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Visuospatial functioning is associated with sleep disturbance and hallucinations in nondemented patients with Parkinson's disease

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Abstract

Introduction: Cognitive impairment is a common symptom of Parkinson's disease (PD) associated with reduced quality of life and a more severe disease state. Previous research has shown an association between visuospatial dysfunction and worse disease course; however, it is not clear whether this is separable from executive dysfunction and/or dementia. This study sought to determine whether distinct cognitive factors could be measured in a large PD cohort, and if those factors were differentially associated with other PD-related features, specifically to provide insight into visuospatial dysfunction.

Methods: Non-demented participants with PD from the Pacific Udall Center were enrolled (n = 197). Co-participants (n = 104) completed questionnaires when available. Principal components factor analysis (PCFA) was utilized to group the neuropsychological test scores into independent factors by considering those with big factor loading (>=.40). Linear and logistic regression analyses were performed to examine the relationship between the cognitive factors identified in the PCFA and other clinical features of PD.

Results: Six factors were extracted from the PCFA: 1) executive/processing speed, 2) visual learning & memory/visuospatial, 3) auditory working memory, 4) contextual verbal memory, 5)

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Disclosure of interest

The authors report no conflict of interest.

semantic learning & memory, and 6) visuospatial. Motor severity (p = 0.001), mood (p <0.001), and performance on activities of daily living scores (informant: p<0.001, patient: p=0.009) were primarily associated with frontal and executive factors. General sleep disturbance (p <0.006) and hallucinations (p=0.002) were primarily associated with visuospatial functioning and visual learning/memory.

Conclusions: Motor symptoms, mood, and performance on activities of daily living were primarily associated with frontal/executive factors. Sleep disturbance and hallucinations were associated with visuospatial functioning and visual learning/memory only, over and above executive functioning and regardless of cognitive disease severity. These findings support that visuospatial function in PD may indicate a more severe disease course, and that symptom management should be guided accordingly.

Keywords

Aging; Cognition; Neuropsychological Assessment; Parkinson's disease

Introduction

Cognitive impairment is a common non-motor symptom of Parkinson's disease (PD) and is associated with reduced quality of life, loss of independence, and increased mortality (Aarsland, Larsen, Tandberg, & Laake, 2000; Levy et al., 2002; Schrag, Jahanshahi, & Quinn, 2000). The nature and extent of cognitive impairment within PD is variable, however, and specific cognitive deficits may be differentially associated with severity of other disease-related features (Caballol, Marti, & Tolosa, 2007). Given the variability in PD symptom presentation, a precision medicine approach, in which treatment strategies are tailored to an individual's specific disease-related characteristics, may be particularly appropriate for PD (B. Cholerton et al., 2016; Titova and Chaudhuri, 2017). The identification of distinct cognitive factors and their associations with other PD-related clinical features may thus provide a foundation for specific interventions aimed at alleviating distress associated with non-motor symptoms in PD.

Visuospatial dysfunction is commonly reported in PD (Armstrong, 2017; Curtis, Masellis, Camicioli, Davidson, & Tierney, 2018). Previous reports have shown an association between visuospatial dysfunction and severity of visual hallucinations, gait dysfunction, REM sleep behavior disorder, and dementia, all of which may impact quality of life and independence and are markers for more severe disease (Factor et al., 2014; Jozwiak et al., 2017; Kelly et al., 2015). The etiology of visuospatial dysfunction in PD is multifactorial and not well-understood, with some evidence that deficits on visuospatial tasks are largely related either to the increased task demand associated with impaired executive function, or to the presence of more advanced disease and dementia associated with cortical Lewy body accumulation (Pal et al., 2018; Papagno and Trojano, 2018). Alternatively, visuospatial dysfunction may be separable from executive function in PD and largely the result of disruptions in striatal pathways to occipital and/or parietal lobes (Pereira et al., 2009; Siepel et al., 2014).

We previously reported a relationship between reduced visuospatial performance and the presence of glucocerebrosidase (*GBA*) gene variants in the PD Cognitive Genetics

Consortium (PDCGC), a large cohort of cognitively and clinically characterized participants with PD (Mata et al., 2016). Given this association and to better assess visuospatial functioning, we implemented an expanded cognitive battery, with augmented visuospatial and visual learning and memory measures in the Pacific Udall Center, a subset of the PDCGC. Here, we aim to determine the underlying cognitive factors measured by the expanded cognitive battery in non-demented participants with PD, and specifically whether distinct visuospatial factors are identified. Secondly, we sought to identify whether the resulting cognitive factors are differentially associated with other clinical features of PD, and whether these associations can provide insight into visuospatial dysfunction in PD.

Materials and Methods

Participants

Participants were drawn from the Pacific Udall Center of Excellence in Parkinson's Disease Research, a multicenter collaboration with a focus on harmonized clinical and neuropsychological evaluation among a prevalent PD cohort (B. A. Cholerton et al., 2013). The current study enrolled participants from two Pacific Udall Center sites: the University of Washington/Veterans Affairs Puget Sound Health Care System and Oregon Health Sciences University/Veterans Affairs Portland Health Care System. All participants met the United Kingdom Parkinson's Disease Society Brain Bank (UKBB) clinical diagnostic criteria for PD and were assigned a cognitive diagnosis at a consensus diagnosis conference as previously described (B. A. Cholerton, et al., 2013). Those participants aged 50–85 who completed at least one visit with an extended cognitive battery (see below) were included (n = 248). Thirty-five participants with a dementia diagnosis were excluded and 16 were missing cognitive test data, for a total of 197 participants included in the analyses. Co-participants (n=104) were enlisted to complete questionnaires when available. The institutional review board at both sites provided formal approval for the study. All participants and co-participants provided written informed consent.

Cognitive variables

The original PUC neuropsychological battery included the Montreal Cognitive Assessment (MoCA)(Nasreddine et al., 2005), Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict, Schretlen, Groninger, & Brandt, 1998), Logical Memory I and II from the Wechsler Memory Scale-Revised(Wechsler, 1987b), Letter-Number Sequencing from the Wechsler Adult Intelligence Scale – III (Wechsler, 1997), Digit Symbol and Digit Span subtests from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1987a), Trailmaking Test, parts A and B (Strauss, Sherman, & Spreen, 2006), Stroop test (Golden version) (Golden, 1978), semantic verbal fluency (animals and vegetables), phonemic verbal fluency (FAS) (Strauss, et al., 2006), Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983), and Benton Judgment of Line Orientation (Benton, Sivan, Hamsher, Varney, & Spreen, 1994). Participants included in the current analyses completed an extended neuropsychological battery with additional visuospatial and visual learning and memory measures: the Brief Visual Memory Test-Revised (BVMT-R) learning trials, recall, and copy(Benedict, Schretlen, Groninger, Dobraski, & Sphritz, 1996), a 10-point command

clock drawing test, and a 10-point clock copy test (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992) (Supplemental table).

Clinical variables and covariates

Participants and study partners completed a variety of questionnaires and clinical measures to assess neuropsychiatric status and performance of activities of daily living. Part 1 of the Unified Parkinson's Disease Rating Scale, Movement Disorders Society revision (MDS-UPDRS) (Goetz et al., 2008) briefly assesses hallucinations, depression, anxiety, sleep problems, and apathy among participants. Depression was further evaluated using the 15-item Geriatric Depression Scale (GDS) (Yesavage et al., 1982). The 12-item Neuropsychiatric Inventory (NPI) (Cummings, 1997) was administered to co-participants to assess participant delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, sleep disturbances, and appetite/eating abnormalities (npitest.net). Detailed sleep information was gathered from the co-participant using the Mayo Sleep Questionnaire (Boeve et al., 2013; Boeve et al., 2011). The Penn Parkinson's Daily Activities Questionnaire – 15 (PDAQ-15) (Brennan et al., 2016) was completed separately by the participant and co-participant to assess impairment in daily activities.

A movement disorders specialist assessed the severity of motor symptoms using the MDS-UPDRS Part III. Levodopa equivalent daily dose (LEDD) was calculated as described by Tomlinson et al. (Tomlinson et al., 2010). The entire coding region of the *GBA* gene was sequenced and *APOE* alleles ε2/ε3/ε4 were genotyped as previously described (Mata, et al., 2016; Mata et al., 2014). The presence of *GBA* variants and *APOE* ε4 were included in the analyses due to previous associations with cognitive decline.

Statistical analyses

Principal components factor analysis (PCFA) was used to reduce the 23 neuropsychological test scores into a smaller number of independent factors that account for most of the variation and the underlying correlation pattern. Raw test scores were treated as dependent variables in linear regression analyses that adjusted for age, education, disease duration, and sex, and the resulting standardized residuals were entered into the PCFA. Factors with an eigenvalue of 1 or greater were extracted and rotated using a varimax orthogonal rotation. Factors were interpreted by considering those with a factor loading magnitude >=.40. Factor scores were calculated using the regression method (Thompson, 1951). In the subsequent analyses examining the association between the identified factors and other clinical features, linear and logistic regression analyses were performed as appropriate with factor scores as the independent variables, additionally controlling for total MoCA score, site, *APOE* ε4, and GDS score. Results are presented both before and after controlling for LEDD. Due to missing values in *GBA* carrier status and MDS-UPDRS, these variables were not adjusted in the main analyses. However, we include them in follow up sensitivity analyses by excluding observations with missing values. The Bonferroni adjustment was used to control the family wise type I error set a priori at 0.05; since there were six factor scores, a significance level of 0.05/6 = 0.008 was used. All analyses were performed in Stata 15.1.

Results

Participant demographics, clinical characteristics, and cognitive test scores are detailed in Table 1. From the 23 cognitive variables, 6 factors were extracted from an independent PCFA. These factors accounted for 63% of the total variance and were characterized by those measures with the strongest factor loadings: 1) executive/processing speed, 2) visual learning & memory/visuospatial, 3) auditory working memory, 4) contextual verbal memory, 5) semantic learning & memory, and 6) visuospatial. PCFA results are presented in Table 2.

The relationship between factor scores resulting from the PCFA and several concomitantly collected clinical measures were evaluated (Figure 1):

Motor

Factor 1 (executive/processing speed) was significantly negatively associated with the MDS-UPDRS, Part III, the primary measure of motor severity ($\beta = -0.22$, SE = 0.81, p = 0.001). This relationship remained after controlling for LEDD ($\beta = -0.24$, SE = 0.85, p = 0.001).

Mood

Factor 3 (auditory working memory) was significantly negatively associated with depression, as measured by the GDS ($\beta = -0.26$, SE=0.10, p <0.001). This association remained after controlling for LEDD ($\beta = -0.29$, SE = 0.10, p <0.001). GDS score was also associated with Factor 5 (semantic learning & memory; $\beta = -0.15$, SE=0.10, p = 0.04), but the association is not significant after correcting for multiple comparisons or controlling for LEDD. Mood items from the MDS-UPDRS Part I and NPI were not significantly associated with the cognitive factors.

Sleep

Section K (“Nighttime Behaviors”) on the NPI was negatively associated with Factor 6 (visuospatial) only (OR = 2.4, 95% CI 1.4 – 4.0, p = 0.001), an association that remained after controlling for LEDD (OR = 2.1, 95% CI 1.2 – 3.6, p = 0.006). NPI-K subquestions indicated that Factor 6 (visuospatial) was significantly negatively associated with difficulty falling asleep (OR = 2.9, 95% CI 1.6 – 5.4, p < 0.001; after controlling for LEDD: OR = 2.3, 95% CI 1.2 – 4.4, p = 0.009) and getting up during the night (OR = 2.2, 95% CI 1.3 – 3.7, p = 0.002; after controlling for LEDD: OR = 2.1, 95% CI 1.2 – 3.7, p = 0.009). Factor 5 (semantic learning and memory) was significantly *positively* associated with waking the spouse/partner during the night (OR=2.8, 95% CI 1.1 – 7.2, p = 0.01); however, this was not significant after correcting for multiple comparisons.

The sleep item from the MDS-UPDRS was also significantly associated with Factor 6 when a binary variable (none/slight/mild = 0, moderate/severe = 1) was the dependent variable (OR = 1.7, 95% CI 1.2 – 2.5, p = 0.004; after controlling for LEDD: OR = 1.5, 95% CI 1.0–2.2, p = 0.04).

Internal consistency for the Mayo Sleep questionnaire items was low (Cronbach’s $\alpha = 0.49$), thus items for this measure were examined individually. There were no significant associations between the cognitive factors and questions related to REM behavior disorder

(RBD), sleepwalking, or disrupted breathing. There was a pattern of a negative relationship between reported restless leg-associated symptoms and Factor 6 (although none is statistically significant after correcting for multiple comparisons): 1) “Do the patient’s legs repeatedly jerk or twist during sleep?” (OR = 1.8, 95% CI 1.1 – 3.0, p = 0.02); 2) “Does the patient complain of a restless, nervous, tingly, or creepy-crawly feeling in his/her legs that disrupts his/her ability to fall asleep?” (OR = 1.8, 95% CI 1.1 – 3.1, p = 0.03); and 3) “Does the patient have leg cramps at night?” (OR = 1.7, 95% CI 1.1 – 2.8, p = 0.03). However, after controlling for LEDD, the first two questions were no longer significantly associated with any of the cognitive factors. General level of daytime alertness was positively associated with Factor 1 (more alert = better executive function/processing speed, OR = 1.5, 95% CI 1.0 – 2.2, p=0.04) and *negatively* associated with Factor 2 (more alert = worse performance on visual learning and memory/visuospatial, OR=1.6 95% CI 1.1 – 2.4, p = 0.02), both before and after controlling for LEDD, although these associations were not significant after correcting for multiple comparisons.

Hallucinations

The presence of co-participant reported hallucinations on the NPI (Y, N) was significantly negatively associated with Factor 2 (visual learning & memory/visuospatial; OR=3.0, 95% CI 1.4 – 6.6, p=0.006). This association remained after controlling for LEDD (OR = 12.1, 95% CI 2.5 – 57.6, p = 0.002)

NPI subquestions indicated that Factors 2 (visual learning & memory/visuospatial; OR = 2.6 95% CI 1.2 – 6.1, p <0.02; after controlling for LEDD: OR = 8.3 95% CI = 1.6 – 43.1, p = 0.01) and 6 (visuospatial; OR = 2.4, 95% CI 1.1 – 4.9, p = 0.02; after controlling for LEDD, not significantly associated with Factor 6) were negatively associated with the presence of visual hallucinations, although these do not meet significance after correcting for multiple comparisons.

Activities of daily living

For both patient and informant, Factor 1 (executive/processing speed) was significantly associated with PDAQ score, both before (informant: β = 0.35, SE=0.91, p=0.001, patient: β = .21, 95% CI SE=0.61, p=0.005) and after (informant: β = 0.39, SE=0.90, p<0.001, patient: β = .21, 95% CI SE=0.62, p=0.009) controlling for LEDD. For the informant scores only, Factor 6 (visuospatial) was also associated with activities of daily living (β = 0.28, SE=0.77, p=0.007; after controlling for LEDD: β = 0.25, SE=0.81, p=0.02). However, these association are not statistically significant after correcting for multiple comparisons.

GBA status was not associated with any of the cognitive factors, while the presence of an *APOE* ε4 allele was associated with Factors 1 (p=0.03) and 2 (p=0.007); thus APOE allele was included as a covariate in all analyses. Follow up sensitivity analyses that additionally adjusting for MDS-UPDRS and *GBA* status did not substantially change the results for the above analyses.

Discussion

In the current study, we sought to identify the underlying cognitive factors in non-demented participants diagnosed with PD and specifically hypothesized that distinct visuospatial factors would be identified. Our analyses showed that the 23 cognitive variables loaded predominantly on six factors, including those associated most strongly with visual learning and memory and visuospatial function. Secondly, we hypothesized that the cognitive factors would be differentially associated with concomitantly collected disease-related features. We found that motor, mood, and performance on activities of daily living scores were primarily associated with frontal/executive factors, while sleep and hallucinations were primarily associated with visuospatial functioning and visual learning/memory.

As expected in participants with PD, the executive/processing speed factor accounted for the largest proportion of variance of all cognitive factors (Dirnberger and Jahanshahi, 2013), while the other factors, including visual learning and memory/visuoperceptual, verbal contextual memory, auditory working memory, semantic learning and memory, and visuospatial function, highlight the variability of cognitive profiles in PD(Kehagia, Barker, & Robbins, 2010). Interestingly, the BNT, a measure of confrontational naming, loaded on Factor 2 along with visual learning and memory. This is consistent, however, with prior literature that found the BNT to correlate more strongly with visuoperceptual skills than other naming tasks (Yochim, Kane, & Mueller, 2009). In addition, Mitrushina and Satz (Mitrushina and Satz, 1995) examined repeated BNT testing in older adults and found a shift between predominantly verbal information processing on the BNT during the first testing to predominantly visuospatial processing by the third administration. In the current study, the expanded visuospatial battery was implemented at the third or later visit for 60% of sample. Impaired confrontational naming in PD is rare (Hoogland et al., 2018), thus it is not surprising that reduced performance on the BNT in this sample may be more closely related to visual perception than to pure language per se.

We found that the most common cognitive features reported in PD (executive function, processing speed, and working memory) were associated most strongly with motor symptom severity, depression, and performance of activities of daily living. This is unsurprising, as the fronto-striatal circuit disruption from nigro-striatal dopaminergic depletion, which is a hallmark of the disease, has previously been associated with both the near-ubiquitous executive function decline and myriad motor deficits reported early in PD (Elgh et al., 2009; Foltynie, Brayne, Robbins, & Barker, 2004; Kudlicka, Clare, & Hindle, 2011; Uekermann et al., 2004). Prior studies have also shown a relationship between depression and worse motor function in PD, likely due to dopamine loss in the caudate and subsequent impaired signaling in fronto-striatal circuits (Borgonovo et al., 2017; Larsen, Dalen, Pedersen, & Tysnes, 2017; Vriend et al., 2014). Finally, performance of activities of daily living are associated with executive function and control in both demented and nondemented participants with PD (Giovannetti et al., 2012; Higginson, Lanni, Sigvardt, & Disbrow, 2013; Koerts, Van Beilen, Tucha, Leenders, & Brouwer, 2011).

Of primary interest in the current study, however, were the identified visuospatial factors. Outside of executive functions, these cognitive factors were most strongly associated with

the clinical measures examined, and were the only factors associated with both sleep problems and hallucinations over and above all the other factors. We found significant associations between reduced visuospatial function and measures of general sleep disturbance (e.g., the NPI and MDS-UPDRS), both before and after controlling for LEDD. A wide range of sleep problems, including insomnia, RBD, fragmentation of sleep, and daytime drowsiness, are common in PD (Chahine, Amara, & Videnovic, 2016), and reduced cognition has been reported in both PD and non-PD populations with sleep disorders (Ju et al., 2013; Stavitsky, Neargarder, Bogdanova, McNamara, & Cronin-Golomb, 2012; Tsapanou et al., 2016; Tsapanou et al., 2017). Although many studies report primary associations between impaired sleep and executive/attention dysfunction, daytime sleepiness, fatigue, restless leg symptoms, and obstructive sleep apnea have also been correlated with visuospatial dysfunction (Goldman et al., 2013; Kluger et al., 2017; Li et al., 2018; Olaithe, Bucks, Hillman, & Eastwood, 2018). Visuospatial deficits in PD are related to pathology in posterior cerebral regions, including decreased dopamine uptake in the occipital lobes and synucleinopathy/Lewy body spreading from subcortical regions to the posterior cortex (Armstrong, 2017; Bayram et al., 2019). Posterior lesions have also been associated with sleep dysfunction (Radziunas et al., 2018) which may coincide with visuospatial deficits in PD. Indeed, Latreille et al. (Latreille et al., 2015) found that lower sleep spindle amplitude on EEG in the parietal and occipital areas was specifically associated with poorer visuospatial function in participants with PDD.

In contrast to general measures of sleep disturbance, our investigation into specific sleep problems commonly associated with PD (e.g., RBD and restless leg symptoms) either found no association with the cognitive factors or weak associations that disappeared after controlling for LEDD. This is contrary to findings by others, who report reduced cognitive function in participants in both RBD alone and among participants with both PD and RBD, including attention/executive function, episodic verbal memory, nonverbal learning, and visuospatial performance (Chahine et al., 2018; Chahine et al., 2016; Jozwiak, et al., 2017; Manni et al., 2013). Generally, however, the presence of RBD is associated with more severe overall cognitive impairment, and the combination of cognitive impairment and RBD may be a marker for disease severity (Huang et al., 2018; Jozwiak, et al., 2017; Meles et al., 2018). Our analyses did not include participants with dementia and controlled for global cognitive status. Finally, the questions related specifically or non-specifically to restless leg syndrome (e.g., leg cramps), may also be associated with influences outside of the central nervous system; thus, our weak associations might be spurious. Additional investigation into the relationship between RBD, restless leg syndrome, and cognition in nondemented patients with PD is needed.

We further report a relationship between visual learning/memory and visuoperception and hallucinations. This is consistent with previous literature, where associations between visuospatial dysfunction, visual memory, and visuoperception and severity and incidence of visual hallucinations have been reported (Factor, et al., 2014; Ramirez-Ruiz, Junque, Marti, Valldeoriola, & Tolosa, 2007). However, previous reports commonly included participants with dementia in their analyses; as such, visual hallucinations may simply signal a more advanced disease state. Importantly, we excluded participants with dementia, controlled for executive dysfunction and global cognitive status, and still found a relationship between

hallucinations and reduced visual learning/memory and visuoperception. A meta-analysis of neuroimaging in PD with visual hallucinations by Lenka et al. (Lenka, Jhunjhunwala, Saini, & Pal, 2015) gives insight into the possible underlying pathology, suggesting that visual hallucinations may arise from dysfunction in more than one region, but almost uniformly result from abnormal top-down visual processes in combination with aberrant functioning in frontal lobe structures and frontostriatal circuits. In our study we found that a visual learning and memory task loaded on Factor 2 which supports a possible role for the medial temporal lobe in visual memory and visual hallucinations in nondemented participants with PD. Dopamine signaling modulates long-term potentiation in the hippocampus and hippocampal-striatal circuits have been shown to be important in visual learning and memory (DeCoteau et al., 2007; Frey, Schroeder, & Matthies, 1990), and participants with PD and visual hallucinations have reduced hippocampal size and connectivity with the occipital lobe as well as reduced metabolism in the temporal lobes (Ibarretxe-Bilbao et al., 2008; Park et al., 2013). Our results support that, at least prior to dementia onset, visual hallucinations may be associated with disruptions in hippocampal-striatal pathways. As hallucinations may also occur in response to antiparkinsonian treatments (Factor, Molho, Podskalny, & Brown, 1995), it is important to note that these associations remained significant after controlling for LEDD.

This study has limitations. First, as this is a prevalent sample, we were unable to evaluate most participants *de novo*. Further, although data collection is ongoing, the expanded neuropsychological battery was only recently implemented and we were not able to assess the progression of cognitive impairment and concomitant changes in clinical symptoms. Additionally, co-participant inclusion was limited, thus we did not have data for the full sample for the NPI or Mayo Sleep Questionnaire. Those with co-participant data were older and had worse motor function than those without co-participant data. Thus, the results reported here may be less applicable in certain groups. Alternatively, the reason we did not see more associations with NPI data, unlike other studies, may be largely due to reduced power or failure to collect in the entire sample. Further, the Mayo Sleep Questionnaire has not been validated as a full instrument, and thus may not have sufficiently queried sleep issues associated with PD. Finally, we did not find an association between *GBA* carrier status and cognition; however, we previously found this association in a much larger sample and the lack of association in the current study is likely due to inadequate power.

In this study, we found that principal cognitive domains, including visuospatial ability, can be assessed with an expanded neuropsychological battery in the Pacific Udall Center. Interestingly, we found that visuospatial dysfunction relates to sleep impairment and hallucinations. These symptoms are associated with a worse disease outcome and cognitive profile over and above executive functioning and in the absence of dementia. Our findings suggest that clinicians should be attuned to changes in visuospatial function in PD as this may indicate a more severe disease course. Hopefully, these findings will help guide potential cognitive interventions and lead to treatments that can simultaneously address multiple distressing symptoms of PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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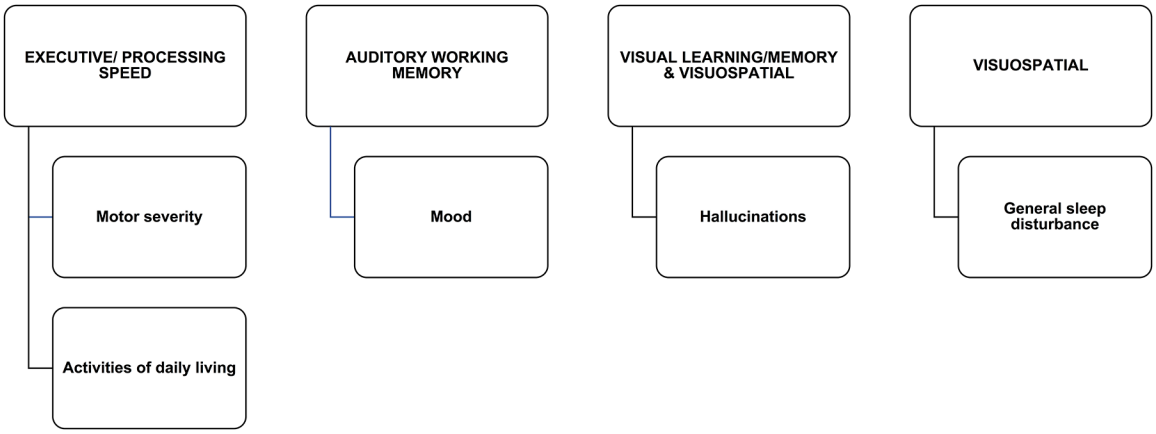

Figure 1.

Associations between cognitive factors and clinical features in Pacific Udall Center participants with PD.

Table 1.

Pacific Udall Center participant characteristics

Demographic characteristics	**n = 197**
Age at visit, years mean (sd) range	67.5 (7.4) 50.1 – 84.8
Education, years mean (sd) range	16.3 (2.3) 12 – 20
Gender n male (% male)	127 (64.1%)
Disease duration, years mean (sd) range	11.7 (6.7) 1 – 41
MDS-UPDRS, part 3 mean (sd) range	23.9 (12.0) 1 – 63
Hoehn & Yahr median range	2 1 – 4
Geriatric Depression Scale mean (sd) range	5.5 (1.4) 1 – 10
LEDD, mg mean (sd) range	730.0 (563.3) 0 – 2960.0
Cognitive tests	
MoCA mean (sd) range	25.9 (2.7) 19 – 30
HVLT-R immediate recall mean (sd) range	24.7 (5.0) 12 – 35
HVLT-R delayed recall mean (sd) range	8.8 (2.4) 1 – 12
Logical Memory I mean (sd) range	12.9 (3.9) 3 – 23
Logical Memory II mean (sd) range	11.8 (4.1) 2 – 22
BVMT-R immediate recall mean (sd) range	19.2 (6.8) 2 – 35
BVMT-R delayed recall mean (sd) range	8.1 (2.7) 2 – 12
BVMT-R copy mean (sd) range	11.6 (0.7) 8 – 12
Clock-copy mean (sd) range	9.3 (1.0) 4 – 10
Clock-command mean (sd) range	9.0 (1.3) 0 – 10
Judgment of Line Orientation mean (sd) range	12.4 (2.1) 5 – 15
Stroop – words mean (sd) range	86.9 (17.1) 32 – 139
Stroop – colors mean (sd) range	61.2 (12.4) 26 – 107
Stroop – color/word mean (sd) range	35.1 (9.8) 8 – 72
Trailmaking, Part A, seconds mean (sd) range	34.1 (18.5) 15 – 150
Trailmaking, Part B, seconds mean (sd) range	88.1 (46.0) 26 – 300
Digit Span Forward mean (sd)	9.0 (1.8)

Demographic characteristics	**n = 197**
range	4 – 12
Digit Span Backward mean (sd) range	6.6 (2.2) 2 – 12
Digit Symbol mean (sd) range	44.4 (11.3) 12 – 75
Letter-Number Sequencing mean (sd) range	9.9 (2.2) 3 – 16
Verbal fluency: animals mean (sd) range	19.8 (5.9) 5 – 34
Verbal fluency: vegetables mean (sd) range	13.1 (4.2) 2 – 24
Verbal fluency: letter mean (sd) range	45.5 (13.6) 20 – 105
Boston Naming Test mean (sd) range	28.8 (1.3) 24 – 30

Abbreviations: BVMT-R, Brief Visual Memory Test, Revised; LEDD, levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; HVLT-R, Hopkins Verbal Learning Test, Revised; sd, standard deviation; MDS-UPDRS, United Parkinson's Disease Rating Scale, Movement Disorders Society revision

Table 2.

Principal component factor analysis: Results from the Pacific Udall Center

	Factor 1: Executive/ processing speed	Factor 2: Visual learning/ memory & visuospatial	Factor 3: Auditory working memory	Factor 4: Contextual verbal memory	Factor 5:Semantic learning & memory	Factor 6: Visuospatial
HVLT-immediate recall	0.16	0.03	0.11	0.38	**0.72**	0.16
HVLT-delayed recall	0.03	0.11	−0.20	0.32	**0.71**	0.23
Logical Memory I	0.08	0.10	0.12	**0.90**	0.14	−0.003
Logical Memory II	0.04	0.19	0.07	**0.91**	0.14	0.01
BVMT-R immediate recall	0.19	**0.85**	0.06	0.17	0.07	0.08
BVMT-R delayed recall	0.11	**0.87**	−0.02	0.20	0.07	0.05
BVMT-R copy	0.05	**0.46**	0.20	−0.05	0.01	0.35
Clock-copy	0.18	0.16	0.11	0.01	0.17	**0.75**
Clock-command	0.17	0.15	0.01	−0.10	0.33	**0.50**
Benton JLO	0.19	**0.47**	−0.12	0.08	−0.08	**0.40**
Stroop - word	**0.72**	0.07	0.33	−0.06	0.14	0.10
Stroop – color	**0.80**	0.13	0.22	−0.03	0.08	−0.004
Stroop – color/word	**0.73**	0.22	0.24	0.10	0.07	0.02
Trailmaking, Part A	**−0.69**	0.02	0.20	−0.03	−0.11	−0.30
Trailmaking, Part B	**−0.66**	−0.05	−0.07	−0.15	−0.11	−0.15
Digit Symbol	**0.80**	0.19	0.04	0.18	0.01	0.10
Digit Span Forward	0.14	−0.04	**0.81**	0.08	−0.13	−0.03
Digit Span Backward	0.15	0.07	**0.75**	0.20	0.01	0.09
Letter-Number Sequencing	0.27	0.09	**0.60**	0.12	0.29	0.08
Verbal fluency: animals	**0.51**	0.15	−0.07	0.16	**0.44**	−0.34
Verbal fluency: vegetables	**0.41**	0.14	0.11	−0.03	**0.52**	−0.28
Verbal fluency: letter	**0.47**	0.08	0.36	−0.10	0.32	−0.11
Boston Naming Test	0.08	**0.46**	0.19	−0.05	0.27	−0.35
Total proportion of variance	0.18	0.10	0.10	0.09	0.09	0.07

Raw test scores were entered into a linear regression that adjusted for age, education, disease duration, and sex, and the resulting standardized residuals were entered into the PCFA. Factors with an eigenvalue of 1 or greater were extracted and rotated using a varimax orthogonal rotation. Factors were interpreted by considering those with a factor loading magnitude >=.40.

Abbreviations: BVMT-R, Brief Visual Memory Test, Revised; HVLT-R, Hopkins Verbal Learning Test, Revised; JLO, Judgment of Line Orientation