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Cognitive impairment in Parkinson's disease: Association between patient-reported and clinically measured outcomes

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ABSTRACT

Background: In Parkinson's disease, the association between objective and patient-reported measures of cognitive dysfunction is unknown and highly relevant to research and clinical care.
Objective: To determine which cognitive domain-specific Montreal Cognitive Assessment (MoCA) sub-scores are most strongly associated with patient-reported cognitive impairment on question 1 (Q1) of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS).
Methods: We analyzed data from 759 PD participants and 481 persons without PD with in a retrospective, cross sectional analysis using data from the NINDS Parkinson's Disease Biomarkers Program (PDBP), a longitudinal, multicenter biomarker study. The relationship between a patient-reported cognitive rating (MDS-UPDRS q1.1) and objective cognitive assessments (MoCA) was assessed using multinomial logistic regression modeling and the outcomes reported as conditional odds ratios (cOR's) representing the relative odds of a participant reporting cognitive impairment that is "slight" versus "normal" on MDS-UPDRSq1.1 for a one unit increase in a MoCA sub-score, adjusted for age and education.
Results: In PD participants, changes in visuospatial-executive performance and memory had the most significant impact on subjective cognitive impairment. A 1-point increase in visuospatial-executive function decreased the chance of reporting a MDS-UPDRS Q1 score of "slight" versus "normal" by a factor of 0.686 ($p < 0.001$) and each 1 point improvement in delayed recall decreased the odds of reporting "slight" cognitive impairment by a factor of 0.836 ($p < 0.001$).
Conclusions: Conversion from a PD patient's report of "normal" to "slight" cognitive impairment may be associated with changes in visuospatial-executive dysfunction and memory more than other cognitive domains.

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1. Introduction

Parkinson's disease is a multisystem neurodegenerative disease with motor, autonomic, and neuropsychiatric symptoms. Cognitive impairment is observed in up to 24% of newly diagnosed PD patients [1], with up to 46% of patients developing dementia by 10 years of disease [2] and up to 80% of patients develop dementia after 20 years of PD [3]. Even in the absence of frank dementia, early, mild cognitive impairment is an independent contributor to

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poorer quality of life [4,5] and disability even when motor symptoms are controlled with medications [6].

Fortunately, there are interventions that may potentially address early, mild cognitive deficits in PD. Effective treatment of motor symptoms can sometimes exacerbate cognitive dysfunction [7,8], so adjustments in motor therapy may mitigate these deficits to a certain extent. Futhermore, cognitive enhancers, such as cholinesterase inhibitors have shown some efficacy in treating inattention and executive dysfunction in PD [9,10]. Cognitive rehabilitation, possibly effective in Alzheimer's disease [11], is now being explored in PD [12]. Early identification of cognitive deficits may also influence recommendations regarding employment, financial decision-making, and even driving.

Detection of the earliest cognitive deficits in PD can be difficult given the heterogenous cognitive phenotypic presentations [13] (executive dysfunction vs. visuospatial etc.) due to the influence of multiple pathological [14] processes affecting normal cognitive function. In a large cohort of newly diagnosed PD participants in the Parkinson's Progression Markers Initiative, 22% of participants scored in the "impaired" range on the Montreal Cognitive Assessment (MoCA) [15] while verbal memory and processing speed were found to be the most frequently impaired domains when "impairment" was defined as a score 1.5 standard deviations below normative values.

Despite significant knowledge regarding the earliest objectively measured cognitive impairments in PD, the literature regarding patients' subjective experience with early cognitive symptoms is limited and most studies show discordance between subjective and objective cognitive impairment. While Dujardin et al. showed that subjective cognitive complaints were more commonly detected with the Cognitive Complaint Interview (CCI) in patients with significant cognitive impairment (Mattis dementa rating scale <130) [16], the CCI score was not a good predictor of performance on the Mattis dementia rating scale and the study did not evaluate objective deficits in *early* cognitive impairment. A more recent publication suggested that subjective (patient- and caregiver-reported) and objective deficits in specific domains are usually disocordant [17] due to the tendency to describe most cognitive deficits as difficulty with "memory" (ie "forgetting" how to program a new remote control rather than recognizing this as an executive function task). Exploring the specific impairments that drive patients to first report even slight cognitive impairment will create a greater understanding of the degree of patient awareness and direct the use of patient-oriented outcomes in therapeutic research targeting cognition in early PD. Recognition of the domain-specific cognitive deficits that underly the earliest subjective experience of overall cognitive decline will also help clinicans respond to early cognitive complaints with recommendations specific for the domains most likely to be affected. To this end, we evaluated the association between the subjective report of slight overall cognitive impairment (MDS-UPDRS question 1.1) and objective deficits as measured by MoCA sub-scores in a large cohort of well-characterized PD patients and controls.

2. Methods

2.1. Setting

Objective and subjective cognitive assessments and demographic variables were extracted from the NIH Parkinson's Disease Biomarker Program (PDBP) dataset. The PDBP is a consortium of 11 centers, each with its own research project related to biomarker development. Five of the PDBP sites enroll participants, each collecting longitudinal data on elderly control participants without parkinsonism, PD participants, and atypical parkinsonism syndromes using common data elements [18]. Participants were enrolled at academic centers but are followed by either academic or community neurologists, in Dallas, TX, Hershey, PA, Baltimore, MD, Boston, MA, and Birmingham, AL. Data collection began in 2012 and data for this study were initially extracted on March 17, 2016.

2.2. Patients and data

Participants' data were extracted from the PDBP database if they 1) had a diagnosis of "probable or possible idiopathic Parkinson's disease" or "Control" and 2) had at least one visit with both a MoCA and a Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) reported. Subjects with a diagnosis of "parkinsonism" were excluded because the focus of our study was on subjective cognitive complaints in idiopathic PD and we would expect different results in atypical parkinsonian disorders given the differential cortical and subcortical pathology. Diagnosis of probable or possible PD was defined by the UK Brain Bank Criteria [19]. Inclusion and exclusion criteria for PD participants and controls have been previously published [20], but generally, volunteers were enrolled as controls if they had "no evidence of a clinically significant neurological disorder" and were often spouses of PD participants. Neither controls nor PD subjects were excluded based on the presence of cognitive impairment (PD-MCI or PD dementia) or comorbid psychiatric conditions. Psychiatric conditions are likely to co-occur with cognitive impairment in PD, and excluding patients with psychiatric disease would limit generalizability of our findings to the larger population of PD patients. Each PDBP Center's local IRB has approved the protocol, and all participants were consented for the study. Aggregate data are released immediately and are publically available.

Because the 5 sites recruited participants for different protocols, the study duration and number of serial assessments varied across sites. Though our study evaluated cross-sectional associations between objective and subjective cognitive assessments, visits within the same participant were clustered to correct for repeated measures with a robust standard error. From each patient-visit, the following data were collected: age, diagnosis (PD or control), gender (self-reported: male or female), education level (17 possible responses), MDS-UPDRS (32 subjective scores, 33 objective motor scores) [21], and MoCA [22] scores. The MoCA contains 10 sections which assess six proposed cognitive domains [22], confirmed by factor analysis [23,24] to roughly characterize separate cognitive domains with construct validity. Though the positive and negative predictive value of individual MoCA item performance does not replace a detailed cognitive evaluation [25], it is a reasonable screen for individual cognitive domains in a large study sample [15]. In question 1.1 of the MDS-UPDRS, patients are asked, "Over the past week, have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town?" Possible answers include that cognition is "normal", or that cognitive impairment is present and, "slight, mild, moderate, or severe". This was used as the subjective cognitive measure.

2.3. Statistical analysis

2.3.1. Analytic overview

Our aim was to observe relationships between objective and subjective cognitive dysfunction to determine objective cognitive deficits that are most likely to be present when a PD patient first perceives the mildest degree of impairment reportable on the MDS-UPDRS question 1.1. To do this, we used multinomial logistic regression modeling to determine the conditional odds ratio (cOR) of answering "slight" versus "normal" to the question of cognitive

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