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Anxiety predicts impulsive-compulsive behaviours in Parkinson’s Disease: clinical relevance and theoretical implications

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| Abstract: | Patients with Parkinson’s Disease (PD) often present symptoms of anxiety, depression and apathy. These negative affect manifestations have been recently associated with the presence of Impulsive-Compulsive Behaviours (ICBs). However, their relation with the use of dopamine replacement therapy (DRT), a renewed risk factor for ICBs, is still not fully understood. Elucidating the role of these different ICBs predictors in PD could inform both prevention/intervention recommendations as well as theoretical models. In the present study we have analyzed data collected in 417 PD patients, 50 patients with parkinsonian symptoms but with scan without evidence of dopaminergic deficit (SWEDD), and 185 healthy controls (HC). We examined their clinical profile over a two-year’s time window, investigating the role of both negative affect and DRT on ICBs. Results confirmed the presence of higher levels of anxiety in both the clinical groups, and of higher level of ICBs in SWEDD patients, respect to both PD and HC. Mixed model analysis’ results also revealed a significant association between anxiety and ICBs in the SWEDD patients, who did not take any DRT. Findings suggest the independence between the role of anxiety and DRT in ICBs development and provide new evidence for the motivational opponency theoretical framework. |

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Highlights

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* Patients with Parkinson’s Disease with- and- without dopaminergic deficits show higher level of anxiety symptoms when compared with healthy controls
* Anxiety (STAI-Y total score) significantly predicts impulsive-compulsive behavior in patients with Parkinson’s Disease without dopaminergic deficits
* Anxiety management may represent important prevention strategy for the development of impulsive-compulsive behavior in Parkinson’s Disease

Abstract

# Abstract

Patients with Parkinson’s Disease (PD) often present symptoms of anxiety, depression and apathy. These negative affect manifestations have been recently associated with the presence of Impulsive Compulsive Behaviours (ICBs). However, their relation with the use of dopamine replacement therapy (DRT), a renewed risk factor for ICBs, is still not fully understood. Elucidating the role of these different ICBs predictors in PD could inform both prevention/intervention recommendations as well as theoretical models.

In the present study, we have analyzed data collected in 417 PD patients: 50 patients with parkinsonian symptoms but with scan without evidence of dopaminergic deficit (SWEDD), and 185 healthy controls (HC). We examined each patient’s clinical profile over a two-year time window, investigating the role of the negative affect on both DRT on ICBs. Results confirmed the presence of higher levels of anxiety in both the clinical groups, and of higher level of ICBs in SWEDD patients, respect to both

PD and HC. Mixed model analyses revealed results supporting a statistically significant association between anxiety and ICBs in the SWEDD patients, who did not take any DRT. Findings suggest the independence between the role of anxiety and DRT in ICBs development and provide new evidence for the motivational opponency theoretical framework.

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## **1. Introduction**

Behavioural impulsivity and negative affect manifestations are common symptoms in several disorders mainly characterised by abnormal dopaminergic modulation, such as gambling disorder (e.g., Mallorquí-Bagué, et al., 2019), obsessive compulsive disorder (Dong et al., 2020) attention-deficit/hyperactivity disorder (Sagvolden et al., 2005; Paloyelis et al., 2009),

Huntingdon’s disease (e.g., Johnson et al., 2017) and Parkinson’s Disease (e.g., Antonelli et al., 2011; Martini et al., 2018). At the same time, they are also common in both Mood and Anxiety Disorders (DSM-5) characterized by abnormal functioning of the serotoninergic system, as exemplified in disorders such as bipolar disorder II (e.g., Perugi et al., 1999; Ballani et al., 2012) major depressive disorder (e.g., Moustafa et al., 2017; Fields et al., 2021), cyclothymic disorder (e.g., Perugi et al., 2011), separation anxiety disorder (e.g., Kayha & Taskale, 2019), panic disorder such as agoraphobia (e.g., Besirli, 2018), and generalized anxiety disorder (e.g., Taylor et al., 2008; Moustafa et al., 2017; Ferreira-Garcia et al., 2019; Gecaite-Stonciene et al., 2020).

Recent neuroscientific evidence has further established that both dopamine (DA) and serotonin (5-HT) play a crucial role in the regulation of impulsive behavior (Dalley and Roiser, 2012) and negative affect manifestations such as depression, anxiety, and apathy (Peciña et al., 2017; de la Mora et al., 2010; Dunlop and Nemeroff, 2007). Moreover, as suggested by the motivational opponency theoretical framework, the two neurotransmitters would have an interactive partnership, with the 5-HT mostly involved in coding the aversive behaviours, and the DA playing a critical role in coding the appetitive ones (Boureau, & Dayan, 2011; Boureau, et al., 2011; Tops et al., 2009; Daw et al., 2002).

Despite this framework has been supported by important results coming from animal and robotic studies (Cardinal et al, 2001; Winstanley et al, 2003, Krichmar, 2013), evidence from human pathological conditions would provide importantly complementary insights to the study of the relation between impulsivity and negative affect. Indeed, while the interaction of DA and 5-HT in the regulation of both approach and avoidance behavior would explain the transdiagnostic evidence of these two symptomatology across different diseases, an unresolved issue is the fact that the mechanisms on which each symptom relies appear to be orthogonal. On the one hand, negative affect is associated with avoidance behaviour and an excessive focus on threat-related stimuli, and, on the other hand, approach and impulsive behaviours are related to elevated levels of physiological arousal (Phaf et al., 2014). Hence, studies investigating the relation between impulsivity and negative affect manifestations in humans would be extremely valuable from both a theoretical and clinical point of view.

One of the clinical conditions where both these symptoms are present is Parkinson’s Disease (PD). A neurodegenerative disease caused by an initial DA depletion in the midbrain, PD is a multisystem disorder involving different anatomical structures and neurotransmitters such as 5-TH, and is characterized not only by motor abnormalities, but also by several non-motor ones, including negative affect manifestations, such as depression, anxiety and apathy, as well as impulsive compulsive behaviors (ICBs).

Negative affect manifestations are indeed very common in PD patients (for a review, see Dan et al., 2017; Garlovsky et al., 2016; Langston, 2006) and have been associated with the pathophysiology of the disease itself and, more specifically, with the impairment of both the DA and the 5-HT systems (Jolig at el., 2019; Thobois et al., 2017; Maillet et al., 2017; Menza et al., 1999). Indeed, their incidence exceeds the rates in both the general population as well as in other chronic and/or neurodegenerative diseases (Chaduri et al., 2006; Nègre-Pagès et al., 2010; Stein et al. 1990), with up to 89% of PD patients having at least one negative affect symptom(Aarsland et al., 2007). Recent statistics indicated that that while depression prevalence (Chuquilín-Arista et al., 2020) widely varies from 2.7% to 90% (Aarsland et al., 2012), and apathy affects between 30% and 51% of PD patients (Radakovic et al., 2018), anxiety is one of the most frequent neuropsychiatric disorders in PD, with higher incidence than in other chronic diseases (38% vs 11%) (Pincus & Tucker, 2002). These symptoms are also highly comorbid in PD (Dan et al., 2017) and have been associated with negative health outcomes(Barone et al., 2009). Recently, it has been shown that negative affect manifestations represent a risk factor for the development of ICBs in PD patients (Jesus et al., 2021; Zhang et al., 2021; Scott et al., 2020; Vriend, 2018; Martini et al., 2018). Symptoms of ICB in PD patients include, namely, pathological gambling, hypersexuality, compulsive shopping and eating. Yet, despite being object of numerous studies so far, ICB’s underlying neural mechanisms are still not fully understood (Zhang et al., 2021; Paz-Alonso et al., 2020; Nombela et al., 2014). Indeed, together with the aforementioned studies link negative affect to ICBs, several previous evidence recently reviewed by Zhang and colleagues (2021) identified in the dopaminergic replacement therapy (DRT), especially DA-agonists, the main risk factor for the development of ICBs in PD patients (Zhang et al., 2021; Nirenberg & Waters, 2006; Melchionda & Cuzzolaro, 2019; De Micco et al., 2108). There is a complex interplay between the pathophysiology of PD and the use DRT. Specifically, while it provides a major symptomatic relief from the PD motor symptoms, recent neuroimaging studies have illustrated that DRT can disrupt the homeostatic relationship between the ventral striatum and the dorsal striatum (Cools et al., 2006; Vaillancourt et al., 2013; Nonnekes et al, 2016; Vo et al., 2018; Dogan et al., 2021).

The imbalance between ventral and dorsal striatal dopaminergic activity would consequently lead to deficient inhibitory capacity and aberrant reward processing, which may be linked to the development of ICBs in around 40% of PD patients in the past five (Cao et al., 2021; Marković et al., 2020; Martini et al., 2020).

The association of ICBs with both DRT and negative affect gives rise to a main question: are these two risk factors equally important? In other words, is there a prevalent role of one respect to the other one? Unfortunately, studies conducted so far were not able to answer this question yet, and because of the high prevalence of negative affect manifestations in PD, and of the almost essential use of DRT in PD patients. Thus, in order to disentangle the effect of DRT from the one of the negative affect manifestations, new evidence on ICBs in PD is needed. The present study aims to overcome this limitation studying ICBs in patients affected by a particular clinical condition called Scan Without Evidence of Dopaminergic Deficit (SWEDD). This condition is also often referred to as “non-DA deficient PD,” since patients with a SWEDD diagnosis show a similar Parkinsonian symptomatology, but do not present any deficiency of the DA active transporter (DAT) binding. Although the actual etiology of this clinical condition still controversial (Lee et al., 2021; Erro et al., 2016), the lack of DA-deficit, the well documented presence of negative affect manifestations (Marek et al., 2018; Taylor et al., 2016; Demerdash et al., 2014) as well as the fact that the majority of SWEDD patients is not treated with a DRT, makes this condition the ideal one for the purpose of the present study. We analyzed longitudinal data collected in a group of unmedicated SWEDD patients, a group of PD patients, and a sample of neurologically healthy control (HC). We hence investigated the presence of ICBs symptoms in these three groups, over a two-year’s time window, and we examined their relationship with negative affect manifestations, the DRT used by PD patients, as well as other indices of disease severity, such as motor and cognitive deficits.

To our knowledge, this is the first study examining the predictor of ICBs comparing PD and SWEDD patients. For this reason, we did not formulate specific predictions, but we hypothesized that either the presence of ICBs in SWEDD or their relation with negative affect manifestations, would be a result towards the independency between negative affect and DRT on ICBs development in PD patients.

## **2. Methods**

### 2.1 Participants

Data used in the preparation of this article were obtained from the [Parkinson's Progression Marker Initiative](https://www.ppmi-info.org/)  (PPMI) database (Marek et al., 2011), an ongoing observational, international, multicenter study aiming to study PD progression with longitudinal follow-up in a large cohort. PPMI enrolled patients with early and untreated (de novo) PD, patients without evidence of dopaminergic deficits (SWEDD) as well as healthy controls (HC) of similar age (Marek et al., 2018).

This study initially considered data from 64 SWEDD patients, 423 PD patients, and 197 HC. From these groups, we excluded participants who, at either the 12- or 24-months follow-up, changed diagnosis and/or developed other neurological disorders, as well as SWEDD patients who took any DRT. The final sample consisted therefore in 50 SWEDD patients, 417 PD patients, and 185 HC at baseline (T0). Attrition rates at 12 (T1) and 24 months (T2) are reported in Figure 1. The study was approved by the Institutional Review Board at each site, and participants provided written informed consent. Data were downloaded on May 2020.

## Figure 1 around here please

### 2.2 Selected clinical measures

As measure of ICBs, scores at the Questionnaire for Impulsive Compulsive Disorders in PD (QUIP-Short; Weintraub et al., 2009) were considered as the main outcome measure. As indices of negative affect manifestation, the total score from the State-Trait Anxiety Inventory Form Y (STAI-Y; Spielberger et al., 1983) was utilized as a means to measure levels of anxiety. The Geriatric Depression Scale (GDS-15; Sheikh & Yesavage, 1986) was used to measure the index of depressive symptomatology, and the part I apathy scale of the Movement Disorder Society- Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) was selected for this study to serve as a means to quantify severity of symptoms related to apathy, as per Goetz et al. 2008.

As an index of general cognitive status, the Montreal Cognitive Assessment Test (MoCA; Nasreddine et al. 2005) score was employed, while the scores at the Benton Line Orientation Judgement Test (BLOJT; Benton & Hamsher, 1978) were considered as an index of visuospatial processing. Composite measures of memory and executive function were obtained as mean of standardize scores of the following tests: Symbol Digit Modalities test (Smith, 1973), Semantic Fluency test (Spreen & Benton, 1977) and Wechsler Memory Scale III Letter Number Sequencing (Wechsler 1997) for the executive function score; Hopkins Verbal Learning Test–Revised (HVLT) for Delayed Recall and Delayed Recognition (Benedict et al., 1998) for the memory one. For PD patients only, information on the use of DRT was obtained considering both the total levodopa equivalent daily dose (LEDD) and the use of dopaminergic agonist (yes or no). For both patients’ groups, disease duration in years and motor symptoms severity (MSD-UPDRS part III score) were also considered (see Tables 1-3).

### 2.3 Statistical analysis

In a first set of analyses, the presence of between groups differences in each of the outcome measure considered and in three time-points was assessed conducting a set of multivariate analysis of variance (MANOVA) and Chi square tests, respectively for the continuous and the categorical ones. We employed Tukey's honestly significant difference test (HSD test) for post-hoc analyses, and, to reduce the chance of Type I error, we have applied Bonferroni correction for multiple comparisons.

In a second set of analysis, conducted considering SWEDD and PD patient’s data, a mixed model regression was performed to assess the predictors of ICBs (QUIP-Short scores) in two year’s time window. Specifically, a first model was conducted with the fixed factors Group (SWEDD vs PD) and Time (Time 0 vs Time 1 vs Time 2), and with the following variables as covariates: age, gender, years of education, current general cognitive status (MoCA score), depression (GDS score), anxiety (STAY-Y score), apathy (MSD-UPDRS scale I score), visuospatial processing (BLOJT score), memory and executive function composite scores; disease duration, motor symptom severity (UPDRS-III score); LEDD and use of DA-agonist.

Participant identification number was entered as a random factor.

### 3. Results

**3.1 *Between group differences at baseline (T0).***

As shown in Table 1, the three groups were matched for age, gender and education.

Despite the data suggested a group difference in terms of ICBs, with higher levels in the SWEDD group compared to both PD and HC, factor group resulted to be not significant after applying Bonferroni correction for multiple comparisons (p = .007; cut of p-value = .004). On the contrary, group differences emerged when analyzing negative affect manifestations, with both SWEDD and PD groups showing more symptoms of anxiety and depression when compared to the HC (for both, p< .001).

Results also showed that current general cognitive status (MoCA score), as well as scores at memory and executive function tests were significantly lower in both SWEDD and PD patient groups, when compared to the HC (for both, p <.001). Finally, motor symptoms severity was significantly higher in PD patients, when compared to the SWEDD (p <.001). No other group difference emerged as statistically significant (see Table 1 for a detailed results description). For the sake of clarity, LEDD and DA-agonist use data are not present in Table 1 because both PD and SWEDD patients were unmedicated at baseline.

## Table 1 around here please

### 3.2 Between group differences after 1 year (T1)

Attrition rates from baseline to T1, for the SWEDD, PD, and HC were 12.9%, 21.8% and 6.5%, respectively. Despite this, the three groups remained matched for demographic characteristics. The neuropsychological and neuropsychiatric profiles evident at baseline were replicated at T1, with two exceptions. The first concerns the ICBs symptomatology, that in

SWEDD, with significantly higher levels if compared with both HC and PD patients’ group (p <.001). The second concerns the MoCA score, where a significant difference was present only between PD patients and HC in this time point (p <.001). Motor symptoms continued to be more severe in PD patients when compared with the SWEDD (p <.001), despite in this time point, 54% of the patients was under DRT, and the 20% of this sub-group under DAagonist (see Table 2).

## Table 2 around here please

### 3.3 Between group differences after 2 years (T2)

Attrition rates from T1 to T2, for SWEDD, PD and HC were 6.4%, 7.6% and 6.8%, respectively. The three groups remained matched for demographic features, and there were no changes in the relative status of neuropsychological, neuropsychiatric and clinical features, apart from the change in ICBs levels in SWEDD, which despite appearing to be higher if compared with both PD and HC groups, were not significantly different (p=.05; see Table 3 for a detailed results summary).

## Table 3 around here please

### 3.4. ICBs predictors in SWEED and PD

The results of regression mixed models are presented in Tables 4 and 5. The first model showed that, between the covariates considered, only the presence of anxiety symptoms emerged as significant predictor of ICBs in the two-year’s time windows considered (respectively: B= 0.0280, *t*= 2.78, *p*< .01). Importantly, the presence of ICBs presence were also predicted by the fixed factor Group (B= 0.2953, *t*= 3.70, *p*< .001). Therefore, two post-hoc models were run separately for each patient’s group. Results of these two models showed a significant role of anxiety in explaining ICBs in SWEDD patients (B= 0.001, *t*= 2.63, *p*< .01), and a similar trend in PD patients, despite the result was not significant after correcting for multiple comparison (B= 0.05, *t*= 4.08, *p*< .005; see Figure 2). In each of the two models, no other predictor emerged to significantly predict ICBs.

## Tables 4 and 5 around here please

## Figure 2 around here please

### 4. Discussion

The main objective of the present study was to disentangle the role of DRT and negative affect manifestations, such as depression, anxiety, and apathy, on ICBs development in PD, over a two-year’s time window. To do so, we analyzed longitudinal data collected in a group of patients with SWEDD, that is, a form of PD where there is no evidence of DA deficit. More specifically, from the PPMI database, we selected a group of SWEDD patients who did not show any evidence of DA deficit and did not use any DRT over a two-year’s time window, and we analyzed their profile comparing it with the one of a group of “traditional” PD patients, and with a group of matched HC. Comparing the SWEDD with both PD patients and HC not only allowed us to add new knowledge about the non-motor symptoms characterizing this peculiar clinical condition. Indeed, it permitted us to obtain new knowledge useful for both the clinical practice and the theoretical advancement. Hence, we will discuss the results first on the light of their clinical relevance and, second, we will talk about their possible theoretical implications. Finally, together with a review of the limitations of the present study and with our conclusions, we provide some ideas for future investigation within this research field.

#### 4.1 Anxiety predicts ICBs in SWEDD patients: clinical relevance

The first set of results of the present study showed that SWEDD and PD patients present similar symptomatologies, albeit with different levels of severity. Specifically, at the time of diagnosis as well as after one and two years, those with PD presented more severe motor dysfunctions when compared with SWEDD. At the same time, both PD and SWEDD show the presence of lower cognitive performance and of higher levels of depressive and anxiety symptoms, when compared with matched HC, but with no differences between them. Finally, results also showed that SWEDD patients presented higher level of ICBs, if compared with both PD patients and HC, after one year from the diagnosis.

These findings are partly coherent with a previous study conducted analyzing the PPMI baseline data, which reported similar motor and cognitive deficits in PD and SWEDD, as well as higher level of ICBs and depressive symptoms in the SWEDD group, when compared with PD (Marek et al. 2018). These discrepancies, however, could be explained by the two main differences between our study and the one of Marek et al. 2018.

These discrepancies, however, could be explained by the two main differences between our study and the one of Marek et al. 2018.

First, the fact we have excluded from the analysis the SWEDD who changed diagnosis after one or two years from the baseline, as well as the ones who took any DRT in this same time window. Second, the fact that we have applied the Bonferroni correction for multiple comparisons in our statistical analyses.

Indeed, considering the relatively high number of variables in our analysis as well as the lomngitudinal design, we wanted to reduce the chances of Type I error and to produce robust findings. To the best of our knowledge, this is the first study reporting the differences in both motor and non-motor symptoms between PD and SWEDD adopting a longitudinal approach.

The second set of results, yielded by the first mixed model conducted, show that in both SWEDD and PD patients, anxiety represents a significant risk factor for the development of ICBs. Moreover, results also show that the kind of diagnosis itself, SWEDD vs PD, also was a significant predictor of ICBs, coherently with the results of the previous set of analysis showing higher level of ICBs in SWEDD, respect to both PD and HC after one year from the diagnosis. Most notably, when we analyzed the two groups separately, the effect of anxiety in predicting ICBs remained significant in the SWEDD group only. For the sake of clarity, we remind that both PD and SWEDD had higher level of anxiety symptoms at each of the three time points, when compared with HC. However, SWEDD had higher level of ICBs when compared with both PD and HC, especially after one year from the diagnosis. Hence, results indicate that, despite abnormal levels of anxiety are present in both clinical conditions, anxiety leads to ICBs especially in the SWEDD group. As far as the authors are aware, this is the first study to show that anxiety is a significant predictor of ICBs in SWEDD patients.

From a clinical point of view, this result can be interpreted considering the peculiarity of the SWEDD condition itself. Indeed, if compared with PD, SWEDD patients experience the absence of a ‘definitive’ diagnosis and prognosis, as well as the lack of an effective treatment plan for their motor distressing symptoms (Schneider et al., 2007; Schwingenschuh et al., 2010; Bain, 2009). This increased level of uncertainty might therefore lead to a pathological cascade of uncontrolled worry and deficient cognitive control. More specifically, as suggested by the intolerance of uncertainty model (Freeston et al., 1994; see also Shihata et al., 2017; Ouellet et al, 2019), individuals with pathological anxiety find uncertainty very distressing and, when confronted with an uncertain or ambiguous situation, which the SWEDD diagnosis could represent, are subject to worrying (Einstein, 2014; McEvoy & Mahoney, 2012). Indeed, always according to the uncertainty model (Freeston et al., 1994; Shihata et al., 2017; Ouellet et al, 2019), anxiety leads to a first loop of “negative problem orientation,” associated with the belief that problems are threatening, as well as with a low problem-solving confidence, which in turn increases the intensity of worry (Koerner, N., & Dugas, 2006; Einstein, 2014). Moreover, a second feedback loop would be involved too, suggesting that anxiety also leads to cognitive avoidance, whereby the individual is motivated to engage in unhelpful strategies such as thought suppression, distraction, and thought replacement (Freeston et al., 1994; McEvoy & Mahoney, 2012; Shihata et al., 2017; Ouellet et al, 2019). In the short-term these strategies might be negatively reinforced by a reduction in worrisome thoughts and anxiety. However, they also prevent underlying threat appraisals from being modified, which ultimately results in more worrisome thoughts, thereby completing the cycle.

The mechanism through which pathological anxiety would lead to abnormal avoidance and to a deficient cognitive control has been also taken into account by the recent review of Kenwood et al., 2021. In detail, authors suggest that uncertainty about outcomes, combined with bias towards threat, can create a persistently aroused and hypervigilant state, which in turn can bias an anxious individual towards avoidance (Kenwood et al., 2021; Arnaudova et al., 2017; Barlow, 2004). Importantly, adaptive avoidance strategies selection would depend on coordinated actions between subcortical regions, such as amygdala and striatum, and cortical ones such as orbitofrontal and ventromedial cortex (Kenwood et al., 2021). Therefore, leading to maladaptive avoidance behavior, abnormal anxiety may lead to abnormal PFC activity and, consequently, to cognitive control impairment (Paulus, 2015; Braver et al.., 2007; Hoshino and Tanno, 2017; Eysenck et a., 2007). Taken together, this set of evidence suggests a possible mechanism to link abnormal anxiety to ICBs in individuals who experience high level of uncertainty, such as PD and particularly the SWEDD.

Our results may have implications for treatment as well. While the present data suggests that the presence of anxiety symptoms augment the risk of ICB, it is not possible to assess whether an early treatment of such symptoms may prevent the onset of ICB. While specific treatments for anxiety in PD are recommended to improve quality of life and treatment adherence (Reynolds et al., 2019), future randomized controlled trials should evaluate their potential preventive role on ICB development as well. Specifically, both pharmacological and psychological interventions should be tested and in turn, as their efficacy as preventive strategies may help to understand better the relationship between the former and the latter.

Taken together, we believe these results represent an important missing piece of information for the clinicians working with patients with undefined diagnosis, such as SWEDD. In fact, being aware of the detrimental effect of uncertainty on anxiety levels and therefore on cognitive control could help establishing effective strategies to prevent the development of disabling behavioural problems like ICBs. Secondly, on the light of the theoretical implications we are now going to discuss, our finding could also help clinicians working with PD patients too, motivating them in the implementation of regular anxiety assessment as part of a prevention strategy for ICBs development, especially in the first years from the PD diagnosis.

#### 4.2. Anxiety and ICBs in SWEDD and PD patients: theoretical implications

From a neurobiological perspective, the co-occurrence of negative affect and approach behaviours in ICB is predicted by the motivational opponency framework (Boureau, & Dayan, 2011; Boureau, et al., 2011; Tops et al., 2009; Daw et al., 2002)

In its simplest form, this framework posits that the interaction between systems modulated by dopamine (DA)-serotonin (5-HT) code for affective events, with a DA system modulating positive excursions from baseline and a 5-HT system modulating negative excursionsTo the extent that 5-HT acts as an opponent to DA, rodent studies provide preliminary insight into the extent of the complexities of this interaction. For instance, forebrain serotonergic lesions attenuate the ability of the DA agonist d-amphetamine to decrease impulsivity on a delay-discounting procedure in rats (Cardinal et al, 2001; Winstanley et al, 2003). By the same token, the DA antagonist cis-(z)-flupenthixol only blocked the anti-impulsivity effects of amphetamine in serotonergically lesioned animals, but not in sham-operated controls (Winstanley et al. 2003, 2005). The framework also provides a rationale for the addition of low dose dopamine receptor antagonists when patients with OCD fail to respond to selective serotonin reuptake monotherapy.The motivational opponency framework has also been examined in a neurobiologically inspired robot called CarlRoomba (Krichmar. 2013). This robot was based on a neural network for avoidance-approach behaviour built on the 5-HT/DA oppositional partnership principles, and had a frontal cortex layer too, which loosely corresponds to top-down control by orbitofrontal and medial prefrontal cortices of the DA and 5-HT systems, respectively. Results of Krichmar et al. 2013 showed that upregulating 5-HT activity in the robot’s neural network produced the predicted avoidant behaviours to a bright light, mirroring the increased avoidant behaviours seen 5-HT transporter knockout mice (Holmes et al., 2003; Bregman et al., 2018). On the other hand, upregulating DA resulted in CarlRoomba showing more curiosity and risk taking, similar to DA transporter knockout mice (Gainetdinov et al., 1999; Cinque et al., 2018). The same pattern of avoidant and approach behavioural response to novelty followed lesions of the robot’s medial prefrontal cortex and orbitofrontal ‘cortices’, respectively (Krichmar, 2013).

The motivational opponency framewok also provides a rationale for the presence of ICBs in both de novo PD patients, PD patients medicated with dopamine replacement therapies and SWEDD patients if impulsive behaviour is the sum product of the net interaction of DA and 5-HT and perturbation in either direction isa critical factor in the explaining ICB.

The present results on unmedicated SWEDD patients well integrate with these animal and robotic evidence showing the non-exclusive role of DA on the development of ICBs. Therefore, we speculate that negative affect manifestation, such as anxiety, could play a major role in the development of ICBs in PD patients too, especially in the first stages of the disease, where anxiety levels are higher respect to normal conditions, and DRT is not always prescribed. Indeed, in a recent meta-analysis conducted on a total of 684 PD patients with and 3.382 PD patients without ICBs (Cao et al. 2021), of the four studies that reported both disease duration and DRT as significant predictors, DRT was only a risk factor for ICBs where disease duration had been longer than 2 years (see Figures 7 and 12 of Cao et al., 2021; see also Fan et al., 2009; Marković et al., 2020; Kon et al, 2018; Zhang et al., 2017). And this is in line with our results on PD patients’, where the use of DRT was not significantly related to ICBs symptoms over a two years’ time window.

#### 4.3 Limitations and future directions

Some limitations should be noted when considering our results. First, the lack of imaging data, which prevent us from making more direct conclusion about the neural mechanisms behind the development of ICBs in PD patients, with and without evidence of DA deficiency. Future study should therefore overcome this limitation, assessing disease and symptoms progression in relation to a parallel functional neuroimaging assessment.

Secondly, the high data variability of our SWEDD sample, as well as its smaller size, if compared with the one of PD patients and HC. Although we believe that this limitation does not invalidate our results, a more balanced set of samples would be a desirable target for future studies aimed to replicate our preliminary results.

Last, the relatively short time window considered in this study, two years, which did not allow us to detect any role of DRT on ICBs development in PD patients. Unfortunately, data concerning the desired outcome measures in the clinical samples we included in the present study were not available after the last time point considered. Future studies considering broader time-windows would be therefore preferable, in order to replicate previous evidence concerning the role of DRT in predicting ICBs in PD patients.

(Yee & Braver, 2018)

### 5. Conclusion

Taken together, the key finding of the present study is that ICBs can be present in PD patients without DA deficiency, and that it is significantly triggered by their high level of anxiety. These results represent an important advancement in the research field studying the non-motor symptoms of Parkinsonisms, either PD or SWEDD. At the same time, they are also coherent with the existing literature showing the transdiagnostic nature of negative affect manifestations and impulsivity, co-occurring across a range of different developmental and functional brain disorders. A potential future development of this study could be the direct comparison between the neuropsychiatric profile of SWEDD and PD patients with individuals affected by frontotemporal dementia, a neurodegenerative disease characterized by behavioural impulsivity, and for which negative affect manifestations seems to represent significant risk factors (Collins et al., 2020). Indeed, results of the present study demonstrate the importance of considering multiple clinical conditions in studies focused on multisystem pathologies, such as PD.

Defining and evaluating the transdiagnostic features of different pathological conditions would be in fact extremely informative not only for the research community, but also for who is involved in the clinical practice, especially when talking about neurodegenerative conditions. The rapid aging of the worldwide population, and the consequent increase in the prevalence of pathologies like PD, currently the fastest growing neurological disorder worldwide (Armstrong et al., 2020; Dorsey & Bloem, 2018; Feigin et al., 2017), urgently requires new knowledge, able to help the development of valid and effective strategies able to prevent its disabling symptoms. In our opinion, more attention to the psychological symptoms of these diseases, such as pathological anxiety, would represent a promising preventive approach.

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(www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

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# FIGURE LEGEND

**Figure 1: Flow chart representing attrition rates at baseline (T0), 12 months (T1) and 24 months (T2). From the 683 participants available from the PPMI database on May 2020, 31 participants (14 SWEDD; 6 PD; 11 HC) were excluded according to the following criteria: missing variables of interest; change of diagnosis; presence of other neurological conditions; use of dopaminergic medication for SWEDD and HC**

**Figure 1**

**Figure 2: Scatterplot representing the statistically significant role of anxiety (STAI-Y total score) in predicting the presence of Impulsive-Compulsive behaviours (QUIP-RS score) in both SWEDD and PD patients, over a two-year’s time window.**

Figure 1 [Click here to download Figure Figure1.tif](https://www.editorialmanager.com/jpsychiatrres/download.aspx?id=175902&guid=06b3e419-85d2-46a5-bdae-5c8e32f2851c&scheme=1)

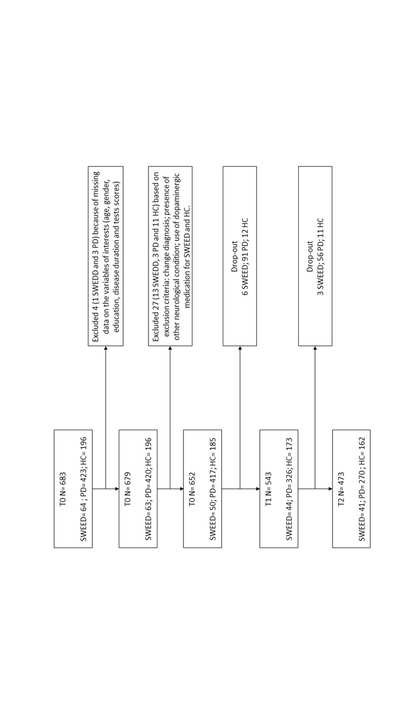
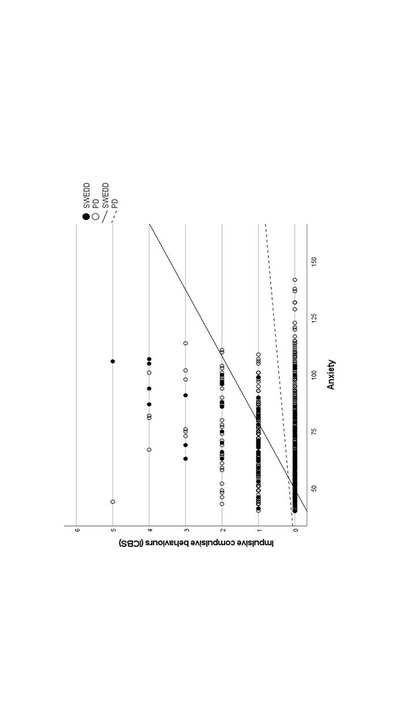


Figure 2 [Click here to download Figure Figure2.tif](https://www.editorialmanager.com/jpsychiatrres/download.aspx?id=175903&guid=97868eec-5ee2-4dc1-9a97-29eaed756b09&scheme=1)



**Table 1. Demographic, neuropsychological, and clinical characteristics by group at baseline (T0).**

SWEDD (n=50)

PD (n=417)

HC (n=185)

Test value

a

*p*

*-*

*value*

*Effect size (*

*η2*

*)*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | M (SD) | M (SD) | M (SD) |  |  |  |
| Gender (Female=1; Male=0) | 60.00% | 65.70% | 65.40% | 0.65 | .724 |  |
| Age (years) | 60.57 (10.23) | 61.55 (9.69) | 60.62 (11.29) | 0.64 | .530 | 0.002 |
| Education (years) | 15.26 (3.65) | 15.57 (2.97) | 16.12 (2.87) | 2.75 | .065 | 0.008 |
| General cognitive status (MoCA) | 27.12 (2.52)\* | 27.12 (2.33)\* | 28.24 (1.11) | 19.35 | <.001^ | 0.056 |
| Visuospatial processing (BJLO) | 13.06 (2.41) | 12.79 (2.11) | 13.19 (1.93) | 2.53 | .080 | 0.008 |
| Composite memory | -0.21 (1.01)\* | -0.08 (0.84)\* | 0.24 (0.72) | 11.21 | <.001^ | 0.033 |
| Composite executive function | -0.14 (0.84)\* | -0.06 (0.74)\* | 0.25 (0.74) | 12.85 | <.001^ | 0.038 |
| Anxiety (STAI-Y) | 68.74 (17.01)\* | 65.37 (18.36)\* | 56.98 (13.76) | 18.27 | <.001^ | 0.053 |
| Depression (GDS) | 2.80 (3.40)\* | 2.33 (2.45)\* | 1.28 (2.11) | 14.23 | <.001^ | 0.042 |
| Impulsive-compulsive behaviour (QUIP-Short) | 0.60 (0.95) | 0.28 (0.63) | 0.28 (0.70) | 5.07 | .007 | 0.015 |
| Apathy (MDS-UPDRS-I apathy scale) | 0.16 (0.42) | 0.20 (0.49) | − | 0.33 | .566 | 0.001 |
| Disease duration (years) | 7.06 (7.75) | 6.61 (6.48) | − | 0.21 | .646 | 0.000 |
| Motor symptom severity (MDS-UPDRS-III score) | 12.50 (9.08)‡ | 20.77 (8.80) | − | 39.13 | <.001^ | 0.078 |

MoCA: Montreal Cognitive Assessment; BJLO: Benton Line Orientation Judgement Test; STAI-Y: State-Trait Anxiety Inventory Form Y; GDS: Geriatric Depression Scale; QUIP-short:

Questionnaire for Impulsive‐Compulsive Disorders in PD- Short version; MSD-UPDRS= Movement Disorder Society Unified Parkinson’s Disease Rating Scale.

\*Significantly different from controls; ‡significantly different between patient groups; ^ significant after applying Bonferroni correction for multiple comparisons (p-value < .004). aF-test values are reported for all variables except Gender, for which Chi square test value is reported. *η2*: partial eta square*.*

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**Table 2. Demographic, neuropsychological, and clinical characteristics by group after one year from the baseline (T1).**

SWEDD (n=44)

PD (n=326)

HC (n=173)

Test

a

*p*

*-*

*value*

*η*

2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | M (SD) | M (SD) | M (SD) |  |  |  |
| Gender (Female=1; Male=0) | 56.80% | 66.60% | 64.70% | 1.65 | .439 |  |
| Age (years) | 60.42 (10.55) | 61.04 (9.71) | 60.80 (11.25) | 0.08 | .918 | 0.000 |
| Education (years) | 14.82 (3.27) | 15.63 (2.90) | 16.08 (2.83) | 3.56 | .029 | 0.013 |
| General cognitive status (MoCA) | 26.32 (2.55) | 26.24 (2.81)\* | 27.23 (2.23) | 8.38 | <.001^ | 0.030 |
| Visuospatial processing (BJLO) | 12.55 (2.41) | 12.40 (2.35) | 12.75 (2.42) | 1.16 | .313 | 0.004 |
| Composite memory | -0.10 (0.77)\* | -0.14 (0.88)\* | 0.29 (0.70) | 16.02 | <.001^ | 0.056 |
| Composite executive function | -0.10 (0.79)\* | -0.11 (0.74)\* | 0.26 (0.77) | 14.34 | <.001^ | 0.050 |
| Anxiety (STAI-Y) | 64.68 (17.12)\* | 65.03 (18.79)\* | 56.23 (16.71) | 13.93 | <.001^ | 0.049 |
| Depression (GDS) | 2.12 (2.65)\* | 2.43 (2.68)\* | 1.45 (2.42) | 8.50 | <.001^ | 0.031 |
| Impulsive-compulsive behaviour (QUIP-Short) | 0.55 (1.09)‡\* | 0.17 (0.48) | 0.27 (0.63) | 7.86 | <.001^ | 0.028 |
| Apathy (MDS-UPDRS-I apathy scale) | 0.25 (0.49) | 0.33 (0.64) | − | 0.61 | .437 | 0.002 |
| Disease duration (years) | 7.67 (8.07) | 6.65 (6.51) | − | 0.90 | .343 | 0.002 |
| Motor symptom severity (MDS- UPDRS-III score) | 11.68 (9.43)‡ | 25.05 (10.81) | − | 60.95 | <.001^ | 0.142 |
| Levodopa equivalent daily dose (LEDD) | − | 154.29 (220.67) | − |  |  |  |
| Dopamine Agonist use (yes= 1; no = 0) | − | 20.20% | − |  |  |  |

MoCA: Montreal Cognitive Assessment; BJLO: Benton Line Orientation Judgement Test; STAI-Y: State-Trait Anxiety Inventory Form Y; GDS: Geriatric Depression Scale; QUIP-short:

Questionnaire for Impulsive‐Compulsive Disorders in PD- Short version; MSD-UPDRS= Movement Disorder Society Unified Parkinson’s Disease Rating Scale.

\*Significantly different from controls; ‡significantly different between patient groups; ^ significant after applying Bonferroni correction for multiple comparisons (p-value < .004).

aF-test values are reported for all variables except Gender, for which Chi square test value is reported. *η2*: partial eta square*.*

**Table 3. Demographic, neuropsychological, and clinical characteristics by group after two years from the baseline (T2).**

SWEDD (n=41)

PD (n=270)

HC (n=162)

Test

a

*p*

*-*

*value*

*η*

2

M (SD)

M (SD)

M (SD)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Gender (Female=1; Male=0) | 61.00% | 66.70% | 63.00% | 0.91 | .633 |  |
| Age (years) | 61.10 (10.57) | 61.73 (9.72) | 60.48 (11.33) | 0.73 | .481 | 0.003 |
| Education (years) | 15.05 (3.64) | 15.84 (2.81) | 16.16 (2.91) | 2.42 | .090 | 0.010 |
| General cognitive status (MoCA) | 26.12 (3.11) | 26.17 (3.19)\* | 27.08 (2.38) | 6.44 | .002^ | 0.027 |
| Visuospatial processing (BJLO) | 12.76 (2.48) | 12.92 (2.14) | 13.07 (2.10) | 0.43 | .653 | 0.002 |
| Composite memory | -0.14 (0.80)\* | -0.11 (0.81)\* | 0.22 (0.77) | 8.98 | <.001^ | 0.037 |
| Composite executive function | -0.17 (0.93)\* | -0.11 (0.79)\* | 0.26 (0.72) | 12.52 | <.001^ | 0.051 |
| Anxiety (STAI-Y) | 63.68 (14.61)\* | 65.19 (19.18)\* | 55.48 (14.08) | 16.39 | <.001^ | 0.065 |
| Depression (GDS) | 2.90 (3.34)\* | 2.56 (2.65)\* | 1.19 (1.95) | 17.43 | <.001^ | 0.069 |
| Impulsive-compulsive behaviour (QUIP-Short) | 0.51 (1.05) | 0.25 (0.63) | 0.24 (0.59) | 3.01 | .050 | 0.013 |
| Apathy (MDS-UPDRS-I apathy scale) | 0.27 (0.67) | 0.33 (0.64) | − | 0.28 | .596 | 0.001 |
| Disease duration (years) | 8.08 (8.17) | 6.71 (6.27) | − | 1.55 | .214 | 0.005 |
| Motor symptom severity (MDS- UPDRS-III score) | 10.88 (8.17)‡ | 27.25 (11.20) | − | 80.97 | <.001^ | 0.208 |
| Levodopa equivalent daily dose (LEDD) | − | 314.19 (345.01) | − |  |  |  |
| Dopamine Agonist use (Yes= 1; No = 0) | − | 27.40% | − |  |  |  |

MoCA: Montreal Cognitive Assessment; BJLO: Benton Line Orientation Judgement Test; STAI-Y: State-Trait Anxiety Inventory Form Y; GDS: Geriatric Depression Scale; QUIP-short:

Questionnaire for Impulsive‐Compulsive Disorders in PD- Short version; MSD-UPDRS= Movement Disorder Society Unified Parkinson’s Disease Rating Scale.

\*Significantly different from controls; ‡significantly different between patient groups; ^ significant after applying Bonferroni correction for multiple comparisons (p-value < .004).

aF-test values are reported for all variables except Gender, for which Chi square test value is reported. *η2*: partial eta square*.*

**Table 4. Results of the mixed models’ analyses conducted to assess ICBs predictors in SWEDD and PD patients over the two-years time window. First mixed model (**A) considered both the clinical groups together. Models B and C considered, respectively, SWEED and PD patients only.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **A** | **PD and SWEDD (n=467)** | |  | **B** | **SWEDD (n=50)** | |  | **C** |  | **PD (n=417)** | |  |
| Predictors Strength? | **B** | **SE** | **t** | **p** | **B** | **SE** | **t** | **p** | **B** |  | **SE** | **t** | **p** |
| **Group (1=SWEDD, 0=PD)** | **0.2953** | **0.0799** | **3.70** | **<.001^** |  |  |  |  |  |  |  |  |  |
| Year | -0.0424 | 0.0243 | -1.74 | .082 | -0.0157 | 0.0833 | -0.19 | .851 | -0.0407 |  | 0.0255 | -1.60 | .111 |
| Gender (1=Female, 0=Male) | -0.0267 | 0.0533 | -0.50 | .616 | -0.0856 | 0.1999 | -0.43 | .671 | 0.0081 |  | 0.0512 | 0.16 | .875 |
| Age (years) | -0.0019 | 0.0027 | -0.69 | .488 | -0.0013 | 0.0101 | -0.13 | .898 | -0.0017 |  | 0.0027 | -0.63 | .528 |
| Education (years) | 0.0110 | 0.0083 | 1.32 | .187 | 0.0604 | 0.0274 | 2.21 | .033 | 0.0029 |  | 0.0081 | 0.36 | .719 |
| General cognitive status (MoCA) | 0.0034 | 0.0085 | 0.40 | .689 | -0.0130 | 0.0353 | -0.37 | .715 | 0.0016 |  | 0.0084 | 0.19 | .851 |
| Visuospatial processing (BJLO) | 0.0096 | 0.0099 | 0.96 | .335 | -0.0023 | 0.0373 | -0.06 | .950 | 0.0119 |  | 0.0100 | 1.20 | .232 |
| Composite Memory | 0.0081 | 0.0290 | 0.28 | .780 | 0.0828 | 0.1206 | 0.69 | .494 | 0.0090 |  | 0.0285 | 0.31 | .754 |
| Composite Executive Functions | -0.0320 | 0.0389 | -0.82 | .411 | -0.2261 | 0.1580 | -1.43 | .156 | 0.0096 |  | 0.0379 | 0.25 | .799 |
| **Anxiety (STAI-Y)** | **0.0048** | **0.0015** | **3.33** | **.001^** | **0.0218** | **0.0054** | **4.08** | **<.001^** | 0.0039 |  | 0.0015 | 2.63 | .009 |
| Depression (GDS) | 0.0280 | 0.01P01 | 2.78 | .005 | 0.0776 | 0.0286 | 2.71 | .008 | 0.0169 |  | 0.0108 | 1.57 | .117 |
| Apathy (MDS-UPDRS-I apathy scale) | 0.0288 | 0.0347 | 0.83 | .406 | 0.0801 | 0.1518 | 0.53 | .598 | 0.0338 |  | 0.0342 | 0.99 | .323 |
| Disease duration (years) | 0.0009 | 0.0036 | 0.25 | .800 | 0.0049 | 0.0123 | 0.40 | .694 | 0.0021 |  | 0.0035 | 0.60 | .548 |
| Motor symptom severity (MDS- UPDRS-III score) | -0.0021 | 0.0021 | -0.98 | .329 | -0.0057 | 0.0097 | -0.59 | .559 | -0.0018 |  | 0.0021 | -0.85 | .395 |
| Levodopa equivalent daily dose (LEDD) | 0.0001 | 0.0001 | 1.00 | .319 |  |  |  |  | 0.0001 |  | 0.0001 | 0.99 | .321 |
| Dopamine Agonist use (Yes= 1; No = 0) | 0.0255 | 0.0607 | 0.42 | .674 |  |  |  |  | 0.0222 |  | 0.0568 | 0.39 | .696 |

B= estimate; SE= standard error of the mean; t= Student t-test; MoCA: Montreal Cognitive Assessment; BJLO: Benton Line Orientation Judgement Test; STAI-Y: State-Trait Anxiety Inventory Form Y; GDS: Geriatric Depression Scale; QUIP-short: Questionnaire for Impulsive‐Compulsive Disorders in PD- Short version; MSD-UPDRS= Movement Disorder Society Unified Parkinson’s Disease Rating Scale. ^ significant after applying Bonferroni correction for multiple comparisons (p-value < .003).