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Journal
Parkinsonism & Related Disorders, 20(12)

ISSN
1353-8020

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Publication Date
2014-12-01

DOI
10.1016/j.parkreldis.2014.10.007

Peer reviewed

Published in final edited form as:
Parkinsonism Relat Disord. 2014 December ; 20(12): 1430–1433. doi:10.1016/j.parkreldis.2014.10.007.

Sensitive measures of executive dysfunction in non-demented Parkinson's disease

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Abstract

Background—We examined the sensitivity of different executive function measures for detecting deficits in Parkinson's disease patients without dementia.

Methods—Twenty-one non-demented PD subjects and 21 neurologically healthy controls were administered widely used clinical executive functioning measures as well as the NIH EXAMINER

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Author Roles and Financial Disclosures

Bott: Led the design and execution of analyses and writing of the manuscript. Mr. Bott has no disclosures to report.
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Kramer: Oversaw all aspects of this project including study design, data interpretation, and manuscript review and critique. Dr. Kramer receives research support from NIH grants P50 AG023501 R01AG022983 and R01AG032289. He receives honoraria for serving on the University of Indiana Alzheimers Disease Center external advisory board. He receives royalties from the California Verbal Learning Test. He previously received support from Novartis Pharmaceuticals for a prior study.
Possin: Oversaw all aspects of this project including study design, data interpretation, and manuscript review and critique. Dr. Possin has received support from K23AG037566, the Hellman Family Foundation, and the Michael J. Fox Foundation. She is employed by UCSF.

battery, which produces Cognitive Control, Working Memory, and Verbal Fluency scores, along with an overall Executive Composite score, using psychometrically matched scales.

Results—No significant differences between groups were observed on widely used clinical measures. The PD patients scored lower than controls on the EXAMINER Executive Composite, Cognitive Control, and Working Memory Scores.

Conclusions—The NIH EXAMINER Executive Composite and Cognitive Control Scores are sensitive measures of executive dysfunction in non-demented PD, and may be more sensitive than several widely used measures. Results highlight the importance of careful test selection when evaluating for mild cognitive impairment in PD.

Keywords

Parkinson's disease; Mild cognitive impairment; Executive function; Cognitive control; Working memory

Introduction

Mild cognitive impairment (MCI) describes a state of cognitive decline exceeding that which is associated with typical aging and often precedes the extent of impairment associated with dementia. Prevalence estimates of MCI in Parkinson's disease without dementia (ndPD) range from 19% to 38% [1]. Non-amnestic, single domain impairment is the most common subtype [2], and executive function (EF) and attention deficits are common. A wide variety of tests are used for the assessment of EF in PD, but it is not clear which are most sensitive. The accurate identification of MCI in ndPD patients is critical, as cholinesterase inhibitors have been associated with improved attention [3] and increased frontal brain activity in cognitively impaired PD [4]. In addition, studies have shown that cognitive dysfunction is a risk factor for the subsequent development of Parkinson's disease dementia [5], and cognitive impairment in ndPD predicts disability, impaired driving, and increased risk for falls, which results in increased medical care costs [6].

Recently, diagnostic criteria for MCI in PD (PD-MCI) were proposed by the Movement Disorders Society (MDS) to improve the clinical characterization of PD-MCI for the development of early interventions and the prediction of conversion to dementia [7]. Two diagnostic models have been proposed, an abbreviated Level I model, and a more comprehensive Level II model. Level II PD-MCI single-domain criteria require abnormalities on at least two tests within a single cognitive domain (e.g., EF), with other domains unimpaired. Impairment is defined by performance approximately 1 to 2 SDs below appropriate norms. While the MDS PD-MCI criteria provides unified diagnostic criteria for PD-MCI across research and clinical settings, and give examples of tests by domain, the authors indicated that research on test selection and how this affects PD-MCI classification is needed. The choice of tests within each domain is important to investigate, as this can affect the sensitivity of detecting PD-MCI and has consequences for patient care and research outcomes.

The NIH EXAMINER battery generates 4 composite scores to measure overall executive dysfunction, cognitive control, working memory, and fluency [8]. Recent studies

demonstrate its psychometric properties [9] and clinical utility across a number of adult populations including behavioral variant frontotemporal dementia [10] and premanifest Huntington's disease [11]. NIH EXAMINER composite scores are generated using item response theory based on a sample of 1248 neurologically healthy patients and controls [8]. Item response theory provides psychometrically-matched scales with linear scaling properties across the ability spectrum without floor or ceiling effects and that take into account item difficulty. These scores have been shown to be more sensitive than individual test scores [12].

In this study we investigated the sensitivity of the 4 NIH EXAMINER scores and several widely used clinical EF measures to ndPD-related executive dysfunction. We hypothesized that the EXAMINER Executive Composite, Cognitive Control Score, and the Working Memory Score would be sensitive to ndPD-related executive dysfunction, with lower scores in ndPD than in NCs, based on prior studies that have shown PD patients to be frequently impaired on these sub-domains [13,14].

Methods

Subjects

The University of California – San Francisco (UCSF) Committee on Human Research approved this study, and written informed consent was obtained for each subject. All twenty-one ndPD subjects who were administered the NIH EXAMINER battery at UCSF between 2012 and 2013 were included in this study. The ndPD subjects were recruited through clinic, participation in other research studies at our center, the Michael J. Fox Foundation trial finder website, the UCSF PD Center website, and PD conference brochures. We included all 21 NC subjects who participated in both the NIH examiner validation study and a study on healthy aging at UCSF, who were in the same age and education range as the ndPD subjects. The groups did not differ in age (ndPD: 63.7 +/− 8.0, NC: 66.4 +/− 8.3), percent male (ndPD: 67%, NC: 62%), or years of education (ndPD: 16.5 +/− 2.5, NC: 16.9 +/− 2.2), all ps of independent samples t-tests > .10.

The ndPD participants were diagnosed with Parkinson's disease by a neurologist with specialty in movement disorders. The Movement Disorders Society –Unified Parkinson's Disease Rating Scale Part III scores ranged from 12 – 51 with a mean of 27.1 +/− 11.3. Global cognition was assessed in ndPD using the Montreal Cognitive Assessment (MoCA), with a cutoff below 26 indicating mild cognitive impairment. MoCA scores for our sample ranged from 22 to 30 with a mean of 27.2 +/− 2.1, with only 2 subjects falling in the mild cognitive impairment range based on this global screen.

Consensus diagnoses of Parkinson's disease and absence of dementia, and neurologically healthy status of controls were made by a team of neurologists, nurses, and neuropsychologists based on the results from a comprehensive diagnostic evaluation that included a neurological exam, neuropsychological assessment, and an informant interview. Additionally, 16 ndPD patients were administered the Clinical Dementia Rating Scale; 9 patients had a total score of 0, indicating no cognitive symptoms, and 7 had a score of 0.5, indicating mild cognitive symptoms.

Executive Function Assessment

Participants were administered eight tests from the NIH EXAMINER battery (see Table 1). A standard 15.4″ Dell Latitude D830 laptop was used for the computerized portions of the battery. Standardized scoring and scale construction procedures based on item response theory for the eight donor scales, which are part of the NIH EXAMINER, produced Working Memory, Cognitive Control, and Fluency Scores, as well as an overall Executive Composite score [8].

In addition, participants were administered a battery of widely used clinical EF measures consistent with MDS PD-MCI criteria recommendations, including: total seconds to completion on Trails B, total colors named in 1-minute on the interference condition of the Stroop, D-KEFS Design Fluency Filled Dots total correct, and digits backward maximum span. One control was missing data on Design Fluency. Two patients were missing data on Trails B; one on Design Fluency. All patients were administered the EF battery while receiving their typical regimen of PD medication.

Data Analysis

IBM SPSS Statistics 21.0 for Mac (IBM Corp., Armonk, NY) was used to perform statistical analyses. Group differences in traditional measures of executive function and NIH EXAMINER scores were evaluated using independent samples t-tests. We used a threshold for significance of p-values < .05, and p-values <.10 were considered trends for all analyses. In order to correct for multiple comparisons performed in the analysis of the Executive Composite, which includes Working Memory, Cognitive Control, and Fluency scores, we lowered the threshold for significance of p-values to < .016. Cohen's d effect sizes are reported for group difference analyses. Following the diagnostic guidelines of the MDS, EF scores of all subjects were converted to z-scores relative to NCs, and performance was defined as impaired if it was more than 1.5 standard deviations (SD) below the NC mean. Frequency of impaired scores was compared between the groups using Chi Square.

Results

The ndPD subjects scored lower than the NCs on the Executive Composite, the Cognitive Control Score, and the Working Memory Score, all ps < .05 (Table 2). There was a trend towards lower scores in ndPD on Trails B and the Stroop, ps < .10. No significant differences between groups were observed on Design Fluency, Digits Backward, and EXAMINER Verbal Fluency scores, all *ps* >.10.

Employing the MDS PD-MCI guidelines, the ndPD patients were more frequently impaired than the NC patients (>1.5SD below NC mean) on the Executive Composite, χ^2= 7.00, p = .01, the Cognitive Control Score, χ^2 = 4.29, p = .04, and there was a trend for Digits Backward χ^2 = 3.22, p = .07. The patients were not more frequently impaired on any of the other EF measures, all *ps* >.10.

Discussion

In this study we found that ndPD subjects scored significantly lower than NCs on the NIH EXAMINER Executive Composite, Cognitive Control, and Working Memory Scores. No significant differences in performance were observed between groups on Trails B, Stroop, Design Fluency, Digits Backward, and the Verbal Fluency Score. Our findings suggest that the NIH EXAMINER battery, particularly the Executive Composite and the Cognitive Control Score, may be more sensitive than several traditional tests of executive function in assessing MCI in PD.

The results from the present study underscore how test selection can alter PD-MCI classification. The most sensitive and specific measure of impairment in this study was the NIH EXAMINER Executive Composite, detecting impairment in six patients with ndPD, zero NCs, and with an effect size of .94. Other measures were less sensitive; for example, our verbal fluency score detected impairment in 4 ndPD and 1 NC, with an effect size of .21. Studies of fluency impairment in nondemented PD patients are mixed, with studies reporting deficits in only letter fluency, others in only semantic fluency, others reporting deficits in both, and still others reporting no deficits; furthermore, these deficits can be affected by PD medication [15]. The reasons for the enhanced sensitivity of the Executive Composite are two-fold. First, this composite combines performance across aspects of executive functioning consistently reported to be impacted by PD, including cognitive control and working memory. Studies employing cognitive control tasks such as set-shifting and flanker have found PD patients to be impaired inhibiting prepotent responses and shifting set, particularly under speeded conditions [13]. Working memory deficits have also been frequently reported [14]. In addition, the Executive Composite and other NIH EXAMINER scores are derived using item response theory, which can improve sensitivity and increase statistical power over standard scoring methods [12].

Aarsland and colleagues examined the cognitive profiles of 1346 patients with PD without dementia in a pooled analysis and found 25.8% to have MCI as defined by 1.5 SD below the mean in memory, attention/executive function, and/or visuospatial functioning [2]. 10.1% of patients had attention/executive function impairment using widely used tests, which is comparable to the 14.3% with impairment in this domain in our sample on at least two of four widely used executive function tests. In contrast, 28.5% of our sample was impaired on the EXAMINER Executive Composite, which highlights how results can vary based on measure selection or sample differences.

Beyond sensitivity and specificity to PD, a cognitive measure is valuable if it correlates with real world deficits, is sensitive to change over time, predicts future cognitive decline or disability, and measures well treatment effects. The Executive Composite has been shown to correlate with real world executive deficits in patients with a variety of neurological disorders, including PD [9], and further validation in a larger sample of PD patients is needed. Broeders and colleagues found that while newly-diagnosed PD patients performed worse than NCs across several executive functioning tasks, decline was detected on only the Wisconsin Card Sorting Task (categories and perseverations) [16]. While the Executive Composite demonstrates good sensitivity cross-sectionally, validation of its sensitivity to

change over time is needed. The literature on whether executive deficits are harbingers of incipient dementia is conflicting. Future research using more sensitive and psychometrically robust executive measures could clarify this important question. Selection of the most sensitive outcome measures for treatment studies maximizes power to detect a treatment effect, an important consideration for PD given the impact of cholinesterase inhibitors on this cognitive domain [3].

In conclusion, test selection should be considered in the application of MDS Level II PD-MCI criteria for the identification of executive dysfunction in ndPD. Our study includes several strengths, such as a well-defined PD cohort, diagnosis by specialists in movement disorders, and the application of the MDS PD-MCI Level II criteria for executive function. The small sample size represents a limitation of this study, and while the effect sizes (Cohen's d) were substantial, replication is needed.

Acknowledgments

This study was supported by the National Institute on Aging (Possin: K23AG037566; Kramer: R01AG032289; Miller: P50AG023501), the Larry L. Hillblom Foundation (Miller, 2007/2I), the Hellman Family Foundation, and MJFF2011, MRI signature of Parkinson's disease from the Michael J. Fox Foundation

We are grateful to our research participants for their generous time and efforts.

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Highlights

- We demonstrate the sensitivity of the NIH EXAMINER battery to executive dysfunction in non-demented Parkinson's disease.
- We demonstrate increased sensitivity to executive dysfunction in non-demented Parkinson's disease with the NIH EXAMINER as compared with widely used measures of executive function.
- Our study provides support for the Movement Disorders Society's indication that further research on test selection and its effects on Parkinson's disease mild cognitive impairment classification is needed.
- Our study highlights the importance of careful test selection when evaluating for mild cognitive impairment in Parkinson's disease.

Table 1

NIH EXAMINER Scores, Donor Scales, and Administration Times

Working Memory Score		
1-back	Accuracy in identifying whether a series of locations match the location presented 1 before, corrected for response bias.	5-minute trial
2-back	Accuracy in identifying whether a series of locations match the location presented 2 before, corrected for response bias.	5-minute trial
Dot counting total	Examinees count blue dots on a series of screens and then recall the number of dots across screens. Score is the total number of counts correctly recalled.	7-minute trial
Cognitive Control Score		
Flanker score	The sum of accuracy and reaction time scaled scores on incongruent trials, on which subjects must indicate the direction of an arrow that is flanked by arrows pointing in the opposite direction.	5-minute trial
Set-shifting score	The sum of accuracy and reaction time scaled scores on shift trials, on which subjects must shift between matching targets based on shape or color.	5-minute trial
Verbal Fluency Score		
Letter Fluency	Total number of F and D words generated.	1-minute trials
Category fluency	Total number of animals generated.	1-minute trial
Executive Composite		
Comprise of all measures		

Table 2

Mean Executive Function Scores, Group Differences and Frequency of Impairment on Executive Measures Ordered by Effect Size Magnitude

	ndPD Mean(SD)	NC Mean(SD)	Cohen's d	p-value	Impaired Range (≤1.5 SD)
Executive Composite	.80(.42)	1.21(.45)	.94	.004	ndPD=6; NC=0
Cognitive Control Score	.41(.69)	.84(.49)	.74	.02	ndPD=6; NC=1
Working Memory Score	.36(.60)	.75(.58)	.65	.04	ndPD=6; NC=2
Trails B	74.37(33.07)	57.33(20.5)	.62	.06	ndPD=3; NC=1
Stroop	49.33(8.26)	54.71(10.57)	.57	.07	ndPD=2; NC=1
Design Fluency	10.55(3.19)	12.15(3.8)	.46	>.10	ndPD=2; NC=0
Digits Backward	5.00(1.48)	5.52(1.03)	.41	>.10	ndPD=3; NC=0
Verbal Fluency Score	1.12(.69)	1.26(.56)	.21	>.10	ndPD=4; NC=1

Cohen's d is the average score difference between ndPD and NC in standard deviation units, with ndPDs scoring lower than NCs on all measures

Parkinsonism Relat Disord. Author manuscript; available in PMC 2015 December 01.