Neuropsychologia 90 (2016) 25–32

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Associative reinstatement memory measures hippocampal function in Parkinson's Disease

Melanie Cohn [a,c,*], Irene Giannoylis [b], Maya De Belder [d], Jean A. Saint-Cyr [a], Mary Pat McAndrews [a,b,c]

[a] Toronto Western Hospital UHN, 399 Bathurst Street, Toronto, Canada M5T 2S8
[b] Krembil Research Institute, 399 Bathurst Street, Toronto, Canada M5T 2S8
[c] Dept. of Psychology, University of Toronto, 100 St. George Street, Toronto, Canada
[d] Dept. of Experimental Psychology, Ghent University, Henri Dunantlaan 2, Ghent, Belgium

ARTICLE INFO

Article history:
Received 11 December 2015
Received in revised form
26 April 2016
Accepted 28 April 2016
Available online 29 April 2016

Keywords:
Associative memory
Recognition
Hippocampus
FMRI
Parkinson's Disease

ABSTRACT

In Parkinson's Disease (PD), hippocampal atrophy is associated with rapid cognitive decline. Hippocampal function is typically assessed using memory tests but current clinical tools (e.g., free recall) also rely on executive functions or use material that is not optimally engaging hippocampal memory networks. Because of the ubiquity of executive dysfunction in PD, our ability to detect true memory deficits is suboptimal. Our previous behavioural and neuroimaging work in other populations suggests that an experimental memory task – *Associative Reinstatement Memory* (ARM) – may prove useful in investigating hippocampal function in PD. In this study, we investigated whether ARM is compromised in PD and we assessed its convergent and divergent validity by comparing it to standardized measures of memory and of attention and executive functioning in PD, respectively. Using fMRI, we also investigated whether performance in PD relates to degree of hippocampal engagement. Fifteen participants with PD and 13 age-matched healthy controls completed neuropsychological testing as well as an ARM fMRI recognition paradigm in which they were instructed to identify word pairs comprised of two studied words (intact or rearranged pairs) and those containing at least one new word (new or half new pairs). ARM is measured by the differences in hit rates between intact and rearranged pairs. Behaviourally, ARM was poorer in PD relative to controls and was correlated with verbal memory measures, but not with attention or executive functioning in the PD group. Hippocampal activation associated with ARM was reduced in PD relative to controls and covaried with ARM scores in both groups. To conclude, ARM is a sensitive measure of hippocampal memory function that is unaffected by attention or executive dysfunction in PD. Our study highlights the benefit of integrating cognitive neuroscience frameworks and novel experimental tasks to improve the practice of clinical neuropsychology in PD.

1. Introduction

Progressive cognitive impairment is recognized as a prevalent non-motor symptom associated with Parkinson's disease (PD) and a high proportion of people with PD will develop Mild Cognitive Impairment (PD-MCI) and dementia (PDD) (Emre et al., 2007). While the classic cognitive profile of people with PD is characterized by deficits in attention and executive functioning which are attributed to dopaminergic depletion, other cognitive domains such as visuospatial skills and memory are also often compromised. The latter are related in part to cholinergic depletion and lewy body pathology affecting temporal and parietal regions, and are thought to be predictive of the development of PDD (Hobson and Meara, 2004; Kehagia et al., 2010; Levy et al., 2002; Williams-Gray et al., 2007; Williams-Gray et al., 2013). Neuroimaging findings support this proposal. For instance, medial temporal lobe (MTL) atrophy is associated with memory performance in PD (Beyer et al., 2013; Brucket al., 2004; Camicioli et al., 2009; Goldman et al., 2012; Pereira et al., 2013) and is present in PD-MCI and PDD, but not in PD patients with intact cognition (Apostolova et al., 2012; Melzer et al., 2012; Summerfield et al., 2005). Studies also show that some individuals with PD exhibit a pattern of brain atrophy similar to that observed in Alzheimer's disease, which includes volume loss in the hippocampus, and this pattern of atrophy predicts global cognitive decline at 2-year follow-up (Weintraub et al., 2012, 2011).

Whilst it is important to obtain accurate indicators of MTL function and potentially identify individuals at greater risk of rapid

* Corresponding author at: Neuropsychology Clinic, Toronto Western Hospital, 4F-409, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8.
E-mail address: melanie.cohn@uhn.ca (M. Cohn).

http://dx.doi.org/10.1016/j.neuropsychologia.2016.04.026
0028-3932/

cognitive decline, our ability to detect true episodic memory deficits in the clinic is suboptimal due to the ubiquity of executive dysfunction in PD. Clinical episodic memory tests, such as word-list free recall, rely heavily on executive functions during encoding (generation and elaboration of strategies) and retrieval (search strategies and post-retrieval monitoring) and memory dysfunction in PD is at least in part accounted for by those deficits. For instance, differences in memory performance between PD and healthy control groups are minimized when encoding strategies are provided explicitly (Knoke et al., 1998) or when encoding is done under incidental conditions (Vingerhoetset al., 2005). Furthermore, a common pattern of performance in PD is characterized by impaired free recall but intact or less severely impaired recognition memory, suggesting difficulties with the executive control of retrieval processes (Emre et al., 2007). Some individuals with PD do, nonetheless, show recognition memory deficits (Higginson et al., 2005; Whittington et al., 2000) suggesting the presence of memory and possibly MTL dysfunction. Standardized recognition tasks do minimize executive demands by providing retrieval support but they are not without limitations. Few tasks equate encoding strategies, and post-retrieval monitoring may impact retrieval. Lastly, these tasks usually assess memory for single items, while the cognitive neuroscience literature demonstrates that hippocampal engagement is greatest when the material used involves novel associations (Eichenbaum et al., 2007; Konkel and Cohen, 2009). This may be also important in PD given that some studies documented dissociations between intact item memory and impaired associative memory in PD on experimental recognition tasks (Cohn et al., 2010; Drag et al., 2009; Rodriguez et al., 2014).

Based on our work on associative memory, we believe an associative reinstatement memory (ARM) task would be best suited to provide a sensitive and selective measure of memory function in PD. In this task, we impose an optimal encoding strategy (deep processing of items and associations) and provide support at retrieval (recognition). While classic tests of associative memory require the overt identification of studied associations (*were items paired together at study?*), reinstatement tasks are more indirect measures which further minimizes the impact of executive deficits at retrieval. In reinstatement tasks, participants are solely asked about their memory for the items. The gain observed in item memory when test items are presented with their studied associate (intact pairs) versus when they are not (test items are presented alone or in a novel pairing) indexes their memory for the associations. Unlike direct measures of associative memory, this reinstatement effect is immune to manipulations that interfere with effortful retrieval processes, such as post-retrieval monitoring and verification (Cohn and Moscovitch, 2007), and is intact in healthy older adults relative to young adults (Cohn et al., 2008) unlike the more direct and effortful measures of associative memory. Reinstatement is associated with hippocampal engagement in an fMRI study in young adults (Cohn et al., 2009b) when it triggers a recollection process, which is characterized by the retrieval of rich contextual information. ARM is also impaired, like other measures of associative memory, in people with temporal lobe damage (Cohn et al., 2009a).

In this study, we investigated whether ARM is compromised in PD and we assessed its convergent validity by comparing it to standardized measures of memory, and its discriminant validity by contrasting it to measures of attention and executive functioning in PD. We also investigated the neural substrate of ARM using fMRI to determine whether hippocampal engagement is reduced in PD and whether it correlates with this associative memory measure. We hypothesize that ARM will be impaired in PD and will be correlated with neuropsychological tests of verbal memory but, unlike those tests, not with attention or executive functioning. Based on our previous imaging findings, we also predict that ARM will be associated with hippocampal activation and that any group differences in hippocampal activation will mirror differences observed at the performance level.

2. Material and methods

2.1. Participants

Sixteen individuals diagnosed with idiopathic Parkinson's Disease according to the UK brain bank criteria were recruited from the Movement Disorder Clinic at the Toronto Western Hospital and 15 age-matched healthy control participants were recruited from the community. One individual from the PD group was excluded due to claustrophobia during scanning and two controls were excluded because their cognitive testing was consistent with a diagnosis of Mild Cognitive Impairment. The final sample size was 15 PD participants and 13 age-matched controls. All subjects were between the ages of 40 and 70 years old, were fluent English speakers, were right-handed, and had no gross cognitive deficits on a screening test (Montreal Cognitive Assessment - MoCA score >25, (Nasreddine et al., 2005)) nor did they report significant difficulties with instrumental activities of daily living on a modified version of the Functional Assessment Questionnaire (FAQ score <9, (Pfefferet al., 1982)). They had no history of severe psychiatric conditions, concomitant neurological conditions, cardiovascular problems or diabetes, and did not use anticholinergic medications. PD participants were at stage I or II of the Hoehn and Yahr scale (Hoehn and Yahr, 1967), had relatively good control of their PD symptoms with medications and did not experience significant motor fluctuations or dyskinesia. Motor symptoms were assessed using the MDS-UPDRS – Part 3, which was completed after scanning approximately 2 h after medication intake (intermediate to end of dose). In the PD group, one participant was not medicated, one took dopamine agonist only, four took L-dopa only, and nine took a combination of L-dopa with COMPT inhibitors, dopamine agonists and/or MAOB inhibitors. Levodopa equivalent daily dosage (LEDD) was calculated for all participants (Tomlinson et al., 2010). All patients were assessed on medication with the exception of the patient who was not taking any Parkinson's medications. Cognitive testing and scanning were completed on a single day for all but two PD participants who preferred to complete the study on different days. They received $100 compensation for their participation. Clinical and demographic variables are presented in Table 1.

2.2. Behavioural measures

2.2.1. Neuropsychological assessment

All participants underwent a neuropsychological examination. The test battery included an estimate of premorbid intellectual function (Wechsler Test of Adult Reading - WTAR) and measures assessing five cognitive domains. Attention/processing speed was assessed using oral Symbol Digit Modalities Test (SDMT-oral) and Color Trail-Making Test A (C-TMTA); executive functioning was assessed using the Color Trail-Making Test B (C-TMTB), the Wisconsin Card Sorting Test-64 (WCST-

Table 1
Demographic and clinical characteristics.

	Controls	Parkinson's Disease
n	13	15
Age	53.9 (8.1)	59.1 (8.0)
Sex (Male:Female)	8:5	9:6
Education	17.7 (3.4)	17.3 (2.8)
Premorbid IQ	112.5 (6.1)	112.7 (7.4)
2-scale IQ	117.2 (15.3)	116.7 (11.9)
MoCA	28.0 (1.5)	28.2 (1.3)
Disease duration	–	6.2 (3.6)
MDS-UPDRS part III – intermediate/end of dose	–	18.7 (8.1)
Side of PD onset		2R:13L
1st symptom at PD onset		5 akinesia, 10 tremor
Levodopa equivalent daily dose (LEDD)	–	600.0 (322.4)
Cognitive diagnosis*	–	6 Intact; 9 Multi-domain MCI
Cognitive domains	–	7xMemory, 6xExecutive, 2xAttention; 3xVisuospatial 1xLanguage

* Diagnosis of MCI is based on MDS task force level 2 (Litvan et al., 2012) using cutoff scores of 1.5 SD below normative data for individual with average premorbid estimate, or 1SD below normative data for individuals with high average or superior premorbid levels of ability, on two independent neuropsychological tests.