Parkinsonism and Related Disorders 20 (2014) 1430–1433

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

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

Nicholas T. Bott [a, *], Erica T. Johnson [a], Norbert Schuff [b, c], Nicholas Galifianakis [d], Trishna Subas [a], Jessica Pollock [b, c], Peter Pressman [a], Joel H. Kramer [a], Katherine L. Possin [a]

[a] Department of Neurology, Memory and Aging Center, University of California, San Francisco, USA
[b] Department of Radiology and Biomedical Imaging, University of California, San Francisco, USA
[c] Department of Veterans Affairs Medical Center, San Francisco, CA, USA
[d] Parkinson's Disease Research, Education, and Clinical Center, San Francisco Veteran's Affairs Medical Center, San Francisco, USA

ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form
29 September 2014
Accepted 7 October 2014

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

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 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.

1. 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 1–2 SDs below appropriate norms. While the MDS PD-MCI criteria provides unified diagnostic criteria for PD-MCI across research and

☆ 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.
* Corresponding author. 675 Nelson Rising Lane, Suite 190, Box 1207, San Francisco, CA 94158, USA. Tel.: +1 650 814 9383.
E-mail address: nbott@stanford.edu (N.T. Bott).

http://dx.doi.org/10.1016/j.parkreldis.2014.10.007
1353-8020/

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].

2. Methods

2.1. 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 to 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 .5, indicating mild cognitive symptoms.

2.2. 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.

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		

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.

2.3. 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.

3. 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, $\chi^2 = 7.00$, $p = .01$, the Cognitive Control Score, $\chi^2 = 4.29$, $p = .04$, and there was a trend for Digits Backward $\chi^2 = 3.22$, $p = .07$. The patients were not more frequently impaired on any of the other EF measures, all *ps* > .10.

4. Discussion

In this study we found that ndPD subjects scored significantly lower than NCs on the NIH EXAMINER Executive Composite,