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Association of cognitive domains with postural instability/gait disturbance in Parkinson's disease

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ABSTRACT

Introduction: Research suggests an association between global cognition and postural instability/gait disturbance (PIGD) in Parkinson disease (PD), but the relationship between specific cognitive domains and PIGD symptoms is not clear. This study examined the association of cognition (global and specific cognitive domains) with PIGD symptoms in a large, well-characterized sample of individuals with PD.
Methods: Cognitive function was measured with a detailed neuropsychological assessment, including global cognition, executive function, memory, visuospatial function, and language. PIGD symptoms were measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, Motor Examination subscale. Multiple linear regression analyses were performed to assess the relationship between cognition and PIGD symptoms with models adjusting for age, sex, education, enrollment site, disease duration, and motor symptom severity.
Results: The analysis included 783 participants, with mean (standard deviation) age of 67.3 (9.7) years and median (interquartile range) MDS-UPDRS Motor Subscale score of 26 (17, 35). Deficits in global cognition, executive function, memory, and phonemic fluency were associated with more severe PIGD symptoms. Deficits in executive function were associated with impairments in gait, freezing, and postural stability, while visuospatial impairments were associated only with more severe freezing, and poorer memory function was associated only with greater postural instability.
Discussion: While impairments in global cognition and aspects of executive functioning were associated with more severe PIGD symptoms, specific cognitive domains were differentially related to distinct PIGD components, suggesting the presence of multiple neural pathways contributing to associations between cognition and PIGD symptoms in persons with PD.

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1. Introduction

Cognitive dysfunction is a common non-motor feature of Parkinson disease (PD), with estimated point prevalence rates of up to 60% for mild cognitive impairment (PD-MCI) [1] and 30% for dementia (PD-D) [2]. Cognitive impairments in PD-MCI and PD-D are among the most consequential features of the disease, contributing to reduced quality of life [3] and increased risk for disability and mortality [4,5].

Previous research suggests a relationship between global cognitive dysfunction and motor symptoms of postural instability/gait disturbance (PIGD). Compared to those with tremor-dominant phenotype, people with PIGD-dominant phenotype have greater impairment on measures of global cognition [6], a higher frequency of PD-MCI [7], and an increased risk for developing dementia [8]. However, the relationship between specific cognitive domains and PIGD symptoms is not well characterized, with varying reports of distinct associations between PIGD symptoms and visuospatial function [9] or language [7]. Importantly, associations between specific cognitive domains and PIGD symptoms could implicate distinct neural pathways underlying cognitive dysfunction and PIGD symptoms in PD.

The aim of this study was to examine the association between global cognition as well as specific cognitive domains and PIGD symptoms in a large, well-characterized cohort of individuals with PD. An improved understanding of this relationship is important to elucidate common mechanisms underlying cognitive and PIGD symptoms and to tailor interventions specific to the cognitive and motor status of each individual with PD.

2. Methods

2.1. Participants

Participants were recruited and enrolled through the Pacific Northwest Udall Center (PANUC) of Excellence for Parkinson's Disease Research, a collaboration among the University of Washington and the Veterans Administration (VA) Puget Sound Health Care System in Seattle, Washington, and Oregon Health and Science University and the Portland VA Medical Center in Portland, Oregon; the University of Cincinnati in Cincinnati, Ohio; and the Emory University Movement Disorders Program in Atlanta, Georgia. Eligibility criteria included: (1) fulfillment of the United Kingdom Parkinson's Disease Society Brain Bank (UKBB) criteria for idiopathic PD; and (2) no history of other neurologic disorders known to impact cognition. Participants were recruited without consideration of cognitive diagnostic status in order to examine associations between cognition and PIGD symptoms across a range of cognitive functions. Approval for studies involving human subjects was received from the institutional review boards of all participating sites. All participants (or their legally authorized representative, as appropriate) provided written informed consent in accordance with approved procedures.

2.2. Study design and data collection

Cross-sectional data reported here were collected continuously across the four sites from February 2010 through April 2014 as part of an ongoing longitudinal study. Data collection procedures were aligned across all sites. Each participant was assessed while on their regular medication regimen, with motor and cognitive testing sessions completed within a 30-day time frame.

2.3. Clinical examination

Participants completed a focused interview to determine demographic characteristics, symptom history, medications, and past medical history. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III, Motor Examination subscale was used to assess the severity of motor symptoms (performed in the "on" state, if receiving medication), with higher scores indicating more severe impairments [10]. The total PIGD score was calculated as the sum of scores on the gait (3.10), freezing of gait (3.11), and postural stability (3.12) items, based on recommended MDS-UPDRS Part III items for determining the PIGD phenotype [11]. Each item is rated on a 5-point ordinal scale, with a score of 0 indicating no impairment and a score of 4 indicating severe impairment.

2.4. Neuropsychological assessment

Participants completed a comprehensive cognitive assessment based on published consensus guidelines [12]. We selected tests common to all study sites to assess global cognition as well as specific cognitive domains. Global cognitive function was assessed using the total scores for the Montreal Cognitive Assessment (MoCA) and the Mattis Dementia Rating Scale-2 (DRS-2). Executive function, including attention, processing speed, and working memory, was assessed using the total scores for Letter-Number Sequencing, Trail Making, and Digit Symbol tests. Memory was assessed with the Hopkins Verbal Learning Test-Revised (HVLT-R), delayed recall score. Visuospatial function was assessed using the total score for the Judgment of Line Orientation (JoLO). Language was assessed using semantic verbal fluency ('animals' category) and phonemic verbal fluency (sum of F-A-S); however, it is recognized that phonemic fluency is a more frontally mediated task that depends heavily on and is often considered a measure of executive function [13]. For a subset of participants, additional assessments of memory and language were available and included Logical Memory (delayed recall score) from the Wechsler Memory Scale-Revised and the Boston Naming Test, respectively.

2.5. Statistical analysis

Multiple linear regression analysis was used to examine the relationship between cognitive domains and PIGD symptoms after adjusting for age, sex, years of education, enrollment site, time since symptom onset (disease duration), and motor symptom severity. Motor symptom severity was calculated by the MDS-UPDRS Part III total score minus the total PIGD score (as described above, the sum of items 3.10, 3.11, 3.12). Analyses of Trail Making Test Part B times were also adjusted for Part A times to control for motor slowing or tremor. The primary analysis examined associations between neuropsychological tests (global cognition and specific domains of executive function, memory, visuospatial function, and language) and total PIGD scores. Secondary analyses utilized separate models to examine: (1) associations between neuropsychological tests and item scores for gait, freezing of gait, and postural stability; and (2) associations between Logical Memory and Boston Naming and PIGD symptoms (both total and item scores) in the smaller subset of participants completing these neuropsychological tests. All available participant data were used for each analysis, regardless of whether a participant completed all tests in the neuropsychological assessment. Statistical analyses were performed using Stata 12.0 (Stata Corp., College Station, Texas), with significance set at $\alpha \leq 0.05$ for all tests. As these were exploratory analyses, no adjustments for multiple comparisons were made in order to identify all potential associations for follow-up study in additional cohorts.

3. Results

3.1. Participant characteristics

Table 1 shows demographic characteristics and cognitive status of eligible participants. A total of 850 people were enrolled at the participating sites. Individuals were excluded due to missing data for disease duration (n = 22), incomplete MDS-UPDRS (n = 19), not fully meeting UKBB criteria (n = 16), absent neuropsychological assessment (n = 2), having an additional diagnosis impacting cognition (n = 1), or completing motor and cognitive testing more than 30 days apart (n = 7). The final sample included 783 individuals. Participants had a mean (standard deviation) age of 67.3 (9.7) years and 67.8% were male. Mean disease duration was 9.4 (6.5) years, and motor symptom severity was moderate as reflected by a median MDS-UPDRS Part III score of 26 (interquartile range: 17, 35). Cognitive diagnostic status was established at clinical consensus conferences [1] at three of the four sites (91.2% of the sample), with 18.9% of the sample classified as having no cognitive impairment, 53.1% having mild cognitive impairment, and 19.2% having dementia. Also shown are the numbers of participants in each analysis, as some participants did not complete all neuropsychological tests.

3.2. Association between cognition and total PIGD scores

Table 2 summarizes associations between neuropsychological test performance and total PIGD scores. In fully adjusted models, poorer performance on measures of global cognitive function (MoCA, DRS-2), working memory (LNS), processing speed (Digit

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