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Neurodegeneration and cognition in Parkinson's disease: a review

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Abstract. – Parkinsons Disease (PD) is a neurodegenerative disorder of the dopaminergic neurons in the substantia nigra. Much of the scientific literature on the Parkinson's disease has been focused on the evaluation and management of motor conditions in PD. Much less stress has been laid on evaluating and managing the cognitive disturbances found comorbidly in this condition. Studies have suggested that the cognitive dysfunction observed in PD can range anywhere from individual cognitive deficits to the clinical picture of minimal cognitive impairment to as much as a full-blown dementia like clinical picture. Perhaps because of this poor understanding, the treatments for this comorbidity have not been able to be adequately developed. Right now, only rivastigmine is the approved drug of choice for treatment of dementia associated with PD. In this review we aim at elaborating the individual cognitive deficits associated with PD instead of focusing on full-blown dementia. Our aim at focusing on individual symptoms is important because these symptoms should be evaluated even at the most beginning stages of PD rather than waiting for the patient to report for the symptoms. Therefore, we will aim at elaborating the prevalence, symptomatology and implications for treatment for these cognitive dysfunctions individually. Because covering all the domains of cognitive dysfunctions are not possible here, we will focus on three cognitive impairments which are most commonly observed in the PD patients. These are the (1) Executive function deficits (2) Memory deficits and (3) visuospatial deficits. We will, finally, have an overview of the condition of minimal cognitive deficits observed in PD.

Key Words:
Parkinson's disease, Cognitive function, Memory deficit, Rivastigmine, Dementia, Visiospatial deficits, Mild cognitive impairment.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder of the dopaminergic neurons in the substantia nigra. It is chronic and progressive in nature with an asymmetric onset. Motor and non-motor deficits are characteristic features of this disease. Previously it was believed that intellect is preserved in PD, but several recent researches report of cognitive deficits and impairment. It is rather strange to note that not enough of stress has been laid on this disorder from the neuropsychological perspective because it seems that almost all kinds of cognitive dysfunctions are prevalent in the PD. Studies have suggested that the cognitive dysfunction observed in PD can range anywhere from individual cognitive deficits to the clinical picture of minimal cognitive impairment to as much as a full-blown dementia like clinical picture. Perhaps because of this poor understanding, the treatments for this comorbidity have not been able to be adequately developed. Right now, only rivastigmine is the approved drug of choice for treatment of dementia associated with PD. In this review we aim at elaborating the individual cognitive deficits associated with PD. Our aim at focusing on individual symptoms is important because we are of the opinion that these symptoms should be evaluated even at the most beginning stages of PD rather than waiting for the patient to report for the symptoms. Therefore, we will aim at elaborating the prevalence, symptomatology and implications for treatment for these cognitive dysfunctions individually. Because covering all the domains of cognitive dysfunctions are not possible here, we will focus on three cognitive impairments which are most commonly observed in the

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PD patients. These are the (1) Executive function deficits (2) Memory deficits and (3) visuospatial deficits. We will finally have an overview of the condition of minimal cognitive deficits observed in PD.

Prevalence of Cognitive Deficits in PD

Few studies have explored the prevalence of cognitive deficits in PD patients. In a population based cohort study by Foltynie et al (Brain 2004; 127: 550-560), it was observed that one of three cognitive tasks (the Mini-Mental State Examination, a pattern recognition task, and the tower of London task) were performed poorly by 36% of PD patients in a. In other follow up studies[1], it was found that dementia eventually developed in 20% to as many as 75%[2] of the PD patients. However, the incidences of individual cognitive impairments has not been assessed earlier. Aarsland et al[2] compared early, untreated Parkinson disease subjects with controls and found a twofold increase in the proportion of cognitive impairment. One of the problems with these studies which prevents these results from being acceptable is that there is no clear cut guideline in literature to define cognitive impairment in old age. Usually these studies have used a MMSE, score below 24 as indicative of cognitive impairment. Similarly, scores of 16/24 on the PRM and 8/14 on the tower of London (TOL) are greater than 1 SD below expected for unaffected age- and IQ-matched individuals therefore indicating cognitive impairment. However, there is a lack of well validated criteria for diagnosing the cognitive impairments in PD patients.

Executive Function Deficits

A set of faculties essential to take decision in day to day life are named by the umbrella term of executive functions. A number of cognitive functions like planning, monitoring, cognitive flexibility, inhibition of automated responses, retrieval from declarative memory and the maintenance and manipulation of information in working memory are grouped in this category. Several studies have reported attentional and executive function impairments in PD in addition to the hallmark symptoms of motor abnormalities[3-7]. Executive function deficits in PD have been found to be particularly sensitive to neuropsychological tests like Wisconsin Card Sorting Test (WCST), Trail Making Test (TMT) and TOL test[8-10]. The patient's quality of life can be foreseen based on deficits in executive functions[11]. In a study it was observed that the impairment of shifting conceptual sets of executive dysfunction was higher during the initial period of PD than in age matched normal control subjects. These findings were replicated by other studies using cognitive tests such as TMT or Stroop Color-Word test which assesses the set shifting abilities[8,12]. Other tests have also revealed cognitive impairments. For example, the initial thinking time was impaired in a mild stage of PD and the minimum move solution was revealed at a severe stage of PD in studies using the TOL. However in the advanced disease, disturbance in almost every cognitive parameter have demonstrated[9]. "Behavioural Assessment of the Dysexecutive Syndrome" (BADS), is a neuropsychological array of subtests which includes the Rule Shift Cards Test, Action Program Test, Key Search Test, Temporal Judgement Test, Zoo Map Test, and Modified Six Elements Test[13]. BADS has been found to be a sensitive tool for the assessment of executive dysfunction. It offers a broad assessment of executive dysfunction, which includes the planning of behaviour under concept formation to novel situations, problem solving and reasoning in addition to set shifting and inhibition control. This is proven to be more apt tool, in comparison to the traditional tests like WCST, Trail making test, Porteus Maze Test, Controlled Oral Word Association Test, and Tinker Toy Test[14,15]. Perfetti et al (Parkinsonism Relat Disord 2010; 16: 46-50) reported the total score of BADS and its six subsets to be more sensitive a parameter followed by TOL for assessment of executive functions. This was reported after examining the BADS with other traditional tests like WCST, TMT, Jigsaw puzzle test in 25 non-demented PD and 24 demographically matched controls.

Kamei et al (Mov Disord 2008; 23: 566-573) conducted a study on 63 non-demented PD patients to assess executive dysfunction using BADS along with UPDRS. All of the non-demented PD patients attained a score of ≥24 on the Mini-Mental State Examination. To evaluate the predisposing factors to executive dysfunction, they used multiple logistic regression analysis, which was defined as <70 points on the age-controlled standardized score. It was observed that the total score on the UPDRS was a significant independent predisposing factor for executive dysfunction Moreover, UPDRS part II was specifically found to be a significant factor for executive dysfunction. A significantly lower pro-

file score was noticed in patients with executive dysfunction in all subtests on the BADS when compared to patients without executive dysfunction. They also noticed that executive dysfunction in non-demented PD with was a predisposing factor for greater severity of PD, leading to impairment of daily living activities. A wide-range of components of executive dysfunction was found in non-demented PD. With the increasing severity of PD, all components of executive dysfunction were impaired and diversity was shown in the patterns of each component.

Variations in the impairment of executive functions with PD subgroups was also taken into consideration. These subgroups included young onset versus late onset PD, tremor predominant versus akinetic-rigid form, non-tremor subgroup, PD with dementia versus without dementia. It was observed that intelligence, age, education, medication etc were the variables which played a significant role in the cognitive impairments of PD.

Liozidou et al (J Geriatr Psychiatry Neurol 2012; 25: 215-221) compared 73 non-demented PD patients with 48 healthy participants on the tasks of working memory (digit span backward), information processing speed (digit symbol subscale-WAIS, and trail making (TMT) part A). They observed that in PD without dementia there was a significant association between working memory (digit span backward) and inflexible behavior (perseverative errors on WCST). They also studied two categories of PD groups, which were based on their performance on the Weschler adult intelligence scale (WCST). The first group completed 0-2 categories whereas the second group completed 3-6 categories. They found that age and general level intelligence (full IQ) significantly affected the perseverative errors on WCST committed by the second subgroup, when both these parameters were controlled. This signifies the importance of age and level of intelligence in executive functions.

Memory Deficits

Memory impairments in PD deviate on several lines when compared to other neurodegenerative disorders. Impairment in memory depends on many factors like the age of onset of the disease, disease duration and severity of clinical symptoms[16]. In PD short-term memory is impaired with intact long term memory[17]. Sagar et al (Brain 1988; 111: 525-539) reported recency discrimination deficits and impaired short term memory processing in PD through short stimulus-test in which there was deficit in content recognition. Short-term memory deficits related with scores on tests of working memory, attention and executive function showed that attention deficits influence both short-term memory and working memory[18]. Visual short-term memory was affected but not verbal short-term memory. Defects in visual short-term memory corresponded with the severity of the disease and motor performance[19].

It has been observed that the impairment in declarative memory in PD is more pronounced when compared to that seen in age matched healthy elderly subjects. Procedural memory deficits observed were a loss of automatism and was linked with age and pathology[20]. Verbal recall of words and drawing were impaired where as recall of faces was intact, reflecting partial loss of explicit memory[21]. Impairments in working memory have been reported in many studies[22-24]. In treated PD patients with severe clinical symptoms, spatial, verbal and visual working memory were affected in direct proportion to the severity of clinical symptoms and progression of the disease[25].

Both immediate and delayed visual recognition memory was found to be normal (in whom?). This kind of memory was not affected by age, motor dysfunction or duration of the disease[27]. Hence previously it was thought that the impairments in patients with PD are primarily in recall rather than in recognition domain[26-28]. However impairment in recognition memory in PD was reported in several consequent studies[29-31].

Infact, recognition memory deficits have been observed in PD with or without dementia. This was reported by Whittington et al (Neuropsychology 2000; 14: 233-246), after performing power analysis and meta-analysis. They proposed that these recognition memory deficits may progress with disease progression and the largest deficits occur in PD with dementia. In recall component, deficits are mainly evident in recall of temporal sequence source[5,28,32], recollection of sources[33] and self-ordered pointing[28,34].

Visuospatial and Visuoconstructive Abilities

PD is known to cause visuospatial deficits[35,36] and even in the presence of minimal motor involvement these deficits are obvious[37] reported visuospatial deficits in PD. They did this by examining visuospatial function in 76 patients with idiopathic PD and then comparing them with 76

matched normal controls. Both the groups were administered Benton's Judgement of Line Orientation (JLO) test. A greater proportion of complex intra quadrant errors and horizontal line errors were observed in idiopathic PD when compared to the controls. In addition they also administered JLO twice in a time interval of 20 minutes to rule out the possibility of practice effect and they found no significant difference between two administrations. Another work[38] conducted extensive evaluation of the visuospatial functioning in patients with Parkinson's disease by administering the neuropsychological tests of basic visual perception, complex perceptual discrimination, and spatial orientation to assess. Results demonstrated that the three variables, age, duration of disease and degree of dementia were major determinants of the differences of the findings observed in the groups. They concluded that decreases in spatial orientation functioning in Parkinson's disease may reflect the rate of progression of the disease as reflected by the effects of these three variables on the outcome.

Studies have suggested that motor involvement as a major criterion for visuospatial deficits in PD. This is reflected in the fact that even in the initial stages of the illness[39]. It was reported that when the task had some degree of involvement of motor component visuospatial deficits were observed and were absent on the tasks not having motor component involvement[40,41].

Mild Cognitive Impairment (MCI)

An important development in exploring the cognitive declines in PD patients has been the exploration of MCI. There is no consensus over the uniform diagnostic criteria of MCI in PD. were by The Movement Disorder Society (MDS) Task Force[42] proposed two levels of diagnostic guidelines. The first level consists of following criteria: (1) A diagnosis of PD based on the UK PD Brain Bank Criteria, (2) gradual decline in cognitive ability reported by either patient or informant, or observed by the clinician (3) cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities, and (4) cognitive deficits are not sufficient to interfere significantly with functional independence. The level two diagnostic criteria consisted of a more precise diagnostic criteria which were based on comprehensive assessment. These include the following (1) neuropsychological testing which should have two tests within each of the five cognitive domains: attention and working memory, executive, language, memory, visuospatial functions; (2) impairment on at least two neuropsychological tests in one cognitive domain, or one impaired test in two different cognitive domains, and (3) impairment below appropriate norms *or* significant decline on serial cognitive testing *or* significant decline from estimated premorbid levels.

Diagnosis of MCI based on neuropsychological assessment, requires longer time and specialized personnel and reliable, valid and culture specific tools, which is a major disadvantage. This is usually not possible for the clinician in clinical and community practice settings for which a lesser time consuming is needed which could be administered with lesser training skills. Hence, a globally accepted tool for assessment of MCI is still deficient. However, to identify subtle cognitive deficits there are some self-reported and care giver-reported questionnaire. [43, 44] Studies indicate that these subtle deficits are more likely to lead to dementia like features in later age and hence an early detection of subtle cognitive deficits is vital. A 4-year community based longitudinal follow up study reported that 62% of PD-MCI in comparison to only 20% of patients without cognitive deficits had developed dementia[45].

Neurodegeneration and Impaired Cognition in PD: Gross Pathology

Parkinson's disease is essentially a progressive neurodegenerative disorder. However, contrary to the earlier understanding that only nigro-striatal pathway undergoes degeneration, atrophy of several brain regions have been found in PD. Hence, analyzing the areas of atrophy in brain can be used in studying the association of cognitive impairments with the gross pathology of PD. The executive function deficits in PD are primarily due to frontal lobe dysfunction secondary to pathophysiological alterations in the basal ganglionic-dorsolateral frontal loops[46] and are also thought to be due to degeneration of the fronto-striatal circuitry[47]. Melzer et al[47] observed that the grey matter loss in PD correlated with global cognitive score but not with motor impairment in most of the brain regions. He came to this conclusion by comparing PD with normal cognition (PD-N), PD with MCI (PD-MIC) and PD with dementia (PD-D) with matched controls. He found that the brain regions implicated in PD-MCI showed partial grey matter atrophy in the temporal, parietal and frontal cortex as well as

the bilateral caudal hippocampus, amygdala and right putamen. A more wide spread atrophy was observed in PD-D subjects in regions involved in PD-MCI but in addition they also had reduced grey matter volume in other large areas of the temporal lobe (including the parahippocampi), the intracalcarine and lingual gyri, posterior cingulate gyrus, frontal regions and bilateral caudate.

Similarly, Mak et al[48,49] comparing PD-NIC (no cognitive impairment) with PD-MIC, found that patients with PD-MCI had lower global cognition scores compared with PD-NCI (Mini-Mental State Examination: 26.9 vs 28.4, p = 0.011; Montreal Cognitive Assessment: 24.5 vs 27.0, $p < 0.001$). A significantly poorer performance was exhibited by PD-MIC group on almost all of the cognitive domains including the executive function, attention, memory and language abilities. At the same time, the neuropathological findings of greater reductions in grey matter volumes in the left insular, left superior frontal and left middle temporal areas were also observed in patients with PD-MCI compared to PD-NCI. When multiple regressions were performed by on the variables like age, education and cardiovascular risk factors, a significant positive correlation was noticed between left insular atrophy and executive-attention dysfunction.

The degree of degeneration in the thalamus was examined in a series of studies by Halliday (Parkinsonism Relat Disord 2009; 15(Suppl 3): S152-155). He reported that in levodopa-responsive Parkinson's disease patients a selective degeneration of the intralaminar thalamic nuclei was seen. The caudal intralaminar nuclei (the centre-median/parafascicular complex), the parataenial, cucullar and central lateral nuclei were the nuclei involved.

Neurodegeneration and Impaired Cognition in Pd: the Cellular Neuropathology

In patients with PD it is difficult to find a direct correlation between the cellular neuropathology and cognitive decline. But cellular pathological findings with cognitive deficits in PD patients are correlated in some of the current studies. Gomperts et al (Neurology 2008; 71: 903-910) report that amyloid contributes to cognitive, but not motor, decline over time. However at baseline measurements, there is no distinction between cognitively impaired and unimpaired subjects with PD without dementia on amyloid burden. A worsening in executive function, as well as visuospatial function, activation retrieval, and performance on the Mini-Mental State Examination was related to the APOE 4 allele.

The fronto-striatal dysfunction presumed to result from dopamine deficiency may lead to mild cognitive deficits[50,51]. This may be a contributing factor for the cognitive decline in PD as it has been observed that in the initial stages of PD, particularly evident cortical thinning ensues in frontotemporal regions. This dopamine deficiency has been observed more closely recently when Barut et al (Acta Neurol Belg 2013; 113: 117-125) conducted a comparative study between ET (essential tremor) with PD (ET-PD) with the groups having ET only or PD only. They found that ET-PD patients demonstrated more frequent familial tremor histories and lower levodopa responsiveness than PD patients. Severe cognitive impairments were seen in ET-PD patients' population when compared to pure-ET patients. This study concludes that a more extensive neurodegeneration is seen in ET-PD patients which are a subset of ET patients. Such as overlap between ET and PD may indicate the presence of a syndrome.

In PD patients with MCI regional cerebral glucose metabolism has been studied and its deficiencies have been implicated. For example, extensive hypometabolism has been observed in temporo parietal regions of PD patients[50,51]. Recently it has been hypothesized that the non-coding RNA oxidation could be a major neuropathological reason for cognitive loss in PD[52].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Bowm FP, Hoehn MM, Yahr MD. Parkinsonism: alterations in spatial orientation as determined by a route walking test. Neuropsychologia 1972; 10: 355-361.
2) Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003; 60: 387-392.
3) Brown RG, Marsden CD. Internal versus external cues and the control of attention in Parkinson's disease. Brain 1988; 111: 323e45.

4) Wright MJ, Burns RJ, Geffe GM, Geffen LB. Covert orientation of visual attention in Parkinson's disease: an impairment in the maintenance of attention. Neuropsychologia 1990; 28: 151e9.

5) Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early untreated Parkinson's disease and its relationship to motor disability. Brain 1991; 114: 2095-2122.

6) Van Spaendonk KPM, Berger HJC, Horstink MWI, Buytenhuijs EL, Cools AR. Executive functions and disease characteristics in Parkinson's disease. Neuropsychologia 1996; 34: 617e26.

7) Richard M, Cote LJ, Stern Y. Executive function in Parkinson's disease: set shifting or set-maintenance? J Clin and Exp Neuropsychol 1993; 15: 266e79.

8) Hietanen M, Teravainen H. Cognitive performance in early Parkinson's disease. Acta Neurol Scand 1986; 73: 151-159.

9) Vingerhoets G, Verleden S, Santens P, Miatton M, De Reuck J. Predictors of cognitive impairment in advanced Parkinson's disease. J Neurol Neurosurg Psychiatry 2003; 74: 793-796.

10) Lewis SJ, Cools R, Robbins TW, Dove A, Barker RA, Owen AM. Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. Neuropsychologia 2003; 41: 645-654.

11) Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000; 69: 308-312.

12) Dujardin K, Degreef JF, Rogelet P, Defebvre L, Destee A. Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J Neurol 1999; 246: 783-788.

13) Wilson BA, Alderman N, Burgess PW, Emslie H, Evans JJ. Behavioural assessment of the dysexecutive syndrome. Bury St. Edmunds, England: Thames Valley Test Company, 1996.

14) Bennett PC, Ong B, Ponsford J. Assessment of executive dysfunction following traumatic brain injury: comparison of the BADS with other clinical neuropsychological measures. J Int Neuropsychol Soc 2005; 11: 606-613.

15) Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment, 4th ed. Oxford: Oxford University Press, 2004; pp. 636-637.

16) Zakharov VV, Akhutina TV, Yakhno NN. Memory impairment in Parkinson's disease. Neurosci Behav Physiol 2001; 31: 157-163.

17) Sullivan EV, Sagar HJ. Double dissociation of short term and long term memory for nonverbal material in Parkinson's disease and global amnesia. A further analysis. Brain 1991; 114: 893-906.

18) Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. Brain 1991; 114: 2095-2122.

19) Bruna O, Junqué C, Vendrell P, Roig C, Grau-Veciana JM. Memory changes in Parkinson's disease. Relation with clinical variables. Neurologia 1992; 7: 55-60.

20) Allain H, Lieury A, Quemener V, Thomas V, Reymann JM, Gandon JM. Procedural memory and Parkinson's disease. Dementia 1995; 6: 174-178.

21) Allain H, Lieury A, Thomas V, Reymann JM, Gandon JM, Belliard S. Explicit and procedural memory in Parkinson's disease. Biomed Pharmacother 1995b; 49: 179-186.

22) Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW. Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 1997; 35: 519-532.

23) Beato R, Levy R, Pillon B, Vidal C, du Montcel ST, Deweer B, Bonnet AM, Houeto JL, Dubois B, Cardoso F. Working memory in Parkinson's disease patients: clinical features and response to levodopa. Arq Neuropsiquiatr 2008; 66: 147-151.

24) Bradley VA, Welch JL and Dick DJ. Visuospatial working memory in Parkinson's disease. J Neurol Neurosurg Psychiatry 1989; 52: 1228-1235.

25) Rottschy C, Kleiman A, Dogan I, Langner R, Mirzazade S, Kronenbuerger M, Werner C, Shah NJ, Schulz JB, Eickhoff SB, Reetz K. Diminished activation of motor working memory networks in Parkinson's disease. PLoS One 2013; 8: e61786.

26) Breen EK. Recall and recognition memory in Parkinson's disease. Cortex 1993; 29: 91-102

27) Brown RG, Marsden CD. How common is dementia in Parkinson's disease? Lancet 1984; 2: 1262-1265.

28) Flowers KA, Pearce I, Pearce JMS. Recognition memory in Parkinson's disease. J Neurol Neurosurg Psychiatry 1984; 47: 1174-1181.

29) Gabriel JDE, Singh J, Stebbins GT, Goetz CG. Reduced working memory span in Parkinson's disease: Evidence for the role of a frontostriatal system in working and strategic memory. Neuropsychology 1996; 10: 322-332.

30) Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M, Robbins TV. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. Brain 1988; 111: 695-718.

31) Owen AM, Beksinska M, James M, Leigh PN, Summers BA, Marsden CD, et al. Visuospatial memory deficits at different stages of Parkinson's disease. Neuropsychologia 1993; 31: 627-644.

32) Stebbins GT, Gabrieli JD, Masciari F, Monti L, Goetz CG. Delayed recognition memory in Parkinson's disease: a role for working memory? Neuropsychologia 1999; 37: 503-510.

33) Sullivan EV, Sagar HJ, Cooper JA, Jordan N. Verbal and nonverbal short term memory impairment in untreated Parkinson's disease. Neuropsychology 1993; 7: 396-405.

34) Taylor AE, Saint-Cyr JA, Lang AE. Memory and learning in early Parkinson's disease: Evidence for a frontal lobe syndrome. Brain Cognition 1990; 13: 211-232.

35) Owen AM, James M, Leigh PN, Sumers BA, Marsden CD, Quinn NP, Lange KW, Robbins TW. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992; 115: 1727-1751.

36) Lee AJ, Smith E. Cognitive deficits in the early stages of Parkinson's disease. Brain 1983; 106: 257-270.

37) Levin BE, Llabre MM, Weiner WJ. Cognitive impairments associated with early Parkinson's disease. Neurology 1989; 39: 557-561.

38) Montse A, Pere V, Carme J, Frances V, Eduardo T. Visuospatial deficits in Parkinson's Disease assessed by Judgement of Line Orientation Test: Error analysis and practice effects. J Clin Exp Neuropsychol 2001; 23: 592-598.

39) Raskin SA, Borod JC, Wasserstein J, Bodis-Wollner I, Coscia L, Yahr MD. Visuospatial orientation in Parkinson's Disease. Int J Neurosci 1990; 51: 9-18.

40) Bollek F, Passafiume D, Keefe NC, Rogers K, Morrow L, Kim Y. Visuospatial impairment in Parkinson's disease: role of perceptual and motor factors. Arch Neurol 1984; 41: 485-490.

41) Bowen FP, Burns MM, Brady EM, Yahr MD. A note on alterations of personal orientation in Parkinsonism. Neuropsychologia 1976; 14: 425-429.

42) Brown RG, Marsden CD. Visuospatial function in Parkinson's disease. Brain 1986; 109: 987-1002.

43) Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, Mollenhauer B, Adler CH, Marder K, Williams-Gray CH, Aarsland D, Kulisevsky J, Rodriguez-Oroz MC, Burn DJ, Barker RA, Emre M. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012; 27: 349-356.

44) Naismith SL, Lewis SJG. 'DASH' symptoms in patients with Parkinson's disease: red flags for early cognitive decline. J Clin Neurosci 2011; 18: 352-355.

45) Naismith SL, Pereira M, Shine JM, Lewis SJG. How well do caregivers detect mild cognitive change in Parkinson's disease? Mov Disord 2011; 1: 161-164.

46) Janvin CC, Aarsland D, Larsen JP. Cognitive predictors of dementia in Parkinson's disease: a community-based, 4-year longitudinal study. J Geriatr Psychiatry Neurol 2005; 18: 149-154.

47) Cummings J. Frontal subcortical circuits and human behavior. Arch Neurol 1993; 50: 873-880.

48) Melzer TR, Watts R, MacAskill MR, Pitcher TL, Livingston L, Keenan RJ, Dalrymple-Alford JC, Anderson TJ. Grey matter atrophy in cognitively impaired Parkinson's disease. J Neurol Neurosurg Psychiatry 2012: 83: 188-194.

49) Mak E, Zhou J, Tan LC, Au WL, Sitoh YY, Kandiah N. Cognitive deficits in mild Parkinson's disease are associated with distinct areas of grey matter atrophy. J Neurol Neurosurg Psychiatry 2014; 85: 576-580.

50) Mak E, Bergsland N, Dwyer MG, Zivadinov R, Kandiah N. Subcortical atrophy is associated with cognitive impairment in mild Parkinson disease: a combined investigation of volumetric changes, cortical thickness, and vertex-based shape analysis. AJNR Am J Neuroradiol 2014: 35: 2257-2264.

51) Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. J Neurol Neurosurg Psychiatry 2007; 78: 254-259.

52) Tinaz S, Courtney MG, Stern CE. Focal cortical and subcortical atrophy in early Parkinson's disease. Mov Disord 2011; 26: 436-441.