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Brief Communication

Examining the Diagnostic Accuracy of a Novel Performance-Based Test for Alzheimer's Disease Screening

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Abstract

Affordable, rapid methods for identifying mild Alzheimer's disease (AD) are needed. A simple, brief performance-based test involving the learning of functional upper-extremity movements has been developed and is associated with AD pathology and functional decline. However, its specificity to AD relative to other neurodegenerative diseases that present with motor impairment is unknown. This study examined whether this novel test could distinguish between 34 participants diagnosed with mild AD (Clinical Dementia Rating Scale = 0.5-1) from 23 participants with mild-to-moderate Parkinson's disease (PD) (Hoehn & Yahr = 2-3) using Receiver Operating Characteristic analysis of secondary data from two separate clinical trials. Indicators of diagnostic accuracy demonstrated that the test identified participants with AD, who had worse scores than those with PD, suggesting it may be a viable screening tool for mild AD. Exploratory analyses with a control group (n=52) further showed that test scores were not sensitive to motor dysfunction.

Key words: Disease screening, performance-based test, sensitivity, specificity.

Introduction

Advancements in our understanding of Alzheimer's disease (AD) have led to the development of methods that can screen for the disease in its preclinical or early stages, including plasma biomarkers (1). These are helpful for monitoring patients over time, and can assist in directing patients to appropriate therapeutics or clinical trials. However, these methods can be costly, possibly invasive, and require extensive equipment, personnel, and/or patient time (e.g., 2), which many patients may not be able to afford or access. Thus, there is a critical need for the development of alternative screening methods for AD in its early stages that are more accessible and feasible in various settings, including in primary care and at home.

To address this need, a novel performance-based test has been developed that uses upper-extremity movement and can be collected in <5 minutes without any computer or wearable technology. Specifically, participants are timed on multiple trials of a novel upper-extremity motor task that requires skilled, dexterous movement. Final scores are objective (rather than based on self-report or observer ratings) and reflect the extent to which an individual learned the task. Prior work has demonstrated the potential of this measure to provide quantitative information about an individual's level of cognition (specifically visuospatial) (3–5), procedural learning (6), and daily functioning (7). It is noted that historically, procedural learning has thought to be relatively spared in AD, but there are mixed findings in the literature about whether or not procedural learning remains intact (8,9). Specifically, research has shown that the learning of this motor-based test is mediated by visuospatial memory and executive function (as evidenced by both neuroimaging and neuropsychological data) in both cognitively intact and impaired individuals (5, 10). This test may also be prognostic of one's trajectory, given that worse scores predicted more functional decline over one year in patients with amnestic Mild Cognitive Impairment (aMCI), when measured by both subjective and objective measures of daily function (the Alzheimer's Disease Cooperative Study-Activities of Living Scale and the Independent Living Scale) (7). Furthermore, cognitively unimpaired older adults score better than those with aMCI and mild AD (11), and scores were related to AD pathology (brain volume on MRI and amyloid burden on PET) (10, 12). Finally, this test can be reliably self-administered at home without supervision (13), opening opportunities for remote assessment that can minimize clinical burden.

Since this test involves voluntary movement, it is important to determine the extent to which motor impairments affect test scores. In other words, this test should be sensitive and specific to AD while also not being influenced by motor dysfunction (e.g., tremors, bradykinesia, weakness) associated with other neurodegenerative diseases like Parkinson's disease (PD) or normal aging (i.e., relatively resistant to motor impairment). This study therefore compared scores on this test between participants with mild AD and participants with mild-to-moderate PD. Based on

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prior studies, it was hypothesized that AD participants would have significantly higher (worse) test scores that those with PD, and that test scores would be able to accurately classify participants based on diagnosis (AD vs. PD). In addition to this primary purpose of this study, exploratory analyses included a control group of cognitively unimpaired adults with no diagnosis to further test the extent to which scores on the novel test were affected by motor dysfunction.

Methods

Participants

This study was a secondary analysis of data from 34 participants with mild AD and 23 participants with PD from prior studies registered on clinicaltrials.gov. AD participants were originally recruited into NCT03466736, and PD participants were originally recruited into NCT02600858. The original trial involving AD participants was observational, and was designed to demonstrate that individuals with low short-term practice effects on cognitive testing are more likely to be identified as «positive» on amyloid imaging than individuals with high short-term practice effects. The original trial involving PD participants was interventional (randomized trial), and was designed to determine whether standard medical care (dopamine) affects learning and retention of an upper limb feeding task in people with PD. For AD participants, the mean±SD age was 77.2±6.4 years and mean±SD education was 16.0±2.3 years. All were Caucasian and 55% were female. Self-ratings of depression symptoms were minimal on the 15-item Geriatric Depression Scale (1.2±1.1). AD participants were identified through the University of Utah Center for Alzheimer's Care Imaging and Research via a medical records review, especially based on prior neuropsychological testing, neurological exam, and brain imaging. Confirmation of mild AD was made with the Alzheimer's Disease Neuroimaging Initiative (ADNI) (14) classification battery, which included the Mini Mental Status Examination (15) (AD = 20-26), the Clinical Dementia Rating Scale (16) (AD = 0.5–1), and the Wechsler Memory Scale – Revised (17) Logical Memory II (AD: ≤8 if education ≥ 16 years, ≤4 if education 8–15 years, ≤2 if education 0–7 years). AD participants were classified by one of the authors, a board-certified neuropsychologist (KD).

For PD participants, the mean±SD age was 71.1±6.9 years and mean±SD education was 16.3±2.5 years. All were Caucasian and 52% were female. Participants were recruited via advertisements posted at a Movement Disorders Center, local PD support groups, and through a PD wellness exercise group in Salt Lake City, USA. Individuals were included in the original trial if they had idiopathic PD diagnosed by a neurologist, were aged 50–80 years, and had been on a stable antiparkinsonian medication regime for one month prior to enrollment. Individuals were excluded if they were not taking levodopa medication, had prior deep brain stimulation surgery, any health conditions that would interfere with safe participation, or a Montreal Cognitive Assessment score<18 (mean±SD score was 26.6±2.04). It is noted that this criterion was intended to exclude potential PD participants with significant cognitive impairment, rather than to only select those who were cognitively normal. Participants were evaluated with the motor section of the Movement Disorders Society-sponsored version of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (18) while "off" medication following overnight withdrawal of levodopa-carbidopa, then subsequently "on" medication 30–60 minutes after participants had taken their usual morning dose of levodopa-carbidopa. Participants continued to take other antiparkinsonian medications as usual (e.g., dopamine agonists) to minimize participant burden. All PD participants had a modified Hoehn and Yahr score of 2 (91%) or 3 (9%), and a mean±SD motor MDS-UPDRS score of 30.5±8.8 "on" medication (45.7±8.7 "off" medication). Self-rating of depression symptoms was also minimal on the 15-item Geriatric Depression Scale (2.6±3.4). In the original PD trial, participants were randomized to complete the novel test "on" vs. "off" medication (12 "on" vs. 11 "off"). Due to a lack of difference in test scores between the "on" vs. "off" medication subgroups (see Results), the PD group was collapsed across testing-related medication status.

Data from 52 neurologically intact participants were also included from NCT03466736 (mean±SD age=72.5±4.9; 61% female; 16.7±2.1 years of education; 100% Caucasian) and used as a control group for exploratory analyses to 1) compare the magnitude of scores on the novel test relative to the AD and PD samples and 2) test the extent to which scores were affected by motor dysfunction in the PD group. This control group was a convenience sample and not intended to match either the AD or PD groups based on clinical or demographic factors. Demographic data are summarized in Table 1.

Table 1. Participant demographics (N=109)

	AD (n=34)	PD (n=23)	Control (n=52)
Age	77.2±6.4	71.1±6.9	72.5±4.9
Sex			
Female	19 (55%)	12 (52%)	32 (61%)
Male	15 (45%)	11 (48%)	20 (39%)
Years of Education	16.0±2.3	16.7±2.5	16.3±2.5
Race			
White	34 (100%)	23 (100%)	52 (100%)
Ethnicity			
Not Hispanic or Latino	34 (100%)	23 (100%)	52 (100%)

Values are shown as Mean±SD or n (%)

Novel performance-based test and other clinical measures

A full visual description of the test apparatus and a partial trial can be viewed on Open Science Framework (https://osf.io/phs57/wiki/Functional_reaching_task/), and its methods have been published previously (10, 11). To summarize, participants use a standard plastic spoon to acquire two raw kidney beans at a time from a central cup to one of three distal cups arranged at a radius of 16 cm at -40°, 0°, and 40° relative to the central cup. All cups are the same size (9.5cm diameter and 5.8cm deep). Participants in this study were tested using their nondominant hand and started by moving to the cup ipsilateral of the hand used. They then returned to the central cup to acquire two more beans at a time to transport to the middle cup, then the contralateral cup, and then repeated this sequence four more times for a total of 15 out-and-back movements. Performance for each trial was measured as trial time (in seconds, i.e., how long it took to complete 15 movements). A single test score was calculated based on trial times across six consecutive trials for each participant based on the variability (standard deviation) in trial time, where higher scores (i.e., more variability and less task learning (10, 11)) are considered worse.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and Trail-Making Test (A and B) were also administered in both original trials. The RBANS (19) consists of 12 subtests measuring immediate memory, visuospatial/constructional, language, attention, and delayed memory, yielding standardized Total Score that has a mean score of 100 with a standard deviation of 15, and a score range from 40 to 160 with higher scores indicating better cognitive performance. The RBANS has been shown to have excellent estimates of diagnostic accuracy and is a useful screening tool in detection of cognitive deficits (20). Administration of the RBANS takes ~20–40 minutes. Raw scores for the Trail-Making Test were included in this study, where lower values indicate better cognitive performance and processing speed. These measures assisted in further characterizing cognitive differences between the AD and PD groups. Although there were no common motor measures collected between the AD and PD groups, grip strength was recorded (via hand dynamometry) for 30% (10/34) of the AD group and 8% (4/52) of the cognitively unimpaired control group. None of the participants had values outside of the normal range based on age and sex (21).

Statistical analyses

All statistical analyses were completed using JMP Pro 16 (SAS Institute, Cary NJ, USA). Primary analyses of the AD and PD groups included nominal logistic regression to determine the extent to which scores on the novel test could accurately identify participants as having AD, with and without controlling for age, given that the AD group was older (95%CI [75.0, 79.5]) than the PD group (95%CI [68.1, 74.0]). In order to examine the diagnostic accuracy of the test, subsequent receiver operating characteristic (ROC) analysis was used to determine the area under the curve (AUC), as well as sensitivity, specificity, and predictive value (positive and negative) (22) of the novel test in classifying participants with AD from those with PD. Confusion matrices were used to identify these ROC values based on a threshold score from the novel test that was associated with the lowest misclassification rate and highest Matthew's correlation coefficient (23). The positive predictive value (PPV) is interpreted as how well a test score above the threshold predicted whether the participant had AD, and negative predictive value is how well a test score below the threshold predicted whether the participant had PD. A positive likelihood ratio >1 indicates that test scores above the threshold are associated with AD, whereas a negative likelihood ratio <1 indicates that test scores below the threshold are associated with PD. The further likelihood ratios deviate from 1, the stronger the evidence for the presence or absence of disease (24). An exploratory nominal logistic regression analysis was done between the PD and control groups to further evaluate the novel test's sensitivity to motor dysfunction.

Separate one-way analyses of variance (ANOVA) were used to compare scores on the novel test, RBANS, and Trail-Making Tests between the AD, PD, and control groups, followed by Tukey HSD tests when warranted.

Results

Scores on the novel test were not significantly affected by whether PD participants completed it "on" vs. "off" their levodopa-carbidopa medication (p=0.40). Thus, data for the PD group were collapsed across medication status for subsequent analyses. In ROC curve analysis, an AUC = 0.83 (95%CI [0.73, 0.93]) for identifying participants with AD was observed, without including participant age in the model (AUC = 0.86 when controlling for age). Confusion matrices identified an optimal threshold test score of 8.3 (units are in seconds) as having the lowest misclassification rate of 23.64% and a Matthews correlation coefficient of 0.52. Table 2 shows the sensitivity, specificity, predictive values, and likelihood ratios associated with this threshold score. Likelihood ratios indicate that for a test score above 8.3, the result of the participant having AD was obtained nearly three times more frequently than having PD (positive likelihood ratio of 2.99). An exploratory ROC analysis comparing the PD and cognitively unimpaired control groups yielded an AUC = 0.53 (95%CI [0.41, 0.64]), indicating that the novel test was not better than chance at differentiating between these two groups. This result demonstrated that novel test scores were not affected

by the motor dysfunction present in the PD group, suggesting that although the test uses motor behavior to evaluate cognition and daily function, it in and of itself should not be considered or used as a test of motor function.

Table 2. Receiver operating characteristic results for classifying Alzheimer's disease versus Parkinson's disease

	Estimate	Lower 95% CI	Upper 95% CI
Sensitivity	0.78	0.63	0.89
Specificity	0.74	0.54	0.87
Positive PV*	0.81	0.64	0.91
Negative PV*	0.71	0.51	0.85
Positive LR†	2.99	1.47	6.10
Negative LR†	0.30	0.15	0.59

*PV: Predictive value; †LR: Likelihood ratio.

ANOVA results showed that scores on the novel test varied by group ($F_{2,106} = 9.59$; $p<0.0001$). Post-hoc analyses showed that scores were higher (worse) for the AD group compared to the PD group ($p<0.0004$) and control group ($p<.0013$). Importantly, scores on the novel test for the PD group were not statistically different from those for the control ($p=0.54$), further indicating that the presence of motor impairment does not affect test performance and that the PD group was not functionally or cognitively impaired. Neuropsychological measures further confirmed that the PD group was not cognitively impaired, given that the RBANS Total Scale Index scores were within normal range (95%CI [85.7, 96.3]). The PD group was also not significantly different from the control group on Trails A ($p=0.13$) or Trails B ($p=0.65$). As expected, however, the AD group had RBANS Total Scale Index scores close to the 1st percentile (95%CI [64.8, 74.5]) and had significantly worse Trails A ($p<0.0001$) and Trails B ($p<0.0001$) scores compared to the control group.

Discussion

Primary analyses from this study compared scores on a novel performance-based learning test between participants with mild-to-moderate PD (i.e., individuals with motor impairment based on clinical diagnosis) and participants with mild AD (i.e., individuals with cognitive and functional impairments based on clinical diagnosis). Results supported the hypothesis, such that despite engaging voluntary movement, the novel test discriminated between a cognitive disorder (AD) and a movement disorder (PD), with higher (worse) scores being associated with AD. Furthermore, results from exploratory analyses indicated that novel test scores were comparable between the PD group and the cognitively unimpaired control group, meaning they were able to learn and complete the test despite having a movement disorder. This strongly suggests that the novel test in this study is likely detecting deficits in cognition and daily functioning associated with dementia while being resistant to deficits in motor control. While our data suggest that the RBANS could also accurately distinguish AD patients from PD patients who are cognitively unimpaired, the RBANS takes longer to administer (~20-40 minutes), requires a clinician or trained staff to administer, and is affected by demographic variables (e.g., age, education, sex) (25). In contrast, the novel test used in this study is briefer (~5 minutes) and has not shown significant effects of age, sex, and education (10, 11, 26). It can also be reliably completed at home and unsupervised (13), opening up new avenues for making AD screening more affordable and accessible.

Results from this study are consistent with some studies showing procedural learning deficits within MCI and AD (8), although this literature is equivocal (8, 9). This type of learning appears to span across multiple brain regions (27) and structures (including the hippocampus, cerebellum, and the motor cortex) and this novel test has been associated with atrophy in several of these regions (10, 11). At the same time, other motor measures like gait speed that are not designed to measure procedural learning may also be sensitive to (or prognostic of) AD (28). However, the measure of gait speed is not specific to AD, given that other neurologic conditions and even normal aging are associated with slow gait speeds, and the proposed mechanism for gait slowing for AD is not well established at this time, thereby limiting the ability for gait speed tests to differentiate between motor and cognitive symptoms of various neurodegenerative diseases.

There were several limitations to this study. First, the sample sizes are relatively small and the findings may not necessarily generalize, particularly since this study was a secondary analysis of two existing datasets (one observational and one randomized trial). Since observational studies in general tend to have higher selection bias than randomized trials, methods have been proposed for combining data from observational studies and randomized trials (29). These instances are most often to supplement randomized trial data to better predict real-world effectiveness of a given intervention (30), which was not the purpose of this study; no intervention is under consideration, thereby minimizing concerns related to combining data from two different trial designs. Second, none of the participants with PD were cognitively impaired, at least based on the tests they completed (MoCA, RBANS, and Trail-Making). As such, it remains unknown if the novel test can differentiate between the pathologies of AD and other dementias, such as frontotemporal dementia, Parkinson's disease dementia, or dementia with Lewy bodies. Future work aims to collect data in patients with non-AD dementias, while also exploring the proposed mechanism by which the novel test may selectively assay AD pathology and

progression. Prior work suggests that the test may probe the integration of visuospatial abilities into daily activities (3–5). Third, there were limited data on motor function in the AD participants, although this is common among AD studies since AD is historically and clinically not considered to be a movement disorder. Lastly, the novel test was administered to some PD participants while "on" their typical dose of levodopa-carbidopa medication and others while "off" due to the original clinical trial study design, although results indicated that medication status did not significantly affect scores. It is critical for future studies to consider the effects of other medications, including those targeting AD (e.g., symptom-managing or novel monoclonal antibodies), on test scores and changes in test scores over time.

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Conflict of interest: Sydney Schaefer is a co-founder and managing member of Neurosessments LLC. No other authors hold any financial or personal conflicts of interest relative to the content of this manuscript.

Ethical standards: The primary studies were approved by the University of Utah Institutional Review Board. Prior to enrollment in the studies, participants either provided written informed consent, or provided assent with a collateral person (e.g., spouse, adult child) providing consent.

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