CORTEX XXX (2015) 1–17

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Research report

Evidence of an amnesia-like cued-recall memory impairment in nondementing idiopathic Parkinson's disease

N.M.J. Edelstyn [a,*], C.M. John [a], T.A. Shepherd [a], J.L. Drakeford [b], D. Clark-Carter [b], S.J. Ellis [c] and A.R. Mayes [d]

[a] School of Psychology, Keele University, Staffordshire, UK
[b] School of Psychology, Sport and Exercise, Staffordshire University, Staffordshire, UK
[c] University Hospital of North Midlands and Keele University, Staffordshire, UK
[d] Psychological Sciences, University of Manchester, Manchester, UK

ARTICLE INFO

Article history:
Received 15 September 2014
Reviewed 3 May 2015
Revised 16 June 2015
Accepted 23 June 2015
Action editor H. Branch Coslett
Published online xxx

Keywords:
Recall/recollection
Familiarity
Medial temporal lobe
Prefrontal cortex
Parkinson's disease

ABSTRACT

Medicated, non-dementing mild-to-moderate Parkinson's disease (PD) patients usually show recall/recollection impairments but have only occasionally shown familiarity impairments. We aimed to assess two explanations of this pattern of impairment. Recollection typically improves when effortful planning of encoding and retrieval processing is engaged. This depends on prefrontally-dependent executive processes, which are often disrupted in PD. Relative to an unguided encoding and retrieval of words condition (C1), giving suitable guidance at encoding alone (C2) or at encoding and retrieval (C3) should, if executive processes are disrupted, improve PD recollection more than control recollection and perhaps raise it to normal levels. Familiarity, being a relatively automatic kind of memory, whether impaired or intact, should be unaffected by guidance. According to the second explanation, PD deficits are amnesia-like and caused by medial temporal lobe dysfunction and although poorer recollection, which is caused by hippocampal disruption, may be improved by guidance, it should not improve more than control recollection. Familiarity impairment will also occur if the perirhinal cortex is disrupted, but will be unimproved by guidance. Without guidance, recollection/recall was impaired in thirty PD patients relative to twenty-two healthy controls and remained relatively equally impaired when full guidance was provided (C1 *vs* C3), both groups improving to broadly the same extent. Although impaired, and markedly less so than recollection, familiarity was not improved by guidance in both groups. The patients showed elevated rates of subclinical depressive symptoms, which weakly correlated with recall/recollection in all three conditions. PD executive function was also deficient and correlated with unguided/C1 recollection only. Our results are

* *Corresponding author*. School of Psychology, Keele University, Keele, Staffordshire ST5 5BG, UK.
E-mail address: n.edelstyn@keele.ac.uk (N.M.J. Edelstyn).

http://dx.doi.org/10.1016/j.cortex.2015.06.021
0010-9452/

consistent with a major cause of the patients' recall/recollection impairments being hippocampal disruption, probably exacerbated by subclinical depressive symptoms. However, the results do not exclude a lesser prefrontal cortex contribution because patient executive functions were impaired and correlated solely with unguided overall recollection.

1. Introduction

Idiopathic nondementing Parkinson's disease (PD) is dominated by tremor, bradyphrenia, rigidity and postural instability (Parkinson, 2002) , which each have a good response to dopaminergic medication. The motor problems that characterise PD are caused by progressive degenerative changes that occur primarily in the dopaminergic nuclei of the midbrain (Fearnley & Lees, 1991; Hornykiewicz, 1966; Obeso, et al., 2008). However, PD is not 'just' a motor disorder. Patients are often impaired at recalling recently experienced information, such as facts and personal events, but have usually been found to be less impaired at recognition of recently encountered stimuli (e.g., Beatty, Staton, Weir, Monson, & Whitaker, 1989; Breen, 1993; Edelstyn, Mayes, Condon, Tunnicliffe, & Ellis, 2007; Edelstyn, Shepherd, Mayes, Sherman, & Ellis, 2010; Flowers, Pearce, & Pearce, 1984; Higginson, Wheelock, Carroll, & Sigvardt, 2005; Shepherd, Edelstyn, Mayes, & Ellis, 2013; Taylor, Saint-Cyr, & Lang, 1986).

The most plausible explanation of why recall is typically more impaired than recognition in PD is provided by the widely accepted dual process view according to which recognition is supported by two kinds of memory, recollection and familiarity, that depend on distinct processes and different systems of brain structures (see Montaldi & Mayes, 2010; but also see Wixted & Squire, 2011 for a contrasting view). Recollection is a kind of memory in which a recognition test stimulus cues recall of detail(s) from one or more previous episodes where the stimulus was encountered. This kind of cued recall is often diagnostic of an earlier encounter with the stimulus. It is functionally and neurally very similar to other kinds of recall, which also depend on cues (even free recall is cued by context). Tests of recall, therefore, depend solely on recollection or kinds of recall very similar to it whereas recognition test performance can often be strongly supported by familiarity. Familiarity-driven recognition memory supports a subjective experience of memory for a previously encountered stimulus in the absence of any cued recall of associated details from previous encounters with the stimulus. Whereas recollection and other kinds of recall often depend on effortful and planned processing at study and test, familiarity is believed to be a relatively automatic activity (see Jacoby, 1991; Yonelinas, 2002). In general, the dual process view explains the typical PD memory impairment as being the result of a brain dysfunction in a region that primarily mediates recollection and other kinds of recall, leaving the familiarity brain system functioning relatively normally. The dual process view can also explain cases where recognition is clearly impaired because, although familiarity often makes a major contribution to recognition, the relative contribution of recollection and familiarity to different kinds of recognition varies and some kinds mainly depend on recollection (Holdstock et al., 2002).

Two hypotheses are consistent with PD patients having a greater recall than recognition deficit. Both hypotheses propose that the PD memory disorder is caused by dysfunction (but also possibly damage) of brain regions that are modulated by the dopaminergic midbrain structures the atrophy of which underlies PD. According to the prefrontal cortex/organizational hypothesis, the death of dopamine-producing cells in the *ventral tier* of the substantia nigra pars compacta (Fearnley & Lees, 1991) results in a progressive loss of dopamine innervation in the basal ganglia (Hornykiewicz, 1966). Since a close relationship exists between the basal ganglia and prefrontal areas (Alexander, Delong, & Strick, 1986), it is not surprising to find evidence of PD-dependent deficits of forms of cognition, such as working memory (Gabrieli, Singh, Stebbins, & Goetz, 1996), planning and problem-solving (Beatty & Monson, 1990; Morris et al., 1988), and verbal fluency (Hanes, Andrewes, Smith, & Pantelis, 1996), that depend upon the integrity of the prefrontal cortex (Owen, Doyon, Dagher, Sadikot, & Evans, 1998). Common to each of these kinds of cognition is the requirement to select and implement appropriate strategies. Evidence of poor performance of these executive processes (for a review see Dirnberger & Jahanshahi, 2013) and functional brain imaging evidence of reduced (medial) prefrontal activation and elevated false alarm rate during a yes/no item recognition memory task in PD (e.g., Segura, et al., 2012) has led to proposals that the prefrontal dependent executive deficits underlie the breakdown of recall, which often depends on effortful and organized encoding and retrieval processes. The impaired executive control processes normally underlie the organization of material at encoding and the search for better cues at retrieval as well as retrieval-related activities, such as response monitoring and decision-making (e.g., Gabrieli, et al., 1996; Mayes & Daum, 1996; Savage, et al., 2001).

The claim of the prefrontal cortex/organisational hypothesis that prefrontal dysfunction disrupt recall is supported by findings from lesion patients. Like PD patients, patients with frontal lesions are not amnesic; however, they do exhibit deficits on tests of free recall (Gershberg & Shimamura, 1995; Turner, Cipolotti, Yousry, & Shallice, 2007; Wheeler, Stuss, & Tulving, 1995) and source recall, particularly when the tests depend heavily on the use of memory strategies as applies

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

when multiple learning trials are used (Duarte, Ranganath, & Knight, 2005; Gershberg & Shimamura, 1995; Janowsky, Shimamura, & Squire, 1989a; Janowsky, Shimamura, Kritchevsky, & Squire, 1989b). On the other hand, when the demands on effortful executive control processes are reduced by the provision of category cues at test and/or strategic instruction, recall performance has been shown to be less affected (Gershberg & Shimamura, 1995); and item recognition memory is relatively normal (Janowsky et al., 1989a; Parkin, Bindschaedler, Harsent, & Metzler, 1996; Schacter, Curran, Galluccio, Milberg, & Bates, 1996; Shimamura, Jurica, Mangels, & Gershberg, 1995). These findings suggest that a deficit in the initiation and use of organisational strategies explains the free recall deficits following frontal lobe damage. If this is so, then provision of strategic instruction at encoding and/or retrieval should remediate these deficiencies as has been reported (Della Rocchetta & Milner, 1993; Gershberg & Shimamura, 1995; Hirst & Volpe, 1988; Jetter, Poser, Freeman & Makowitsch, 1986).

Although prefrontal damage can disrupt familiarity (e.g., Duarte et al., 2005; MacPherson et al., 2008), and fMRI studies also indicate that activation of various prefrontal regions occurs during familiarity processing (e.g. Henson, Rugg, Shallice, Josephs, & Dolan, 1999), there is very poor correspondence of prefrontal sites between the two approaches and relatedly what they are doing. There is also behavioural evidence from older healthy adults showing better executive functioning is associated with greater recollection, but is unrelated to familiarity performance (Anderson et al., 2008). This is consistent with the view that familiarity is a much more automatic kind of memory and depends much less on executive function than intentional recollection, and consequently, the prefrontal/organizational hypothesis would predict that familiarity should be relatively spared, as has been reported (e.g., Mayes & Daum, 1996).

The second hypothesis that explains why recall is typically more impaired than recognition in PD proposes that hippocampal dysfunction selectively disrupts recall memory in the same way that it is disrupted in organic amnesia. This hypothesis is derived from the neuroanatomical development of the dual process view (e.g., Aggleton & Brown, 1999), a central tenet of which is that the hippocampus and its connections via the fornix in the midline diencephalon and the retrosplenial cortex play a selective role in mediating recollection and other kinds of recall. Based on this, the medial temporal lobe/amnesia-like hypothesis proposes that impaired dopaminergic modulation predominantly of the hippocampus is caused by atrophy of the *dorsal* tier of the substantia nigra pars compacta and the ventral tegmental area (Bunzeck, et al., 2007; Fearnley & Lees, 1991; Lisman & Grace, 2005). The hypothesis also allows that direct neuropathology of the hippocampus may occur in PD. This neuropathology may involve several hippocampal subregions and, particularly if PD is accompanied by subclinical depressive symptoms or clinical depression, probably includes suppression of neurogenesis in the dentate gyrus (for a full discussion of adult hippocampal neurogenesis in depression, see Kemperman & Kroneberg, 2003; Sahay & Hen, 2007). However, whether these neuropathologies result directly and solely from atrophy of midbrain dopaminergic structures remains uncertain (e.g., Laakso, et al., 1996). Whatever the source of dysfunctionality of the hippocampus, the dual process view proposes that this structure's impaired efficiency disrupts recollection and other kinds of recall selectively, leaving familiarity intact, and recognition intact to the extent that it is supported by familiarity (see Aggleton & Brown, 1999; Edelstyn, Grange, Ellis, & Mayes, 2015; Montaldi & Mayes, 2010). There is also longstanding evidence that amnesic patients' impaired recognition memory improves to the same extent as that of their controls when they are given precise elaborative encoding instructions rather than encode in a spontaneous way (e.g., Mayes, Meudell, & Neary, 1980). This is consistent with their usually preserved executive functions and intelligence and strongly suggests that they process and represent informational inputs normally even when their elaborative processing at study and test is self-driven (i.e., spontaneous) rather than guided (see Mayes, 1988 for a review).

Unlike the prefrontal cortex/organizational hypothesis, which cannot explain PD familiarity deficits if they are indeed disruptions of a largely automatic kind of memory, the medial temporal lobe/amnesia-like hypothesis can explain a PD familiarity impairment, provided the hypothesis is extended so as to exploit the full neuroanatomical development of the dual process view. The full dual process view also proposes that item familiarity memory is critically mediated by the perirhinal cortex (e.g., Aggleton, et al., 2005; Bowles et al., 2007; Montaldi & Mayes, 2010; Montaldi, Spencer, Roberts, & Mayes, 2006) and its connection to the medial subdivision of the mediodorsal thalamus (Edelstyn, et al., 2015; see also Kaftas & Montaldi, 2014 for a review). Therefore, the medial temporal lobe/amnesia-like hypothesis proposes that, although the hippocampus typically becomes dysfunctional first in PD, the perirhinal cortex eventually will do so also typically later in the disease as Braak, Del Tredici, Rüb, de Vos, Jansen Steur & Braak, (2003) have argued. Less commonly, the perirhinal cortex may become dysfunctional at the same time and rate as the hippocampus or, perhaps in rare cases, even earlier so that in unusual cases of PD familiarity may be as impaired as recollection and other kinds of recall or even more impaired (e.g., Davidson, Anaki, Saint-Cyr, Chow, & Moscovitch, 2006; Weiermann, Stephan, Kaelin-Lang, & Meier, 2010).

Recognition and recall memory have been investigated more in PD than have recollection and familiarity, although several more selective studies of these two kinds of memory have been conducted. These studies have usually found that recollection is impaired, but that familiarity is preserved in mild to moderate nondementing PD (Algarabel, et al., 2010; Edelstyn et al., 2007; Edelstyn et al., 2010; Hay, Moscovitch, & Levine, 2002; RodrÍguez, Algarabel, & Escudero, 2014; Shepherd et al., 2013). However, familiarity has sometimes been found to be impaired as previously indicated (Davidson, et al., 2006; Weiermann, et al., 2010).

These findings may differ for two main reasons. First, the differences may have related to how familiarity and recollection were measured. For example, in the Davidson et al. study, it was claimed that familiarity impairments and spared recollection were evident across 3 estimation methods, although in reality, the same data set was used for 2 of these methods (remember-know procedure and word-frequency mirror effect). This is a serious problem given the recognized

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

difficulties with measuring familiarity and recollection accurately and in relatively noise free or unbiased ways, particularly when only small groups are used as they were in Davidson et al.'s study (see Migo, Mayes, & Montaldi, 2012). Davidson and his colleagues' third method was the process dissociation procedure. The procedure assumes that the ability to discriminate between intact and recombined word pairs so as to select only intact pairs must depend on recollection alone because it cannot depend on item familiarity. However, it is known that associative familiarity can be found for several kinds of association, including those between words (Bastin, Van der Linden, Schnakers, Montaldi, & Mayes, 2010; Harlow, MacKenzie, & Donaldson, 2010). If this kind of memory was operating in the Davidson et al. study to an appreciable extent, as seems very likely, then the levels of estimated recollection and item familiarity may have been seriously inaccurate given how the process dissociation equations work. This is because the simultaneous equations, related to the inclusion and exclusion conditions of process dissociation procedure, cannot solve three unknowns: recollection, item familiarity and associative familiarity. Indeed, as the conditions were run separately, there may be further unknowns that correspond to the possibly distinct criteria adopted in the two rather different conditions. Second, there may be differences between the patients used in the studies with respect to the stage of their disease, their medication, the pattern of their disease, or specific features such as the severity of PD-related depressive symptoms and executive dysfunction.

However, even if all the different findings reflect PD patient-related differences, they are all consistent with the medial temporal lobe/amnesia-like hypothesis provided unknown factors differentially affect the rate at which hippocampal versus perirhinal cortex dysfunction develops. This is not the case for the prefrontal/organizational hypothesis, which cannot explain on its own impaired familiarity and a fortiori familiarity that is more impaired than recollection in PD unless it is argued, contrary to most evidence, that making accurate familiarity judgements is at least as effortful as recollection. It is, of course, possible (indeed likely) that all PD patients show different combinations of prefrontal and medial temporal lobe dysfunction, in which case the possible diversity of familiarity versus recollection deficits indicated above can be explained by the two hypotheses.

There is only one PD study, the design of which seems similar to our study reported here, but the findings of which, if reliable, are inconsistent with any combination of the above two hypotheses. In this study, Cohn, Moscovitch, and Davidson (2010) argued for a double dissociation between familiarity and recollection as a function of how semantically unrelated word pairs were encoded. When patients encoded the word pairs as they chose, familiarity was impaired and recollection intact, whereas when they generated sentences intended to link the unrelated words together, recollection was impaired and familiarity was intact. However, there are a number of reasons for exercising caution about the reliability of their findings. First, only 9 PD patients and 9 controls were included, when much larger groups are probably needed to provide reliable and replicable results given that the recollection and familiarity deficits are relatively small and PD patients as a group are highly heterogeneous. Second, familiarity and recollection were estimated using a process dissociation procedure. Concerns about the ability of this procedure to provide accurate estimates of familiarity and recollections have already been discussed in relation to earlier work published by the same group (Davidson, et al., 2006). Third, possibly related to the previous problem, control recollection estimates were surprisingly low in the spontaneous encoding condition, and were similar to that of their PD group, as well as a previously studied group of mildly amnesic patients who had undergone unilateral medial temporal lobe resections (Cohn, McAndrews, & Moscovitch, 2009).

Cohn, et al. (2010) argued that the PD recollection deficit suggests hippocampal dysfunction whereas the PD familiarity deficit reflects a strategic (organizational) and related attention deficit caused by striato-frontal dysfunction. However, there is evidence that providing a good semantic elaborative encoding strategy improves PD recall (e.g., Knoke, Taylor, & Saint-Cyr, 1998; Van Spaendonck, Berger, Horstink, Borm, & Cools, 1996), and similar effects have been noted in amnesics (e.g., Mayes et al., 1980). Further, even if PD familiarity was increased by giving sentence generation instructions (because it is not completely automatic), contrary to what was reported, it would be expected to increase less than recollection, which is typically more effortful. Finally, executive functioning was not assessed. However, it seems likely that, to the extent that they were typical PD patients, it would have been impaired and the patients and their controls would not have performed the unguided sentence generation task in the same way, raising the possibility that the patients may have produced sentences that did not improve recollection.

The purpose of the current study was to explore whether memory impairment in PD patients without dementia is better predicted by the prefrontal/organizational hypothesis or by the medial temporal lobe/amnesia-like hypothesis using a design that was not constrained by the limitations identified in the previous Cohn et al. (2010) study. To this end, using a large group of patients and controls, we compared the effects of guided elaborative encoding as well as guided elaborative encoding and retrieval versus spontaneous encoding and retrieval on PD and healthy matched control word recognition, familiarity and two kinds of recollection. These kinds of memory were examined using a slightly modified version of the remember/know procedure that fitted well with a source recall task. Executive functions as well as depression were also carefully assessed. The prefrontal/organizational hypothesis predicts that, when guided elaborative encoding (or guided encoding and retrieval) remove the need to use effortful executive processes in order to encode efficiently for subsequent recollection, PD recollection will improve markedly more than that of their controls or possibly even become completely normal. In contrast, the medial temporal lobe/amnesia-like hypothesis predicts that, assuming the piloting was successful, the patients' recollection will improve in the guided conditions relative to the spontaneous encoding condition, but to the same extent as that of the controls. Whether one or both of the hypotheses

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

applies to PD patients, familiarity should not be affected by the two guided conditions. This was because according to the prefrontal/organisational hypothesis, familiarity, depends much less on executive function than intentional recall, and according to the medial temporal lobe/amnesia-like hypothesis, familiarity, is relatively automatic kind of memory. Therefore, this kind of memory should not be affected by elaborative guided encoding designed to enhance semantic links between the paired words and more indirectly the links between the words and thoughts during the more elaborate encoding activity rather than systematically affect the encoding of individual words.

By chance, our study's unguided condition (C1) in which encoding was spontaneous and unguided at encoding and retrieval and our partial guidance condition (C2) in which guidance was only provided at encoding were quite similar to the read and sentence generation conditions respectively in the Cohn, et al. (2010) study, although the full guidance condition in which guidance was given both at encoding and at retrieval (C3) was unique to our study. However, although both studies required participants to study unrelated word pairs, there was a major difference between C2 and the Cohn et al. sentence generation task. Whereas they left participants to generate their own sentences we actually provided sentences known to be beneficial to memory and required participants to judge how well they linked the paired words to ensure that attention was paid to the sentences' meaning. To the extent that executive function was disturbed in the PD patients, one would expect them to be impaired at generating suitable sentences or even generating them at all, and Cohn et al. do not report whether this was so. Incidentally, our study allowed us to determine whether anything like Cohn et al.'s different encoding-dependent patterns of memory results were produced in a much larger group of PD patients where we could be much more confident that patients really did encode in a similar way to their controls in C2 and C3. We also estimated familiarity and recollection using a modified form of the remember/know (R/K) procedure (Tulving, 1985) rather than the process dissociation procedure (or other procedures for estimating familiarity and recollection) because we believed that the R/K procedure is more reliable if used with care (see Migo et al., 2012 for a discussion of this issue). Our modification also allowed us to measure both objectively scorable source recall of the paired word with which tested words were encoded at study as well as the more standard subjective recollection that scored recall of any other study associates of the tested word. We piloted the three encoding conditions to increase the likelihood that the guided encoding conditions would improve recognition and recollection in healthy older controls.

As PD executive function impairments are expected according to the prefrontal/organizational hypothesis we measured some aspects of executive function in our participants and also measured depressive symptoms. As both executive dysfunction and subclinical depressive symptoms were present in the patients, we tested whether they may have contributed to any of the observed memory deficits by correlating them with familiarity and a combined measure of the two kinds of recollection in the three conditions.

2. Materials and method

2.1. Participants

Thirty patients were recruited from the PD outpatient clinic in the Department of Neurology, University Hospital of North Staffordshire. Patients were screened for adverse clinical events or issues (e.g. drastic medication changes, fatigue, distress) that might affect performance in the study. The PD group were in the moderate stages of the condition with a mean illness duration of 6.31 years (SD, 3.34 years), mean medicated modified Hoehn and Yahr disease severity rating of 2.53 (SD, .9, Hoehn & Yahr, 1967) and mean medicated Unified PD Rating motor subsection score of 13.38 (SD, 5.08, Fahn & Elton, 1987).

A group of twenty-two healthy controls provided control data for the recognition memory tasks. They were matched to the PD patients for age and current levels of functioning (*Minimental state examination*, Folstein, Folstein, & McHugh, 1975; *Wechsler Abbreviated Scale of Intelligence*, Wechsler, 1999).

The demographic, neuropsychological and clinical (patients only) characteristics of the healthy control and PD groups are provided in Table 1.

Patients were tested in a medicated state (within 90 min of taking their morning medication), and at the time of testing, were on a mixture of medication regimens that included either L-dopa, a second generation dopamine agonist (pramipexole, ropinirole or rotigotine) or a monoamine B enzyme inhibitor as either monotherapy or in various combinations. The mean L-dopa equivalent dose was 635.71 mg (SD, 463.86).

Exclusion criteria for all participants included a *Minimental* score of 25 or less, presence or a history of a psychiatric or neurological illness including diagnosable dementias such as Alzheimer's Disease (apart from the PD patients in the index group), history of substance abuse (such as alcoholism), currently taking antidepressants, learning difficulty

Table 1 – The demographic, neuropsychological and clinical (patients only) characteristics for the groups of controls and patients.

Parameter	Healthy controls ($n = 22$)	Parkinson's patients ($n = 30$)
	Mean (SD)	Mean (SD)
Age (years)	65.50 (5.25)	64.38 (6.51)
Current levels of functioning		
MMSE[a]	29.00 (.95)	29.06 (1.12)
WASI[b] (full scale IQ)	108.83 (8.67)	109.69 (14.1)
Illness duration (years)	–	6.31 (3.34)
Modified Hohn and Yahr disease severity rating	–	2.53 (.90)
UPDRS[c] (motor subsection)	–	13.38 (5.08)
Equivalent Dopamine Load (mg/day)	–	635.71 (463.86)

Notes and abbreviations.
[a] MMSE, Mini Mental State Examination.
[b] WASI, Wechsler Abbreviated Scales of Intelligence.
[c] UPDRS, motor subsection of the Unified Parkinson's Disease Rating Scale.

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

(including dyslexia), or English as a second language. Additional exclusion criteria for the patients included a history of visual hallucinations and/or delusions, dyskinesias, impulse control disorders, and commencement of dopaminergic medication within the two months prior to entering the study.

The study was approved by the Keele University Faculty of Humanities and Social Sciences Research Committee and South Staffordshire NHS Research Ethics Committee, and conducted in accordance with Good Clinical Practice.

2.2. *Experimental recognition memory test*

2.2.1. *Stimuli*

Three Yes-No recognition memory tests (RMT) were constructed from a pool of 150 verbal paired associates (VPAs). The VPAs were created by asking fifteen undergraduates to generate an associate for each of one hundred and fifty words (mean imagery 6.05, SD .49; mean concreteness 6.27, SD .65; mean frequency 3.39, SD .90). The VPAs that were least frequently associated to the first word formed the second word in each word pair. This process created further one hundred and fifty weakly associated VPA. The VPAs were randomly assigned to the three recognition memory tests, with each version containing fifty word pairs. In the spontaneous encoding and retrieval condition, the target stimuli comprised word pairs (e.g. **IRON – CREASE**).

A further one hundred and fifty nouns (mean imagery 5.52, SD .68; mean concreteness 5.33, SD, 1.13, mean frequency 3.28, SD, 1.34) formed the lures (i.e. new words) for the test sessions. None of the lures appeared in the target VPAs used during the study phase. The distracters were randomly assigned to three packs, each containing fifty words. At test, first or second words from the VPAs and never both words from any one pair were randomly selected and presented in a random mixed order, intermixed with fifty lures. Assignment of packs of lures and target VPAs, and whether the first or second word from each word pair was presented at test, were counterbalanced across participants.

2.2.2. *Procedure*

All participants completed the same three RMT conditions, administered in the same sequence (C1, followed by C2, in turn, followed by C3). The sequence in which the conditions were completed was not counterbalanced to prevent carry-over of organisational strategies between C3 and C2, and between each guidance condition and the baseline/no guidance condition (C1). Each RMT was completed at the same time of day on three non-consecutive days. Each condition was presented and delivered in exactly the same manner in all respects apart from the form in which the target VPAs were presented at study and the accompanying instructions provided at study and test.

In the first RMT condition, C1, participants viewed the VPA and were given standard encoding and retrieval instructions (see the following section for details). In the second and third RMT conditions, C2 and C3, the VPA were embedded in sentences that provided a connection between the two associates. For example, for the VPA '**TELEPHONE – PLUG**', the target sentence read "The **TELEPHONE** was located close to the wall **PLUG**". Directed encoding guidance was combined with standard retrieval instructions in C2, and with directed retrieval guidance in C3.

The target VPAs in C1, and sentences in C2 and C3, were each displayed for 9000 msec during the *study* phase, and participants also had a 9000 msec window in which to either endorse or reject the probe during the test phase. The second test stage for endorsed items which required participants to make a *remember*, *know* and source recall response was not time constrained.

A 25 min interval that separated the *study* and *test* phases was filled with non-verbal neuropsychological testing (see below). The session occurred at the same time in the morning for all of the participants. Prior to administering the first RMT, participants were familiarized with the experimental set-up, stimuli and task requirements, including types of responses they were required to make using tailored practice tests. None of the word pairs or new words used in the practice test appeared as new words or word pairs in the main RMT.

2.2.3. *Instructions*

The following "standard" instructions were given to participants prior to commencing the study phase in C1: '*I am going to show you fifty pairs of words written in bold letters that are slightly related to each other. Read each word pair aloud. Do your best to commit them to memory because I will be testing your memory for the items later*'. The "standard" retrieval instructions provided immediately prior to test in C1 and C2 were: "*Now, I am going to test your memory for the words I have just shown you.*"

The guided encoding instructions in C2 and C3 were: '*I will show you fifty pairs of words in bold letters. Each will appear in a sentence that helps connect the words. I want you to read the sentence aloud and say whether you think that it relates the words well or not. This will help you remember the words when I test your memory shortly after the study session has finished. We have tried to make the sentences so that they help relate the words so do not worry if you think that most or, even all, the sentences do this.*'

The additional guidance provided at test in C3 was '*It* will help you to do the task if you try to remember the sentence that you were shown during the study session.'

2.2.4. *Performance measures*

Correct identification of a target item was defined as a *hit*, whilst false recognition of a lure was termed a *false alarm*. Following each endorsement, irrespective of whether it was a hit or false alarm, participants were first asked to make a judgement about whether their recognition was accompanied by either recollection of specific details, in addition to the word paired with the tested word at study associated with studying the tested word earlier ('*remember*' response) or by feelings of familiarity without any recollection ('*know*' response). Recall of the source word was prompted by the experimenter if it had not already been spontaneously produced.

A correction has been made to the data to eliminate extreme scores in accordance with Snodgrass and Corwin's (1988) recommendation. Familiarity and recollection memory discrimination scores were made by first computing the familiarity and recollection hit rates and false alarm rates. In order to calculate the hit and false alarm rates for familiarity, it was assumed that recollection and familiarity are

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

stochastically independent at retrieval, and therefore, Yonelinas and Jacoby's (1995) independence formula has been applied to the corrected *know* scores (Familiarity = *know*/[1−*remember*]) . Estimates of recognition and familiarity were calculated using signal detection theory (*d'*), and a threshold measure (*pr*) is reported for subjective recollection and source recall (i.e. hit rate minus false alarm rate). Based on fMRI data, introspective experience and general plausibility arguments, there are strong reasons to suppose that this assumption is much nearer to reality than that familiarity and recollection have an exclusivity relationship or that, every recollection response is always accompanied by a familiarity response (redundancy) (see Migo et al., 2012 for a full development of these arguments).

2.2.5. *Remember-know instructions*

Participants were instructed that a *remember* response could be given only if, when presented with a probe item, they recollected at least one of the following: (i) the item that appeared just before or after the currently being tested "probe" item during the study session; (ii) personal memories, mental images, or words that came to mind when the probe was presented during the study session; (iii) an emotional reaction that the currently being tested probe triggered during the study session. These instructions aim to ensure that recollection is only reported when a participant has recalled one or more things that they were thinking of when they were processing the probe during study. It is important to stress that remember judgements specifically *did not* include source recall of the word paired at study with the tested word.

Know responses were only recorded if participants recognised the probe as having been presented in the study session, but did not recall any specific details, including the paired word about it from the study session. Although guess responses are sometimes also included in the *remember/know* procedure, they were not used for two reasons. Their use is unwarranted because familiarity memory discrimination scores were corrected using the familiarity false alarm rate so if any familiarity response was really a guess rather than a weak familiarity response, this was fully corrected. The second reason that we did not use guess responses was that it is likely that the extra complexity will confuse participants. Such confusion is highly undesirable because there is evidence that unless instructions are kept simple and are fully understood, participants can too frequently fail to follow them properly (see Migo et al., 2012 for a full discussion of these points).

Participants were asked to justify each *remember* and *know* judgement throughout the test phase to ensure that they maintained a full understanding of the criteria for making these types of decisions in line with published recommendations on measuring recollection and familiarity using the *remember/know* procedure recommended by Migo et al. (2012).

2.3. *Neuropsychological tests*

Controls and patients completed a depression questionnaire (*Hamilton Depression Inventory*, Reynolds & Koback, 1995) , a test of executive function (*The Brixton Test of Spatial Anticipation*, Burgess & Shallice, 1997) and an independent measure of delayed verbal recall (*Logical Memory* delayed verbal recall subtest from *The Wechsler Memory Scales*, Wechsler, 1997), which previous studies indicate are impaired in PD (e.g., Cooper, Sagar, Jordan, Harvey & Sullivan, 1991; Crescentini, Mondolo, Biasutti, & Shallice, 2008; Edelstyn et al., 2007; Shepherd et al., 2013) . The questionnaire and both tests were administered according to their respective manuals.

2.4. *Data analysis*

To examine the effects of guidance instructions on the performance measures, a series of 2 by 3 mixed analyses of variance (ANOVA) were conducted with Group (PD group *vs* healthy controls) as the between subjects factor; and memory condition (C1 *vs* C2 *vs* C3) as the within subjects factor. Significant main effects and interactions were investigated further using planned pair-wise comparisons.

The effect of increasing strategic guidance on memory performance within each group was also examined using paired samples *t*-tests.

A series of bivariate correlational analyses, using Pearson's product moment coefficients, explored the relationship between the measures of subclinical depressive symptoms, executive function, delayed verbal recall, RMT performance measures (familiarity [d'] and a composite measure of recollection [pr] in C1, C2 and C3) in a subset of participants (17 PD patients and 10 healthy controls). The reported correlations have not been corrected for multiple comparisons as their purpose was to examine whether there was any evidence, however, weak, that impaired dysexecutive processing driven by prefrontal dysfunction and/or subclinical depression might also be contributing, at least to a small extent to the PD memory deficits.

3. Results

The raw hit and false alarm rate (HR, FAR, respectively) means and standard deviations for item recognition memory (RM), *know*, *remember* and source recall by group are shown in Table 2. The estimates of item RM (*d'*), familiarity (*d'*), subjective recollection (*pr*) and source recall (*pr*) are also shown in Table 2 and in Fig. 1.

3.1. *Comparisons between PD patients and controls*

Analysis of item recognition (*d'*) revealed main effects of *Group* [$F(1,50) = 12.81$, $\eta^2 = .23$, $p = .001$] and *Condition* [$F(2,50) = 3.83$, $\eta^2 = .08$, $p = .026$], but the *Interaction* between *Group* and *Condition* was not significant [$F(2,50) = .78$, $\eta^2 = .02$, $p = .46$]. Item recognition in the PD patients was significantly lower than in the healthy controls in C1 [$t(50) = -3.53$, $p = .001$] C2 [$t(50) = -2.34$, $p = .02$] and C3 [$t(44) = -2.85$, $p = .01$].

The second ANOVA of familiarity (*d'*) showed a main effect of *Group* [$F(1,50) = 4.01$, $\eta^2 = .0.84$, $p = .051$] but not of *Condition* [$F(2,50) = 2.38$, $\eta^2 = .05$, $p = . 9$], and the interaction was also not significant [$F(2,50) = 2.00$, $\eta^2 = .04$, $p = . 14$]. Familiarity in the PD patients was significantly lower than in the healthy controls in C1 [$t(50) = -2.18$, $p = .034$] but not in either C2

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

Table 2 – Mean hit rate, false alarm rate for recognition memory, know, remember, source recall, and estimates of recognition memory (*d'*), familiarity (*d'*), subjective recollection (pr) and source recall (pr) are shown for the groups of controls and patients for each the three experimental recognition memory test conditions.

	Recognition memory			Know			Remember			Source recall		
	HR	Far	RM (*d'*)	HR	Far	Fam (*d'*)	HR	Far	Recoll (pr)	HR	Far	Source (pr)
Condition 1: Spontaneous encoding and retrieval												
Controls	37.41	4.23	2.23	10.45	2.55	2.02	25.64	1.86	.47	19.41	2.41	.30
1 SD	7.34	2.71	.89	4.55	2.20	2.14	9.52	2.03	.22	5.42	2.12	.10
Patients	28.67	5.17	1.55	17.20	4.70	1.25	10.50	.57	.20	8.47	.90	.15
1 SD	7.98	4.03	.53	8.00	4.12	.53	634.00	.94	.12	7.34	1.49	.15
Condition 2: Partial guidance (encoding only)												
Controls	36.95	3.73	2.33	9.00	2.64	1.51	24.32	1.95	0.5	20.56	2.88	.33
1 SD	7.85	2.71	.63	3.99	2.50	.62	10.83	1.76	.22	6.75	2.91	.17
Patients	30.43	3.50	1.87	11.77	3.30	1.23	15.57	.40	.30	12.87	.33	.25
1 SD	8.85	3.36	.58	6.12	3.57	.69	6.35	.77	.13	8.92	.66	.18
Condition 3: Full guidance (encoding and retrieval)												
Controls	37.75	2.81	2.38	6.31	2.13	1.34	30.38	1.50	.57	23.00	2.09	.41
1 SD	8.39	1.83	.53	4.21	1.63	.53	11.47	.68	.23	9.00	2.07	.18
Patients	28.7	2.80	1.90	9.83	2.47	1.22	16.93	.33	.33	13.45	.43	.26
1 SD	7.72	5.57	.56	4.71	3.42	.42	6.63	.66	.13	9.37	.63	.19

Notes and abbreviations: HR, FAR, Hit rate and False alarm rate, respectively; Recoll, subjective recollection; Source, source recall; *d'*, signal detection mesure of discrimination accuracy; pr, threshold measure of accuracy; 1 SD, one standard deviation. Six PD patients and four controls were lost to follow up between conditions 2 and 3.

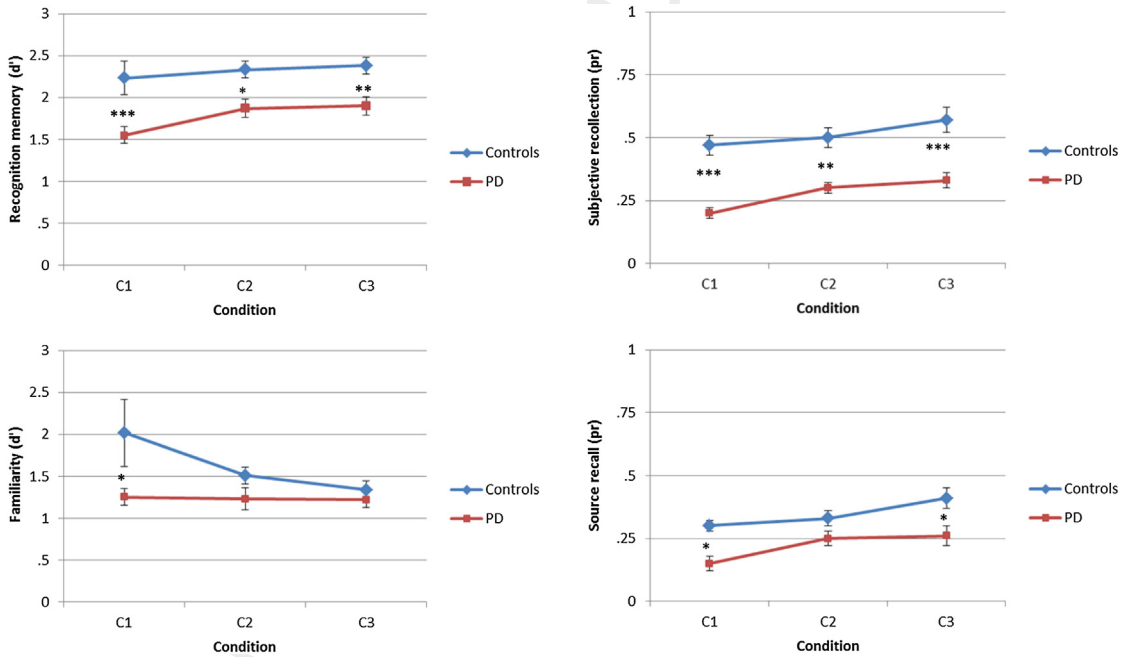

Fig. 1 – Estimates of recognition memory (*d'*), familiarity (*d'*), subjective recollection (pr) and source recall (pr) are shown for the groups of controls and patients for the three experimental recognition memory test conditions. Notes and abbreviations: Significant at $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. C1, baseline condition where participants are reliant on spontaneously generated encoding and retrieval strategies; C2 and C3 provide guidance at encoding (C2) and additionally at retrieval (C3).

[$t(50) = -1.39$, $p = .17$], or C3 [$t(44) = -.83$, $p = .39$] where partial and full guidance were provided respectively.

Analysis of subjective recollection (*pr*) was marked by main effects of *Group* [$F(1,50) = 27.46$, $\eta^2 = .38$, $p < .001$] and *Condition* [$F(2,50) = 17.50$, $\eta^2 = .29$, $p < .001$], but the interaction was not significant [$F(2,50) = 1.69$, $\eta^2 = .04$, $p = .19$]. Subjective recollection in the PD patients was significantly lower than in the healthy controls in each of the three conditions [C1: $t(50) = -6.21$, $p < .001$; C2: $t(50) = -2.99$, $p = .004$ and C3: $t(44) = -4.62$, $p < .001$].

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

The final ANOVA of source recall (*pr*) showed main effects of *Group* [$F(1,50) = 7.58$, $\eta^2 = .16$, $p = .009$] and *Condition* [$F(2,50) = 6.14$, $\eta^2 = .14$, $p = .003$], but the interaction was not significant [$F(2,50) = 7.03$, $\eta^2 = .03$, $p = .30$]. Source recall in the PD patients was significantly lower than in the healthy controls in C1 and C3 [C1: $t(50) = -2.44$, $p = .02$; C3: $t(39) = -2.35$, $p = .02$] but not in C2 [$t(50) = -.41$, $p = .69$].

To compare the relative severity of impairment, estimates of familiarity, subjective recollection and source recall in the unguided/spontaneous encoding and retrieval condition (C1) were converted to standard scores. A paired-samples *t*-test showed familiarity ($z = -.32$) to be significantly less impaired than both subjective recollection [$z = -1.45$, t (29) = 10.0, $p < .001$] and source recall [$z = -1.65$, t (29) = 5.83, $p < .001$], whereas subjective recollection and source recall showed comparable levels of decline [t (29) = .96, $p = .34$].

3.2. *Effects of guidance within each group*

Paired sample *t*-tests showed PD patients' RM, subjective recollection and source recall each improved with guidance (C2, C3) compared to baseline (C1). But the amount of memory improvement did not increase when guidance was given both at retrieval and encoding (C3) compared to encoding alone (C2) [RM, C1–C2: $t(29) = -2.8$, $p = .009$; C1–C3: $t(29) = -2.92$, $p = .007$; C2–C3: $t(29) = -.28$, $p = .78$; subjective recollection, C1–C2: $t(29) = -5.12$, $p < .001$; C1–C3: $t(29) = -5.0$, $p < .001$; C2–C3: $t(29) = -1.14$, $p = .26$; source recall, C1–C2: $t(29) = -2.7$, $p = .011$; C1–C3: $t(29) = -2.69$, $p = .01$; C2–C3: $t(29) = -.37$, $p = .71$].

In contrast, there was no effect of guidance on PD familiarity between any of the contrasted guidance conditions [C1–C2: $t(29) = .16$, $p = .88$; C1–C3: $t(29) = .3$, $p = .77$; C2–C3: $t(29) = .08$, $p = .93$].

The healthy controls showed improvements in both subjective recollection and source recall between the unguided (C1) and full guidance (C3) conditions [subjective recollection, $t(15) = -3.1$, $p < .01$ and source recall: $t(10) = -2.51$, $p = .03$, respectively]; partial and full guidance conditions C2–C3 [subjective recollection: $t(15) = -2.55$, $p = .02$; source recall: $t(10) = -2.23$, $p = .05$] but not between unguided (C1) and partial guidance (C2) [subjective recollection: $t(21) = .78$, $p = .44$; source recall: $t(22) = -.36$, $p = .72$].

A borderline decrease in familiarity was present between unguided and partial guidance conditions [$t(21) = 2.04$, $p = .06$] but not between unguided and full guidance or between partial and full guidance [C1–C3: $t(15) = 1.94$, $p = .072$; C2–C3: $t(15) = 1.24$, $p = .23$].

There were no changes in RM between any of the guidance conditions [RM, C1–C2: $t(21) = -.49$, $p = .63$; C1–C3: $t(15) = -.85$, $p = .41$; C2–C3: $t(15) = -.38$, $p = .64$].

In summary, patients with mild to moderate PD (mean HY 2.53) displayed deficits in source recall and subjective recollection whereas item familiarity was markedly less impaired. There was no evidence that the PD group gained more advantage from partial guidance (at study only) than the controls (compare C1 with C2). However, patient subjective recollection and source recall remained impaired even with full guidance at test as well as at study, and, critically, the two groups improved to the same extent when C3 was compared to C1. These findings are illustrated in Fig. 2.

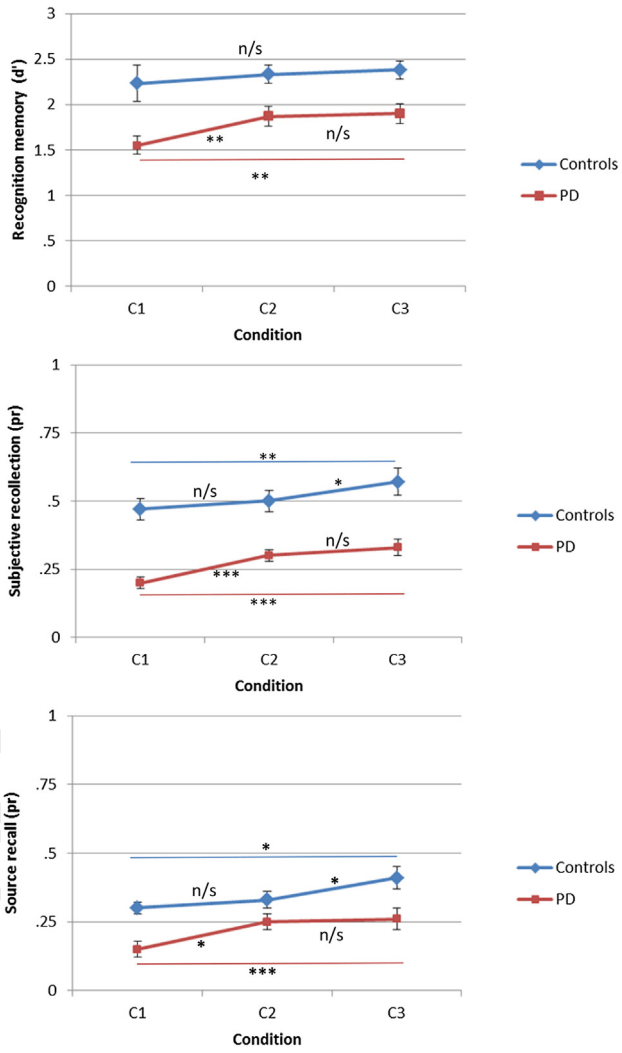

Fig. 2 – Effect of the three experimental recognition memory test conditions on within group estimates of recognition memory (*d'*), subjective recollection (pr) and source recall (pr) for the groups of controls and patients. Notes and abbreviations: Significant at $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. C1, baseline condition where participants are reliant on spontaneously generated encoding and retrieval strategies; C2 and C3 provide guidance at encoding (C2) and additionally at retrieval (C3). N/s, not significant $p > .05$.

3.3. *Neuropsychological and depression scores*

Scores on the Brixton Test, Logical Memory and Hamilton Depression Inventory are shown in Table 3.

Compared to the healthy controls, PD patients showed evidence of executive dysfunction [*Brixton Test*, t (25) = −2.6, $p = .02$], impairment in delayed verbal recall [*Logical Memory*

Table 3 – Neuropsychological and depression scores for the groups of controls and patients.

Parameter	Healthy controls ($n = 17$)	Parkinson's patients ($n = 10$)
	Mean (SD)	Mean (SD)
Brixton Test	5.85 (.8)	3.39 (2.51)***
Logical Memory (30 min delay)	31.39 (4.48)	21.59 (7.05)***
Hamilton Depression Inventory	4.61 (2.93)	11.92 (6.16)**

Notes and abbreviations: significant at *$p < .05$, **$p < .001$, ***$p < .001$.

delayed verbal recall, $t\ (25) = -5.07$ $p < .001$] and significantly elevated rates of subclinical depressive symptoms [*Hamilton Depression Inventory [HDI]*, $t\ (25) = -2.45$ $p = .021$].

3.3.1. *The PD group*

HDI scores weakly correlated with overall recollection in the unguided, partial and full guidance conditions, respectively [C1: $r(17) = -.36$, $p = .077$; C2: $r(17) = -.46$, $p = .03$; C3: $r\ (17) = -.36$, $p = .078$, respectively]. HDI scores also failed to correlate with the C3–C1 difference score for overall recollection ($r = -.04$, $p = .83$).

Delayed story recall correlated with overall recollection in each of the three conditions [C1: $r\ (17) = .62$, $p = .004$; C2: $r\ (17) = .59$, $p = .007$ and C3: $r(17) = -.48$, $p = .024$].

Executive function was correlated with unguided overall recollection rates in C1 only [$r\ (17) = .46$, $p = .03$], and failed to correlate with overall recollection in the presence of partial guidance at encoding [C2: $r\ (17) = .31$, $p = .11$] and full guidance at encoding and retrieval [C3: $r\ (17) = .13$, $p = .31$]. Executive function also failed to correlate with the C3–C1 difference score for overall recollection ($r = -.11$, $p = .64$).

Familiarity rates in the unguided and guided conditions failed to correlate with HDI scores [C1: $r\ (17) = -.07$, $p = .39$; C2: $r\ (17) = .14$, $p = .29$; C3: $r\ (7) = .09$, $p = .37$], executive function [C1: $r\ (17) = .27$, $p = .14$; C2: $r\ (17) = -.34$, $p = .09$; C3: $r\ (17) = -.08$, $p = .38$], delayed recall [C1: $r\ (17) = .27$, $p = .15$; C2: $r\ (17) = -1.02$, $p = .35$; C3: $r\ (17) = -.04$, $p = .44$] and overall recollection [C1: $r\ (17) = .26$, $p = .15$; C2: $r\ (17) = -.20$, $p = .23$; C3: $r\ (17) = -.22$, $p = .20$].

Finally, HDI scores showed border-line correlations with delayed recall and executive function [$r\ (21) = -.39$, $p = .06$; $r\ (21) = -.41$, $p = .05$, respectively].

In summary, PD executive function correlated with unguided overall recollection only, and failed to correlate with the C3–C1 difference score for overall recollection. HDI scores weakly correlated with overall recollection in the unguided, partial guided and fully guided conditions, but failed to correlate with the C3–C1 difference score for overall recollection.

3.3.2. *The healthy controls*

Overall recollection failed to correlate with HDI scores and familiarity estimates and in the unguided and guided conditions [depression, C1: $r\ (10) = .28$, $p = .22$; C2: $r\ (10) = .12$, $p = .37$; C3: $r\ (10) = -.38$, $p = .14$; familiarity,C1: $r\ (10) = .03$, $p = .46$; C2: $r\ (10) = .47$, $p = .09$; C3: $r\ (10) = .42$, $p = .12$]. Executive function was not correlated to overall recollection in any of the conditions [C1: $r\ (10) = -.23$, $p = .26$; C2: $r\ (10) = .19$, $p = .30$; C3: $r\ (10) = -.20$, $p = .29$]. Delayed recall weakly correlated to overall recollection in C2 but not in either C1 or C3 [C1: $r\ (10) = .14$, $p = .35$; C2: $r\ (10) = -.52$, $p = .06$; C3: $r\ (10) = -.36$, $p = .16$].

Estimates of familiarity correlated to executive function and delayed recall in the full guidance condition only [executive function, C1: $r\ (10) = .34$, $p = .17$; C2: $r\ (10) = -.21$, $p = .28$; C3: $r\ (10) = -.6$, $p = .034$; delayed recall, C1: $r\ (10) = .23$, $p = .26$; C2: $r\ (10) = .07$, $p = .4$; C3: $r\ (10) = .05$, $p = .05$]. There were no correlations between familiarity and depression rates [C1: $r\ (10) = -.33$, $p = .18$; C2: $r\ (10) = .04$, $p = .46$; C3: $r\ (10) = -.06$, $p = .43$]. There were also no correlations between depression levels and executive function [$r\ (10) = -.33$, $p = .18$], depression levels and delayed recall [$r\ (10) = .02$, $p = .48$], or executive function and delayed recall [$r\ (10) = -.36$, $p = .16$].

4. General discussion

In all three of the learning and test conditions used in our study, a large group of non-dementing mild to moderate PD patients were impaired at the two kinds of cued recall examined: source recall of words paired at study with the tested words and subjective recollection of other associations with the tested words from the study episode. Contrary to the findings in our previous work, the patients were also impaired at word familiarity, although their familiarity deficit was very modest and significantly smaller than their impairments in both kinds of cued recall. Given the dependence of recognition test performance on both familiarity and recollection, it was unsurprising that the patients showed an overall deficit in word recognition in each of the 3 conditions. In separate tests, the patients also were clearly impaired at delayed free recall of short stories (i.e., delayed logical memory) and, as is often found with mild to moderate PD patients, they showed impaired executive functions as well as significantly elevated levels of subclinical depressive symptoms relative to their controls.

Most importantly, in the PD patients as well as their controls, both kinds of cued recall were significantly increased with full guidance at encoding and retrieval compared to the unguided condition (C3 *vs* C1). As the amount of cued recall improvement shown by patients and controls was similar, this indicates that full guidance relative to no guidance for both groups was equally beneficial for their cued recall. This finding fits broadly with what should be expected if the PD patients' cued-recall impairment is primarily driven by a medial temporal lobe/amnesia-like deficit rather than a breakdown in prefrontal cortex-dependent organisational processes.

However, although there was no cued recall interaction between group and degree of guidance, individual *t*-tests suggested that PD patients' main cued recall benefit was provided by encoding guidance and that they gained little extra from additional retrieval guidance. In contrast, with controls, these effects were the other way round with them gaining little from encoding guidance, but significantly from retrieval guidance. There is a danger of overinterpreting this effect, which may be a statistical anomaly and can at most only

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

indicate a weak effect. Such a weak effect may or may not turn out to be genuine when examined by a future study that would have to include many more patients than did the current study (probably around 100) to have sufficient power for a convincing examination. If it did prove to be a real but weak effect, it would most likely indicate that patients and controls used a slightly different strategy with the guidance offered. For example, the less confident patients might have tried to think of what they had encoded when tested even when not given explicit retrieval instructions to do this whereas the more confident controls did this much less unless explicitly asked to do so in the full guidance condition. Whether or not this happened, however, the fact that full guidance improved patient and control cued recall to the same significant degree, is incompatible with the PD recollection deficit being appreciably affected by a prefrontal/executive impairment.

PD word familiarity, on the other hand, did not differ across the 3 conditions, being unaffected by the kinds of guidance which we provided. Although the group by guidance condition was not significant, the controls showed an insignificant tendency to perform more poorly on this measure in the guided conditions (C2 and C3) than in the spontaneous condition (C1), which accounted for the hint of a PD familiarity deficit in the spontaneous versus guided conditions. However, the lack of a guidance condition interaction with group for familiarity together with the lack of effect of condition indicates that the weakly significant PD familiarity deficit noted in C1, if reliable, is more likely to reflect perirhinal cortex/medial temporal cortex dysfunction rather than frontal cortex dysfunction, contrary to the proposal of Cohn et al. (2010). This point has been discussed previously in the Introduction in relation to functional imaging work (see Henson et al., 1999), prefrontal lesion studies (Duarte et al., 2005; MacPherson, et al., 2008) and behavioural evidence from older adults (Anderson, et al., 2008), and is explored further in later sections of the Discussion with reference to modulation of hippocampal function by the dopaminergic midbrain, evidence of hippocampal atrophy in nondementing PD, and Braak et al.'s (2003) staging model of PD.

The significant correlation of delayed free recall of short stories with the measure of overall recollection, a composite measure of both kinds of cued-recall, but not word familiarity, in all three conditions was consistent with the view that these kinds of cued-recall memory have overlapping functional and neural mechanisms whereas they have relatively distinct underlying processes and neural bases from item familiarity. This view is further reinforced by the failure of familiarity to correlate with overall recollection in guided as well as unguided conditions.

The significant correlation of executive functions in the PD patients only with unguided overall recollection in C1 suggests that the patients' impaired executive functions may have slightly worsened their spontaneous processing, but that the guided conditions markedly reduced the need to rely on these dysexecutive functions. The patients' executive function failed to correlate with the C3–C1 difference score for overall recollection which is again consistent with the view that a frontal dysexecutive impairment is not a major cause of the PD memory disorder. Finally, the absence of a correlation between the patients' executive functions and familiarity in any of the conditions is compatible with familiarity being unhelped by guidance. This finding is expected because familiarity seems to be a relatively automatic kind of memory, which is dependent on the perirhinal cortex and its connections. However, weak and, as yet unspecified, prefrontal contributions may be present that need not involve the frontal executive processes that probably support intentional cued-recall. Even if such executive processes are involved, our results suggest that familiarity depends on them much less than the typically more demanding and effortful cued recall memory.

The tendency for subclinical depressive symptoms in the PD patients to correlate with overall recollection, but not word familiarity, in all three conditions, is consistent with subclinical depressive symptoms contributing to their recollection deficit but not their poorer familiarity memory.

This pattern of results is broadly what would be expected if hippocampal dysfunction/degeneration was a major contributor to our patients' impaired recollection and a smaller degree of dysfunction/degeneration in the perirhinal cortex was a major contributor to their slight impairment in word familiarity. In other words, our findings are broadly consistent with the medial temporal lobe/amnesia-like hypothesis of PD memory. Hippocampal dysfunction would, of course, give rise to inefficient working of a more extended neural system that mediates the kind(s) of memory that underlie recall, whereas perirhinal cortex dysfunction would give rise to inefficient working of a distinct, more extended system that mediates the kind(s) of memory that underlie familiarity.

This interpretation of our findings is consistent with evidence that dopaminergic inputs from the dopaminergic midbrain ventral tegmental area modulate activity in the hippocampus and perirhinal cortex as well as the parahippocampal and entorhinal cortices within the medial temporal lobes through feedback circuits involving projections from the hippocampus via the nucleus accumbens and perirhinal cortex respectively (see Lisman, Grace, & Duzel, 2011 for a review). The role of hippocampal dysfunction in the PD recollection and recall impairment is specifically supported by rodent and imaging studies of healthy human adults, which show that the hippocampus and the ventral tegmental area form a functional loop controlling the entry of novel and salient/goal-directed information into long-term memory (e.g., Bethus, Tse, & Morris, 2010; Bunzeck, et al., 2007; Chowdhury, Guitart-Masip, Bunzeck, Dolan, & Duzel, 2012; Gasbarri, Sulli, & Packard, 1997; for a review see Lisman & Grace, 2005). Dopamine D1 and D2 receptors are also implicated in the persistence/slow consolidation of hippocampal-dependent memories (Hammad & Wagner, 2006; Laszy, Laszlovszky, & Gyertyan, 2005; Lisman, et al., 2011; O'Carroll, Martin, Sandin, Frenguelli, & Morris, 2006; Takahashi, et al., 2008) . However, although functional Q9 disruption of the hippocampal recall-related circuits will result from ventral tegmental area degeneration even if the hippocampus remains largely structurally intact, there is also evidence that indicates there is hippocampal neuropathology in nondementing PD with volume loss particularly associated with the CA2-4 subfields/dentate gyrus (Pereria et al., 2013). Volumetric imaging studies in nondementing PD also report an association between recall but not recognition and

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

hippocampal neuropathology (e.g., Bouchard, et al., 2008; Carlesimo et al., 2012; Filoteo, Reed, Litvan, & Harrington, 2014; Ibbarretxe-Bilbao, et al., 2008; Junqué, et al., 2005; Laakso, et al., 1996; Riekkinen et al., 1998; however, for a counter argument see Apostolova, et al., 2010; Camicioli et al., 2003; Nagano-Saito, et al., 2005; Tam, Burton, McKeith, Burn, & O'Brien, 2005) .

However, the overall pattern of our data (for example, the statistically weaker correlational evidence, which should be taken as suggestive rather than conclusive) indicates that our main findings do not eliminate the possibility that there is a weak contribution from impaired dysexecutive processing driven by prefrontal dysfunction. Furthermore, if it occurs, the extent of prefrontal contribution is likely to vary across different PD patients, although the factors underlying this remain to be fully clarified so a significant effect may not always be found except within very large groups of patients.

Our finding that subclinical depressive symptoms weakly correlated with overall recollection, but not familiarity, in all three conditions suggests that depression in PD may impair recollection selectively in a way that does not need to depend strongly on its effect on executive functions. This is what would be expected if depression causes an amnesia-like memory problem by disrupting the hippocampus because this should impair recollection/source recall equally regardless of whether processing is spontaneous or guided so as to depend less on frontal executive functions, i.e., in all three conditions. In contrast, if depression also acts on the frontal cortex to disrupt executive functions, then the strongest effect should be on the spontaneous condition because this depends more on these functions. This suggests that, if depression also disrupts overall recollection via its disruptive effect on executive functions, then it should correlate with the difference in overall recollection between the spontaneous and most guided condition, i.e., C3 and C31. However, it did not, which also suggests that depression primarily disrupts overall recollection via its effect on the hippocampus to produce an amnesia-like condition, although all these correlations were weak so future work should use much larger participant numbers.

It is well-established that prolonged depression is particularly associated with hippocampal atrophy, which is believed to play a key role in the memory disorder found in depression (e.g., Gradin & Pom, 2008). An interesting, if speculative, possibility is that a component of this atrophy is decreased adult neurogenesis in the dentate gyrus of the hippocampal (for reviews, see Kemperman & Kroneberg, 2003; Sahay & Hen, 2007) . Such decreased neurogenesis in the anterior dentate gyrus would negatively disrupt cellular processes underlying pattern separation in the CA1-4/dentate gyrus subfields of the hippocampus (e.g., Sahay, et al., 2011). . This kind of processing is believed to underlie the kind of associative memory that supports cued recall (e.g., Clelland, et al., 2009).

There is also evidence for less marked and more delayed degeneration in the perirhinal cortex in PD, which is predicted by the staging model according to which neuropathology emerges in the CA2 fields of the hippocampus before it extends to the medial portion of perirhinal cortex (Braak et al., 2003, see also Braak & Del Tredici, 2008; Braak, Del Tredici, et al., 2006; Braak, Rüb, Del Tredici, 2006; see also Pereira, et al., 2013) . However, the relationship of the staging of these degenerative changes and their associated memory changes to clinical severity needs further exploration. In particular, the factors that underlie the relative rates at which hippocampal and perirhinal cortex degeneration occur and the precise mechanisms underlying the degeneration are currently unknown.

Interestingly, if perirhinal cortex atrophy is mainly responsible for our patients' marginal decline in familiarity this may help explain why we have not previously found this kind of memory to be impaired in mild to moderate PD. Unlike our other studies (Edelstyn et al., 2007, 2010; Shepherd et al., 2013), in this one, before testing memory, we used a 25 min delay during which participants were occupied with other tasks. This would have produced interference, which, according to Sadeh, Ozubko, Winocur, and Moscovitch (2014), is the main mechanism responsible for forgetting of perirhinally-supported familiarity memory. This suggestion is consistent with the two previous PD studies reporting a selective familiarity deficit, where a filled delay of 10 min (Davidson, et al., 2006) and 30 min (Weiermann, et al., 2010) was introduced between study and test. In addition, it has been argued that, following perirhinal cortex damage, object/item inputs can no longer be integrated at the highest level in the ventral stream so that item representations are likely to become more similar to each other. As interference is a similarity-based process, it will increase following perirhinal cortex damage so that familiarity impairments will be greater after a delay (Saksida & Bussey, 2010).

Our findings do not preclude the possibility of a PD-related impairment in executive functions contributing to our patients' verbal memory disorder, but they were only very weakly supportive of the possibility. The patients' executive function scores did show a tendency to correlate with overall recollection only in the unguided, spontaneous condition (C1), but if this correlation reflected a causal influence on recollection of the patients' executive impairment, they should have gained more from guidance, particularly full guidance (C3) than their controls. But the interactions between both kinds of recollection and condition were not significant. Recollection/recall did improve more in the patients between C1 and C2, but, this effect was reversed between C2 and C3 with control recollection tending to improve more than patient recollection, albeit not significantly so. This finding is consistent with a recent PD study reporting executive function to be weakly related to verbal episodic recall using factor analysis, canonical regression and structural equation modelling (Alfonso Recio, Martin, Carvajal, Ruiz, & Serrano, 2013).

Future research on different kinds of guidance may clarify whether PD recall memory is disproportionately improved by any kinds of guidance, but our evidence is not suggestive that it does. This would be expected in so far as PD disrupts the functioning of frontal regions that mediate executive functions that facilitate processing at encoding and retrieval. PD has long been associated with dysfunction in some frontal regions and there is evidence that early non-demented PD patients show prefrontal cortex atrophy (e.g., Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004). Although whether the

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

frontal impairments found in PD impair executive functions that disrupt recall remains to be convincingly shown, depression is known to disrupt executive functions and to impair recall (e.g., see Channon & Green, 1999) as well as to disrupt frontal functioning (e.g., Baxter, et al., 1989) so PD patients with subclinical depressive symptoms may well suffer from executive function deficits that exacerbate their amnesia-like recall deficits that are caused by hippocampal dysfunction. In so far as subclinical depressive symptoms contributes to both prefrontal and hippocampal dysfunction, resolution would require a very large study that uses a regression analysis or the use of structural and possibly functional MRI in quite a large study to discover how strongly each structural region relates to the recollection deficit.

Even though our study may seem, on the surface, similar to that of Cohn et al. (2010), particularly with respect to our conditions C1 and C2 and their spontaneous ("Read-only") and guided ("Sentence generation") conditions, the fact that they used process dissociation procedure meant that they tested half the word pairs their participants encoded with a word recognition test and half with an associative word recognition test. Our participants, in contrast, were only tested on word recognition and had to recall the paired words rather than recognize them. Also, Cohn and her colleagues did not set out to deliberately test the hippocampal/amnesia-like hypothesis against the prefrontal/organizational hypothesis. The failure of the sentence generation task to improve recollection in Cohn et al.'s patients unlike in their controls may have arisen because their patients' presumed executive deficits led to their not generating suitable sentences. The need to do this was obviated in our study by the provision of appropriate sentences. However, this difference does not explain the very poor estimated recollection scores of Cohn et al.'s controls in their Read condition, which led to the apparently normal recollection scores of their patients in this condition. We believe it to be more likely that this strange finding as well as Cohn et al.'s findings with word familiarity arose because of distortions resulting from their use of the process dissociation procedure. In particular, associative familiarity may have contributed to different degrees in the two groups across the conditions so that their estimated familiarity and recollection scores were distorted differently.

Although our results suggest that dysfunction in medial temporal lobe structures, perhaps particularly the hippocampus, contributes in a major way to the memory problems in mild to moderate non-dementing PD, this conclusion should be viewed with some caution for several reasons and some qualifications need to be made.

First, the idea of compensating for impaired executive functions by providing easy-to-follow instructions remains to be fully explored. It could be that other compensating tasks will be more likely to lead to a disproportionate improvement in PD recall. Even without such disproportionate improvement, however, patients may find that using better but simple encoding and retrieval procedures produces valuable benefits to everyday recall abilities.

Second, we are not yet sure which kinds of frontally-related executive function disruptions relate most closely to memory impairments. For example, apathy, a common feature of PD (e.g., Barone, et al., 2009; Dujardin, et al., 2007; Pluck & Brown, 2002), contributes to impaired memory (e.g., Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010) and future studies should be careful to control for this.

Third, as previously discussed, there is some evidence that some frontal lesions can impair familiarity. It seems unlikely that this deficit is related to executive function impairment and more likely that the effective damage is to frontal sites that form part of the perirhinal cortex familiarity memory system. However, precisely what the relevant frontal region is and what its exact familiarity-related function is has not yet been explored.

Fourth and related to the previous point, future research will need to use structural and functional MRI to identify the extent to which damage or dysfunction of the hippocampus, perirhinal cortex, parts of the frontal lobes, or other structures relate to recollection/recall and familiarity deficits in PD patients. In such research, it will also be critical to measure structure and functionality of the midbrain dopaminergic systems, damage to which underlies PD.

Fifth, PD is a heterogeneous disorder. Disruption of familiarity and recollection is likely to be influenced by these variable factors, such as the severity of depression, executive functions, and the severity of different kinds of medial temporal lobe dysfunction. This occurs because PD is a syndrome, defined in terms of its characteristic motor symptoms, the severity of which does not always related straightforwardly to cognitive symptoms that are caused by the atrophy of related but distinct structures. In addition, PD patients are treated with a variety of drugs and there is direct evidence that particular drugs can disrupt recall/recollection (e.g., Edelstyn et al., 2010; MacDonald et al., 2013; Shepherd et al., 2013).

Finally, familiarity and recollection are hard to measure so great care must be taken in their measurement. Recollection can be measured directly (as with our source recall measure) and this should be done where possible. But familiarity should either be measured with the RK procedure or a modification of this, such as the familiarity only procedure (see Mayes, Montaldi, & Migo, 2007), ensuring that very careful instructions are given and that checks are made throughout to ensure that participants are following the instructions to the letter.

In summary, medicated, non-dementing mild-to-moderate PD patients exhibited impairments in source recall and subjective recollection as well as a marginal and less severe overall decline in familiarity. Providing full guidance at encoding and retrieval improved source recall and subjective recollection to the same extent in PD and their age matched controls so that PD subjective recollection and source recall remained deficient. On the other hand, familiarity was unaffected by guidance provided at either encoding alone or at retrieval as well as at encoding. The PD pattern of recollection and familiarity response to strategic guidance suggests that their free recall, subjective recollection and source recall impairments are amnesia-like deficits caused at least in part by damage or dysfunction to the hippocampus whereas their milder familiarity impairment may have been caused by perirhinal cortex damage or dysfunction. However, the patients' response to guidance also suggests that their recall and recollection impairments may often arise partly because of a kind of dysexecutive problem caused by damage or dysfunction of parts of the prefrontal cortex. Either way our

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

results provide the hope that poor PD recall and recollection may be usefully helped by given patients guidance to steer more effective encoding and retrieval.

Acknowledgements and funding

The work was supported a grant from by the North Staffordshire Medical Institute. We are also grateful to all our participants for their co-operation.

REFERENCES

Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behavioural Brain Sciences, 122*, 425–489.

Aggleton, J. P., Vann, S. D., Denby, C., Dix, S., Mayes, A. R., Roberts, N., et al. (2005). Sparing of the familiarity component of recognition memory in a patient with hippocampal pathology. *Neuropsychologia, 43*, 1810–1823.

Alexander, G. E., Delong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience, 9*, 357–381.

Alfonso Recio, L., Martin, P., Carvajal, F., Ruiz, M., & Serrano, J. M. (2013). A holistic analysis of relationships between executive function and memory in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 35*, 147–159.

Algarabel, S., Escudero, J., Peset, V., Combita, L.-M., Rodriguez, L.-A., Fuentes, M., et al. (2010). Recognition by familiarity is preserved in Parkinson's without dementia and Lewy-Body disease. *Neuropsychology, 24*, 599–607.

Anderson, N. D., Ebert, P. L., Jennings, J. M., Grady, C. L., Cabeza, R., & Graham, S. J. (2008). Recollection- and familiarity-based memory in healthy aging and amnestic mild cognitive impairment. *Neuropsychology, 22*, 177–187.

Apostolova, L. G., Beyer, M., Green, A. E., Hwang, K. S., Morra, J. H., Chou, Y. Y., et al. (2010). Hippocampal, caudate and ventricular changes in Parkinson's disease with and without dementia. *Movement Disorders, 25*, 687–688.

Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T. P., et al. (2009). The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Movement Disorders, 24*, 1641–1649.

Bastin, C., Van der Linden, M., Schnakers, C., Montaldi, D., & Mayes, A. R. (2010). The contribution of familiarity to within- and between-domain associative recognition memory: use of a modified remember/know procedure. *European Journal of Cognitive Psychology, 22*, 922–943.

Baxter, L. R., Schwartz, J. M., Phelps, M. E., Mazziota, J. C., Guze, B. H., Selin, C. E., et al. (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry, 46*, 243–250.

Beatty, W. W., & Monson, N. (1990). Problem solving in Parkinson's disease: comparison of performance on the Wisconsin and California card sorting tests. *Journal of Geriatric Psychiatry and Neurology, 3*, 163–171.

Beatty, W. W., Staton, R. D., Weir, W. S., Monson, N., & Whitaker, H. A. (1989). Cognitive disturbances in Parkinson's disease. *Journal of Geriatric Psychiatry and Neurology, 2*, 22–33.

Bethus, I., Tse, D., & Morris, R. G. (2010). Dopamine and memory: modulation of the persistence of memory for novel hippocampal NMDA receptor dependent paired associates. *The Journal of Neuroscience, 30*, 1610–1618.

Bouchard, T. P., Malykhin, N., Martin, W. R., Hanstock, C. C., Emery, D. J., Fisher, N. J., et al. (2008). Age and dementia-associated atrophy predominates in the hippocampal head and amygdala in Parkinson's disease. *Neurobiology of Aging, 29*, 1027–1039.

Bowles, B., Crupi, C., Mirsattari, S. M., Pigott, S. E., Parrent, A. G., & Pruessner, J. C. (2007). Impaired familiarity with preserved recollection after anterior temporal-lobe resection that spares the hippocampus. *Proceedings of the National Academy of Science (USA), 104*, 16382–16387.

Braak, H., & Del Tredici, K. (2008). Reply to "Controversies over the staging of α-synuclein pathology in Parkinson's disease". *Acta Neuropathology, 116*, 129–131.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2006). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging, 24*, 197–211.

Braak, H., Rüb, U., & Del Tredici, K. (2006). Cognitive decline correlates with neuropathological stage in Parkinson's disease. *Journal of Neurological Sciences, 248*, 255–258.

Breen, E. K. (1993). Recall and recognition memory in Parkinson's disease. *Cortex, 29*, 91–102.

Bruck, A., Kurki, T., Kaasinen, V., Vahlberg, T., & Rinne, J. O. (2004). Hippocampal and prefrontal atrophy with early non-demented Parkinson's disease is related to cognitive impairment. *Journal of Neurology, Neurosurgery and Psychiatry, 75*, 1467–1469.

Bunzeck, N., Schütze, H., Stallforth, S., Kaufmann, J., Düzel, S., Heinze, H.-J., et al. (2007). Mesolimbic novelty processing in older adults. *Cerebral Cortex, 17*, 2940–2948.

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton tests*. Bury St. Edmunds: Thames Valley Test Co. Ltd.

Butterfield, L., Cimino, C. R., Oelke, L. E., Hauser, R. A., & Sanchez-Ramos, J. (2010). The independent influence of apathy and depression on cognitive functioning in Parkinson's disease. *Neuropsychology, 24*, 721–730.

Camicioli, R., Moore, M. M., Kinney, A., Corbridge, E., Glassberg, K., & Kaye, J. A. (2003). Parkinson's disease is associated with hippocampal atrophy. *Movement Disorders, 18*, 784–790.

Carlesimo, G. A., Piras, F., Assogna, F., Pontieri, F. E., Caltagirone, C., & Spalletta, G. (2012). Hippocampal abnormalities and memory deficits in Parkinson's disease. *Neurology, 78*, 1939–1945.

Channon, S., & Green, P. S. S. (1999). Executive function in depression: the role of performance strategies in aiding depressed and non-depressed participants. *Journal of Neurology, Neurosurgery and Psychiatry, 66*, 162–171.

Chowdhury, R., Guitart-Masip, M., Bunzeck, N., Dolan, R. J., & Duzel, E. (2012). Dopamine modulates episodic memory persistence in old age. *The Journal of Neuroscience, 32*, 14193–14204.

Clelland, C. D., Choi, M., Romberg, C., Clemenson, G. D., Fragniere, A., Tyre, P., et al. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science, 325*, 210–213.

Cohn, M., McAndrews, M. P., & Moscovitch, M. (2009). Associative reinstatement: a novel approach to assessing associative memory in patients with unilateral temporal lobe excisions. *Neuropsychologia, 47*, 2989–2994.

Cohn, M., Moscovitch, M., & Davidson, P. S. R. (2010). Double dissociation between familiarity and recollection in Parkinson's disease a function of encoding tasks. *Neuropsychologia, 48*, 4142–4147.

Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E. V. (1991). Cognitive impairment in early untreated Parkinson's disease and its relationship to motor disability. *Brain, 114*, 2095–2122.

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

Crescentini, C., Mondolo, F., Biasutti, E., & Shallice, T. (2008). Supervisory and routine processes in noun and verb generation in nondemented patients with Parkinson's disease. *Neuropsychologia, 46*, 434–447.

Davidson, P. S. R., Anaki, D., Saint-Cyr, J. A., Chow, T. W., & Moscovitch, M. (2006). Exploring the recognition memory deficit in Parkinson's disease: estimates of recollection versus familiarity. *Brain, 129*, 1768–1779.

Della Rocchetta, A. I., & Milner, B. (1993). Strategic search and retrieval inhibition: the role of the frontal lobes. *Neuropsychologia, 31*, 503–524.

Dirnberger, G., & Jahahshahi, M. (2013). Executive dysfunction in Parkinson's disease: a review. *Journal of Neuropsychology, 7*, 193–224.

Duarte, A., Ranganath, C., & Knight, R. T. (2005). Effects of unilateral prefrontal lesions on familiarity, recollection and source memory. *The Journal of Neuroscience, 25*, 8333–8337.

Dujardin, K., Sockeel, P., Devos, D., Delliaux, M., Krystkowiak, P., Destee, A., et al. (2007). Characteristics of apathy in Parkinson's disease. *Movement Disorders, 22*, 778–784.

Edelstyn, N. M. J., Grange, J. A., Ellis, S. J., & Mayes, A. R. (2015). A deficit in familiarity-driven recognition in a right-sided mediodorsal thalamic lesion patient. *Neuropsychology*. In press. Q13 Q14

Edelstyn, N. M. J., Mayes, A. R., Condon, L., Tunnicliffe, M., & Ellis, S. J. (2007). Recognition, recollection, familiarity and executive function in patients with moderate Parkinson's disease. *Journal of Neuropsychology, 1*, 131–147.

Edelstyn, N. M. J., Shepherd, T. A., Mayes, A. R., Sherman, S. M., & Ellis, S. J. (2010). Effect of disease severity and dopaminergic medication on recollection and familiarity in patients with idiopathic nondementing Parkinson's. *Neuropsychologia, 48*, 1367–1375.

Fahn, S., & Elton, R. L. (1987). The unified Parkinson's disease rating scale. In S. Fahn, C. D. Marsden, D. B. Calne, & M. Goldstein (Eds.), *Recent developments in Parkinson's disease* (pp. 293–304). Florham Park, N.J: Macmillan.

Fearnley, J. M., & Lees, A. J. (1991). Ageing and Parkinsons disease: substantia nigra regional selectivity. *Brain, 114*, 2283–2301.

Filoteo, J. V., Reed, J. D., Litvan, I., & Harrington, D. L. (2014). Volumetric correlates of cognitive functioning in nondemented patients with Parkinson's disease. *Movement Disorders, 29*, 361–367.

Flowers, K. A., Pearce, I., & Pearce, J. M. S. (1984). Recognition memory in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 47*, 1174–1181.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research, 12*, 189–198.

Gabrieli, J. D. E., Singh, J., Stebbins, G. T., & Goetz, C. G. (1996). Reduced working memory span in Parkinson's disease: evidence for the role of a frontostriatal system in working and strategic memory. *Neuropsychology, 10*, 322–332.

Gasbarri, A., Sulli, A., & Packard, M. G. (1997). The dopaminergic mesencephalic projections to the hippocampal formation in the rat. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 21*, 1–22.

Gershberg, F. B., & Shimamura, A. P. (1995). Impaired use of organizational strategies in free recall following frontal lobe damage. *Neuropsychologia, 33*, 1305–1333.

Gradin, V. B., & Pom, A. (2008). The role of hippocampal atrophy in neuropsychiatric disorders. *Journal of Biological Physics, 34*, 107–120.

Hammad, H., & Wagner, J. J. (2006). Dopamine-mediated disinhibition in the CA1 region of rat hippocampus via D_3 receptor activation. *The Journal of Pharmacology and Experimental Therapeutics, 316*, 113–120.

Hanes, K. R., Andrewes, D. G., Smith, D. J., & Pantelis, C. (1996). A brief assessment of executive control dysfunction: discriminant validity and homogeneity of planning, set shift, and fluency measures. *Archives of Clinical Neuropsychology, 11*, 185–191.

Harlow, I. M., MacKenzie, G., & Donaldson, D. A. (2010). Familiarity for associations? A test of the domain dichotomy theory. *Journal of Experimental Psychology: Learning, Memory and Cognition, 36*, 1381–1388.

Hay, J. F., Moscovitch, M., & Levine, B. (2002). Dissociating habit and recollection: evidence from Parkinson's disease, amnesia and focal lesion patients. *Neuropsychologia, 40*, 1324–1334.

Henson, R. N. A., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *The Journal of Neuroscience, 19*, 3962–3972.

Higginson, C. I., Wheelock, V. L., Carroll, K. E., & Sigvardt, K. A. (2005). Recognition memory in Parkinson's disease with and without dementia: evidence inconsistent with the retrieval deficit hypothesis. *Journal of Clinical and Experimental Neuropsychology, 27*, 516–528.

Hirst, W., & Volpe, B. T. (1988). Memory strategies with brain damage. *Brain and Cognition, 8*, 379–408.

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology, 17*, 427–442.

Holdstock, J. S., Mayes, A. R., Roberts, N., Cezayirli, E., Isaac, C. L., & O'Reilly, R. C. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans. *Hippocampus, 12*, 341–351.

Hornykiewicz, O. (1966). Dopamine (3-hydroxytyramine) and brain function. *Pharmacology Review, 18*, 925–964.

Ibarretxe-Bilbao, N., Ramirez-Ruiz, B., Tolosa, E., Marti, M. J., Valldeoriola, F., Bargallo, N., et al. (2008). Hippocampal head atrophy predominance in Parkinson's disease with hallucinations and with dementia. *Journal of Neurology, 255*, 1324–1331.

Jacoby, L. L. (1991). A process dissociation framework: separating automatic from intentional uses of memory. *Journal of Memory and Language, 30*, 513–541.

Janowsky, J. S., Shimamura, A. P., Kritchevsky, M., & Squire, L. R. (1989b). Cognitive impairment following frontal lobe damage and its relevance to human amnesia. *Behavioural Neuroscience, 103*, 548–560.

Janowsky, J. S., Shimamura, A. P., & Squire, L. R. (1989a). Source memory impairment in patients with frontal lobe lesions. *Neuropsychologia, 27*, 1043–1056.

Jetter, W., Poser, U., Freeman, R. B., Jr., & Markowitsch, H. J. (1986). A verbal long-term memory deficit in frontal lobe damaged patients. *Cortex, 22*, 229–242.

Junqué, C., Ramīrex-Ruiz, B., Tolosa, E., Summerfield, C., Marti, M. J., Pastor, P., et al. (2005). Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. *Movement Disorders, 20*, 540–544.

Kaftas, A., & Montaldi, D. (2014). Two separate, but interacting, neural systems for familiarity and novelty detection: a dual-route mechanism. *Hippocampus, 24*, 516–527.

Kemperman, G., & Kroneberg, G. (2003). Depressed new Neurons?—Adult hippocampal neurogenesis and a cellular plasticity hypothesis of major depression. *Biological Psychiatry, 54*, 499–503.

Knoke, D., Taylor, A. E., & Saint-Cyr, J. A. (1998). The differential effects of cueing on recall in Parkinson's disease and normal subjects. *Brain and Cognition, 38*, 261–274.

Laakso, M. P., Partanen, K., Riekkinen, P., Lehtovirta, M., Helkala, E. L., Hallikainen, M., et al. (1996). Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. *Neurology, 46*, 678–681.

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

Laszy, J., Laszlovszky, I., & Gyertyan, I. (2005). Dopamine D_3 receptor antagonists improve the learning performance in memory-impaired rats. *Psychopharmacology, 179*, 567–575.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron, 46*, 703–713.

Lisman, J. E., Grace, A. A., & Duzel, E. (2011). A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends in Neuroscience, 34*, 536–547.

MacDonald, A. A., Seergobin, K. N., Owen, A. M., Tamjeedi, R., Monchi, O., Ganjavi, H., et al. (2013). Differential effects of Parkinson's disease and dopamine replacement on memory encoding and retrieval. *Plos One, 8*, 1–9.

MacPherson, S. E., Bozzali, M., Cipolotti, L., Dolan, R. J., Rees, J. H., & Shallice, T. (2008). Effect of frontal lobe lesions on the recollection and familiarity components of recognition memory. *Neuropsychologia, 46*, 3124–3132.

Mayes, A. R. (1988). *Human organic memory disorders*. Cambridge University Press.

Mayes, A. R., & Daum, I. (1996). How specific are the memory and other cognitive deficits caused by frontal lobe lesions? In P. Rabbitt (Ed.), *Methodology of frontal and executive functions* Hove: Erlbaum.

Mayes, A. R., Meudell, P. R., & Neary, D. (1980). Do amnesics adopt inefficient encoding strategies with faces and random shapes? *Neuropsychologia, 18*, 527–541.

Mayes, A. R., Montaldi, D., & Migo, E. M. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Sciences, 11*, 126–135.

Migo, E. M., Mayes, A. R., & Montaldi, D. (2012). Measuring recollection and familiarity: Improving the remember/know procedure. *Consciousness and Cognition, 21*, 1435–1455.

Montaldi, D., & Mayes, A. R. (2010). The role of recollection and familiarity in the functional differentiation of the medial temporal lobes. *Hippocampus, 20*, 1291–1314.

Montaldi, D., Spencer, T. J., Roberts, N., & Mayes, A. R. (2006). The neural system that mediates familiarity memory. *Hippocampus, 16*, 504–520.

Morris, R. G., Downes, J. J., Sahakian, B. J., Evenden, J. L., Heald, A., & Robbins, T. W. (1988). Planning and spatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 51*, 757–766.

Nagano-Saito, A., Washimi, Y., Arahata, Y., Kachi, T., Lerch, J. P., Evans, A. C., et al. (2005). Cerebral atrophy and its relation to cognitive impairment in Parkinson's disease. *Neurology, 64*, 224–229.

Obeso, J. A., Cruz Rodriguez-Oroz, M., Benitez-Temino, B., Blesa, F. J., Guridi, J., Marin, C., et al. (2008). Functional organisation of the basal ganglia: therapeutic implications for Parkinson's disease. *Movement Disorders, 23*, S548–S559.

Owen, A. M., Doyon, J., Dagher, A., Sadikot, A., & Evans, A. C. (1998). Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. *Brain, 121*, 949–965.

O'Carroll, C. M., Martin, S. J., Sandin, J., Frenguelli, B., & Morris, R. G. (2006). Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. *Learning and Memory, 13*, 760–769.

Parkin, A. J., Bindschaedler, C., Harsent, L., & Metzler, C. (1996). Pathological false alarm rates following damage to the left frontal cortex. *Brain and Cognition, 32*, 14–27.

Parkinson, J. (2002). An essay on the shaking palsy. *Journal of Neuropsychiatry and Clinical Neurosciences, 14*, 223–236.

Pereria, J. B., Junqué, C., Bartrés-Faz, D., Ramrex-Ruiz, B., et al. (2013). Regional vulnerability of hippocampal subfields and memory deficits in Parkinson's disease. *Hippocampus, 23*, 720–728.

Pluck, G. C., & Brown, J. (2002). Apathy in Parkinson's disease. *Neurology, Neurosurgery and Psychiatry, 73*, 636–642.

Reynolds, W. M., & Koback, K. A. (1995). Reliability and validity of the Hamilton depression inventory: a paper-and-pencil version of the Hamilton depression rating scale clinical interview. *Psychological Assessment*.

Riekkinen, P., Kejonen, K., Laakso, M. P., Soininen, H., Partanen, K., & Riekkinen, M. (1998). Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients. *NeuroReport, 9*, 1507–1511.

RodrÍguez, R. A., Algarabel, S., & Escudero, J. (2014). Exploring recollection and familiarity impairments in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 36*, 494–506.

Sadeh, T., Ozubko, J. D., Winocur, G., & Moscovitch, M. (2014). How we forget may depend on how we remember. *Trends in Cognitive Science, 18*, 26–36.

Sahay, A., & Hen, R. (2007). Adult hippocampal neurogenesis in depression. *Nature Neuroscience, 10*, 1110–1115.

Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., et al. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature, 472*, 466–470.

Saksida, L. M., & Bussey, T. J. (2010). The representational-hierarchical view of amnesia: translation from animal to human. *Neuropsychologia, 48*, 2370–2384.

Savage, C. R., Deckersbach, T., Heckers, S., Wagner, A. D., Schacter, D. L., Alpert, N. L., et al. (2001). Prefrontal regions supporting spontaneous and directed application of verbal learning strategies. Evidence from PET. *Brain, 124*, 219–231.

Schacter, D. L., Curran, C., Galluccio, L., Milberg, W. P., & Bates, J. F. (1996). False recognition and the right frontal lobe: a case study. *Neuropsychologia, 34*, 793–808.

Segura, B., Ibarretxe-Bilbao, N., Sala-Llonch, R., Baggio, H. C., Marti, M. J., Valldeoriola, F., et al. (2012). Progressive changes in a recognition memory network in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*. http://dx.doi.org/10.1136/jnnp-2012-302822.

Shepherd, T. A., Edelstyn, N. M. J., Mayes, A. R., & Ellis, S. J. (2013). Second generation dopamine agonists and recollection impairments in Parkinson's disease. *Journal of Neuropsychology, 7*, 284–305.

Shimamura, A. P., Jurica, P. J., Mangels, J. A., & Gershberg, F. B. (1995). .Susceptibility to memory interference effects following frontal lobe damage: findings from tests of paired-associate learning. *Journal of Cognitive Neuroscience, 7*, 144–152.

Snodgrass, J. G., & Corwin, J. (1988). Pragmatics of measuring recognition memory. Applications to dementia and amnesia. *Quarterly Journal of Experimental Psychology A, 117*, 34–50.

Takahashi, H., Kato, M., Takano, H., Arakawa, R., Okumura, M., Otsuka, T., et al. (2008). Differential contributions of prefrontal and hippocampal dopamine D1 and D2 receptors in human cognitive functions. *The Journal of Neuroscience, 28*, 12032–12038.

Tam, C. W., Burton, E. J., McKeith, I. G., Burn, D. J., & O'Brien, J. T. (2005). Temporal lobe atrophy on MRI in Parkinson disease with dementia: a comparison with Alzheimer disease and dementia with Lewy bodies. *Neurology, 64*, 861–865.

Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1986). Frontal lobe dysfunction in Parkinson's disease and depression. *Brain, 109*, 845–883.

Tulving, E. (1985). Memory and consciousness. *Canadian Psychologist, 26*, 1–12.

Turner, M. S., Cipolotti, L., Yousry, T. A., & Shallice, T. (2007). Confabulation: damage to a specific inferior medial prefrontal system. *Cortex, 44*, 637–648.

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021

Van Spaendonck, K. P. M., Berger, H. J. C., Horstink, M. W. I. M., Borm, G. F., & Cools, A. R. (1996). Memory performance under varying cueing conditions in patients with Parkinson's disease. *Neuropsychologia, 34*, 1159–1164.

Wechsler, D. (1997). *Wechsler memory scale III*. Harcourt Brace & Co: The Psychological Corporation.

Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence*. Harcourt Brace & Co: The Psychological Corporation.

Weiermann, B., Stephan, M. A., Kaelin-Lang, A., & Meier, B. (2010). Is there a recognition memory deficit in Parkinson's disease: evidence from estimates of recollection and familiarity. *International Journal of Neuroscience, 120*, 211–216.

Wheeler, M. A., Stuss, D. T., & Tulving, E. (1995). Frontal lobe damage produces episodic memory impairment. *Journal of International Neuropsychological Society, 1*, 525–536.

Whittington, C. J., Podd, J., & Kan, M. M. (2000). Recognition memory impairment in Parkinson's disease: power and meta-analyses. *Neuropsychology, 14*, 233–246.

Wixted, J. T., & Squire, L. R. (2011). The medial temporal lobes and attributes of memory. *Trends in Cognitive Science, 15*, 210–217.

Yonelinas, A. P. (2002). The nature of recollection and familiarity: a review of 30 years of research. *Journal of Memory and Language, 46*, 441–517.

Yonelinas, A. P., & Jacoby, L. L. (1995). The relation between remembering and knowing as bases for recognition: effects of size congruency. *Journal of Memory and Language, 34*, 622–643.

Please cite this article in press as: Edelstyn, N. M. J., et al., Evidence of an amnesia-like cued-recall memory impairment in non-dementing idiopathic Parkinson's disease, Cortex (2015), http://dx.doi.org/10.1016/j.cortex.2015.06.021