gli Sperimentatori principali dei siti, e deve ottenere il consenso da tutti loro per permettere allo Sponsor Coordinatore e terzi coinvolti nello studio di usare i dati personali per qualsiasi proposito permesso dalla legge. 10. RISERVATEZZA 10.1 Tutte le informazioni legate allo studio saranno informazioni confidenziali e nessuna parte potrà, per la durata di questo accordo e per un periodo di cinque (5) anni dopo il termine di questo accordo, senza il previo permesso scritto della parte divulgante, divulgarli a soggetti terzi ad eccezione di quanto richiesto per eseguire lo studio qui in oggetto, a meno che non venga richiesto dalla legge applicabile.
10.2 These provisions shall not apply to: 10.2.1 any of the information which at the time of receipt by the receiving Party is in the public domain; 10.2.2 any of the information which after its receipt by the receiving Party is made public by a third party acting without impropriety in so	



doing; 10.2.3 any of the information which the receiving Party can establish was in its possession before receipt from the disclosing Party and was developed independently or acquired directly or indirectly from a source wholly independent of the disclosing Party; 10.2.4 any reference to the Study made by a Site or by the National Coordinating Investigator in the report of its/his activities, that is requested by competent authorities; 10.2.5 Is required to be disclosed by any law, competent jurisdiction or court or government regulation, act or order. 10.3 Nothing contained in this Agreement shall prevent the submission of a thesis to examiners or internal reports in accordance with the normal regulations of either Party subject where appropriate to such examiners or third parties being bound by conditions of confidentiality in no less terms than those contained herein, nor to the placing of such thesis in the library of the relevant party provided that access to such thesis shall only be available on conditions of confidentiality no less onerous than those contained herein. 11. INSURANCE 11.1 The National Coordinating Centre is responsible for and will maintain appropriate insurance cover or equivalent indemnity arrangements, as required by applicable legal and regulatory requirements, for claims arising against the National Coordinating Centre in regard to their responsibilities as detailed in Schedule 1, and shall provide evidence of the same to the Coordinating Sponsor upon request. 11.2 The National Coordinating Centre shall ensure that all Sites (including the National Coordinating Centre if it is acting as a Site) have appropriate insurance (or equivalent indemnity arrangements) to cover clinical care and any clinical negligence on their part. The Coordinating Sponsor is responsible for and will obtain adequate insurance to cover negligent harm under its responsibilities as the Coordinating Sponsor as set out in Schedule 1 including Protocol design and shall provide evidence of the same to the National Coordinating Sponsor upon request.	10.2 Tali disposizioni non si applicano a: 10.2.1 qualsiasi informazione al tempo della ricezione da parte della Parte ricevente sia di pubblico dominio; 10.2.2 qualsiasi informazione che dopo essere stata ricevuta dalla Parte ricevente sia resa pubblica da una terza parte che non agisce impropriamente; 10.2.3 qualsiasi informazione che la parte ricevente possa stabilire fosse in suo possesso prima della rizione dalla parte divulgante e che era stata sviluppata indipendentemente o acquisita direttamente o indirettamente dalla fonte interamente indipendente dalla parte divulgante; 10.2.4 qualsiasi riferimento allo studio fatto dal sito o dallo sperimentatore coordinatore nazionale nel riportare le proprie attività se sia richiesto dalle autorità competenti; 10.2.5 sia richiesto di essere divulgata da qualsiasi legge, giurisdizione competente o corte o regolamentazione governativa, atto o ordine. 10.3 Niente di ciò che è contenuto in questo accordo dovrà impedire la sottomissione di una tesi agli esaminatori o un report interno in accordo con la usuale regolamentazione di entrambe le parti ove risulti appropriato a tali esaminatori o terze parti che siano legate da condizioni di confidenzialità in non minori termini di quelle qui contenute, nè può impedire che tale tesi venga posta nella libreria della parte rilevante ove garantito che l'accesso a tale tesi sia possibile solo a condizioni di confidenzialità non meno vincolanti di quelle qui riportate. 11. ASSICURAZIONE 11.1 Il Centro di Coordinamento Nazionale è responsabile di avere e mantenere una appropriata copertura assicurativa o equivalente accordo di indennizzo, come richiesto dalla legge applicabile e dai requisiti regolamentari, per richieste di risarcimento che sorgano contro il Centro di Coordinamento Nazionale rispetto alle sue responsabilità come dettagliato nell'Allegato 1, e dovrà fornire prova della stessa allo Sponsor Coordinatore ove richiesto. 11.2 Il Centro di Coordinamento Nazionale deve assicurare che tutti i siti (inclusi il Centro di Coordinamento Nazionale se agisce in qualità di sito) abbiano un'assicurazione appropriata (o equivalenti disposizioni di indennità) per coprire la cura clinica

12. LIABILITY AND INDEMNITY

12.1 The National Coordinating Centre is and shall remain liable for any negligent harm, claims, actions or expenses (including legal expenses) resulting from or connected with the negligence, breach, omission or fault on its or its Sub-Contractors including but not limited to the Sites, part in undertaking the role of the National Coordinating Centre under this Agreement or the National Coordinating Investigator. The National Coordinating Centre shall indemnify the Coordinating Sponsor against any negligent harm, claims, actions or expenses (including legal expenses) made against them as a result of such claims unless the claim is a result of the negligence or wilful misconduct of the Coordinating Sponsor.

12.2 As far as any such action or claim is brought against the Coordinating Sponsor, the National Coordinating Centre shall co-operate with the Coordinating Sponsor in defending such action or claim.

12.3 The Coordinating Sponsor is and shall remain liable for any negligent harm, claims, actions or expenses (including legal expenses) resulting from or connected with the negligence, breach, omission or fault on the part of the Coordinating Sponsor. The Coordinating Sponsor shall indemnify the National Coordinating Centre and (as appropriate) the National Coordinating Investigator against any negligent harm, claims, actions or expenses (including legal expenses) made against them as a result of such claims unless the claim is a result of the negligence or wilful misconduct of the National Coordinating Centre or the National Coordinating Investigator. In the event that a claim is made against the National Coordinating Centre as a result of the Protocol design and only where the National Coordinating Centre has not been negligent then the Coordinating Sponsor will be liable for such claim and will have full control over the handling of the claim. As far as any other action or claim is brought against the National Coordinating Centre, the Coordinating Sponsor shall co-operate with the National Coordinating Centre in defending

ed ogni negligenza clinica da parte loro.

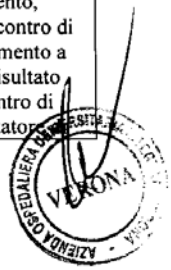
Lo Sponsor Coordinatore è responsabile e sottoscriverà adeguata copertura assicurativa per coprire danni dovuti alla negligenza avvenuti sotto la sua responsabilità in qualità di Sponsor Coordinatore come illustrato in Allegato 1 e nel protocollo, e dovrà fornire prova della stessa al Centro di Coordinamento Nazionale sotto richiesta.

12. RESPONSABILITA' ED INDENNIZZO

12.1 Il Centro di Coordinamento Nazionale è e dovrà rimanere responsabile per qualsiasi danno dovuto alla negligenza, richieste di risarcimento, azioni o spese (incluse le spese legali) risultanti da o connesse con negligenze, violazioni, omissioni o colpe da parte sua o del suo sub-contraente, incluso ma non limitatamente ai siti, la parte che prende il ruolo dei Centro di Coordinamento Nazionale nei termini di questo accordo o lo sperimentatore di coordinamento nazionale. Il Centro di Coordinamento Nazionale deve risarcire lo Sponsor Coordinatore di qualsiasi danno imputabile a negligenza, richieste di risarcimento, azioni o spese (incluse le spese legali) fatte contro di loro come risultato di tali richieste di risarcimento a meno che la richiesta di risarcimento sia il risultato della negligenza o illecito volontario dello Sponsor Coordinatore.

12.2 Se una delle citate azioni o richieste di risarcimento sia avanzata contro lo Sponsor Coordinatore, il Centro di Coordinamento Nazionale deve co-operare con lo Sponsor Coordinatore nella difesa da tale azione o richiesta di risarcimento.

12.3 Lo Sponsor Coordinatore è e deve rimanere responsabile per qualsiasi danno dovuto a negligenza, richieste di risarcimento, azioni o spese (incluse le spese legali) risultanti da o connesse alla negligenza, violazioni, omissioni o colpe da parte dello Sponsor Coordinatore. Lo Sponsor Coordinatore deve indennizzare il Centro di Coordinamento Nazionale e (come appropriato) lo Sperimentatore di Coordinamento Nazionale contro qualsiasi danno dovuto alla negligenza, richieste di risarcimento, azioni o spese (incluse le spese legali) fatte contro di loro come risultato di tali richieste di risarcimento a meno che la richiesta di risarcimento sia il risultato della negligenza o illecito volontario del Centro di Coordinamento Nazionale o dello sperimentatore



such action or claim.	coordinamento nazionale. Nel caso in cui una richiesta di risarcimento sia fatta contro il Centro di Coordinamento Nazionale come risultato del Protocollo e ove il Centro di Coordinamento Nazionale non sia stato negligente, allora lo Sponsor Coordinatore sarà responsabile per tale richiesta di risarcimento e avrà pieno controllo sulla gestione della richiesta di risarcimento. Se una delle citate azioni o richieste di risarcimento sia avanzata contro il Centro di Coordinamento Nazionale, lo Sponsor Coordinatore deve co-operare con il Centro di Coordinamento Nazionale nella difesa contro tale azione o richiesta di risarcimento.
12.4 For the avoidance of doubt, nothing in this clause shall be deemed to exclude or limit in any way either Party's liability for intentional wrongdoing or statutory liability in respect of death or personal injury caused to any person as a result of negligence or any liability that cannot be excluded by law.	12.4 Per evitare qualsiasi dubbio, niente in questa clausola dovrà essere considerato per escludere o limitare in qualsiasi modo sia la responsabilità della parte rispetto alla malcondotta intenzionale o alla responsabilità legale rispetto alla morte o alla lesione personale causata a qualsiasi persona come risultato di una negligenza o di qualsiasi responsabilità che non possa esser esclusa a termini di legge.
13. GENERAL TERMS	13. CONDIZIONI GENERALI
13.1 Neither Party shall have any liability under or be deemed to be in breach of this Agreement for any delays or failures in performance of this Agreement which result from circumstances beyond the reasonable control of that Party. The Party affected by such circumstances shall promptly notify the other Party in writing when such circumstances cause a delay or failure in performance and when they cease to do so. If such circumstances continue for a continuous period of more than 6 months, either Party may terminate this Agreement by written notice to the other Party.	13.1 Nessuna Parte deve avere responsabilità o essere considerata responsabile di una rottura di questo accordo per qualsiasi ritardo o fallimento nell'eseguire questo accordo derivante da circostanze al di là di ogni ragionevole controllo di tale Parte. La Parte che subisce le conseguenze di tali circostanze dovrà prontamente notificare all'altra Parte per iscritto quando tali circostanze hanno causato un ritardo o un fallimento nell'esecuzione e quando hanno cessato di fare ciò. Se tali circostanze continuano per un periodo continuativo di più di 6 mesi, entrambe le Parti possono risolvere questo accordo tramite notifica scritta all'altra Parte.
13.2 This Agreement may only be amended in writing signed by duly authorised representatives of the Parties.	13.2 Questo accordo potrà essere modificato solo per iscritto e firmato dai rappresentanti debitamente autorizzati delle Parti.
13.3 Subject to the following sentence, neither Party may assign, delegate, sub-contract, mortgage, charge or otherwise transfer any or all of its rights and obligations under this Agreement without the prior written agreement of the other Party. A Party may, however, assign and transfer all its rights and obligations under this Agreement to any person to which it transfers all of its business, provided that the assignee undertakes in writing to the other Party to be bound by the obligations of the assignor under this Agreement.	13.3 Secondo la presente disposizione nessuna parte può assegnare, delegare, sub-contrarre, ipotecare, addebitare o altrimenti trasferire qualsiasi dei propri diritti e doveri specificati in questo accordo senza il previo accordo scritto delle altre Parti. Una parte può comunque assegnare e trasferire tutti i suoi diritti e doveri specificati in questo accordo a qualsiasi persona alla quale trasferisce tutti i suoi affari, assicurandosi che l'assegnatario si obblighi per iscritto verso le altre Parti all'adempimento delle
13.4 In the event that either Party needs to assign or sub-contract any of its obligations under this agreement to a third party then the assigning party will remain liable for those obligations and ensure that any contracts entered into with said third party is on terms no less onerous than those contained herein.	

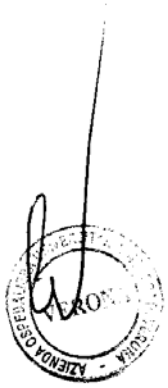
13.5 This Agreement contains the whole agreement between the Parties and supersedes and replaces any prior written or oral agreements, representations or understandings between them. The Parties confirm that they have not entered into this Agreement on the basis of any representation that is not expressly incorporated into this Agreement. Nothing in this Agreement excludes liability for fraud.	obbligazioni del cedente come derivanti dal presente Accordo.
13.6 No failure or delay by either Party in exercising any right, power or privilege under this Agreement shall impair the same or operate as a waiver of the same nor shall any single or partial exercise of any right, power or privilege preclude any further exercise of the same or the exercise of any other right, power or privilege. The rights and remedies provided in this Agreement are cumulative and not exclusive of any rights and remedies provided by law.	13.4 Nel caso in cui qualunque parte debba assegnare o sub-appaltare qualsiasi dei propri doveri specificati in questo accordo ad una terza parte, la parte assegnataria rimarrà comunque responsabile per tali obbligazioni e assicurerà che qualsiasi contratto concluso con la suddetta terza parte sia concluso a condizioni non meno onerose che quelle qui contenute.
13.7 This Agreement shall not constitute or imply any partnership, joint venture, agency, fiduciary relationship or other relationship between the Parties other than the contractual relationship expressly provided for in this Agreement. Neither Party shall have, nor represent that it has, any authority to make any commitments on the other Party's behalf.	13.5 Questo accordo contiene l'intero accordo tra le Parti e annulla e sostituisce ogni precedente accordo scritto o orale, reclamo o intesa tra loro. Le Parti confermano che non hanno concluso questo accordo sulla base di qualsiasi potere di rappresentanza che non sia espressamente menzionata in questo accordo. Niente in questo accordo esclude la responsabilità per frode.
13.8 Each Party to this Agreement shall at the request and expense of the other execute and do any deeds and other things reasonably necessary to carry out the provisions of this Agreement or to make it easier to enforce.	13.6 Nessun inadempimento o ritardo da entrambe le parti nell'esercitare qualsiasi diritto, potere o privilegio specificato in questo accordo deve compromettere lo stesso o operare come una esenzione dello stesso, come neanche ogni parziale o singolo esercizio di qualsiasi diritto, potere o privilegio deve precludere qualsiasi ulteriore esercizio dello stesso o l'esercizio di altro diritto, potere o privilegio. I diritti e rimedi inclusi in questo accordo sono cumulativi con e non esclusivi di ogni altro diritto e rimedio indicato dalla legge.
13.9 If any provision of this Agreement is prohibited by law or judged by a court to be unlawful, void or unenforceable, the provision shall, to the extent required, be severed from this Agreement and rendered ineffective as far as possible without modifying the remaining provisions of this Agreement, and shall not in any way affect any other circumstances of or the validity or enforcement of this Agreement.	13.7 Questo accordo non deve costituire o implicare qualsiasi collaborazione, impresa congiunta, operato, relazione fiduciaria o altra relazione tra le Parti oltre a quelle espressamente sorte sulla base di questo accordo. Nessuna parte deve avere, né affermare di avere, qualsiasi autorità per fare qualsiasi accordo per conto dell'altra parte.
13.10 No Party shall issue or make any public announcement or disclose any Confidential Information regarding this Agreement unless prior to such public announcement or disclosure it furnishes all the Parties with a copy of such	13.8 Ciascuna Parte di questo accordo deve, a richiesta e spese dell'altra, eseguire e fare ogni azione e quanto ragionevolmente necessario per portare a termine le disposizioni di questo accordo o per renderlo più facile da applicare. 13.9 Se qualsiasi disposizione di questo accordo è proibita dalla legge o giudicata da una corte esser illegale, nulla o non applicabile, la disposizione deve, per quanto richiesto, essere separata da questo

announcement or Confidential Information and obtains the approval of such persons to its terms, without prejudice to the provision of clause 6.2. However, no Party shall be prohibited from issuing or making any such public announcement or disclosing such Confidential Information if it is necessary to do so to comply with any applicable law or the regulations of a recognised stock exchange.	accordo e resa inefficace per quanto possibile senza modificare le rimanenti disposizioni di questo accordo, e non dovrà in ogni modo influenzare ogni altra circostanza o la validità o esecuzione di questo accordo.
13.11 In this Agreement unless the context otherwise requires:	13.10 Nessuna Parte deve emettere o fare qualsiasi annuncio pubblico o divulgare qualsiasi informazione confidenziale rispetto a questo accordo a meno che precedentemente a tale pubblico annuncio o divulgazione fornisca tutte le parti con una copia di tale annuncio o informazione confidenziale ed ottenga l'approvazione delle altre parti circa il suo contenuto, fatte salve le disposizioni della clausola 6.2. Comunque, a nessuna Parte viene proibito di emanare o fare tale pubblico annuncio o divulgazione di tale informazione confidenziale se è necessario farlo per attenersi a qualsiasi legge o regolamentazione applicabile di un legittimo scambio.
13.11.1 words importing any gender include every gender; 13.11.2 words importing the singular number include the plural number and vice versa; 13.11.3 words importing persons include firms, companies and corporations and vice versa; 13.11.4 references to numbered clauses and schedules are references to the relevant clause in or schedule to this Agreement; 13.11.5 reference in any schedule to this Agreement to numbered paragraphs relate to the numbered paragraphs of that schedule; 13.11.6 any obligation on any Party not to do or omit to do anything is to include an obligation not to allow that thing to be done or omitted to be done; 13.11.7 the headings to the clauses, schedules and paragraphs of this Agreement are not to affect the interpretation; 13.11.8 any reference to an enactment includes reference to that enactment as amended or replaced from time to time and to any subordinate legislation or byelaw made under that enactment; and 13.11.9 where the word 'including' is used in this Agreement, it shall be understood as meaning 'including without limitation'.	13.11 In questo accordo a meno che il contesto non richieda altrimenti: 13.11.1 Le parole indicanti qualsiasi genere includono ogni genere; 13.11.2 Le parole indicanti il singolare includono il plurale e viceversa; 13.11.3 Le parole indicanti persone includono studi legali, compagnie e società e viceversa; 13.11.4 riferimenti alle clausole numerate e programmate sono riferimenti alle clausole rilevanti in o allegati a questo accordo; 13.11.5 riferimenti in ogni allegato a questo accordo a paragrafi numerati si riferiscono ai paragrafi numerati di tale allegato; 13.11.6 ogni obbligazione di non fare o omettere di fare qualcosa ricadente su qualsiasi Parte include un obbligo di non permettere che quella determinata cosa sia fatta o omessa di fare;
13.12 Any notice to be given under this Agreement shall be in writing and shall be sent by first class mail or air mail to the relevant address of the relevant Party as set out below, or such other address as that Party may from time to time notify to the other Party in accordance with this Clause 13.12. Notices sent as above shall be deemed to have been received five working days after the day of posting (in the case of inland first class mail), or ten working days after the date of	13.11.7 I titoli delle clausole, allegati e paragrafi di questo accordo non sono soggetti ad interpretazione; 13.11.8 ogni riferimento ad una modifica legislativa include un riferimento a tale modifica come modifica o sostituzione di volta in volta e di qualsiasi legislazione subordinata o ordinanza fatta sotto tale modifica; e

posting (in the case of air mail). In the case of notices to the Coordinating Sponsor, sent to: Head of Legal Services Directorate of Engagement & Partnerships Innovation Centre 2 Keele University Science & Innovation Park Keele University Staffordshire ST5 5NH U.K In the case of notices to the National Coordinating Centre sent to: Unità Ricerca Clinica Azienda Ospedaliera Universitaria Integrata Verona, P.le Stefani, 1 (B.go Trento, presso Ospedale Geriatrico, 1° Piano lato Adige) - 37126 Verona, Italy 13.13 If any dispute arises in connection with this Agreement it shall be notified in writing by one Party to the other. 13.14 The validity, construction and performance of this Agreement shall be governed by the law of Italy and shall be subject to the courts of Verona. 13.15 The Agreement has been drawn up in English and Italian languages. In case of discrepancy, the English version will prevail. 13.16 For the purposes of the Contracts (Rights of Third Parties) Act 1999 this Agreement is not intended to, and does not, give any person who is not a party to it any right to enforce any of its provisions. 13.17 The Parties shall not unlawfully discriminate either directly or indirectly on such grounds as gender, race, colour, national origin, disability, sexual orientation or age within the meaning of all legislation, directives and guidance relating to equality and discrimination. 13.18 The Parties shall be entitled to cancel this	13.11.9 dove la parola "incluso" è utilizzata in questo accordo, deve essere intesa come significante 'incluso senza limitazioni'. 13.12 Ogni notifica da dare secondo questo accordo deve essere scritta e deve essere inviata tramite raccomandata o posta aerea all' indirizzo della parte rilevante come di seguito stabilito, o ad altro indirizzo che tale parte abbia notificato all'altra Parte secondo la Clausola 13.12. Notifiche inviate come sopra vanno considerate ricevute dopo cinque giorni lavorativi dopo il giorno dell'invio (in caso di raccomandata), o dopo dieci giorni lavorativi dalla data dell'invio (in caso di posta aerea). In caso di notifica allo Sponsor Coordinatore, mandare a: Head of Legal Services Directorate of Engagement & Partnerships Innovation Centre 2 Keele University Science & Innovation Park Keele University Staffordshire ST5 5NH U.K In caso di notifica al Centro di Coordinamento Nazionale mandare a: Unità Ricerca Clinica Azienda Ospedaliera Universitaria Integrata Verona, P.le Stefani, 1 (B.go Trento, presso Ospedale Geriatrico, 1° Piano lato Adige) - 37126 Verona, Italy 13.13 Se qualsiasi controversia dovesse nascere in relazione a questo accordo, la stessa dovrà essere notificata per iscritto da una delle Parti all'altra. 13.14 La validità, la costruzione e l'esecuzione di questo Accordo è soggetta alla legge Italiana ed alla competenza del Tribunale di Verona. 13.15 L'accordo è stato stilato in inglese ed italiano. In caso di difformità, la versione inglese prevarrà. 13.16 Ai sensi del Contract Act del 1999 (diritti di

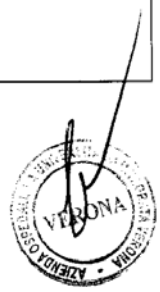
Agreement immediately upon written notice if the other Party or its employees or agents are found to have made, offered, accepted or taken or agreed to make or take any gift, bribe, hospitality or consideration of any kind from any person or body as an inducement or reward for showing or forbearing to show favour or disfavour to any person or for doing or forbearing to do any action in relation to or for the purposes of offering or obtaining an advantage in relation to performance of this Agreement or where such action is in contravention of anti-corruption laws and regulation applicable to each Party.	Parti terze) , questo accordo non è inteso e non dà a nessuna persona che non sia una Parte del presente contratto qualsiasi diritto da applicare sulla base delle sue disposizioni. 13.17 Le Parti non devono discriminare illegittimamente sia direttamente che indirettamente su basi come genere, razza, colore, nazionalità di origine, disabilità, orientamento sessuale o età secondo i limiti della legge, delle direttive e delle rispetto dell'equità e della discriminazione.
IN WITNESS WHEREOF, the parties have executed this Agreement	13.18 Le Parti devono essere autorizzate a risolvere il presente accordo immediatamente tramite notifica scritta se l'altra Parte o i suoi impiegati o agenti abbiano compiuto, offerto, accettato o preso o accettato di fare o fatto qualsiasi regalo, tangente, ospitalità o considerazione di qualsiasi tipo da qualsiasi persona o istituzione come un incentivo o ricompensa per mostrare o sopportare di mostrare favore o sfavore a qualsiasi persona o per fare o sopportare di fare qualsiasi azione in rapporto a o per il proposito di offrire o ottenere un vantaggio in rapporto all'esecuzione di questo accordo o se tale azione è posta in essere in violazione alle leggi anti-corruzione e alle regolamentazioni applicabili in ogni Paese.
1. For and on behalf of the Coordinating Sponsor NAME: Dr Mark Bacon SIGNATURE: DATE:	IN FEDE, le Parti che hanno eseguito questo accordo 1. Per conto dello Sponsor Coordinatore NOME: Dr Mark Bacon FIRMA: DATA:
2. For and on behalf of the National Coordinating Centre NAME: Dott.ssa Giulia Bisoffi SIGNATURE: DATE:	2. Per conto del Centro di Coordinamento Nazionale NOME: Dott.ssa Giulia Bisoffi FIRMA: DATA:
3. Read and Acknowledged by the National Coordinating Investigator I hereby acknowledge that I have read and agree with the terms of this Agreement, and that I will act and perform my duties in the Study in accordance herewith NAME: Dott. Stefano Tamburin SIGNATURE: DATE:	

	3. Letto e sottoscritto dallo Sperimentatore del Centro di Coordinamento Nazionale Io sottoscritto confermo di aver letto e compreso i termini di questo accordo, e che agirò ed eseguirò i miei doveri in relazione allo studio in accordo con le precedenti disposizioni NOME: Dott. Stefano Tamburin FIRMA: DATA:



SCHEDULE 1

Responsibility	Coordinating Sponsor	National Coordinating Centre	Other (specify)
Study Development			
Study Design	✓		
Risk Assessment (if applicable)	✓		
Protocol development	✓		
Develop Information Sheet, Consent Form and other patient focused documents in English	✓		
Case Report Form development	✓		
Develop, test and maintain study database, including randomisation system (if applicable)	✓		
Develop Monitoring Plan (if applicable)	✓		
Provision of finalised essential documents and guidance in English. Including but not limited to: • Risk Assessment • Protocol • Information Sheet, Consent Form • Case Report Form • Monitoring Plan • Coordinating Sponsor proof of insurance	✓		
Train National Coordinating Staff on protocol and responsibilities undertaken as a National Coordinating Centre	✓		
Acceptance and authorisation of protocol in Country		✓	
Develop Country specific Patient Information Sheet, Consent Form and other patient focused documents, including translation and adaption where required, to comply with national requirements Provide copy of Country specific patient documents to		✓	



Coordinating Sponsor			
Develop Country specific guidance documents. Provide copies to Coordinating Sponsor on request (if applicable)		✓	
Provision and sign off of contracts and agreements with Country specific third party suppliers (if applicable) Details of third party suppliers to be provided to Coordinating Sponsor on request		✓	
Funding and Finance			
Obtain funding for conduct of study within Country		✓	
Manage financial budget within Country		Not applicable	
Provide progress reports to Country funder(s) as requested		✓	
Study Authorisation			
Prepare and apply for ethical approval within Country. Provide copy of approval to Coordinating Sponsor		✓	
Apply for additional Country specific authorisations as applicable. Provide copy of approval to Coordinating Sponsor on request		✓	
Ensure Sites obtain appropriate local approval (if applicable). Provide copy of approval to Coordinating Sponsor on request		✓	
Determine which amendments are substantial and supply documentation to the National Coordinating Centre	✓		
Generate and submit Country specific progress reports to ethical committee(s) as required Provide copy to Coordinating Sponsor on request		✓	
Distribute amendments, reports and other documentation (as required) to the Country's Sites		✓	
Study Management			
Ensure study conducted according to protocol and GCP in		✓	

Country			
Conduct Country specific site feasibility		✓	
Ensure investigators in Country are adequately qualified/trained to conduct the study in accordance with national requirements Provide copy of investigator CVs to Coordinating Sponsor on request		✓	
Creation and provision of written agreement between the National Coordinating Centre and Site(s), if present. Copy of signed agreement(s) to be provided to Coordinating Sponsor (if applicable)		✓	
Provision of Investigator Site File to the Country's Sites		✓	
Country specific Site set up and initiation, including training on protocol and preparation of a site initiation report.* Copy of report (with summary in English, if report not written in English) to be provided to Coordinating Sponsor		✓	
Act as a point of contact for routine study management and data management queries in Country*			
Maintain international Study Master File and essential documents	✓		
Maintain Country specific Study Master File and essential documents		✓	
Decide on the need for implementation of urgent safety measures	✓		
Implement urgent safety measure in Country Provide confirmation of implementation to Coordinating Sponsor on request		✓	
Report potential serious breaches of GCP or the Protocol to the Coordinating Sponsor		✓	
Perform assessment of potential serious breaches	✓		
Report serious breaches to the ethics committee as required by Country specific regulations Provide confirmation of submission to Coordinating Sponsor on request		✓	

Decide on need for temporary halt to study	✓ (internationally)	✓ (in country only)	
Notify ethics committee of any temporary halt to the study in Country Provide confirmation to Coordinating Sponsor on request		✓	
Data Management			
Data entry of paper CRF if system unavailable (if applicable)	✓		
Creation of Data Clarification Forms (DCF) (if applicable)	✓		
Distribution of DCF to Country's Sites (if applicable)		✓ (paper DCF on request)	
Distribution of reminders for CRF/DCF to County's Sites (if applicable)		✓	
Provision of statistical data cleaning requests specific for Country	✓		
Distribution of statistical data cleaning requests to Country's Sites		✓	
Notify the Coordinating Sponsor of any potential safety issues		✓	
Notify the ethics committee and investigators of safety issues as specified by the Coordinating Sponsor Provide proof of notification to Coordinating Sponsor on request		✓	
Monitoring and Audit			
Perform on site monitoring of Country's Sites in accordance with GCP, protocol and monitoring plan* Provide copy of monitoring reports to Coordinating Sponsor (if applicable)		✓	
Perform central monitoring in accordance with Monitoring Plan		✓	
Perform audit of National Coordinating Centre (if applicable)	✓		
Data Provision, Statistical Analysis and Publication			

Provide summaries (e.g. number patients recruited, CRF return etc) for inclusion in Country specific reports	✓		
Perform analyses in accordance with the Statistical Analysis Plan	✓		
Preparation and submission of main study publications	✓		
End of Study			
On early termination of study notify ethics committee within regulatory timeframe for reporting Provide confirmation of notification to Coordinating Sponsor on request		✓	
Submit end of study declaration to ethics committee in compliance with regulatory timeframe for reporting (if applicable) Provide confirmation of submission to Coordinating Sponsor on request		✓	
Closure of Country's Sites including preparation of closure report Provide copy to Coordinating Sponsor on request		✓	
Prepare End of Study Report and provide to Country	✓		
Submit Summary of End of Study Report to ethics committee (if required) Provide confirmation of submission to Coordinating Sponsor on request		✓	
Ensure Country's Sites archive investigator site file		✓	
Archiving of Country specific study master file		✓	
Archiving of international study master file	✓		

Area of responsibility	Description	Responsible party
Clinical study management	Day-to-day document distribution and Country-based point of contact	National Coordinating Centre
Funding and finance	To include grant application and development of budget control systems for the Country	National Coordinating Centre

Area of responsibility	Description	Responsible party
Protocol	Coordination of Protocol development and version control	Coordinating Sponsor
	Acceptance and authorisation in the Country	National Coordinating Centre
Case report form (CRF) (if applicable)	Design and development of CRF	Coordinating Sponsor
	Acceptance and authorisation for use in the Country	National Coordinating Centre
Ethics	Complete and submit ethics committee application form	National Coordinating Centre
	Provide appropriate documentation according to local ethics requirements	National Coordinating Centre
	Provide approval letters to Coordinating Sponsor	National Coordinating Centre
Patient information sheet, informed consent form and other patient focused documentation (e.g. general practitioner notification)	Including translation where required, and adaptation to comply with national requirements.	Coordinating Sponsor
	Training of site staff on consent procedure, and review of completed informed consent forms (if local law permits)	National Coordinating Centre
Study master file	Set up of Country study master file, to include investigator site file and maintenance of essential documents	National Coordinating Centre
	Provide investigator site file to Sites as part of Site initiation	Coordinating Sponsor
	Distribute amendments to investigator site file documents to Sites during the study	National Coordinating Centre

Area of responsibility	Description	Responsible party
Site set-up, initiation and management within Country	To include feasibility, Site selection and Site initiation	Coordinating Sponsor
	Written agreement between National Coordinating Centre and Sites	National Coordinating Centre
	Provide copy of signed agreement between National Coordinating Centre and Sites to Coordinating Sponsor if necessary	National Coordinating Centre
	Provide copy of Site initiation reports to National Coordinating Centre	Coordinating Sponsor
	Maintain list of Site contacts (e.g. investigators, research nurses etc.)	National Coordinating Centre
Training within Country	To include training of Site staff in study specifics	Coordinating Sponsor
IT / programming procedures (if applicable)	Produce and maintain study database, including backup of study data	Coordinating Sponsor
	Grant permissions to access study database	Coordinating Sponsor
Data management (if applicable)	Data collection and statistical data cleaning.	Coordinating Sponsor
	Data entry Note: This is by remote data capture with data flowing directly from Country Sites to the Coordinating Sponsor	Coordinating Sponsor
	Distribute data clarifications to Sites	Coordinating Sponsor

Area of responsibility	Description	Responsible party
Amendments	In case of substantial amendment obtain approval from ethics committee (as required)	National Coordinating Centre
	Provide approval letters to Coordinating Sponsor	National Coordinating Centre
	Distribution of amendment and approval documents to Sites	National Coordinating Centre
On-site monitoring within Country	Prepare plan detailing minimal monitoring requirements ("monitoring plan")	Coordinating Sponsor
	Perform on-site monitoring of participating sites in accordance GCP, Protocol and monitoring plan	Coordinating Sponsor
	Provide copy of monitoring visit reports to National Coordinating Centre	Coordinating Sponsor
Statistical procedures (if applicable)	Including statistical design, preparation of statistical analysis plan and analysis	Coordinating Sponsor
Study reports for the responsible country	Provision of study data on request	Coordinating Sponsor
	Submission of reports to ethics committee and funding bodies, where required, and in accordance with national requirements	National Coordinating Centre based on the information provided by Coordinating Sponsor

Area of responsibility	Description	Responsible party
Site/study closure within responsible country	Perform site closure	Coordinating Sponsor
	Provide site closure reports to National Coordinating Centre	Coordinating Sponsor
	Inform National Coordinating Centre of end of study	Coordinating Sponsor
	Submit end of study declaration to ethics committee within 90 days of the end of the study	National Coordinating Centre
	Provide Coordinating Sponsor with confirmation of submission of end of study declaration	National Coordinating Centre
Urgent safety measures	Implement any Urgent Safety Measures notified by the Coordinating Sponsor within required timelines	National Coordinating Centre based on the information provided by Coordinating Sponsor
Serious breaches	Notify Coordinating Sponsor of any events that would be considered a serious breach, as defined within the Protocol	National Coordinating Centre
Temporary halt to study	Following notification by Coordinating Sponsor notify ethics committee of any temporary halt to study within 15 days from when the study is temporarily halted	National Coordinating Centre based on the information provided by Coordinating Sponsor
	Provide Coordinating Sponsor with confirmation of submission	National Coordinating Centre
Early termination of study	Following notification by Coordinating Sponsor, notify ethics committee of early termination of the study within 15 days after the study is terminated	National Coordinating Centre based on the information provided by Coordinating Sponsor
	Provide Coordinating Sponsor with confirmation of submission	National Coordinating Centre

Area of responsibility	Description	Responsible party
End of study report	Produce end of study report	Coordinating Sponsor
	Submit end of study summary report to ethics committee as per national requirements	National Coordinating Centre
	Provide Coordinating Sponsor with confirmation of submission	National Coordinating Centre
Archiving	Country specific investigator site file and study master file	National Coordinating Centre based on the information provided by Coordinating Sponsor
	All other study material	Coordinating Sponsor
Set up and maintenance of quality management system at the National Coordinating Centre in the Country	To include capturing of processes in standard operating procedures, implementing quality checks, and performing audit checks (if applicable)	National Coordinating Centre
Communication	Maintain good communication lines by sharing information regarding issues, best practice etc.	Both Parties

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA
VERONA

(D.Lgs. n. 517/1999 - Art. 3 L.R.Veneto n. 18/2009)

DIPARTIMENTO DIREZIONE MEDICA OSPEDALIERA

COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA
DELLE PROVINCE DI VERONA E ROVIGO
UFFICIO DI SEGRETERIA TECNICO-SCIENTIFICA DEL COMITATO ETICO
c/o SERVIZIO DI FARMACIA
Borgo Trento - P.le A. Stefani, 1 - 37126 Verona - Tel. 045 8123236 - Fax 045 8123177
e-mail: comitatoetico.veronarovigo@aovr.veneto.it
PEC: comitatoetico.aovr@pecveneto.it

Prot n 14811 del 13/03/2019

Sperimentatore: Dr. Tamburin Stefano - Neurologia B - (UOC) - Azienda Ospedaliera Universitaria Integrata - Verona

Direttore U.O.: Prof. Salvatore Monaco - Neurologia B - (UOC) - Azienda Ospedaliera Universitaria Integrata - Verona

Promotore: Keele University

NRC: A.O. UNIVERSITARIA INTEGRATA DI VERONA

Oggetto: Prog. 1456CESC - Emendamento n. 1 del 10/01/2019 - Studio Clinico: Fattori di rischio cognitivi, psicologici e neurobiologici per i disturbi da discontrollo degli impulsi nella malattia di Parkinson: uno studio multicentrico su una coorte italiana di malati di Parkinson (PROACTIVE-PD) - Codice Protocollo: PROACTIVE-PD-001

In riferimento alla richiesta di autorizzazione dell'emendamento in oggetto, si trasmettono le decisioni del Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo riunitosi in data **06/03/2019.**

Si rammenta che per l'attivazione dell'emendamento è necessario attendere:

1. ove previsto, la ricezione dell'autorizzazione della propria Amministrazione

Il Comitato Etico, in osservanza a quanto previsto dalla legislazione vigente in materia di sperimentazione clinica

HA ESAMINATO L'EMENDAMENTO SOSTANZIALE
E, IN PARTICOLARE, LA SEGUENTE DOCUMENTAZIONE:

- **Modulo di domanda per CE per emendamento sostanziale** (versione del *10/01/2019*)
- **Lettera di trasmissione** (versione del *29/01/2019*)
- **Protocollo dello Studio Aggiornato** (versione *6.3* del *23/11/2018*)
- **RIASSUNTO** (versione del *10/01/2019*)
- **CRF (Healthy controls)** (versione *4.2* del *23/11/2018*)
- **CRF (Parkinson's)** (versione *3.1* del *23/11/2018*)
- **Boston Naming test**
- **Dimensional Apathy Scale**
- **Documento informativo (gruppo di controllo sano)** (versione *5.1* del *23/11/2018*)
- **Consenso informato (gruppo di controllo sano)** (versione *3.3* del *23/11/2018*)
- **Documento informativo (Parkinson)** (versione *5.1* del *23/11/2018*)
- **Consenso informato** (versione *3.3* del *23/11/2018*)
- **Lettera per il medico di base** (versione *4.0* del *23/11/2018*)

- **Modulo per il consenso al trattamento dei dati personali**
- **Aggiornamento sullo stato di avanzamento dello studio a livello locale (modulo)** (versione del *20/02/2019*)

Data arrivo documentazione completa:25/02/2019

HA ESPRESSO IL SEGUENTE PARERE:
PARERE FAVOREVOLE

Note/richieste: In data 25/02/2019 è pervenuta presso la Segreteria del CESC la documentazione relativa all'emendamento sostanziale n. 1 del 10/01/2019.

Il CESC procede con l'approvazione dell'emendamento e dei documenti ad esso correlati.

APPROVATO

Componenti del Comitato Etico per la Sperimentazione Clinica delle Province di Verona e Rovigo presenti alla discussione:
Dr. Paolo BIBAN, *Clinico*
Dott. Andrea BONETTI, *Clinico*
Dott. Emanuele CARBONIERI, *Clinico*
Dott.ssa Lucia CAZZOLETTI, *Biostatistico*
Dott.ssa Anita CONFORTI, *Farmacologo*
Dr. Pierluigi DAL SANTO, *Clinico*
Prof.ssa Maria Gloria DE BERNARDO, *Bioeticista*
Dott. Michele GANGEMI, *Pediatra di libera scelta*
Prof. Roberto LEONE, *Farmacologo*
Dott.ssa Anna Rosa MARCHETTI, *Medico di Medicina Generale Territoriale*
Dott.ssa Paola MARINI, *Farmacista*
Avv. Elisa MENGHINI, *Esperto in materie giuridiche e assicurative*
Dr. Giuseppe MORETTO, *Clinico*
Dr. Felice PASINI, *Clinico*
Dott. Dario RANIERO, *Medico legale*
Dott. Giulio RIGON, *Medico di Medicina Generale Territoriale*
Prof. Giuseppe VERLATO, *Biostatistico*
Dott.ssa Elisabetta VERONESE, *Infermiera*
Dott.ssa Teresa ZUPPINI, *Esperto dispositivi medici*

Componenti del Comitato Etico assenti :
Dott.ssa Roberta JOPPI, *Farmacista*
Dott. Flavio MAGARINI, *Rappresentante associazione di volontariato per l'assistenza o associazionismo di tutela dei pazienti*
Prof. Pietro MINUZ, *Clinico*
Prof. Gian Cesare GUIDI - *Sostituto Permanente del Direttore Sanitario AOUI Verona*

I sopraindicati componenti del Comitato dichiarano di astenersi dal pronunciarsi su quelle sperimentazioni per le quali possa sussistere un conflitto di interessi di tipo diretto o indiretto.

Verona, 06/03/2019

D'Ordine del Presidente del Comitato Etico
delle Province di Verona e Rovigo
L'Ufficio di Segreteria
Dott.ssa Ilaria Bolcato

Appendix AC: Study 3 S. Camillo Hospital of Venice Ethical Review Panel approval - *Ethical Review Panel of the Venice Territory*

FONDAZIONE OSPEDALE SAN CAMILLO
OSPEDALE NEURORIABILITATIVO | ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO
SEDE LEGALE: 30126 | VENEZIA-LIDO | VIA ALBERONI, 70 | TEL. 041 22 07 111 | FAX 041 73 13 30
C.F. 94071440278 | P.I. 03953700279 | ISCRITTA PREFETTURA DI VENEZIA: REG. P.G. N. 409
IRCCS

Lido di Venezia, 08 ottobre 2018
Rif. CE: Protocollo 2018.11

Preg.ma
Dr.ssa Roberta Biundo
IRCCS San Camillo

Oggetto: Protocollo 2018.11 "FATTORI DI RISCHIO COGNITIVI, PSICOLOGICI E NEUROBIOLOGICI PER I DISTURBI DA DISCONTROLLO DEGLI IMPULSI NELLA MALATTIA DI PARKINSON: UNO STUDIO MULTICENTRICO SU UNA COORTE ITALIANA DI MALATI DI PARKINSON (PROACTIVE-PD) - PROACTIVE-PD
Parere del Comitato etico

Gent.ma Dr.ssa Biundo,

ho il piacere di comunicarLe che il Comitato Etico per la Sperimentazione Clinica della Provincia di Venezia e IRCCS San Camillo, nella seduta del 18 settembre u.s., vista la documentazione presentata, ha espresso PARERE FAVOREVOLE al protocollo in oggetto.

Si allega alla presente un estratto del Verbale della seduta.

L'occasione è gradita per porgerLe cordiali saluti.

La Segreteria del Nucleo di Ricerca Clinica

Dott.ssa Stefania Rossa

Stefania Rossa

COMITATO ETICO PER LA SPERIMENTAZIONE CLINICA DELLA PROVINCIA DI VENEZIA E IRCCS SAN CAMILLO(CESC)

SEDUTA del 18/09/2018

Verbale N° 90 A/CESC

Il giorno 18/09/2018 alle ore 14.30 presso l'aula 512 – Azienda ULSS 3 SERENISSIMA - si è riunito il Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS San Camillo, istituito in conformità alle disposizioni del DM 15/07/1997 e nominato con deliberazione del Direttore Generale ULSS12 n. 1803 del 25/09/2013 ai sensi del DM 8/2/2013 e della DGRV n°1066 del 28/6/2013 rinnovato con deliberazione del Direttore Generale ULSS 12 n.2665 del 25/10/2016, modificato con decreto del Direttore Generale ULSS 3 n.810 del 7/04/2017 e successive modifiche e che risulta così costituito:

costituito:

	Componente	
A	Bon Dott. Giuseppe	Esperto in Bioetica
P	Bonanome Dott. Andrea	Clinico
P	Bova Prof. Sergio	Farmacologo
P	Burlon Dott.ssa Nerina	Farmacista
P	Carraro Dott. Daniele	Medico legale
P	Crovato Avv. Alberto	Esperto in materia giuridica e assicurativa
P	Della Bianca Dott.ssa Simona	Rappresentante del settore infermieristico
P	Rosetti Dott.Francesco	Clinico
P	Gobbo Sig. Giorgio	Rappresentante del volontariato
P	Cavarzeran Dott. Fabiano	Biostatistico
P	Corrado Dott. Andrea	Clinico
P	Gasparoli Dott.ssa Elisabetta	Clinico
P	Ponzetto Dott. Tiziana	Medico di Medicina Generale
P	Quatrale Dott. Rocco	Clinico
G	Righetti Dott. Andrea	Pediatra
G	Serino Dott. Francesco Saverio	Clinico
P	Spolaor Dott. Alvise	Esperto in dispositivi
G	Agostini Dott.ssa Michela	fisioterapista
P	Stradella Dott. Giovanni	Farmacista

G	Carraro Dott.ssa Maria Grazia (sostituita dalla Dott.ssa Emanuela Salvatico	Direttore Sanitario ULSS 4
P	Lamanna dott. Onofrio (sostituito dalla Dott.ssa Lisa Bertoncello	Direttore Sanitario. ULSS 3
NC	Malatesta Dott. Renzo	Direttore Sanitario P. S.Marco
NC	Cestrone Dott. Adriano	Direttore Sanitario casa di cura Rizzola
NC	Gorini Dott. Mauro	Direttore Sanitario Fatebenefratelli
A	Pietrobon Dott.Francesco (sostituito dal Dott. Francesco Piccione)	Direttore scientifico ff IRCCS San Camillo
NC	Giron Dott. Giampiero	Direttore Sanitario Villa Salus

P	Anglani Dott.ssa Franca	Esperta in genetica
NC	Semenzato Ing. Mara	Ingegnere clinico
NC	Francini Pesenti Dott. Francesco	Esperto in nutrizione
NC	Merenda Prof. Roberto	Esperto clinico per studi di nuove procedure tecniche, diagnostiche e terapeutiche invasive e semiinvasive

Legenda: P=presente A=assente G=assente giustificato NC=non convocato

La Dott.ssa Michela Zanutti, in qualità di Segretario Scientifico è presente alla seduta.

Riscontrato il numero legale dei componenti si procede alla visione e discussione degli argomenti stabiliti nell'ordine del giorno.

Appendix AD: Study 3 persons with Parkinson's disease participants information sheet

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA
VERONA

Dr Stefano Tamburin
Policlinico G.B. Rossi lotto I, Piano VII
Piazzale L.A. Scuro, 10
37134 Verona
Tel: 045/8124285

Patient-Participant Information Sheet (Parkinson's)

Title of Project: Cognitive, **p**sychological and neu**ro**biological risk f**act**ors for Parkinson's disease related **I**mpulse Control Disorder: a multicentre in**ve**stigation of an Italian **P**arkinson's **d**isease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele University

Principal Investigator: Dr Stefano Tamburin, Policlinico G.B. Rossi lotto I, Piano VII, telephone: 045/8124285

Research Team: Dr Stefano Tamburin, Dr Alice Martini, Dr Fabio Lugoboni, Professor Angelo Antonini, Dr Roberta Biundo, Dr Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

Dear Mr/Mrs/Ms……,

You are being invited to consider taking part in a clinical study that we are conducting in our department investigating "Impulse Control Behaviours" in people with Parkinson's.

The study has been organised jointly by Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona, Professor Angelo Antonini, Department of neuroscience, University of Padova, Dr Roberta Biundo and Dr Luca Weis, Fondazione Ospedale S.Camillo of Venice, and researchers in the School of Psychology, Keele University (United Kingdom).

Before you decide, it is important for you to understand why this research is being done and what it will involve. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part. This leaflet aims to provide you with correct and complete information to allow you to make a free, informed choice.

The investigators responsible for the information are

…… …… ……

(name) *(surname)* *(position/role)*

…… …… ……

(name) *(surname)* *(position/role)*

What is the study about?

The movement difficulties in Parkinson's are usually effectively managed with dopamine replacement medications. However these medications can, in up to 35% of people with Parkinson's, cause impulse control behaviour.

Impulse control behaviours (ICBs) are uncontrollable urges, which are usually harmful either to the person with Parkinson's and/or to those around them. Examples include compulsive eating, compulsive gambling, compulsive shopping and repetitive behaviours that serve no purpose such as assembling and disassembling objects. ICBs may also extend to dopamine replacement medication where people take more medication than is prescribed. ICBs cause significant distress to the individual with Parkinson's, their partner/care-giver, wider families and social networks, and, in addition, may have serious social and legal consequences.

Exactly why some people with Parkinson's develop an ICB and others do not is unclear. Factors that may play a role include differences on activation in areas of the brain linked to the control of reward-related behaviour and also behaviour traits such as risk-taking and impulsivity.

The aim of this study is understand if having an ICB means some mental processes, behavioural traits and/or brain functioning are different. Therefore, we need to compare 2 groups of people with Parkinson's: those who have an ICB and those who do not.

What is the drug, procedure or treatment that is being tested?

No drug, procedure or treatment will be tested. We are only interested in comparing mental processes, behavioural traits and brain functioning in people with Parkinson's who have developed ICBs and those who do not.

Why have I been invited to take part?

You are invited to take part because you have a diagnosis of Parkinson's and we would like you to be part of one of our "Parkinson's groups". You may also have an ICB, but not

necessarily. Either way, if you do have an ICB or not, we would like you to consider taking part. The assessment of ICBs will take place with Dr Stefano Tamburin, Consultant Neurologist, in a screening visit.

We are looking for people aged between 35-85 years, and have mild or moderate Parkinson's. There are other criteria that people in the "Parkinson's groups" should meet. Unfortunately, we cannot include you in this study if:

- Italian is your second language (i.e., you are not Italian-mother tongue);
- You have a severe Parkinson's (indicated by a score of 4 or 5 on the Hoehn and Yahr disease severity rating scale, assessed at the screening visit);
- You have a first degree family member with Parkinson's disease, such as parents diagnosed with Parkinson's;
- You have been diagnosed with another neurological illness (other than Parkinson's) such as Alzheimer's, Multiple Sclerosis, epilepsy;
- You are unable to provide informed consent due to cognitive decline (determined at the screening visit);
- You have a history of learning difficulty including dyslexia;
- You have been diagnosed with psychotic phenomenology such as hallucinations or lack of awareness of dyskinesias (to be determined at screening visit);
- You have incapacitating dyskinesias on a stable dose of l-dopa;
- You have a history of drug or alcohol use disorder;
- You are taking any of the following drugs:
  - Centrally acting anticholinergics;
  - Atypical antipsychotics.

This study will take place in two centers (Verona and Venice) in Italy and 68 people with Parkinson's will take part.

Do I have to take part?

No. You are free to decide if you wish to take part or not. If you do not want to take part you do not need to provide any explanation. This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future.

What will happen if I take part?

If you would like to consider the opportunity to take part in this study, you will provided with this information sheet to read and keep. You will have the opportunity to ask all information that you need before to decide to take part.

If you do decide to take part you will be asked to sign a consent form and be given a copy. Only when you will have signed the consent form, Dr Stefano Tamburin will visit you to make sure you fulfil all the medical eligibility criteria for taking part in this study.

How the study will be conducted?

The study comprises of three visits. Below you can find detailed information related to your involvement.

What will I do if I take part?

You will be invited to attend 2 appointments.

The first will be a screening visit with Dr Stefano Tamburin or Dr Alice Martini in the Policlinico G.B. Rossi lotto I, Piano VII. S/he will review eligibility to take part, answer any questions about the study and if you're happy to proceed into the study, S/he will take consent. You will firstly be asked if we could measure your height and weight (vital signs). These signs are used to calculate the amount of your Parkinson's medication on your body. S/he will also complete a number of questionnaires with you concerning your current and past medical history and in particular Parkinson's. You will also be asked about your participation in any other study that you have taken part, now or in the past. At the end of the screening visit you will attend a visit with DrAlice Martini, psychologist and PhD student, and a neurophysiologist in the Policlinico G.B. Rossi lotto I, Piano VII. This visit will last about 90 minutes. During the visit you will complete a computerized task and Electroencephalogram (EEG) data will be recorded. EEG is a safe procedure that involves no health risks. You will wear a cap that records electric signals generated from your brain. **Please, do not wear any hair products the day of the third visit, as this may interfere with the equipment used for the EEG recording. Also, from the night before the visit please**

avoid any coffee, tea, chocolate, alcoholic drinks consumption, as they may alter the EEG results. If you do not wish to be visited with EEG, you will be given with the opportunity to complete the task without EEG being recorded.

The second appointment will be with Dr Alice Martini in the Policlinico G.B. Rossi lotto I, Piano VII. We are aware that coming twice to the hospital might be difficult for you to arrange; if this is inconvenient for you, Dr Alice Martini can schedule the second appointment at your home. Here you will be asked to complete questionnaires and a number of assessments of memory, attention and decision-making. Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. **Please, bring with you your reading glasses if you use them.**

We would like to arrange for these 2 appointments to take place within one week from each other, if possible. The screening visit and EEG assessment will last about 150 minutes (plus breaks), the second session will last about 60-90 minutes. **It's very important that during the second appointment you don't mention anything about your Parkinson's history – especially if you have experienced impulse control behaviours.**

There is a lot of information here! So, please do not hesitate to ask questions either by phoning us before your decide to take part, or at any point during the screening and research visits.

What do I have to do?

If you wish to take part in the study you will be visited by Dr Stefano Tamburin or Dr Alice Martini to check whether you fulfil all inclusion criteria. The neurologist will answer to your questions about the study and, if you would like to take part in the study, you will be asked to sign the consent form.

If you don't want to take part in this study, you can either return the response slip telling us so or do nothing. However, we will be sending out reminder letters to everyone we haven't heard from.

What are the benefits of taking part?

There are no tangible benefits arising from this study for the participants, anyway there is evidence to suggest that some volunteers gain psychological benefit from participating in research such as increases in self-esteem and the knowledge that they are helping others.

However, we want to reduce the number of people affected by Impulse control behaviours. To do this, clinicians need to be provided with the tools for identifying people at risk of impulse control behaviour, so they can provide advice to patients about impulse control behaviours and consider them when making treatment choices. This study is the first step towards achieving this.

What are the risks?

We don't expect any problem to arise in this study.

EEG is a test that records electrical signals in the brain. This is a safety and non-invasive procedure. When the electrode cap is placed in your head you may experience very minimal discomfort. The researcher will try to reduce this discomfort placing carefully the cap and ensuring that it remains confortable during all the research session.

Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. If you will become anxious, distressed or upset as result of the study you can inform Dr Stefano Tamburin. He will inform you where to seek help. Psychological support is available within the Policlinico G.B Rossi for participants who need it.

What will it happen if new information will be available?

If new information that may influence your safety or wiliness to continue with the study will be available, you will promptly informed by Dr Stefano Tamburin.

Can I change my mind after agreeing to take part?

Yes. You are free to withdraw from this study at any time and without giving reason (unless your decision is due to side effects, in this case you have to provide Dr Stefano Tamburin with all the information related to the side-effects experienced). This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future. However any data we have collected from you up until this point will be used for analysis (ex art. 13 del D.lgs 196/2003). The data we collect will be anonymized and there is no way anyone will be able to link the data with you as individual. Issues around how we keep data about you confidential and anonymous are outlined further on in this leaflet.

You can withdraw from the study informing Dr Stefano Tamburin by phoning him (telephone: 045/8124285) all days, from 08.00 am to 04.00 pm.

What types of reproductive risks may I incur if I decide to take part?

There aren't any reproductive risks.

Will my general practitioner doctor be informed?

Subject to your approval, your general practitioner doctor will be informed of your participation in the study with a letter. Your general practitioner doctor will also be able to contact the principal investigator (Dr Stefano Tamburin) for further information.

How long this study will last?

You participation will last about 2 weeks.

Might the study be interrupted or suspended?

Yes. The principal investigator may interrupt the study in any moment, even without your wiliness, if he considers it necessary for your safety or the correct conduction of the study. The study might also be suspended/interrupted by the Sponsor, or by the Regulatory Authority for unknown causes.

What will happen if problems occur: accident or injuries related to the study?

If any side effects, undesired effect, or damage to your health, ascribable to the study will happen, you have to promptly inform the principal investigator. He will provide you with the relevant information. Fro these issues, the Sponsor that commissioned the study has stipulate an insurance with the "Newline Underwriting Management Limited" company. In case of damages, you have to notify the insurance company within 30 days from the event. The insurance policy that covers the civil liability damages due to the study, but do not cover for the value above the maximum coverage (1.500.000 €).

Will I incur in additional costs?

No. Your participation in the study will not involve any additional costs.

Who is organising and supporting the study?

Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences; Miss Alice Martini, PhD student and psychologist, School of Psychology, Keele University; Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona; Professor Angelo Antonini neurologist at the Department of neuroscience, University of Padova; Dr Roberta Biundo, neuropsychologist at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Luca Weis, biotechinician at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Jim Grange, School of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University. The study has been sponsored by Keele University.

Will you be reimbursed for participating in the study?

Travel expenses will be reimbursed (0.45p/mile).

Who has reviewed the study?

The study protocol has been drawn up in agreement with the Good Clinical Practice regulations of European Union, in agreement with the Declaration of Helsinki. It has been approved by the ethic committee of Keele University and the ethic committee for the clinical experimentation (CESC) of Verona and Rovigo counties, located in the Azienda Ospedaliera Universitaria Integrata di Verona.

Will my taking part be kept confidential? How will my data be used?

Your participation in the study will be compulsorily notified in your medical records. However, the principal investigator and the research team will kept all of the research data collected during the study strictly confidential unless you make known to us information relating to a criminal offence, or that could result in harm to yourself or others. In such cases we would be obliged to report this to the appropriate authorities.

Any information which has your name, address and any other identifying information will be kept in a locked place in the Policlinico G.B. Rossi lotto I, Piano VII. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name. Your data and all information will be used and divulgated in agreement with what stated in the "informative note for the personal data protection" (see attached N° .....). Please note that, if anything new is seen on the scan, the researchers will need to pass the information on to the relevant people, such as your regular Consultant.

How will the results of the study be communicated?

At the end of the study, we will send you a letter to thank you for participating. In this letter you will also be informed whether the study was successful and if further work will follow. However, findings from this study will be submitted as part of a PhD for Ms Martini, and also written up for publications in scientific and medical journals, and presented at conferences. However, the data collected will be anonymised before any submissions or presentations. Therefore, your personal data will not be disclosed and no one will be able to link your participation to this study.

Who can I contact for further information?

If you need further information or any problem might raise during the study, please contact Dr Stefano Tamburin on 045/8124285 all days, from 08.00 am to 04.00 pm.

Dr Roberta Biundo
Unità Operativa dipartimentale di Neuropsicologia
Coordinatore unità Parkinson e disturbi del movimento
IRCCS San Camillo di Venezia
Via Alberoni, 70
30126, Lido di Venezia

Patient-Participant Information Sheet (Parkinson's)

Title of Project: Cognitive, **p**sychological and neu**ro**biological risk f**act**ors for Parkinson's disease related **I**mpulse Control Disorder: a multicentre in**ve**stigation of an Italian **P**arkinson's **d**isease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele University

Principal Investigator: Dr Roberta Biundo, Unità Operativa dipartimentale di Neuropsicologia, Coordinatore unità Parkinson e disturbi del movimento, IRCCS San Camillo di Venezia, Via Alberoni 70, 30126 Lido di Venezia, ITALIA

Research Team: Dr Stefano Tamburin, Dr Alice Martini, Dr Fabio Lugoboni, Professor Angelo Antonini, Dr Roberta Biundo, Dr Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

Dear Mr/Mrs/Ms……,

You are being invited to consider taking part in a clinical study that we are conducting in our department investigating "Impulse Control Behaviours" in people with Parkinson's.

The study has been organised jointly by Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona, Professor Angelo Antonini, Department of neuroscience, University of Padova, Dr Roberta Biundo and Dr Luca Weis, Fondazione Ospedale S.Camillo of Venice, and researchers in the School of Psychology, Keele University (United Kingdom).

Before you decide, it is important for you to understand why this research is being done and what it will involve. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part. This leaflet aims to provide you with correct and complete information to allow you to make a free, informed choice.

The investigators responsible for the information are

…… …… ……

(name) *(surname)* *(position/role)*

Keele University

IRCCS Fondazione Ospedale San Camillo

....

(name) *(surname)* *(position/role)*

What is the study about?

The movement difficulties in Parkinson's are usually effectively managed with dopamine replacement medications. However these medications can, in up to 35% of people with Parkinson's, cause impulse control behaviour.

Impulse control behaviours (ICBs) are uncontrollable urges, which are usually harmful either to the person with Parkinson's and/or to those around them. Examples include compulsive eating, compulsive gambling, compulsive shopping and repetitive behaviours that serve no purpose such as assembling and disassembling objects. ICBs may also extend to dopamine replacement medication where people take more medication than is prescribed. ICBs cause significant distress to the individual with Parkinson's, their partner/care-giver, wider families and social networks, and, in addition, may have serious social and legal consequences.

Exactly why some people with Parkinson's develop an ICB and others do not is unclear. Factors that may play a role include differences on activation in areas of the brain linked to the control of reward-related behaviour and also behaviour traits such as risk-taking and impulsivity.

The aim of this study is understand if having an ICB means some mental processes, behavioural traits and/or brain functioning are different. Therefore, we need to compare 2 groups of people with Parkinson's: those who have an ICB and those who do not.

What is the drug, procedure or treatment that is being tested?

No drug, procedure or treatment will be tested. We are only interested in comparing mental processes, behavioural traits and brain functioning in people with Parkinson's who have developed ICBs and those who do not.

Why have I been invited to take part?

You are invited to take part because you have a diagnosis of Parkinson's and we would like you to be part of one of our "Parkinson's groups". You may also have an ICB, but not necessarily. Either way, if you do have an ICB or not, we would like you to consider taking part. The assessment of ICBs will take place in the screening visit.

We are looking for people aged between 35-85 years, and have mild or moderate Parkinson's. There are other criteria that people in the "Parkinson's groups" should meet. Unfortunately, we cannot include you in this study if:

- Italian is your second language (i.e., you are not Italian-mother tongue);
- You have a severe Parkinson's (indicated by a score of 4 or 5 on the Hoehn and Yahr disease severity rating scale, assessed at the screening visit);
- You have a first degree family member with Parkinson's disease, such as parents diagnosed with Parkinson's;
- You have been diagnosed with another neurological illness (other than Parkinson's) such as Alzheimer's, Multiple Sclerosis, epilepsy;
- You are unable to provide informed consent due to cognitive decline (determined at the screening visit);
- You have a history of learning difficulty including dyslexia;
- You have been diagnosed with psychotic phenomenology such as hallucinations or lack of awareness of dyskinesias (to be determined at screening visit);
- You have incapacitating dyskinesias on a stable dose of l-dopa;
- You have a history of drug or alcohol use disorder;
- You are taking any of the following drugs:
  - Centrally acting anticholinergics;
  - Atypical antipsychotics.

This study will take place in two centers (Verona and Venice) in Italy and 68 people with Parkinson's will take part.

Do I have to take part?

No. You are free to decide if you wish to take part or not. If you do not want to take part you do not need to provide any explanation. This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future.

What will happen if I take part?

If you would like to consider the opportunity to take part in this study, you will provided with this information sheet to read and keep. You will have the opportunity to ask all information that you need before to decide to take part.

If you do decide to take part you will be asked to sign a consent form and be given a copy. Only when you will have signed the consent form, the neurologist will visit you to make sure you fulfil all the medical eligibility criteria for taking part in this study.

How the study will be conducted?

The study comprises of four visits. Below you can find detailed information related to your involvement.

What will I do if I take part?

You will be invited to attend 2 appointments.

The first will be a screening visit with the neurologist at the Parkinson's Unit, San Camillo Hospital of Venice, ground floor. The neurologist will review eligibility to take part, answer any questions about the study and if you're happy to proceed into the study, s/he will take consent. The neurologist will also complete a number of questionnaires with you concerning your current and past medical history. You will also be asked about your participation in any other study that you have taken part, now or in the past. At the end of the screening visit you will attend a visit with a psychologist. This visit will last about 90 minutes. During the visit you will complete a computerized task and Electroencephalogram (EEG) data will be recorded. EEG is a safe procedure that involves no health risks. You will wear a cap that records electric signals generated from your brain. **Please, do not wear any hair products the day of the third visit, as this may interfere with the equipment used for the EEG recording. Also, from the night before the visit please avoid any coffee, tea, chocolate, alcoholic drinks consumption, as they may alter the EEG results.**

If you do not wish to be visited with EEG, you will be given with the opportunity to complete the task without EEG being recorded. During the first appointment you will also complete a screening with a radiologist to ensure there are no contraindications for MRI scan, such as metal implanted in your body. MRI is wildly used and safe procedure as long as you do not carry the items not allowed to bring on a MRI scans. You will be then asked to lie down in a large magnetised machine and keep the eyes open for 13 minutes. During this period of time, we will record your brain activity and morphology. If anything new is seen on the scan, the researchers will need to pass the information on to the relevant people, such as your regular Consultant.

The second appointment will take place with a psychologist at the Parkinson's Unit, San Camillo Hospital of Venice, ground floor. We are aware that coming twice to the hospital might be difficult for you to arrange; if this is inconvenient for you, the psychologist can schedule the second appointment at your home. During this visit you will complete questionnaires and a number of assessments of memory, attention and decision-making. Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. **Please, bring with you your reading glasses if you use them.**

We would like to arrange for these 2 sessions to take place within one week from each other, if possible. The screening visit and EEG assessment will last together about 150 minutes (plus breaks) and the MRI scan will last 45 minutes. The second appointment will last about 60-90 minutes. There is a lot of information here! So, please do not hesitate to ask questions either by phoning us before your decide to take part, or at any point during the screening and research visits.

What do I have to do?

If you wish to take part in the study you will be visited by the neurologist to check whether you fulfil all inclusion criteria. The neurologist will answer to your questions about the study and, if you would like to take part in the study, you will be asked to sign the consent form.

What are the benefits of taking part?

There are no tangible benefits arising from this study for the participants, anyway there is evidence to suggest that some volunteers gain psychological benefit from participating in research such as increases in self-esteem and the knowledge that they are helping others.

However, we want to reduce the number of people affected by Impulse control behaviours. To do this, clinicians need to be provided with the tools for identifying people at risk of impulse control behaviour, so they can provide advice to patients about impulse control behaviours and consider them when making treatment choices. This study is the first step towards achieving this.

What are the risks?

We don't expect any problem to arise in this study. Providing there are no contraindications, MRI is safe. Please, fill very carefully the questionnaire for checking contraindications to perform MRI scan. You will be asked to remove all metal items on your body (e.g., jewellery, heir pin, body piercing, etc.). You cannot bring any metal item on the scanning room since it could be dangerous for you and the other people in the room. Some people might find the scanner claustrophobic or constrained. This feeling might pass after few minutes as you will start to get used to the space. The scanner is loud and noisy, you will be provided with headphones in order to reduce the noise. In any case, you will have a button to press if you want to terminate the session at any time, for any reason. You will also be in contact with the radiologist through the headphone that you will wear inside the scanner. As long as you follow all the safety procedures, there are no known harmful effects from the MRI scan.

EEG is a test that records electrical signals in the brain. This is a safety and non-invasive procedure. When the electrode cap is placed in your head you may experience very minimal discomfort. The researcher will try to reduce this discomfort placing carefully the cap and ensuring that it remains confortable during all the research session.

Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. If you will become anxious, distressed or upset as result of the study you can inform Dr Roberta Biundo. She will inform

you where to seek help. Psychological support is available within the San Camillo Hospital of Venice for participants who need it.

What will it happen if new information will be available?

If new information that may influence your safety or wiliness to continue with the study will be available, you will promptly informed by Dr Roberta Biundo.

Can I change my mind after agreeing to take part?

Yes. You are free to withdraw from this study at any time and without giving reason (unless your decision is due to side effects, in this case you have to provide Dr Stefano Tamburin with all the information related to the side-effects experienced). This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future. However, any data we have collected from you up until this point will be used for analysis (ex art. 13 del D.lgs 196/2003). The data we collect will be anonymized and there is no way anyone will be able to link the data with you as individual. Issues around how we keep data about you confidential and anonymous are outlined further on in this leaflet.

You can withdraw from the study informing Dr Roberta Biundo by phoning her (telephone: 041-2207537) all days, from 10.00 am to 04.00 pm.

What types of reproductive risks may I incur if I decide to take part?

There aren't any reproductive risks.

Will my general practitioner doctor be informed?

Subject to your approval, your general practitioner doctor will be informed of your participation in the study with a letter. Your general practitioner doctor will also be able to contact the principal investigator (Dr Roberta Biundo) for further information.

How long this study will last?

You participation will last about 2 weeks.

Might the study be interrupted or suspended?

Yes. The principal investigator may interrupt the study in any moment, even without your wiliness, if he considers it necessary for your safety or the correct conduction of the study. The study might also be suspended/interrupted by the Sponsor, or by the Regulatory Authority for unknown causes.

What will happen if problems occur: accident or injuries related to the study?

If any side effects, undesired effect, or damage to your health, ascribable to the study will happen, you have to promptly inform the principal investigator. He will provide you with the relevant information. Fro these issues, the Sponsor that commissioned the study has stipulate an insurance with the "Newline Underwriting Management Limited" company. In case of damages, you have to notify the insurance company within 30 days from the event. The insurance policy that covers the civil liability damages due to the study, but do not cover for the value above the maximum coverage (1.500.000 €).

Will I incur in additional costs?

No. Your participation in the study will not involve any additional costs.

Who is organising and supporting the study?

Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences; Dr Alice Martini, PhD student and psychologist, School of Psychology, Keele University; Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona; Professor Angelo Antonini neurologist at the Department of neuroscience, University of Padova; Dr Roberta Biundo, neuropsychologist at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Luca Weis, biotechinician at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Jim Grange, School

of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University. The study has been sponsored by Keele University.

Will you be reimbursed for participating in the study?

Travel expenses will be reimbursed (0.45p/mile).

Who has reviewed the study?

The study protocol has been drawn up in agreement with the Good Clinical Practice regulations of European Union, in agreement with the Declaration of Helsinki. It has been approved by the ethic committee of Keele University and the ethic committee for the clinical experimentation (CESC) of Verona and Rovigo counties, located in the Azienda Ospedaliera Universitaria Integrata di Verona.

Will my taking part be kept confidential? How will my data be used?

Your participation in the study will be compulsorily notified in your medical records. However, the principal investigator and the research team will kept all of the research data collected during the study strictly confidential unless you make known to us information relating to a criminal offence, or that could result in harm to yourself or others. In such cases we would be obliged to report this to the appropriate authorities.

Any information which has your name, address and any other identifying information will be kept in a locked place in the Policlinico G.B. Rossi lotto I, Piano VII. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name. Your data and all information will be used and divulgated in agreement with what stated in the "informative note for the personal data protection" (see attached N° .....). Please note that, if anything new is seen on the scan, the researchers will need to pass the information on to the relevant people, such as your regular Consultant.

How will the results of the study be communicated?

At the end of the study, we will send you a letter to thank you for participating. In this letter you will also be informed whether the study was successful and if further work will follow. However, findings from this study will be submitted as part of a PhD for Ms Martini, and also written up for publications in scientific and medical journals, and presented at conferences. However, the data collected will be anonymised before any submissions or presentations. Therefore, your personal data will not be disclosed and no one will be able to link your participation to this study.

Who can I contact for further information?

If you need further information or any problem might raise during the study, please contact Dr Roberta Biundo (tel: 041-2207537) all days, from 10.00 am to 04.00 pm.

Appendix AE: Questionnaire for Impulsive-compulsive disorders in Parkinson's disease

Questionario sui disturbi impulsivo-compulsivi nel morbo di Parkinson – Scala di valutazione
(Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale, QUIP-RS)

Risposte di: _____ Paziente _____ Persona che fornisce le informazioni _____ Paziente e Persona che fornisce le informazioni

Paziente / Soggetto: _____

Data: _____

1. Quanto pensa ai seguenti comportamenti (ad es. prova difficoltà ad allontanare certi pensieri o prova sensi di colpa)?

Giocare d'azzardo?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare sesso?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare acquisti?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Mangiare?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Svolgere attività o praticare hobby?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Ripetere attività semplici?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Assumere i farmaci per il morbo di Parkinson?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)

2. Avverte un senso di impellenza o desiderio per i seguenti comportamenti che sente come eccessivi o Le provocano disagio (incluso la sensazione di irrequietezza o irritabilità quando non riesce a parteciparvi)?

Giocare d'azzardo?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare sesso?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare acquisti?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Mangiare?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Svolgere attività o praticare hobby?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Ripetere attività semplici?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Assumere i farmaci per il morbo di Parkinson?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)

3. Ha difficoltà a controllare i seguenti comportamenti (ad es. aumentano nel tempo, oppure ha difficoltà a ridurli o arrestarli)?

Giocare d'azzardo?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare sesso?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare acquisti?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Mangiare?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Svolgere attività o praticare hobby?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Ripetere attività semplici?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Assumere i farmaci per il morbo di Parkinson?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)

4. Compie specificatamente delle azioni per continuare nei seguenti comportamenti (ad es. nascondere ciò che sta facendo, mentire, accumulare cose, chiedere in prestito ad altri, fare debiti, rubare o essere coinvolto/a in azioni illecite)?

Giocare d'azzardo?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare sesso?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Fare acquisti?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Mangiare?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Svolgere attività o praticare hobby?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Ripetere attività semplici?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)
Assumere i farmaci per il morbo di Parkinson?	___Mai(0)	___Raramente(1)	___Qualche volta(2)	___Spesso(3)	___Molto spesso(4)

Appendix AF: Study 3 persons with Parkinson's disease participants consent form

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA
VERONA

CONSENT FORM (PARKINSON'S)

Title of Project: Cognitive, **p**sychological and neu**ro**biological risk f**act**ors for Parkinson's disease related **I**mpulse Control Disorder: a multicentre in**ve**stigation of an Italian **P**arkinson's **d**isease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele Univeristy

Principal Investigator: Dr Stefano Tamburin, Policlinico G.B. Rossi lotto I, Piano VII, telephone: 045-8124285

Research Team: Dr Stefano Tamburin, Dr Alice Martini, Dr Fabio Lugoboni, Prof. Angelo Antonini, Dott.ssa Roberta Biundo, Dott. Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

……(place), ……/……/……

……(NAME AND SURNAME), date of birth ……/……/…… . I declare to accept to take part in the no-drugs/devices experimental study.

Consent Form (Parkinson's) V3.3 (20/04/2018)
1 for patient-participant, 1 for hospital record, 1 for site file

Please initial the box

1.	I confirm that I have read and understand the information sheet (version 5.1) dated 20th April 2018 for the above study and have had the opportunity to ask questions.	☐
2.	I have been adequately informed about the aims and procedure of the study. I am aware of the requirement of following the indication and rules that have been illustrated and that I have perfecty understood.	☐
3.	I am aware of the benefit that may arise from the study, and I am also aware of the risks related to.	☐
4.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If the withdraw is due to any side effects, undesired or unpredicted effect, I will agree to promptly inform the principal investigator about the nature and entity of these effects. Data collected until this point will be used for analysis (ex art. 13 del D.Lgs. 196/2003).	☐
5.	I declare that my consent is expressed as free decision, not influenced by money or benefit promises, or gratitude commitments or friendship and/or kinship with the principal investigator.	☐
6.	I authorise the use and divulgation of the results of this study included my clinical data. All data will be used in anonymised form and for scientific and administrative purposes only. Data will be used in compliance of the regulations concerning privacy and confidentiality.	☐
7.	I understand that sections of any of my medical notes may be looked at by authorized individuals where its relevant to my taking part in	☐

research. I give permission for these individuals to have access to my records.

8. If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analyses. ☐

9. I agree to be tested with Electroencephalography (EEG). ☐

I agree ☐ I do not agree ☐ that the news related to the study, limited to the information that may be useful for my health, will be send to my general practitioner doctor, Dr.....

.....,	...../...../.....	.....
Place	*Date*	*Participant Signature*

.....,	...../...../.....	.....
Place	*Date*	*Researcher Signature*

Keele University

IRCCS Fondazione Ospedale San Camillo

CONSENT FORM (PARKINSON'S)

Title of Project: Cognitive, **p**sychological and neu**ro**biological risk f**act**ors for Parkinson's disease related **I**mpulse Control Disorder: a multicentre in**ve**stigation of an Italian **P**arkinson's **d**isease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele Univeristy

Principal Investigator: Dr Roberta Biundo, Unità Operativa dipartimentale di Neuropsicologia, Coordinatore unità Parkinson e disturbi del movimento, IRCCS San Camillo di Venezia, Via Alberoni 70, 30126 Lido di Venezia, ITALIA

Research Team: Dr Stefano Tamburin, Dr Alice Martini, Dr Fabio Lugoboni, Prof. Angelo Antonini, Dott.ssa Roberta Biundo, Dott. Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

……..(place), ……../……../……..

……(NAME AND SURNAME), date of birth ……../……../…… . I declare to accept to take part in the no-drugs/devices experimental study.

Keele University

IRCCS Fondazione Ospedale San Camillo

Please initial the box

1.	I confirm that I have read and understand the information sheet (version 1.0) dated 20th April 2018 for the above study and have had the opportunity to ask questions.	☐
2.	I have been adequately informed about the aims and procedure of the study. I am aware of the requirement of following the indication and rules that have been illustrated and that I have perfecty understood.	☐
3.	I am aware of the benefit that may arise from the study, and I am also aware of the risks related to.	☐
4.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If the withdraw is due to any side effects, undesired or unpredicted effect, I will agree to promptly inform the principal investigator about the nature and entity of these effects. Data collected until this point will be used for analysis (ex art. 13 del D.Lgs. 196/2003).	☐
5.	I declare that my consent is expressed as free decision, not influenced by money or benefit promises, or gratitude commitments or friendship and/or kinship with the principal investigator.	☐
6.	I authorise the use and divulgation of the results of this study included my clinical data. All data will be used in anonymised form and for scientific and administrative purposes only. Data will be used in compliance of the regulations concerning privacy and confidentiality.	☐

Consent Form (Parkinson's) V1.0 (20/04/2018)
1 for patient-participant, 1 for hospital record, 1 for site file

Keele University

IRCCS Fondazione Ospedale San Camillo

7. I understand that sections of any of my medical notes may be looked at by authorized individuals where its relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

8. If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analyses. ☐

9. I agree to be tested with Electroencephalography (EEG). ☐

10. I agree to be scanned with Magnetic Resonance. ☐

I agree ☐ I do not agree ☐ that the news related to the study, limited to the information that may be useful for my health, will be send to my general practitioner doctor, Dr.....

....., .../...../..... .....

Place *Date* *Participant Signature*

....., .../...../..... .....

Place *Date* *Researcher Signature*

Consent Form (Parkinson's) V1.0 (20/04/2018)
1 for patient-participant, 1 for hospital record, 1 for site file

Appendix AG: Study 3 healthy controls information sheet

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA
VERONA

Dr Stefano Tamburin
Policlinico G.B. Rossi lotto I, Piano VII
Piazzale L.A. Scuro, 10
37134 Verona
Tel: 045/8124285

Participant Information Sheet (Healthy controls)

Title of Project: Cognitive, **p**sychological and neu**ro**biological risk f**act**ors for Parkinson's disease related **I**mpulse Control Disorder: a multicentre in**ve**stigation of an Italian **P**arkinson's **d**isease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele University

Principal Investigator: Dr Stefano Tamburin, Policlinico G.B. Rossi lotto I, Piano VII, telephone: 045/8124285

Research Team: Dr Stefano Tamburin, DrAlice Martini, Dr Fabio Lugoboni, Professor Angelo Antonini, Dr Roberta Biundo, Dr Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

Dear Mr/Mrs/Ms……,

You are being invited to consider taking part in a clinical study that we are conducting in our department investigating "Impulse Control Behaviours" in people with Parkinson's.

The study has been organised jointly by Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona, Professor Angelo Antonini, Department of neuroscience, University of Padova, Dr Roberta Biundo and Dr Luca Weis, Fondazione Ospedale S.Camillo of Venice, and researchers in the School of Psychology, Keele University (United Kingdom).

Before you decide, it is important for you to understand why this research is being done and what it will involve. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part. This leaflet aims to provide you with correct and complete information to allow you to make a free, informed choice.

The investigators responsible for the information are

…… …… ……

(name) *(surname)* *(position/role)*

…… …… ……

(name) *(surname)* *(position/role)*

What is the study about?

The movement difficulties in Parkinson's are usually effectively managed with dopamine replacement medications. However these medications can, in up to 35% of people with Parkinson's, cause impulse control behaviour.

Impulse control behaviours (ICBs) are uncontrollable urges, which are usually harmful either to the person with Parkinson's and/or to those around them. Examples include compulsive eating, compulsive gambling, compulsive shopping and repetitive behaviours that serve no purpose such as assembling and disassembling objects. ICBs may also extend to dopamine replacement medication where people take more medication than is prescribed. ICBs cause significant distress to the individual with Parkinson's, their partner/care-giver, wider families and social networks, and, in addition, may have serious social and legal consequences.

Exactly why some people with Parkinson's develop an ICB and others do not is unclear. Factors that may play a role include differences on activation in areas of the brain linked to the control of reward-related behaviour and also behaviour traits such as risk-taking and impulsivity.

The aim of this study is understand if having an ICB means some mental processes, behavioural traits and/or brain functioning are different. Therefore, we need to compare 2 groups of people with Parkinson's: those who have an ICB and those who do not. We also need to compare these Parkinson's' groups with healthy individuals who do not have Parkinson's or an ICB (or any other neurological condition).

We would like you to consider being a member of our healthy participant group.

What is the drug, procedure or treatment that is being tested?

No drug, procedure or treatment will be tested. We are only interested in comparing mental processes, behavioural traits and brain functioning in people with Parkinson's who have developed ICBs and those who do not, and healthy participants.

Why have I been invited to take part?

You are invited to take part in this study because we would like you to be part of our "Healthy participants" group. People in this group do not have Parkinson's and are aged between 35-85 years old. There are other criteria that people in the "healthy participants" group should meet. Unfortunately, we cannot include you in this study if:

- Italian is your second language (i.e., you are not Italian-mother tongue);
- You have a first degree family member with Parkinson's disease, such as parents diagnosed with Parkinson's;
- You have been diagnosed with another neurological illness such as Alzheimer's, Multiple Sclerosis, epilepsy;
- You are unable to provide informed consent due to cognitive decline (determined at the screening visit);
- You have a history of learning difficulty including dyslexia;
- You have been diagnosed with psychotic phenomenology such as hallucinations or delusions;
- You have a history of drug or alcohol use disorder;
- You have a history of ICB, such as pathological gambling or compulsive shopping;
- You are taking any of the following drugs:
  - Centrally acting anticholinergics;
  - Atypical antipsychotics.

This study will take place in two centers in Italy (Verona and Venice) and 68 people with Parkinson's and 34 healthy volunteers will take part.

Do I have to take part?

No. You are free to decide if you wish to take part or not. If you do not want to take part you do not need to provide any explanation. This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future.

What will happen if I take part?

If you would like to consider the opportunity to take part in this study, you will be provided with this information sheet to read and keep. You will have the opportunity to ask all information that you need before to decide to take part.

If you do decide to take part you will be asked to sign a consent form and be given a copy. Only when you will have signed the consent form, Dr Stefano Tamburin or Dr Alice Martini will visit you to make sure you fulfil all the eligibility criteria for taking part in this study.

How the study will be conducted?

The study comprises of three visits. Below you can find detailed information related to your involvement.

What will I do if I take part?

You will be invited to attend 2 appointments.

The first will be a screening visit with Dr Stefano Tamburin or Dr Alice Martini in the Policlinico G.B. Rossi lotto I, Piano VII. S/he will review eligibility to take part, answer any questions about the study and if you're happy to proceed into the study, S/he will take consent. Dr Stefano Tamburin or Dr Alice Martini will also complete a number of questionnaires with you concerning your current and past medical history. You will also be asked about your participation in any other study that you have taken part, now or in the past. At the end of the screening visit you will attend a visit with Dr Alice Martini, psychologist and PhD student, and a neurophysiologist in the Policlinico G.B. Rossi lotto I, Piano VII. This visit will last about 90 minutes. During the visit you will complete a computerized task and Electroencephalogram (EEG) data will be recorded. EEG is a safe procedure that involves no health risks. You will wear a cap that records electric signals generated from your brain. **Please, do not wear any hair products the day of the third visit,**

as this may interfere with the equipment used for the EEG recording. Also, from the night before the visit please avoid any coffee, tea, chocolate, alcoholic drinks consumption, as they may alter the EEG results.

If you do not wish to be visited with EEG, you will be given with the opportunity to complete the task without EEG being recorded.

The second appointment will be with Dr Alice Martini in the Policlinico G.B. Rossi lotto I, Piano VII. We are aware that coming twice to the hospital might be difficult for you to arrange; if this is inconvenient for you, Dr Alice Martini can schedule the second appointment at your home. Here you will be asked to complete questionnaires and a number of assessments of memory, attention and decision-making. Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. **Please, bring with you your reading glasses if you use them.**

We would like to arrange for these 2 appointments to take place within one week from each other, if possible. The screening visit and EEG assessment will last about 150 minutes (plus breaks), the second session will last about 60-90 minutes. There is a lot of information here! So, please do not hesitate to ask questions either by phoning us before your decide to take part, or at any point during the screening and research visits.

What do I have to do?

If you wish to take part in the study you will be visited by Dr Stefano Tamburin or Dr Alice Martini to check whether you fulfil all inclusion criteria. S/he will answer to your questions about the study and, if you would like to take part in the study, you will be asked to sign the consent form.

What are the benefits of taking part?

There are no tangible benefits arising from this study for the participants, anyway there is evidence to suggest that some volunteers gain psychological benefit from participating in research such as increases in self-esteem and the knowledge that they are helping others.

However, we want to reduce the number of people affected by Impulse control behaviours. To do this, clinicians need to be provided with the tools for identifying people at risk of impulse control behaviour, so they can provide advice to patients about impulse control behaviours and consider them when making treatment choices. This study is the first step towards achieving this.

What are the risks?

We don't expect any problem to arise in this study.

EEG is a test that records electrical signals in the brain. This is a safety and non-invasive procedure. When the electrode cap is placed in your head you may experience very minimal discomfort. The researcher will try to reduce this discomfort placing carefully the cap and ensuring that it remains confortable during all the research session.

Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. If you will become anxious, distressed or upset as result of the study you can inform Dr Stefano Tamburin. He will inform you where to seek help. Psychological support is available within the Policlinico G.B Rossi for participants who need it.

What will it happen if new information will be available?

If new information that may influence your safety or wiliness to continue with the study will be available, you will promptly informed by Dr Stefano Tamburin.

Can I change my mind after agreeing to take part?

Yes. You are free to withdraw from this study at any time and without giving reason (unless your decision is due to side effects, in this case you have to provide Dr Stefano Tamburin with all the information related to the side-effects experienced). This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future. However any data we have collected from you up until this point will be used for analysis (ex art. 13 del D.lgs 196/2003). The data we collect will be anonymized

and there is no way anyone will be able to link the data with you as individual. Issues around how we keep data about you confidential and anonymous are outlined further on in this leaflet.

You can withdraw from the study informing Dr Stefano Tamburin by phoning him (telephone: 045/8124285) all days, from 08.00 am to 04.00 pm.

What types of reproductive risks may I incur if I decide to take part?

There aren't any reproductive risks.

Will my general practitioner doctor be informed?

Subject to your approval, your general practitioner doctor will be informed of your participation in the study with a letter. Your general practitioner doctor will also be able to contact the principal investigator (Dr Stefano Tamburin) for further information.

How long this study will last?

You participation will last about 2 weeks.

Might the study be interrupted or suspended?

Yes. The principal investigator may interrupt the study in any moment, even without your wiliness, if he considers it necessary for your safety or the correct conduction of the study. The study might also be suspended/interrupted by the Sponsor, or by the Regulatory Authority for unknown causes.

What will happen if problems occur: accident or injuries related to the study?

If any side effects, undesired effect, or damage to your health, ascribable to the study will happen, you have to promptly inform the principal investigator. He will provide you with the relevant information. For these issues, the Sponsor that commissioned the study has stipulated an insurance with the "Newline Underwriting Management Limited" company. In case of damages, you have to notify the insurance company within 30 days from the event.

The insurance policy that covers the civil liability damages due to the study, but do not cover for the value above the maximum coverage (1.500.000 €).

Will I incur in additional costs?

No. Your participation in the study will not involve any additional costs.

Who is organising and supporting the study?

Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences; Dr Alice Martini, psychologist and PhD student, School of Psychology, Keele University; Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona; Professor Angelo Antonini neurologist at the Department of neuroscience, University of Padova; Dr Roberta Biundo, neuropsychologist at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Luca Weis, biotechinician at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Jim Grange, School of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University. The study has been sponsored by Keele University.

Will you be reimbursed for participating in the study?

Travel expenses will be reimbursed (0.45p/mile).

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Who has reviewed the study?

The study protocol has been drawn up in agreement with the Good Clinical Practice regulations of European Union, in agreement with the Declaration of Helsinki. It has been approved by the ethic committee of Keele University, and the ethic committee for the clinical experimentation (CESC) of Verona and Rovigo counties, located in the Azienda Ospedaliera Universitaria Integrata di Verona.

Will my taking part be kept confidential? How will my data be used?

The principal investigator and the research team will kept all of the research data collected during the study strictly confidential. Any information which has your name, address and any other identifying information will be kept in a locked place in the Policlinico G.B. Rossi lotto I, Piano VII. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name. Your data and all information will be used and divulgated in agreement with what stated in the "informative note for the personal data protection" (see attached N° .....). Please note that, if anything new is seen on the scan, the researchers will need to pass the information on to the relevant people, such as your regular Consultant.

How will the results of the study be communicated?

At the end of the study, we will send you a letter to thank you for participating. In this letter you will also be informed whether the study was successful and if further work will follow. However, findings from this study will be submitted as part of a PhD for Dr Martini, and also written up for publications in scientific and medical journals, and presented at conferences. However, the data collected will be anonymised before any submissions or presentations. Therefore, your personal data will not be disclosed and no one will be able to link your participation to this study.

Who can I contact for further information?

If you need further information or any problem might raise during the study, please contact Dr Stefano Tamburin on 045/8124285 all days, from 08.00 am to 04.00 pm.

Dr Roberta Biundo
Unità Operativa dipartimentale di Neuropsicologia
Coordinatore unità Parkinson e disturbi del movimento
IRCCS San Camillo di Venezia
Via Alberoni, 70
30126, Lido di Venezia

Participant Information Sheet (Healthy controls)

Title of Project: Cognitive, **p**sychological and neu**ro**biological risk f**act**ors for Parkinson's disease related **I**mpulse Control Disorder: a multicentre in**ve**stigation of an Italian **P**arkinson's **d**isease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele University

Principal Investigator: Dr Roberta Biundo, Unità Operativa dipartimentale di Neuropsicologia, Coordinatore unità Parkinson e disturbi del movimento, IRCCS San Camillo di Venezia, Via Alberoni 70, 30126 Lido di Venezia, ITALIA

Research Team: Dr Stefano Tamburin, Dr Alice Martini, Dr Fabio Lugoboni, Professor Angelo Antonini, Dr Roberta Biundo, Dr Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

Dear Mr/Mrs/Ms……,

You are being invited to consider taking part in a clinical study that we are conducting in our department investigating "Impulse Control Behaviours" in people with Parkinson's.

The study has been organised jointly by Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona, Professor Angelo Antonini, Department of neuroscience, University of Padova, Dr Roberta Biundo and Dr Luca Weis, Fondazione Ospedale S.Camillo of Venice, and researchers in the School of Psychology, Keele University (United Kingdom).

Before you decide, it is important for you to understand why this research is being done and what it will involve. Ask us if there is anything that is unclear or if you would like more information. It is important for you to take time to decide whether you wish to take part. This leaflet aims to provide you with correct and complete information to allow you to make a free, informed choice.

The investigators responsible for the information are

.....	.....	.....
(name)	*(surname)*	*(position/role)*
.....	.....	.....
(name)	*(surname)*	*(position/role)*

What is the study about?

The movement difficulties in Parkinson's are usually effectively managed with dopamine replacement medications. However these medications can, in up to 35% of people with Parkinson's, cause impulse control behaviour.

Impulse control behaviours (ICBs) are uncontrollable urges, which are usually harmful either to the person with Parkinson's and/or to those around them. Examples include compulsive eating, compulsive gambling, compulsive shopping and repetitive behaviours that serve no purpose such as assembling and disassembling objects. ICBs may also extend to dopamine replacement medication where people take more medication than is prescribed. ICBs cause significant distress to the individual with Parkinson's, their partner/care-giver, wider families and social networks, and, in addition, may have serious social and legal consequences.

Exactly why some people with Parkinson's develop an ICB and others do not is unclear. Factors that may play a role include differences on activation in areas of the brain linked to the control of reward-related behaviour and also behaviour traits such as risk-taking and impulsivity.

The aim of this study is understand if having an ICB means some mental processes, behavioural traits and/or brain functioning are different. Therefore, we need to compare 2 groups of people with Parkinson's: those who have an ICB and those who do not. We also need to compare these Parkinson's' groups with healthy individuals who do not have Parkinson's or an ICB (or any other neurological condition).

We would like you to consider being a member of our healthy participant group.

What is the drug, procedure or treatment that is being tested?

No drug, procedure or treatment will be tested. We are only interested in comparing mental processes, behavioural traits and brain functioning in people with Parkinson's who have developed ICBs and those who do not, and healthy participants.

Why have I been invited to take part?

You are invited to take part in this study because we would like you to be part of our "Healthy participants" group. People in this group do not have Parkinson's and are aged between 35-85 years old. There are other criteria that people in the "healthy participants" group should meet. Unfortunately, we cannot include you in this study if:

- Italian is your second language (i.e., you are not Italian-mother tongue);
- You have a first degree family member with Parkinson's disease, such as parents diagnosed with Parkinson's;
- You have been diagnosed with another neurological illness such as Alzheimer's, Multiple Sclerosis, epilepsy;
- You are unable to provide informed consent due to cognitive decline (determined at the screening visit);
- You have a history of learning difficulty including dyslexia;
- You have been diagnosed with psychotic phenomenology such as hallucinations or delusions;
- You have a history of drug or alcohol use disorder;
- You have a history of ICB, such as pathological gambling or compulsive shopping;
- You are taking any of the following drugs:
  - Centrally acting anticholinergics;
  - Atypical antipsychotics.

This study will take place in two centers in Italy (Verona and Venice) and 68 people with Parkinson's and 34 healthy volunteers will take part.

Do I have to take part?

No. You are free to decide if you wish to take part or not. If you do not want to take part you do not need to provide any explanation. This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future.

What will happen if I take part?

If you would like to consider the opportunity to take part in this study, you will be provided with this information sheet to read and keep. You will have the opportunity to ask all information that you need before to decide to take part.

If you do decide to take part you will be asked to sign a consent form and be given a copy. Only when you will have signed the consent form, the neurologist will visit you to make sure you fulfil all the eligibility criteria for taking part in this study.

How the study will be conducted?

The study comprises of four visits. Below you can find detailed information related to your involvement.

What will I do if I take part?

You will be invited to attend 2 appointments.

The first will be a screening visit with the neurologist at the Parkinson's Unit, San Camillo Hospital of Venice, ground floor. The neurologist will review eligibility to take part, answer any questions about the study and if you're happy to proceed into the study, s/he will take consent. The neurologist will also complete a number of questionnaires with you concerning your current and past medical history. You will also be asked about your participation in any other study that you have taken part, now or in the past. At the end of the screening visit you will attend a visit with a psychologist. This visit will last about 60-90 minutes. During the visit you will complete a computerized task and Electroencephalogram (EEG) data will be recorded. EEG is a safe procedure that involves no health risks. You will wear a cap that records electric signals generated from your brain. **Please, do not wear any hair products the day of the third visit, as this may interfere with the equipment used for the EEG recording. Also, from the night before the visit please avoid any coffee, tea, chocolate, alcoholic drinks consumption, as they may alter the EEG results.**

If you do not wish to be visited with EEG, you will be given with the opportunity to complete the task without EEG being recorded. During the first appointment you will also complete a screening with a radiologist to ensure there are no contraindications for MRI scan, such as metal implanted in your body. MRI is wildly used and safe procedure as long as you do not carry the items not allowed to bring on a MRI scans. You will be then asked to lie down in a large magnetised machine and keep the eyes open for 13 minutes. During this period of time, we will record your brain activity and morphology. If anything new is seen on the scan, the researchers will need to pass the information on to the relevant people, such as your regular Consultant.

The second appointment will take place with a psychologist at the Parkinson's Unit, San Camillo Hospital of Venice, ground floor. We are aware that coming twice to the hospital might be difficult for you to arrange; if this is inconvenient for you, the psychologist can schedule the second appointment at your home. During this visit you will complete questionnaires and a number of assessments of memory, attention and decision-making. Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. **Please, bring with you your reading glasses if you use them.**

We would like to arrange for these 2 sessions to take place within one week from each other, if possible. The screening visit and EEG assessment will last together about 150 minutes (plus breaks) and the MRI scan will last 45 minutes. The second appointment will last about 60-90 minutes. There is a lot of information here! So, please do not hesitate to ask questions either by phoning us before your decide to take part, or at any point during the screening and research visits.

What do I have to do?

If you wish to take part in the study you will be visited by the neurologist to check whether you fulfil all inclusion criteria. The neurologist will answer to your questions about the study and, if you would like to take part in the study, you will be asked to sign the consent form.

What are the benefits of taking part?

There are no tangible benefits arising from this study for the participants, anyway there is evidence to suggest that some volunteers gain psychological benefit from participating in research such as increases in self-esteem and the knowledge that they are helping others.

However, we want to reduce the number of people affected by Impulse control behaviours. To do this, clinicians need to be provided with the tools for identifying people at risk of impulse control behaviour, so they can provide advice to patients about impulse control behaviours and consider them when making treatment choices. This study is the first step towards achieving this.

What are the risks?

We don't expect any problem to arise in this study. Providing there are no contraindications, MRI is safe. Please, fill very carefully the questionnaire for checking contraindications to perform MRI scan. You will be asked to remove all metal items on your body (e.g., jewellery, heir pin, body piercing, etc.). You cannot bring any metal item on the scanning room since it could be dangerous for you and the other people in the room.

Some people might find the scanner claustrophobic or constrained. This feeling might pass after few minutes, as you will start to get used to the space. The scanner is loud and noisy, you will be provided with headphones in order to reduce the noise. In any case, you will have a button to press if you want to terminate the session at any time, for any reason. You will also be in contact with the radiologist through the headphone that you will wear inside the scanner. As long as you follow all the safety procedures, there are no known harmful effects from the MRI scan.

EEG is a test that records electrical signals in the brain. This is a safety and non-invasive procedure. When the electrode cap is placed in your head you may experience very minimal discomfort. The researcher will try to reduce this discomfort placing carefully the cap and ensuring that it remains confortable during all the research session.

Some of the questionnaire questions could be upsetting. If you will find some of the questions upsetting, then there is no need to answer them. If you will become anxious, distressed or upset as result of the study you can inform Dr Roberta Biundo. She will inform you where to seek help. Psychological support is available within the San Camillo Hospital of Venice for participants who need it.

What will it happen if new information will be available?

If new information that may influence your safety or wiliness to continue with the study will be available, you will promptly informed by Dr Roberta Biundo.

Can I change my mind after agreeing to take part?

Yes. You are free to withdraw from this study at any time and without giving reason (unless your decision is due to side effects, in this case you have to provide Dr Stefano Tamburin with all the information related to the side-effects experienced). This will not affect the care you receive from your doctor or any other healthcare professional either now or in the future. However any data we have collected from you up until this point will be used for analysis (ex art. 13 del D.lgs 196/2003). The data we collect will be anonymized and there is no way anyone will be able to link the data with you as individual. Issues around how we keep data about you confidential and anonymous are outlined further on in this leaflet.

You can withdraw from the study informing Dr Roberta Biundo by phoning her (telephone: 041-2207537) all days, from 10.00 am to 04.00 pm.

What types of reproductive risks may I incur if I decide to take part?

There aren't any reproductive risks.

Will my general practitioner doctor be informed?

Subject to your approval, your general practitioner doctor will be informed of your participation in the study with a letter. Your general practitioner doctor will also be able to contact the principal investigator (Dr Roberta Biundo) for further information.

How long this study will last?

You participation will last about 2 weeks.

Might the study be interrupted or suspended?

Yes. The principal investigator may interrupt the study in any moment, even without your wiliness, if he considers it necessary for your safety or the correct conduction of the study. The study might also be suspended/interrupted by the Sponsor, or by the Regulatory Authority for unknown causes.

What will happen if problems occur: accident or injuries related to the study?

If any side effects, undesired effect, or damage to your health, ascribable to the study will happen, you have to promptly inform the principal investigator. He will provide you with the relevant information. For these issues, the Sponsor that commissioned the study has stipulated an insurance with the "Newline Underwriting Management Limited" company. In case of damages, you have to notify the insurance company within 30 days from the event. The insurance policy that covers the civil liability damages due to the study, but do not cover for the value above the maximum coverage (1.500.000 €).

Will I incur in additional costs?

No. Your participation in the study will not involve any additional costs.

Who is organising and supporting the study?

Dr Stefano Tamburin, Consultant Neurologist at Azienda Ospedaliera Universitaria Integrata Verona and Associate Professor at University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences; Dr Alice Martini, psychologist and PhD student, School of Psychology, Keele University; Dr Fabio Lugoboni, doctor and head of the Addiction Unit, Department of Medicine, University Hospital of Verona; Professor Angelo Antonini neurologist at the Department of neuroscience, University of Padova; Dr Roberta Biundo, neuropsychologist at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Luca Weis, biotechinician at the Parkinson's Unit, IRCCS San Camillo di Venezia; Dr Jim Grange, School of Psychology, Keele University; Professor Nicky Edelstyn, School of Psychology, Keele University. The study has been sponsored by Keele University.

Will you be reimbursed for participating in the study?

Travel expenses will be reimbursed (0.45p/mile).

Who has reviewed the study?

The study protocol has been drawn up in agreement with the Good Clinical Practice regulations of European Union, in agreement with the Declaration of Helsinki. It has been approved by the ethic committee of Keele University, and the ethic committee for the clinical experimentation (CESC) of Verona and Rovigo counties, located in the Azienda Ospedaliera Universitaria Integrata di Verona.

Will my taking part be kept confidential? How will my data be used?

The principal investigator and the research team will kept all of the research data collected during the study strictly confidential. Any information which has your name, address and

any other identifying information will be kept in a locked place in the Policlinico G.B. Rossi lotto I, Piano VII. In addition, the data we collect from you will be fully anonymised, in that it will be assigned a unique study code rather than your name. Your data and all information will be used and divulgated in agreement with what stated in the "informative note for the personal data protection" (see attached N° .....). Please note that, if anything new is seen on the scan, the researchers will need to pass the information on to the relevant people, such as your regular Consultant.

How will the results of the study be communicated?

At the end of the study, we will send you a letter to thank you for participating. In this letter you will also be informed whether the study was successful and if further work will follow. However, findings from this study will be submitted as part of a PhD for Ms Martini, and also written up for publications in scientific and medical journals, and presented at conferences. However, the data collected will be anonymised before any submissions or presentations. Therefore, your personal data will not be disclosed and no one will be able to link your participation to this study.

Who can I contact for further information?

If you need further information or any problem might raise during the study, please contact Dr Roberta Biundo (tel: 041-2207537) all days, from 10.00 am to 04.00 pm.

Appendix AH: Study 3 healthy controls consent form

AZIENDA OSPEDALIERA UNIVERSITARIA INTEGRATA
VERONA

CONSENT FORM (HEALTHY CONTROLS)

Title of Project: Cognitive, psychological and neurobiological risk factors for Parkinson's disease related Impulse Control Disorder: a multicentre investigation of an Italian Parkinson's disease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele Univeristy

Principal Investigator: Dr Stefano Tamburin, Policlinico G.B. Rossi lotto I, Piano VII, telefono: 045-8124285

Research Team: Dr Stefano Tamburin, Dr Alice Martini, Dr Fabio Lugoboni, Prof. Angelo Antonini, Dott.ssa Roberta Biundo, Dott. Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

.....(place), .../...../.....

.....(NAME AND SURNAME), date of birth ...../...../..... . I declare to accept to take part in the no-drugs/devices experimental study.

Consent Form (Healthy controls) V3.3 (20/04/2018)
1 for participant, 1 for hospital record, 1 for site file

Please initial the box

1. I confirm that I have read and understand the information sheet (version 5.1) dated 20th April 2018 for the above study and have had the opportunity to ask questions. ☐

2. I have been adequately informed about the aims and procedure of the study. I am aware of the requirement of following the indication and rules that have been illustrated and that I have perfecty understood. ☐

3. I am aware of the benefit that may arise from the study, and I am also aware of the risks related to. ☐

4. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If the withdraw is due to any side effects, undesired or unpredicted effect, I will agree to promptly inform the principal investigator about the nature and entity of these effects. Data collected until this point will be used for analysis (ex art. 13 del D.Lgs. 196/2003). ☐

5. I declare that my consent is expressed as free decision, not influenced by money or benefit promises, or gratitude commitments or friendship and/or kinship with the principal investigator. ☐

6. I authorise the use and divulgation of the results of this study. All data will be used in anonymised form and for scientific and administrative purposes only. Data will be used in compliance of the regulations concerning privacy and confidentiality. ☐

7. I understand that sections of any of my medical notes may be looked at by authorized individuals where its relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

8. If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analyses. ☐

9. I agree to be tested with Electroencephalography (EEG). ☐

I agree □ I do not agree □ that the news related to the study, limited to the information that may be useful for my health, will be send to my general practitioner doctor, Dr.....

....., .../...../..... .....
Place *Date* *Participant Signature*

....., .../...../..... .....
Place *Date* *Researcher Signature*

Keele University

IRCCS FONDAZIONE OSPEDALE SAN CAMILLO

CONSENT FORM (HEALTHY CONTROLS)

Title of Project: Cognitive, **p**sychological and neu**ro**biological risk f**act**ors for Parkinson's disease related **I**mpulse Control Disorder: a multicentre in**ve**stigation of an Italian **P**arkinson's **d**isease cohort (PROACTIVE-PD)

Protocol Number: PROACTIVE-PD-001

Sponsor: Keele Univeristy

Principal Investigator: Dr Roberta Biundo, Unità Operativa dipartimentale di Neuropsicologia, Coordinatore unità Parkinson e disturbi del movimento, IRCCS San Camillo di Venezia, Via Alberoni 70, 30126 Lido di Venezia, ITALIA

Research Team: Dr Stefano Tamburin, Dr Alice Martini, Dr Fabio Lugoboni Prof. Angelo Antonini, Dott.ssa Roberta Biundo, Dott. Luca Weis, Dr Jim Grange and Professor Nicky Edelstyn.

……(place), ……/……/……

……(NAME AND SURNAME), date of birth ……/……/…… . I declare to accept to take part in the no-drugs/devices experimental study.

Keele University

IRCCS FONDAZIONE OSPEDALE SAN CAMILLO

Please initial the box

1.	I confirm that I have read and understand the information sheet (version 1.0) dated 20th April 2018 for the above study and have had the opportunity to ask questions.	☐
2.	I have been adequately informed about the aims and procedure of the study. I am aware of the requirement of following the indication and rules that have been illustrated and that I have perfecty understood.	☐
3.	I am aware of the benefit that may arise from the study, and I am also aware of the risks related to.	☐
4.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If the withdraw is due to any side effects, undesired or unpredicted effect, I will agree to promptly inform the principal investigator about the nature and entity of these effects. Data collected until this point will be used for analysis (ex art. 13 del D.Lgs. 196/2003).	☐
5.	I declare that my consent is expressed as free decision, not influenced by money or benefit promises, or gratitude commitments or friendship and/or kinship with the principal investigator.	☐
6.	I authorise the use and divulgation of the results of this study. All data will be used in anonymised form and for scientific and administrative purposes only. Data will be used in compliance of the regulations concerning privacy and confidentiality.	☐

Keele University

IRCCS Fondazione Ospedale San Camillo

7. I understand that sections of any of my medical notes may be looked at by authorized individuals where its relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

8. If I decide to withdraw from the study, I agree to my anonymised data being used in subsequent analyses. ☐

9. I agree to be tested with Electroencephalography (EEG). ☐

10. I agree to be scanned with Magnetic Resonance Imaging. ☐

I agree ☐ I do not agree ☐ that the news related to the study, limited to the information that may be useful for my health, will be send to my general practitioner doctor, Dr.....

....., .../...../..... .....

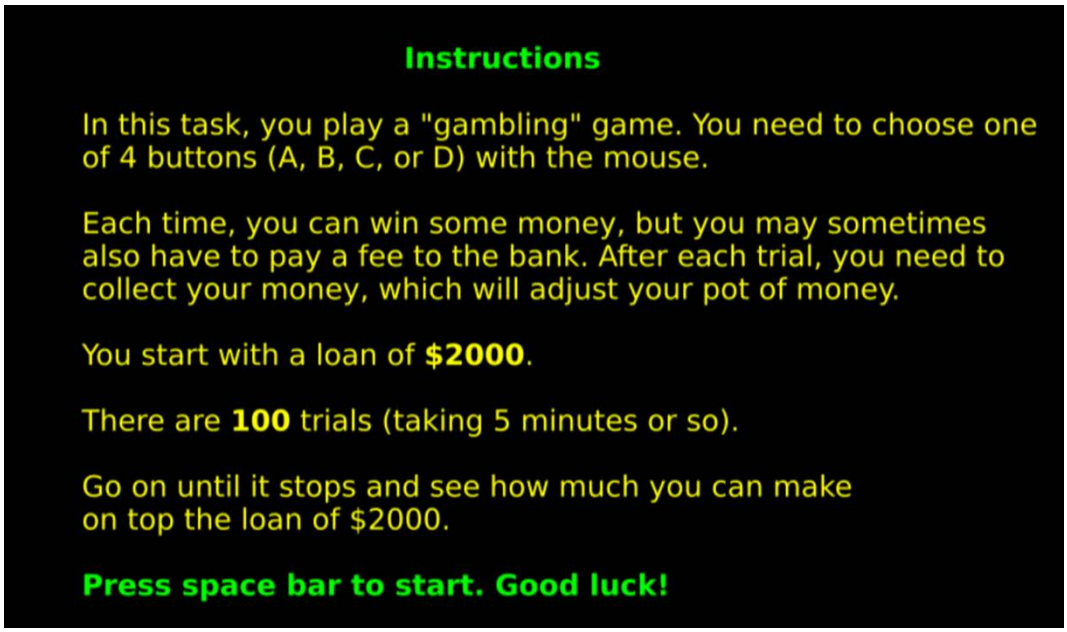
Place *Date* *Participant Signature*

....., .../...../..... .....

Place *Date* *Researcher Signature*

Consent Form (Healthy controls) V1.0 (20/04/2018)
1 for participant, 1 for hospital record, 1 for site file

Appendix AI: Iowa Gambling Task



Appendix AL: Phonological Fluency test

FLUENZA SU CATEGORIA FONEMICA

Data:	Cognome:	Nome:

F	L	P
TOT:	TOT:	TOT:

Punteggio grezzo:
Punteggio corretto:
Punteggio equivalente:
Osservazioni:

Appendix AM: Digit Span Sequencing Task

3. Memoria di cifre *(continuazione)*

Riordinamento di cifre

Interrompere dopo 1 punteggio di 0 ad entrambe le prove di un item.

	Item	Prova	Risposta corretta	Risposta	Punti prova	Punti item
16-90	Es.	2-3-1	1-2-3			
		5-2-2	2-2-5			
16-90	1.	1-2	1-2		0 1	0 1 2
		4-2	2-4		0 1	
	2.	3-1-6	1-3-6		0 1	0 1 2
		0-9-4	0-4-9		0 1	
	3.	8-7-9-2	2-7-8-9		0 1	0 1 2
		4-8-7-1	1-4-7-8		0 1	
	4.	2-6-9-1-7	1-2-6-7-9		0 1	0 1 2
		3-8-3-5-8	3-3-5-8-8		0 1	
	5.	2-1-7-4-3-6	1-2-3-4-6-7		0 1	0 1 2
		6-2-5-2-3-4	2-2-3-4-5-6		0 1	
	6.	7-5-7-6-8-6-2	2-5-6-6-7-7-8		0 1	0 1 2
		4-8-2-5-4-3-5	2-3-4-4-5-5-8		0 1	
	7.	5-8-7-2-7-5-4-5	2-4-5-5-5-7-7-8		0 1	0 1 2
		9-4-9-7-3-0-8-4	0-3-4-4-7-8-9-9		0 1	
	8.	5-0-1-1-3-2-1-0-5	0-0-1-1-1-2-3-5-5		0 1	0 1 2
		2-7-1-4-8-4-2-9-6	1-2-2-4-4-6-7-8-9		0 1	

SRC (Max = 9)	

Riordinamento di cifre (RC) Punteggio grezzo totale (Massimo = 16) ☐

Punteggio grezzo totale della Memoria di cifre (Massimo = 48) ☐

Appendix AN: Stroop Color and Word Test

TEST DI STROOP – Versione breve

Taratura Caffarra et al., 2002

1. Lettura *(W)*		2. Denominazione *(C)*		3. Interferenza *(CW)*	
Item	Errore	Item	Errore	Item	Errore
VERDE		**BLU**		**ROSSO** (verde)	
ROSSO		**ROSSO**		**BLU** (rosso)	
BLU		**BLU**		**ROSSO** (blu)	
ROSSO		**VERDE**		**VERDE** (rosso)	
VERDE		**ROSSO**		**ROSSO** (verde)	
BLU		**BLU**		**VERDE** (blu)	
ROSSO		**VERDE**		**BLU** (rosso)	
VERDE		**ROSSO**		**VERDE** (rosso)	
ROSSO		**BLU**		**ROSSO** (verde)	
BLU		**ROSSO**		**VERDE** (blu)	
BLU		**ROSSO**		**ROSSO** (blu)	
ROSSO		**VERDE**		**BLU** (rosso)	
BLU		**BLU**		**ROSSO** (blu)	
VERDE		**ROSSO**		**BLU** (verde)	
ROSSO		**VERDE**		**VERDE** (rosso)	
BLU		**ROSSO**		**ROSSO** (blu)	
VERDE		**BLU**		**BLU** (verde)	
ROSSO		**VERDE**		**VERDE** (rosso)	
BLU		**BLU**		**ROSSO** (blu)	
ROSSO		**VERDE**		**BLU** (rosso)	
VERDE		**BLU**		**BLU** (verde)	
BLU		**VERDE**		**VERDE** (blu)	
VERDE		**ROSSO**		**BLU** (verde)	
BLU		**BLU**		**ROSSO** (blu)	
ROSSO		**ROSSO**		**BLU** (rosso)	
VERDE		**VERDE**		**ROSSO** (verde)	
ROSSO		**ROSSO**		**BLU** (rosso)	
BLU		**BLU**		**VERDE** (blu)	
VERDE		**ROSSO**		**ROSSO** (verde)	
ROSSO		**VERDE**		**VERDE** (rosso)	

TOTALE ERRORI	**/30**	**/30**	**/30**
TEMPO IMPIEGATO	**sec.**	**sec.**	**sec.**

EFFETTO INTERFERENZA ERRORI E3 – [(E1 + E2)/2]		EFFETTO INTERFERENZA TEMPO T3 – [(T1 + T2)/2]	
PUNTEGGIO CORRETTO		PUNTEGGIO CORRETTO	
PUNTEGGIO EQUIVALENTE		PUNTEGGIO EQUIVALENTE	
Cut-off Eff. Interf. Errori	***4,24***	***Cut-off Eff. Interf. Tempo***	***39,62***

Appendix AO: Prose Memory

MEMORIA DI PROSA - immediata

Ora le leggerò un raccontino; lei mi dovrà ascoltare attentamente perché alla fine dovrà ripetermi tutto quello che ricorda.

	Imm.	Diff.		Imm.	Diff.		Imm.	Diff.
Anna	☐	☐	dei carabinieri	☐	☐	che non mangiavano	☐	☐
Pesenti	☐	☐	che la sera	☐	☐	da due	☐	☐
di Bergamo	☐	☐	precedente	☐	☐	giorni	☐	☐
che lavora	☐	☐	mentre rincasava	☐	☐	e doveva pagare	☐	☐
come donna	☐	☐	era stata aggredita	☐	☐	l'affitto.	☐	☐
delle pulizie	☐	☐	e derubata	☐	☐	I militari	☐	☐
in una ditta	☐	☐	di 150 euro.	☐	☐	commossi	☐	☐
di costruzioni	☐	☐	La poveretta	☐	☐	fecero una colletta.	☐	☐
riferì	☐	☐	aveva quattro	☐	☐			
al maresciallo	☐	☐	bambini piccoli	☐	☐			

Memoria immediata - Punti ...../28 **Memoria differita** - Punti ...../28

Report

Ora le rileggerò questo stesso raccontino. Lei cerchi di tenerlo in mente perché più avanti le chiederò di ripeterlo.

MEMORIA di PROSA – DIFFERITA

MEMORIA DI PROSA - immediata

Ora le leggerò un raccontino; lei mi dovrà ascoltare attentamente perché alla fine dovrà ripetermi tutto quello che ricorda.

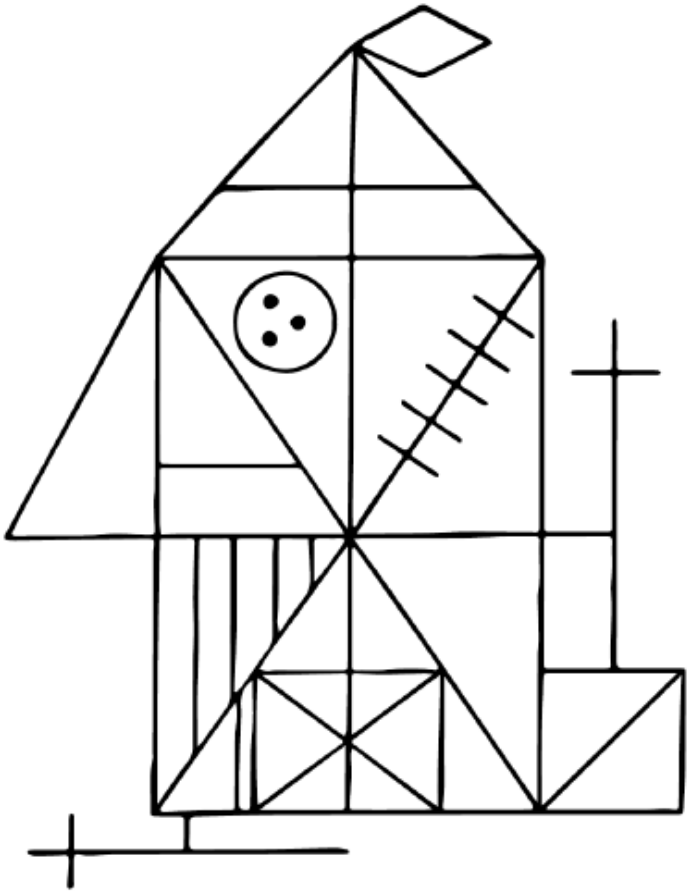
	Imm.	Diff.		Imm.	Diff.		Imm.	Diff.
Anna	☐	☐	dei carabinieri	☐	☐	che non mangiavano	☐	☐
Pesenti	☐	☐	che la sera	☐	☐	da due	☐	☐
di Bergamo	☐	☐	precedente	☐	☐	giorni	☐	☐
che lavora	☐	☐	mentre rincasava	☐	☐	e doveva pagare	☐	☐
come donna	☐	☐	era stata aggredita	☐	☐	l'affitto.	☐	☐
delle pulizie	☐	☐	e derubata	☐	☐	I militari	☐	☐
in una ditta	☐	☐	di 150 euro.	☐	☐	commossi	☐	☐
di costruzioni	☐	☐	La poveretta	☐	☐	fecero una colletta.	☐	☐
riferì	☐	☐	aveva quattro	☐	☐			
al maresciallo	☐	☐	bambini piccoli	☐	☐			

Memoria immediata - Punti ...../28 **Memoria differita** - Punti ...../28

Report

Ora le rileggerò questo stesso raccontino. Lei cerchi di tenerlo in mente perché più avanti le chiederò di ripeterlo.

Appendix AP: Rey-Osterrieth complex figure test



Appendix AQ: Italian Dimensional Apathy Scale

Versione Italiana-Dimensional Apathy Scale (I-DAS)

Nome…….. Età…… Sesso…….
Stato civile…… Scolarità……..

Scegli la risposta che meglio descrive **come ti sei sentito, come ti sei comportato o cosa hai pensato** nelle seguenti situazioni, considerando quanto spesso ti ci sei trovato nel mese scorso (cerchia la frase più adatta):

1. Ho bisogno di un po' d'incoraggiamento per dare inizio alle cose (per far partire le cose)
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

2. *Contatto i miei amici
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

3. *Esprimo le mie emozioni
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

4. *Penso a nuove cose da fare durante il giorno
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

5. *Mi preoccupo di cosa provi la mia famiglia
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

6. Mi ritrovo a guardare nel vuoto
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

7. *Prima di fare qualcosa, penso a come gli altri si sentirebbero se lo facessi
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

8. *Pianifico in anticipo le mie attività quotidiane
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

9. *Quando ricevo cattive notizie mi sento male
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

10. *Sono capace di mantenere l'attenzione su un compito fino a quando non è finito
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

11. Mi manca la motivazione
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

12. Difficilmente comprendo e condivido le emozioni degli altri
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

13. *Mi prefiggo degli obiettivi
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

14. *Provo a fare cose nuove
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

15. Non mi interessa delle emozioni che provano gli altri in risposta al mio comportamento
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

16. *Passo all'azione sulle cose che ho pensato durante il giorno
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

17. Quando svolgo un compito molto impegnativo, ho difficoltà a capire che cosa devo fare
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

18. *Mi tengo occupato
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

Punteggio totale DAS: _____

19. Quando faccio più cose contemporaneamente mi confondo facilmente
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

20. *Mi emoziono facilmente quando guardo qualcosa di triste o felice alla TV
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

21. Ho difficoltà a concentrarmi sulle cose
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

22. * Prendo decisioni di mia spontanea volontà
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

23. Mi distraggo facilmente
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

24. Non provo nessuna emozione rispetto a quello che succede intorno a me
- Quasi sempre
- Spesso
- Occasionalmente
- Quasi mai

Appendix AR: Study 5 List of studies excluded at the full-text screening stage with reason(s) for their exclusions

Authors (year)	Reason(s) for exclusion
Balconi et al. [1]	Unclear whether the ICB- group includes also patients with ICBs other than GD (i.e., QUIP-rs above the cut-off).
Navalpotro et al. [2]	No between groups comparison.
Filip et al. [3]	No ICBs diagnostic procedure defined, therefore it is not clear whether the PD control group was screened for ICBs presence.
Voon et al. [4]	Patients with substance abuse disorder were included; participants included in multiple studies/double.
Voon et al. [5]	Patients with substance abuse disorders were included; participants included in multiple studies/double.
Van Eimeren et al. [6]	Unclear whether patients with ICBs history, other than GD, were included in the ICB- control group; No all ICBs types screened.
Rao et al. [7]	Dementia not clearly excluded.
Cerasa et al. [8]	Patients screened only for GD (i.e., control group might include patients with other types of ICBs).
Yoo et al. [9]	Patients screened only for punding (i.e., control group might include patients with other types of ICBs).

Legend. ICBs: impulsive compulsive behaviours; PD: Parkinson's disease; GD: gambling disorder; QUIP-rs: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease rating scale.

References

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Appendix AS: Study 6 List of studies excluded at the full-text screening stage with reason(s) for exclusions

Authors (year)	Reason(s) for exclusion
Cilia et al. [1]	Brain perfusion
Cilia et al. [2]	Double: Eleven of 15 PwP with GD have been previously described in detail in Cilia et al. (2008)
Joutsa et al. [3]	Double: the group comparisons of the imaging data of PwP with and without ICBs have been published elsewhere (Joutsa et al., 2012)
Kobayakawa et al. [4]	No ICBs; No PET/SPECT
O'Sullivan et al. [5]	Double: Data from six of PwP with ICB have been published elsewhere (Wu et al., 2015)
Ray et al. [6]	Extrastiatal study
Smith et al. [7]	OR and incidence only
Van Eimeren et al. [8]	Brain perfusion
Vriend et al. [9]	No PET/SPECT data: SPECT only during the baseline visit when PwP were unmedicated.

Legend. ICBs: impulsive compulsive behaviours; PwP: Persons with Parkinson's disease; GD: gambling disorder; PET: positron emission tomography; SPECT, single-photon emission computed tomography.

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