Cognitive impairment in Parkinson's disease without dementia

Javier Rodríguez-Ferreiro[1], Fernando Cuetos[2], Elena Herrera[2], Manuel Menéndez[3] &
Renée Ribacoba[3]

[1]University of Barcelona, Spain

[2]University of Oviedo, Spain

[3]Alvarez-Buylla Hospital, Mieres, Spain

Corresponding author at:

Javier Rodríguez-Ferreiro

Dept Psicologia Bàsica,

Universitat de Barcelona,

Mundet, Ponent, Desp. 3509

Pg.Vall D'Hebron, 171

08035, Barcelona, Spain.

E-mail address: rodriguezferreiro@ub.edu

Tel: (+34) 933125151

Fax: (+34) 934021363

Word count: 2697

Running title: Cognitive impairment in Parkinson's disease

Abstract

Some degree of cognitive impairment appears frequently in Parkinson´s disease (PD) patients, even at the onset of the disease. However, due to the heterogeneity of the patients and the lack of standardized assessment batteries, it remains unclear which capacities are primarily affected by this disease. Fifty PD patients were assessed with 15 tests including executive functions, attention, temporal and spatial orientation, memory, and language tasks. Their results were compared to those of 42 age- and education-matched healthy seniors. Semantic fluency, along with visual search appeared to be the most discriminant tasks, followed by temporal orientation and face naming, as well as action naming and immediate recall. PD patients studied showed an impairment of frontal- to posterior-dependent capacities. Executive functions, attention and recall tasks appeared to be significantly impaired in the patients. Nevertheless, significantly poor scores in tasks like action and face naming, as well as semantic fluency, also reveal a mainly semantic deficit.

Introduction

Though there is some heterogeneity in previous data, it is agreed that some
degree of cognitive impairment is present in a considerable number of patients suffering
from Parkinson's disease (PD) [1-6]. Thus, whereas early studies based on DSM-III
criteria had found that 14% of PD patients present dementia[1], more recent work
estimates prevalence rates around 30% [2-6]. Furthermore, when fine-grained
neuropsychological and cognitive measures are used, a certain level of cognitive
impairment can be identified even in some PD patients who cannot be diagnosed with
dementia yet [2, 6, 7]. The diagnostic label Mild Cognitive Impairment (MCI)[8], borrowed
from the domain of Alzheimer's disease (AD), has been applied to these patients with
the intention of describing an intermediate state between preserved cognitive capacity
and fully-established dementia in PD[2, 6]. Given that MCI is considered to be a precursor
of dementia[6] and one of the best predictors of its appearance[9, 10], it is imperative to
conduct a formal neuropsychological examination of PD patients, in order to ascertain
their degree and pattern of cognitive preservation over the course of the disease.
However, given that normative data for extensively used scales, like MMSE or the
Mattis Dementia Rating Scale, is incomplete in PD populations, along with the fact that
the cognitive profile in PD with dementia differs significantly from that in AD [11],
specific tools must be designed to assess the cognitive decline in PD. Several specific
tests have reported their usefulness in PD but the lack of concordance [12] and absence of
studies comparing the performance of PD without dementia patients with controls lead
to question their validity.

The most common deficits described are related to executive functions [3, 4, 6, 13-15],
although visuospatial [14, 16, 17], attentional [14, 18], memory [3, 4, 6, 19, 20], and language [15, 21]
impairments have also been observed in this kind of patients. Some of these disorders

have been detected even in the early stages of the disease [22, 23], while others appear in later stages. In an attempt to put order to the cognitive heterogeneity present in PD patients, signs of cognitive impairment have been proposed to cluster into two main groups [24]. Thus, whereas some of the PD patients present reduced attention and executive capacities, others show a pattern of impairment that is primarily characterized by memory loss. These two cognitive impairment profiles would be the result of frontal lobe- and temporal lobe-dependent pathology respectively [24]. However, it has also been suggested that the executive deficit is the primary cause of the other symptoms including the language and memory impairments [17, 19].

The identification of preclinical dementia in PD patients provides an opportunity to understand cognitive decline in PD and is, thus, crucial for accurate management and prompt treatment. Selecting the cognitive functions to be included in an assessment battery is the first step to build a rational screening test. Obviously, this selection should include the ones that have been affected since the beginning of the disease. Moreover, it is important to assess a variety of cognitive abilities that cover a full range of anterior to posterior-dependent functions, in order to disentangle the contribution of executive function to the expressed deficits.

In this study we conducted a systematic evaluation of a range of cognitive functions including orientation, attention, executive function, memory and language. In some cases, several tasks were designed for each capacity in order to be able to establish fine-grained conclusions regarding the exact origin of the deficit. PD patients without dementia were compared to controls of similar demographic characteristics with the aim of detecting cognitive deficits before the dementia stage.

Materials and methods

Participants

A group of 50 PD patients and a group of 42 healthy seniors took part in the experiment. The two groups of participants were matched on age and years of education, but PD patients presented significantly lower (t(80.54)=-2.76; p=.007) average MiniMental State Evaluation (MMSE) scores. Informed consent was obtained from all the participants or their relatives. PD patients had been diagnosed according to the UK Parkinson's Disease Brain Bank criteria [25] prior to their participation in the experiment. Only native Spanish speakers with no history of alcohol abuse, or neurological or psychiatric disorders other than PD were included in the study. The criteria by the Movement Disorder Society [13, 26] were used to discard dementia. A summary of participant's characteristics is provided in table 1.

Table 1 here

Stimuli and Procedure

Participants were tested with a battery consisting of 15 tasks. The tests were aimed to study those cognitive abilities that are known to be impaired in PD patients, like executive function and attention, but also other capacities like temporal and spatial orientation; semantic and episodic memory; and language production and comprehension. The tasks were:

- Visual search: The participant must mark the number "3" every time it appears on a 12 x 20 grid of the numbers 1 through 9.

- Odd-one-out: Groups of four photographs are presented to the participant, who is asked to indicate which of them is different from the others. Three different criteria are

used: category (e.g., *three apples and a pear*), color (e.g., *three yellow flowers and one red flower*) and number (e.g., *three single gloves and a pair of gloves*).

- Temporal Orientation: The participant is presented with five questions regarding placement in time (e.g., *What day of the week is it? What year is it?*).

- Spatial Orientation: The participant is asked to answer five questions about spatial location (e.g., *What city are we in? What street do you live on?*).

- Immediate recall: The participant is asked five questions about an imaginary friend (e.g., *What's my friend's name? How old is he?*) that is previously described to him (*My friend's name is Arthur, he is 46 years old*, …).

- Delayed recall: The participant is asked the same questions about the imaginary friend several minutes after the immediate recall test.

- Semantic fluency: For 60 seconds, the participant is asked to name as many fruits as he or she can without repeating any.

- Semantic association: The participant is asked to choose which of two drawings presented at the bottom of a page (e.g., a hammer and a padlock) is related to the one presented at the top (e.g., a key).

- Object naming: Ten color drawings of objects are presented, half of them living things and half inanimate objects, for the participant to name.

- Action naming: Ten color drawings of actions are presented for the participant to name.

- Famous faces naming: The participant has to name ten photographs of famous people presented one by one.

- Definition–word pairing: The participant must show which of the four presented words (e.g., *vice*, *insult*, *swindle*, *prayer*) corresponds to a given definition (e.g., *deception with intent to profit*).

- Synonymy: A word (e.g., *plea*) is presented at the top and another three (e.g., *prayer*, *request*, *fervor*) appear at the bottom of a sheet. The participant must indicate which of these three words is synonymous with the word at the top.

- Phonological fluency: For 60 seconds, the participant must name as many words as he or she can that begin with the letter "f" and are not proper nouns.

- Pseudoword repetition: The experimenter articulates ten pseudowords, each with three or four syllables, one by one for the participant to repeat. One point is awarded for each "correctly pronounced" pseudoword.

Each participant was run through the experimental battery individually in two sessions scheduled two or three days apart.

Results

Table 2 presents averages and range of the scores of the two groups in the all the tasks and a summary of the results of the different analyses performed. The control group obtained higher scores than the PD groups on all of the tasks. A MANCOVA analysis conducted with group as an independent variable, the scores on the 16 tasks as dependent variables, and age of the participants as a covariable, yielded significant results [Pillai's trace: V=0.367, F(15,69) = 2.663, p =.003].

Table 2 here

The age of the seniors appeared to be significantly related to their results in all the tasks (ps<.05) except for temporal orientation [F(1,83)=2.025, p=.158]. Between-subjects tests showed significant group differences on seven of the tasks including temporal orientation,

visual search, immediate recall, semantic fluency, face and action naming, as well as odd-one-out. Differences between the scores of the Parkinson and control groups in the delayed recall task approached the significance threshold. In order to ascertain which of the tasks would continue discriminating between healthy seniors and PD patients when global cognitive function is controlled, a second analysis was conducted introducing MMSE scores as a covariable [Pillai's trace: V=0.336, F(16,69) = 2.307, p =.008]. General cognitive decline appeared to be significantly related to scores in all the tasks (ps<.05) but visual search [F(1,88)=0.499, p=.482] and semantic association [F(1,88)=1.067, p=.158]. When this variable was controlled significant differences appeared only between the participants' scores in temporal orientation [F(1,88)=4.545, p=.036], visual search [F(1,88)=11.099, p=.001] and semantic fluency [F(1,88)=5.495, p=.021].

MANCOVA analyses were followed up by a discriminant analysis (see table 2) conducted with diagnosis as the dependent variable and the different tasks as independent variables. The test battery appeared to correctly distinguish 80.4% of the cases, with positive and negative predictive values of 76% and 86% respectively. ROC curves were also computed for each of the comparisons, yielding the area under the curve values also reported in table 2. Semantic fluency, along with visual search appeared to be the most discriminant tasks, followed by temporal orientation, face naming, as well as action naming and immediate recall.

Furthermore, in order to provide a qualitative description of the impairment profiles of PD patients, a classification of their cognitive deficits was attempted. The patient sample was divided according to an established subclassification of MCI[27] on the basis of their scores in the different tests. Whereas 20% of the patients appeared to present normal cognitive abilities, 32% of them were classified as amnestic MCI. The remaining patients

were considered either single non–memory-domain MCI (8%), or multiple-domain MCI (40%).

Discussion

In order to explore the profile of cognitive impairment in PD, a group of 50 non-demented PD patients was assessed with a neuropsychological battery including memory, language, attention, orientation and executive function tasks. In line with previous results in the literature [3, 4, 6, 13-15] the presence of an executive function deficit in PD patients was confirmed in the sample studied here, as significant differences appeared between the scores of the PD and control groups in the odd-one-out test. Yet again, according to previous studies [3, 14, 18] PD patients presented an attention deficit that became apparent in their poor scores in the visual search task. Temporal orientation also appeared to be impaired in the PD group, with patients scoring significantly lower than healthy controls. Spatial orientation, however, was preserved in PD patients, who obtained scores similarly high to those of the control group. Visual search, odd-one-out and temporal orientation turned out to be amongst the four most discriminant tasks in our study. Furthermore, differences between the groups' scores in temporal orientation and visual search appeared to be significant even when global cognitive impairment was controlled entering MMSE scores as a covariable in the analysis. Generally, this pattern of results is congruent with the well established idea [17, 19] that PD patients present a deficit in frontal lobe-dependent capacities.

Concerning language, oral production difficulties can be ruled out in the PD group, as no significant differences appeared between their scores and those of control participants either in the phonological fluency or in the pseudoword repetition tasks. Reading

comprehension also appeared to be preserved in the patient group, with scores comparable to those of healthy seniors in both the synonymy and definition-word pairing tasks.

The episodic memory of PD patients has previously been compared to that of patients suffering from AD. Immediate recall abilities of PD patients have been shown to be similar to those of AD patients [14] but better preserved in the case of delayed recall [28, 29]. Accordingly, PD patients in our study produced significantly less correct responses than healthy seniors in the immediate recall task, although differences disappeared in the delayed recall test. Due to an alleged preservation of recognition abilities of PD patients[30, 31], their episodic memory impairments have been ascribed to retrieval deficits secondary to a general executive impairment [17]. However there is compelling evidence that PD patients do suffer from a recognition deficit[32], so coding difficulties cannot be ruled out as a possible cause of the episodic memory impairment of these patients.

With regards to semantic memory, significant differences appeared in the semantic fluency task, suggesting a relative impairment of this capacity that, nevertheless, was not apparent in the semantic association task. This was probably due to a ceiling effect, as both groups obtained scores close to the maximum in the task. Semantic fluency is agreed to be one of the most sensitive task to detect cognitive impairment in PD patients [15, 17, 19]. This is confirmed in our study, in which semantic fluency together with the visual search task obtained the greatest area under the ROC curve values. Similarly to what happens in the case of recall tasks, even though semantic fluency deficits have repeatedly been reported in previous studies [15, 19], it has been suggested that, rather than having a purely semantic origin, the poor scores obtained by PD samples in this task reveal a deficit of executive functions [14, 19]. This assumption usually relies in the presence of deficits in the phonological fluency task, that is very similar to semantic fluency but with no semantic component [17]. However, there is also evidence that PD patients are more impaired on tests of semantic

than phonemic fluency [15, 33]. As no significant differences appeared between the scores of the PD and control groups in the phonological fluency task in our study, we are inclined to suggest that there is indeed a memory component in the semantic fluency deficit present in patients suffering from PD. Moreover, there is increasing evidence that the pattern of atrophy present in PD extends to medial temporal regions[34, 35], what would explain the appearance of a memory-specific impairment.

Special attention should be paid to the three naming tasks that allow us to assess different aspects of the semantic memory of the patients. No significant differences appeared between the scores of the PD and control groups in the object naming task. Nevertheless action and face knowledge turned out to be significantly impaired in PD patients, making face and action naming appear amongst the most discriminant tasks. Previous studies had noted the appearance of a relative impairment of action knowledge in PD participants [36, 37]. This action-verb deficit has been taken as evidence of the crucial role of movement-related neural structures in the representation of semantic knowledge about verbs. The results of our study replicate these findings adding to the hypothesis that frontal lobe deficiencies influence the semantic impairment present in PD patients. On the other hand, PD patients in our study also presented a face naming deficit. Face processing has consistently been associated to the fusiform area, in the ventral region of the temporal lobe [38-41], and has been suggested to be a useful predictor of dementia in prodromal and initial stages of Alzheimer disease [42]. The results of our study suggest that assessment of face processing should also be conducted in the PD population in order to fully understand their cognitive profile.

Together with the results of previous studies, the experiment presented here points out the existence of a cognitive deficit in PD patients that affects anterior- to posterior-dependent capacities. Although executive functions, attention and recall tasks appear to be

amongst the most sensitive tests to detect cognitive impairment in PD patients, also mainly semantic tasks, like action and face naming, as well as semantic fluency, seem to be good indicators of this condition. Since MCI is believed to be a precursor of dementia[6], and given that different profiles of impairment have been suggested to predict different varieties [43], a wide range of tasks should be applied to these patients in order to fully understand their cognitive deficit.

Acknowledgements

Author Roles

J. Rodríguez-Ferreiro: project conception; statistical design and execution of analyses; manuscript writing, review and critique. F. Cuetos: project conception and organization; statistical analysis review and critique; manuscript writing, review and critique. E. Herrera: project execution, manuscript review and critique. M. Menéndez: project conception and execution, manuscript review and critique. R. Ribacoba: project conception and execution, manuscript review and critique.

References

1.   Girotti F, Soliveri P, Carella F, et al. Dementia and cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51(121):1498-1502.
2.   Aarsland D, Brønnick K, Larsen JP, Tysnes OB, Alves G, Group NPS. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 2009;72:1121-1126.
3.   Elgh E, Domellöf M, Linder J, Edström M, Stenlund H, Forsgren L. Cognitive function in early Parkinson s disease: a population-based study. Eur J Neurol 2009;16:1278-1284.
4.   Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed parkinson's disease. Neurology 2005;65:1239-1245.
5.   Foltynie T, Brayne CEG, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 2004;127:550-560.
6.   Caviness JN, Driver-Dunckley E, Connor DJ, et al. Defining Mild Cognitive Impairment in Parkinson's disease. Mov Disord 2007;22:1272-1277.
7.   Mamikonyan E, Moberg P, Sideworf A, et al. Mild Cognitive impairment is common in Parkinson´s Disease patients with normal MMSE scores. Parkinsonism & related disorders 2009;15:226-231.
8.   Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
9.   Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord 2006;21:1343–1349.
10.   Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain Cogn 2007;130:1787–1798.
11.   Bronnick K, Emre M, Lane R, Tekin S, Aarsland D. Profile of cognitive impairment in dementia associated with Parkinson's disease compared with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2007;78:1064-1068.
12.   Kulisevsky J, Pagonabarraga J. Cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. Mov Disord 2009;24:1103-1110.
13.   Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689-1707.
14.   Goetz CG, Emre M, Dubois B. Parkinson's disease dementia: Definitions, guidelines and research perspectives in diagnosis. Ann Neurol 2008;64:581-592.
15.   Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain 2009;132:2958-2969.
16.   Levin BE, Llabre MM, Reisman S, et al. Visuospatial impairment in Parkinson's disease. Neurology 1991;41:365-369.
17.   Zgaljardic DJ, Borod JC, Foldi NS, Mattis P. A review of the Cognitive and Behavioral sequelae of Parkinson's disease: Relationship to frontoestriatal circuitry. Cogn Behav Neurol 2003;16:193-210.
18.   Rippon GA, Marder KS. Dementia in Parkinson's disease. Adv Neurol 2005;96:95-113.

19.   Almeida GM, Corrêa L, Helena G, Souza A, Bastos A. Dementia and mild cognitive impairment in patients with Parkinson's disease. Arq Neuropsiquiatr 2009;67:423-427.

20.   Emre M. Dementia associated with Parkinson´s disease. Lancet Neurol 2003;2:229-237.

21.   Gurd JM, Ward CD. Retrieval from semantic and letter-initial categories in patients with Parkinson's disease. Neuropsychologia 1989;27:743-746.

22.   Levy G, Jacobs DM, Tang MX, et al. Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord 2002;17:1221-1226.

23.   Mahieux F, Fenelon G, Flahault A, Manifacier MJ, Michelet D. Neuropsychological prediction of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998;64:178-183.

24.   Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. Journal of Neurological Science 2010;289:18-22.

25.   Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745–752.

26.   Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Mov Disord 2007;22:2314-2324.

27.   Petersen RC. Conceptual overview. In: Petersen RC, ed. Mild Cognitive Impairment: Aging to Alzheimer's Disease. New York, NY: Oxford University Press, 2003:1-14.

28.   Noe E, Marder K, Bell KL, Jacobs DM, Manly JJ, Stern Y. Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. Mov Disord 2004;19:60-67.

29.   Starkstein SE, Sabe L, Petracca G, et al. Neuropsychological and psychiatric differences between Alzheimer's disease and Parkinson's disease with dementia. J Neurol Neurosurg Psychiatry 1996;61:381-387.

30.   Levin BE, Torner R, Rey GJ. Cognitive impairments in Parkinson's disease. Neurol Clin 1992;10:471-485.

31.   Pillon B, Deweer B, Agid Y, Dubois B. Explicit memory in Alzheimer's disease, Huntington's disease, and Parkinson's disease. Arch Neurol 1993;50:374-379.

32.   Whittington CJ, Podd J, Kan MM. Recognition memory impairment in Parkinson's Disease: Power and meta-analyses. Neuropsychology 2000;2:231-246.

33.   Henry JD, Crawford JR. Verbal fluency deficits in Parkinson's disease: a meta-analysis. J Int Neuropsychol Soc 2004;10:608-622.

34.   Tam CWC, Burton EJ, McKeith IG, Burn DJ, O'Brien JT. A comparison with Alzheimer disease and dementia with Lewy bodies. Neurology 2005;64:861-865.

35.   Double KL, Halliday GM, McRitchie DA, Reid WGJ, Hely MA, Morris JGL. Regional brain atrophy in idiopathic Parkinson's disease and diffuse Lewy body disease. Dement Geriatr Cogn Disord 1996;7:304-313.

36.   Cotelli M, Borroni B, Manenti R, et al. Action and object naming in Parkinson's disease without dementia. Eur J Neurol 2007;14:632-637.

37.   Rodríguez-Ferreiro J, Menéndez M, Ribacoba R, Cuetos F. Action naming is impaired in Parkinson disease patients. Neuropsychologia 2009;47(14):3271-3274.

38.   Damasio H, Grabowski TJ, Hichwa RD, Damasio AR. A neural basis for lexical retrieval. Nature 1996;380:499-505.

39.   Galton CJ, Patterson K, Graham K, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. Neurology 2001;57:216-225.

40.   Gorno-Tempini ML, Price CJ. Identification of famous faces and buildings: A functional neuroimaging study of semantically unique items Brain 2001;124:2087-2097.
41.   Gorno-Tempini ML, Price CJ, Josephs O, et al. The neural systems sustaining face and proper-name processing. Brain 1998;121:2103-2118.
42.   Werheild K, Clare L. Are faces special in Alzheimer's disease? Cognitive conceptualisation, neural correlates, and diagnostic relevance of impaired memory for faces and names. Cortex 2007;43:898-906.
43.   Gauthier S. Pharmacotherapy of mild cognitive impairment. Dialogues in Clinical Neuroscience 2004;6.

Table Legends:

Table 1. Summary of participants' characteristics.

Table 2. Summary of scores of the two groups in the experimental tasks and results of the different analyses.