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Anterior and Posterior types of Neuropsychological Deficits in Parkinson's Disease: A Subgroup Classification of Cognitive Outcome

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Abstract

Individuals with Parkinson's disease (PD) exhibit cognitive deficits. Recent studies suggest there are distinct cognitive profiles of PD characterized by deficits in abilities that are dependent upon anterior versus posterior areas of the brain. While anterior-based deficits are more prevalent, posterior-based deficits are more predictive of the future occurrence of dementia in PD. The purpose of the current project was to examine these cognitive profiles in more detail. Performance on six tests of anterior function and six tests of posterior function was examined in 34 non-demented PD participants and 27 healthy control participants matched for age and education. Results showed that PD participants performed significantly more poorly than healthy control participants across most measures of cognition. Categorization into profiles was examined using a patient score falling 1.5 standard deviations (SDs) and 2 SDs below the control average. When a deficit was seen on at least two tests within a single domain, the PD participants were identified as having a deficit in that domain. For the 1.5 SD and 2 SD cut-off values, nine of the PD participants exhibited anterior deficits, one had posterior deficits, ten (1.5 cut-off) and five (2 cut-off) had deficits in both domains and 14 (1.5 cut-off) and 19 (2 cut-off) showed no deficits. Further development of this new classification system may allow the prediction of longer-term cognitive outcomes in PD.

Anterior and Posterior types of Neuropsychological Deficits in Parkinson's Disease: A Subgroup Classification of Cognitive Outcome

Parkinson's Disease

Parkinson's disease (PD) is a pervasive neurodegenerative disorder with a prevalence rate of approximately 150 out of 100,000 individuals in the United States and Western Europe (Checkoway & Nelson, 1999). As many as one million people in the United States live with PD, and it is estimated that seven to 10 million people worldwide are afflicted (Parkinson's Disease Foundation, 2013). Roughly 40% of patients develop the disease between 50 and 60 years of age. While early and late onset are possible, it is rare to see disease onset before the age of 40 years. PD is highly variable and can affect men and women of various ages. Disease progression can be rapid resulting in death after only a few years, or a patient can function with PD for decades after diagnosis. Currently, there is no identified biological marker for PD and the pathological diagnosis can only be confirmed via autopsy, thus diagnosis is typically given within the clinical setting. Because there is no test for PD, a physician must evaluate a patient's symptoms and through the process of elimination of other diseases, establish a diagnosis.

The most widely recognized motor symptoms associated with PD include a resting tremor, rigidity, slowness of movement (i.e., bradykinesia), freezing, and gait abnormalities. Non-motor symptoms typically consist of depression, hallucinations, sleep disturbances, fatigue, autonomic nervous system impairment, and cognitive deficits (Hawkes, Tredici, & Braak, 2010; Kaasinen & Rinne, 2002; Stacy, 2011; Ziemssen & Reichmann, 2007). The frequency and severity of these non-motor impairments typically increase with disease duration, and they are not exclusively linked to the motor symptoms (Foltynie, Brayne, Robbins, & Barker, 2004; Yu et al., 2012).

Cognitive impairment is an understudied aspect of PD, which is often present in the early stages of the disease. It has been estimated that approximately 30-90% of patients who suffer from cognitive impairment will eventually develop a form of dementia that is specifically associated with PD, known as Parkinson's Disease Dementia or PD-D (Williams-Gray, Foltynie, Brayne, Robbins, & Baker, 2007). This wide variation in reporting is primarily due to the current lack of criteria in diagnosing dementia in PD and the heterogeneity of the neuropsychological measures used by researchers (Reid et.al, 1996). While age and disease duration are strong predictive markers of PD-D, cognitive impairment in certain domains is also considered to be a major risk factor (Dalrymple-Alford et al., 2011; Williams-Gray et al., 2009).

It is believed that changes in cognition occur between the development of PD and the progression to PD-D. Identifying these changes in cognitive impairment has become an area of great interest for researchers. Termed mild cognitive impairment (MCI), these changes can be measured through neuropsychological tests that focus on anterior (frontal lobes; executive function) and posterior (temporal and parietal lobes; language, memory, and visuospatial abilities) regions of the brain, which can provide great insight into the progression of PD to PD-D (Miller, Neargarder, Risi, & Cronin-Golomb, 2013).

Research suggests that the presence of MCI within the first few years of PD diagnosis can aid in predicting cognitive outcome in patients. In longitudinal studies by Williams-Gray, et al. (2007, 2009) non-demented PD participants completed a battery of neuropsychological tests that included the National Adult Reading Test to estimate premorbid intelligence, anterior-based tests (Tower of London, FAS, Switching), posterior-based tests (Pentagon Copy, semantic fluency, pattern recognition memory, spatial recognition memory), the Beck depression index and the Mini Mental State Exam (MMSE) to measure the presence of dementia. The results

showed that anterior deficits of executive function, shown on performance on the Tower of London test and the FAS test, were the most common types of cognitive impairment in non-demented PD. In the 2.5 year and 5 year follow up, deficits in performance on semantic fluency and Pentagon Copy, both tests of posterior regions of the brain, were the most significant neuropsychological test predictors of dementia within the cohort, whereas the more common anterior deficits were not. Dementia was defined as performing one standard deviation (SD) below published normative data. Based on the results of this longitudinal research, the authors concluded that posterior cognitive impairment was a significant risk factor in the development of PD-D.

Dalrymple-Alford and colleagues (2011) assessed 143 PD patients (including demented and non-demented PD) in the UK in an effort to help characterize MCI in PD. Each PD participant and 50 control participants completed a battery of tests that included anterior-based tests of executive function (e.g. Stroop Color-Word, Trails B, D-KEFS fluency tasks), attention (e.g. Stroop word, Digit forwards and backwards, Trails A), and posterior-based tests of learning and memory (e.g. Rey Complex Figure delay, California Verbal Learning Test), and visuospatial/visuoperceptual function (e.g. Rey Complex figure copy, Judgment of Line Orientation). Researchers compared participant performance on each test and, after analyzing the data, determined that scores of 1.5 SD below the normative score on two or more tests within a single domain or one test from two different domains worked best for characterizing MCI in PD.

Although previous research clearly demonstrates that MCI in PD patients does in fact exist, it remains unclear how best to characterize it. Specifically, should MCI be defined based on performance that falls 1 SD below the normative mean, 1.5 SDs, or 2 SDs? Should data be

compared to published normative data or to an age- and education matched control group wherein assessments are administered in the same environment by the same researcher? If anterior- and posterior-based tests are good predictors of MCI, does an individual have to perform poorly on all tests given within a specific domain (e.g., four out of four anterior tests), or should some other type of criterion be established?

The present project aims to further examine these questions by administering a series of anterior- and posterior-based tests to a group of non-demented PD patients and their age and education matched controls. Various SD cut-offs and the number of domain-specific deficits best characterizing a diagnosis of MCI will be examined. The purpose of this research is to further our understanding of the criteria involved in diagnosing MCI in PD. In the following sections, a review of the neuropsychological and neuropathological evidence for PD, PD-D, and MCI is presented in detail.

Neuropsychological Profile of Non-demented PD Individuals

Cognitive impairment can be seen very early in the course of PD and it is present in approximately 25% of newly diagnosed patients (Aarsland et al., 2010; Aarsland, Bronnick, & Fladby, 2011; Muslimović, Post, Speelman & Schmand, 2005). Most patients with PD experience some degree of cognitive impairment during the course of the disease (Korczyn & Gurevich, 2010).

Non-demented individuals with PD show deficits in anterior and posterior cognitive domains (Aarsland et al., 2010). Many researchers have found anterior executive functioning deficits to be the most common impairment in non-demented PD. Deficits are often seen on attention measures, such as the Stroop Word Test (Janvin, Aarsland, Larsen, & Hugdahl, 2002), attentional set formation, set shifting (Hayashi, Hanyu, & Tamaru, 1998; Lees & Smith, 1983;

Owen et al., 1992) and Digit Span (Dalrymple-Alford et al., 2011) as well as planning and working memory as demonstrated by the Tower of London task (Williams-Gray et al., 2009). Posterior-based deficits of visuospatial abilities are highly selective in PD and often decline with disease duration. In the early stages of PD, non-demented PD patients exhibit visuospatial decline on facial recognition tasks, mental object assembly, and manual visuoconstruction (Levin et al., 1991). Many researchers have investigated cognitive deficits in PD and identified similar patterns of performance (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009; Bronnick, Alves, Aarsland, Tysnes, & Larsen, 2011; Cronin-Golomb & Braun, 1997; Elgh et al., 2009; Ibarretxe-Bibao, Junque, Marti, & Tolosa, 2011; Montse et al., 2001; Pereira et al., 2009; Poletti, Emre, & Bunoccelli, 2011; Yu et al., 2012).

Muslimović, Post, Speelman, & Schmand (2005) examined cognitive abilities of newly diagnosed non-demented PD patients on a battery of neuropsychological tests of psychomotor speed, attention, language, memory, executive function, and visuospatial function. When compared to healthy control participants, PD patients performed significantly worse on most cognitive measures, including all anterior-based measures of executive function (i.e., the modified Wisconsin Card Sorting Test, animal fluency, supermarket fluency, Controlled Oral Word Association Test letter fluency, the Weschler Adult Intelligence Scale-III similarities, and the Tower of London test) and half of the attention measures (i.e., Digit Span backward and Trails B). Posterior-based tasks showed fewer PD deficits compared to healthy control participants, but significant differences were found in memory tasks (i.e., the Rey Auditory Verbal Learning Test (RAVLT): trials 1-5 and delayed recall, the Rivermead Behavioral Memory test: immediate and delayed recall, and the Weschler Memory Scale-III faces: immediate and delayed recall) and visuospatial/visuoconstruction tasks (i.e., the Judgment of

Line Orientation test and the Groninger Intelligence Test: visuo-spatial task). When researchers compared the cognitively impaired PD patients (N=27), they found that the domain of language had the lowest instances of impairment (22% of impaired PDs) and attention/executive function had the highest (100%).

Neuropathology of Non-demented PD

PD is primarily related to the loss of dopaminergic neurons in the substantia nigra, a midbrain structure that is part of the subcortical structure called the basal ganglia, causing a dopamine reduction in the striatum. By the time the first overt symptom of PD is discovered, approximately 50-80% of this neuronal loss has taken place (Jellinger, 1987). A major function of the basal ganglia is to control the fluidity of overlearned and semiautomatic motor programs by connecting to the thalamus and influencing the premotor cortex and other motor areas (Alexander & Crutcher, 1990). Thus, the depletion of dopamine is directly related to the hallmark motor symptoms and rigidity seen in PD.

Another characterization of PD is the formation of Lewy bodies, which are tightly packed granular structures with ring-like filaments found within dying neurons (Colosimo, Hughes, Kilford, & Lees, 2003). Lewy bodies are found in normal aging in the cells of the substantia nigra, but patients with PD have vastly more and may also have concentrations present in the nucleus basalis of Mynert, dorsal raphe, locus coeruleus, substantia nigra, dorsal motor nucleus of the vagus nerve, intermediolateral nucleus and hypothalamic nuclei, then progressing to limbic and neocortical areas when PD progresses to dementia (Gesi et al., 2000; Kövari, Horvath, & Bouras, 2009). Pathological changes in PD occur in a predictable sequence, with the early stages marked by Lewy body deposition in the nigrostriatal system followed by pathological changes in the cortex occurring in later stages (Braak, et.al, 2003).

Impairments in the neural circuitry connecting the basal ganglia and cortex may contribute to cognitive impairments seen in PD (Carbon et al. 2004). Executive and attentional impairments have been associated with the disruption of neuronal circuits involving the caudate and prefrontal cortex, as well as direct loss of ventral tegmental brain stem dopaminergic projections to cortical areas, specifically the prefrontal cortex (Carbon & Marie, 2003). There is a fundamental pattern for the passage of information through the interconnected structures of the basal ganglia. A generic circuit is organized as a large loop, which starts in the cerebral cortex and passes through the corpus striatum, globus pallidus, thalamus, and back to the cerebral cortex (Alexander, DeLong, & Strick, 1986; Chudasama & Robbins, 2006). PD is a progressive disease initially recognized by motor symptoms and signs that follow dopamine decline in the basal ganglia. Throughout the course of the disease, symptoms related to multiple neurotransmitter deficits can be seen in deteriorated areas of the cortices beyond and including the frontal lobe areas (Martinez-Horta & Kulisevsky, 2011). Since the early and mild stages of PD mainly involve the nigrostriatal projections to the putamen and the dorsolateral prefrontal cortex, this may explain why PD patients show worse executive performance when compared to normal control participants (Williams-Gray, et.al 2009).

Additionally, functional structural changes have been found in PD patients. Specifically, in PD patients with cognitive impairment, areas of reduced gray matter in the left frontal and both temporal lobes were found (Barone et al., 2011). In addition, patients who presented with visual hallucinations showed greater cerebral atrophy and suffered from an increased rate of cognitive decline compared to PD patients with no visual hallucinations.

Neuropsychological Profile of Demented PD Individuals

PD-D is associated with increased age, disease duration, severity of symptoms, and cognitive impairment (Litvan et.al, 2011). PD-D is highly variable with some patients developing dementia within 2-3 years of PD diagnosis while others can remain non-demented for decades (Aarsland et al., 2007). A majority of studies report a mean duration of approximately 10 years from onset of PD to the development of dementia and at least 75% of PD patients that survive 10 years or more will go on to develop dementia (Aarsland & Kurz, 2009). When dementia precedes motor symptoms or is present in the first year of PD onset, it is suggestive of alternative diagnoses such as dementia with Lewy bodies (McKeith et al., 2005). However, it is difficult to determine the exact onset of motor symptoms and dementia in a clinical setting. Some studies have found that rigidity, postural instability, and gait disturbances predict more rapid cognitive decline and time to dementia than other tremor symptoms (Aarsland & Kurz, 2009).

Dementia is not a specific disease, but rather a constellation of symptoms with different pathologies. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) defines dementia as an overall decline in intellectual function including difficulties with language, simple calculations, planning and judgment, and motor skills as well as loss of memory (4th ed.; text rev.; DSM-IV-TR; American Psychiatric Association, 2000). Dementia can be caused by a number of different diseases including PD. Patients with PD are six times more likely to develop dementia when compared to healthy control participants (Aarsland, et.al, 2001), and as mentioned earlier, studies have reported dementia rates ranging from 28-90% in the PD population (Janvin, Aarsland, & Larsen, 2005; Janvin, Larsen, Aarsland, & Hugdahl, 2006; Williams-Gray, 2009).

Age is the most prominent risk factor in developing dementia (Aarsland & Kurz, 2010; Williams-Gray et al., 2009). In the general population, 14% of adults 71 years of age and older have dementia and an estimated 35.6 million people worldwide have been diagnosed (World Health Organization, 2012). PD patients categorized as having MCI show an increased risk of developing dementia compared to those without, however, there is no set diagnosis of MCI in PD patients and much variability in the literature in terms of how to categorize it.

To determine the incidence of dementia in PD participants, many researchers use the MMSE to evaluate cognitive impairment. The Mini-mental state examination (MMSE) is a 30-item questionnaire that is used to screen for cognitive impairment and is often used to screen for dementia. The test measures aspects of memory, attention and orientation, visualspatial function, and language. With a maximum possible score of 30, a score of 25 or higher indicates normal cognition (Folstein, Folstein, & Mchugh, 1975). Most research for PD-MCI use cut-off values of between 24 and 26, as scores lower than this can be suggestive of severe cognitive impairment or dementia (Aarsland et al., 2009; Janvin et al., 2002; Williams-Gray et al., 2009).

Individuals with PD-D show global deficits in all domains of cognition. Petrova, Raycheva, and Trykov (2012) evaluated 58 patients with PD-D and 26 normal control participants. PD-D patients were separated into very mild PD-D and moderate PD-D using an MMSE score of 24 or higher for very mild, and 20-23 for moderate PD-D. Cognition in multiple domains was tested using a neuropsychological battery consisting of anterior-based cognitive tests: attention/executive function (Digit Span, Trails A and B, Madrid Card Sorting Test categories, and Stroop Color-Word, as well as posterior-based cognitive tests: visuospatial abilities (copy design and the Clock Drawing Test) and memory (Free and Cued Selective Reminding Test free recall, total recall, intrusions, recognitions, free delayed recall, and total

delayed recall). Both PD-D groups performed significantly worse on anterior tasks for immediate and delayed recall, and delayed total recall. Moderate PD-D had significantly lower scores on recognition tasks and had higher numbers of intrusions in immediate recall than the very mild PD-D group and control group. While both PD-D groups showed lower scores on all anterior measures of attention and executive function, moderate PD-D performed significantly worse than very mild PD-D on Trails A, Trails B, and the Madrid Card Sorting Test. Both groups also performed significantly worse than control participants on posterior-based measures of visuospatial abilities on both the copy design and the clock drawing test (Petrova et al., 2012).

Levin and colleagues (1991) evaluated posterior-based abilities of visuospatial impairment over various stages of PD including PD-D. These tests consisted of Line Orientation, the Hooper Visual Organization Test, Block Design, Facial Recognition, Ghent, and Nonverbal Embedded Figures Task. Their findings suggest that visuospatial abilities do not deteriorate uniformly, but gradually as a function of disease duration. In the early stages, non-demented and PD-D both show visuospatial decline on facial recognition. During the middle stages, PD-D start to diverge and begin showing difficulties with mentally assembling puzzles, formulating angular judgments, and identifying embedded objects and geometric figures. In the advanced stages of PD-D, pervasive impairments are seen on all measures of visuospatial function.

Neuropathology of PD-D

Lewy bodies are specific pathological markers for PD-D and have been the most consistent pathological correlate of dementia in PD patients. Braak staging is a method often used to classify the degree of pathology in PD. According to Braak staging, Lewy bodies first appear in the olfactory bulbs, medulla, and tegmentum. As the disease progresses, Lewy bodies are found in the substantia nigra, areas of the midbrain, and continue upward until they finally

reach the neocortex (Braak, et al. 2003). Apaydin et al (2002) examined 12 post-mortem PD patients with dementia. Their findings suggested that the Lewy body counts were nearly 10-fold in the neocortex and limbic areas compared with 9 post-mortem PD patients examined without dementia. Aarsland et al (2005) described autopsy results from 22 PD participants from a longitudinal study in Norway. All had significant limbic or neocortical Lewy bodies that were significantly associated with the rate of cognitive decline on pre-mortem neuropsychological testing.

Magnetic resonance imaging (MRI) studies have shown that hippocampal, temporal, and parietal lobe volume is decreased in patients with PD-D when compared to healthy control participants (Braak & Braak, 2000; Emre, 2003), but findings in non-demented PD patients have been less conclusive with varying degrees of atrophy when compared to a healthy control group (Weintraub et.al, 2011).

PD-MCI

Mild Cognitive Impairment (MCI) as defined by Petersen (2004) was integral in the understanding of the progression of Alzheimer's disease (AD). MCI originally focused on memory as a risk factor for AD, but the definition of MCI has been expanded to include other domains such as executive functioning and visuospatial abilities. The linear pattern of cognitive impairment in AD differs from that of PD (Martinez-Horta et al., 2011). AD does not have a motor component and often relies on reports of cognition changes by the patient or caregiver. The slight cognitive changes in PD may be overshadowed by the motor abnormalities. Additionally, depression and anxiety are the most common psychiatric symptoms of PD. Changes in cognition may not be easily seen as they might be masked by the symptoms of

depression such as preoccupation with ill health, an inability to work, and loss of desire (Allain, Schuck, & Mauduit, 2000).

In AD, MCI is a transitional state and it is hypothesized to be similar for PD, but the confounding range of neuropsychological abnormalities with predictive cognitive impairment makes it difficult to observe overt signs of later dementia. In studies supported by the Movement Disorders Society, various criteria were used to determine PD-MCI. These criteria were observed in 27% of patients and were associated with the subsequent development of PD-D (Litvan, et.al, 2011).

There is much controversy surrounding the application of MCI to PD, including whether it is appropriate to apply it to PD at all. One of the key factors of MCI in AD is the reporting of cognitive impairment affecting daily life for the patient with an emphasis on memory impairment (Petersen, at al., 1997). Unlike AD, memory function is not an early sign of PD and can often be preceded by executive dysfunction such as changes in behavior and judgment. Additionally, the drug treatments for depression, anxiety, and the motor symptoms may result in changes in cognition that cannot be considered part of the disease progression (Korczyn, 2011). Despite the controversy, many studies now label changes in the cognitive functioning of PD patients as MCI and have shown that the Petersen criteria can be used to identify cognitive impairment between normal cognition and dementia in patients with PD (Sollinger, Goldstein, Lah, Levey, & Factor, 2010).

A uniform definition of MCI in PD is important for the identification of the clinical characteristics of cognitive impairment in the early stages of PD, the effects of MCI in the quality of life for PD patients, and the best predictors of dementia in the PD population (Litvan,

et.al, 2012). However, various studies looking at MCI have used different criteria for defining MCI resulting in inconsistent information.

Neuropsychological profile of MCI

There are currently no definitive criteria for determining MCI in PD, but the Movement Disorder Society recently formed a task force and proposed guidelines for characterizing and diagnosing PD-MCI (Litvan et al., 2012). These guidelines suggest that multiple domains should be assessed with multiple neuropsychological measures. While the task force emphasized the need for additional research in order to determine the exact neuropsychological measures that should be used, they did determine that a diagnosis of MCI should require the presence of deficits on at least two tasks within a variety of cognitive domains (e.g. executive deficits, visuospatial deficits, etc). The guidelines allow for cognitive impairment on neuropsychological tests to be determined in several ways: performance between 1 and 2 SD below matched norms, significant decline on serial cognitive testing or significant decline from estimated premorbid levels, or even less than 1 SD below matched norms in patients who report a change in cognition who have undergone neuropsychological testing and have fallen at least 1 SD below previous test scores (Litvan et al., 2012).

Neuropathology of MCI

Neuropathologies for PD and PD-D have all been shown to involve Lewy bodies. Neuropathological changes in PD-MCI have not been thoroughly described. Adler and colleagues (2010) autopsied patients that had confirmed cases of PD from 1987-2010, eight of which met criteria for PD-MCI before death. In those eight PD-MCI patients, the Lewy body distribution varied between brainstem-predominant, brainstem-limbic, and neocortical. Five of the eight cases had at least limbic cortical Lewy body involvement. Their conclusion was that it

was uncertain if Lewy body pathology is the cause of cognitive impairment in PD-MCI (Adler et al. 2010).

Present Project

The present study examined non-demented PD and healthy control participants (HC) on a large number of tests of cognition that rely on anterior and posterior areas of the brain. The primary goal was to determine the degree of PD-related cognitive deficits on anterior versus posterior tasks. PD participants' performance was compared to HC participants' performance in an effort to determine tests that would be sensitive to the cognitive effects of PD. This study is different from previous research in that the research directly compared PD and HC participants' performance across all cognitive measures. Previous research has primarily compared PD and HC participants' performance against published normative data, with no direct comparisons made with an age and education matched control group. It was hypothesized that PD participants would perform significantly more poorly across all anterior and posterior tests than age and education matched HC participants. A second goal was to examine cognitive performance variation within individuals with PD in an effort to develop subtypes based on patterns of anterior and posterior deficits. Based on previous literature, it was hypothesized that PD participants would fall into one of four cognitive groups (anterior deficit only, posterior deficit only, both deficit, and neither deficit) and that more patients would exhibit anterior-type compared to posterior-type deficits. Examining group and individual neuropsychological profiles on anterior and posterior measures may provide additional information regarding the course of the disease and may provide insight that could help identify early cognitive changes that may result in later dementia. Further, to determine MCI in PD, various criteria were used such as two deficits in a single domain with cut offs of 1.5 SD, and 2 SD below control

participants. Based on previous research (Dalrymple-Alford et al., 2011), it was hypothesized that two deficits of 1.5 SD below the mean in a single domain would provide categorization that is sensitive enough to detect cognitive impairment, yet conservative enough to avoid false positives.

Method

Participants

The study consisted of 61 participants: 34 non-demented PD participants (21 males and 13 females) with average age and education levels of 64.97 years (SD = 7.67) and 17.09 years (SD = 2.09) respectively, and 27 healthy control participants (HCs; 12 males and 15 females) with average age and education levels of 64.85 years (SD = 8.61) and 17.30 years (SD = 2.04) respectively. PD and HC participants did not significantly differ on age [$t(60)=-.57$, $p=.96$] or education [$t(60)=.39$, $p=.67$]. All participants scored above 25 on the Modified Mini-Mental State Exam (mMMSE), indicating the absence of dementia. Median Hoehn & Yahr staging for PD participants was 2.0 and the average duration of PD was 6.9 years. Participants were referred from the Parkinson's Disease Center of Boston University's Medical Center and local support groups, and included individuals who met the clinical criteria for mild to moderate PD as diagnosed by the patients' neurologists. HC participants were recruited from the community. Exclusion criteria included co-existing serious chronic illness (including psychological or neurological), use of psychoactive medication other than antidepressants and anxiolytics in the PD group, use of any psychoactive medication in the HC group, history of intracranial surgery, traumatic brain injury, alcoholism, or other drug abuse, and visual acuity poorer than 20/40. The study protocol was approved by the Boston University Institutional Review Board.

Measures and Procedures

Participants were given a battery of tests as part of a larger study on PD and cognition. Tests were chosen based on literature supporting their utility in identifying deficits among PD patients. These tests measured anterior- and posterior-type abilities. Anterior tests measured frontal lobe abilities including executive functioning, attention, and decision-making skills. Posterior-type tests measured abilities associated with the parietal and temporal lobes and included visuospatial, visuomotor, visual dependence, spatial reasoning, and memory skills. PD patients were categorized into subgroups based on their performance across the various tests relative to healthy control participants.

Anterior-type tests.

The Stroop Color-Word Task. The Stroop Color-Word Task (Stroop, 1935) is a test of executive functioning and measures selective attention, cognitive flexibility, and processing speed. First, participants are presented with a series of "XXXXs" in five columns of 20 words. Each series is presented in one of three colors: green, blue, or red. Participants name the color of each series of "XXXXs" presented as quickly as possible. If the participant is able to complete the list of words, they go back to the beginning to continue reading. The number correct after 45 seconds is recorded. Next, they are presented repeatedly with the words "green," "blue," and "red," that appear in black (the Stroop word portion). Their task is to read the words as quickly as possible within a 45-second time frame. Finally, they are repeatedly presented with the words "green," "blue," and "red," except now the words are colored such that the color of the word is incongruent with what the word says (e.g., the word blue appears in red; the Stroop color-word portion). Participants are asked to name the color in which the words appear (the response to the above example would be red). Participants are timed and the resulting score is equal to the

number correct within a 45-second time frame (dependent variable). The Stroop word portion (reading the color names in black ink) measures attention, while the color-word portion (the color names in incongruent colors) measures executive functioning including cognitive flexibility with lower scores indicating poorer performance.

The Delis-Kaplan Executive Functioning System (D-KEFS) Verbal Fluency task. The D-KEFS (Delis, Kaplan, & Kramer, 2001) measures verbal fluency, specifically, the ability to understand language rules and the ability to switch between rules. Participants were asked to generate as many words as possible that started with the letter F within a period of one minute. The number of words that were said in each 15-second interval was recorded along with set loss errors and repetitions. Proper nouns, non-english words, homophones, variations of the same word (far, farther, farthest), and numbers were not counted toward the final score. Individual words that met the criteria were counted (dependent variable). This procedure was repeated for the letters A and S. The results from each portion (F, A, and S) were summed to generate a total score. For the category switching portion of the D-KEFS, participants are asked to name as many pieces of fruit and furniture as possible while alternating between categories (e.g., apple, table, banana, chair, etc.) for a period of 60 seconds. The number of words that qualify as fruit or furniture and are properly alternated is the dependent variable with lower numbers indicating poorer performance.

The Trail Making Test. The Trail Making Test (Tombaugh, 2004) measures executive function, specifically attention (Trails A) and set-shifting (Trails B). The Trail Making Test consists of two parts. Trails A has 25 circles with numbers (1-25) in them. Trails B has 25 circles with letters or numbers (A-L, 1-13). The circles are scattered throughout the page in no discernable pattern. Participants were asked to connect the dots in order. For Trails A, each dot

was a circle with a number in it and participants were asked to draw a line as fast as they could, connecting all of the dots in numerical order without lifting the pen. The line was required to at least touch the circle. Participants were able to self-correct errors, but if the pen was lifted, the task was started from the first number. The amount of time it took to connect all of the dots was recorded as the dependent variable. For Trails B, each circle had either a number or a letter in it. Participants were asked to connect the dots in order alternating between letters and numbers (1, A, 2, B, etc.) without picking up the pen and making sure the line touched the circles. The amount of time it took to connect all the dots was recorded as the dependent variable with lower time indicating better performance.

Posterior-type tests.

The Cube and Pentagon Copying tests from the modified Mini Mental State Exam (mMMSE). The Cube and Pentagon Copying tests (Stern, Sano, Paulson, & Mayeux, 1987) measure motor abilities related to vision (visuomotor) and abilities related to the perception of spatial relations involving vision (visuospatial). For these tests, participants copied a 3-D cube and two overlapping pentagons without a time limit. Scoring systems previously applied to PD by Maehima and colleagues (cube; Maeshima, Itakura, Nakagawa, Nakai, & Komai, 1997) and Jefferson and colleagues (pentagon; Jefferson et al., 2002) were used to obtain a total score for each. The accuracy of the drawings contingent on the stated criteria was the dependent variable with higher scores indicating better performance.

The D-KEFS Verbal Fluency task. The D-KEFS (Delis et al., 2001) measures semantic fluency, which is the participant's ability to demonstrate verbal fluency within a given category. Participants named as many animals as possible in one minute. The number of words stated in 15-second intervals was recorded as well as set loss errors and repetitions. Types of animals and

specific species can be used. For example, a participant could say "bird," and "seagull." Individual words that met the criteria (dependent variable) were counted resulting in a total score with lower scores indicating poorer performance.

The Landmark Line Bisection task. The Line Bisection task (Davidsdottir, Wagenaar, Young, & Cronin-Golomb, 2008; Lee, Harris, Atkinson, & Fowler, 2001) measures spatial perception without motor demands so that the score was not dependent on the participant's physical abilities. On a computer screen, participants viewed a horizontal line crossed by a vertical mark that began on either the left or right side of the horizontal line. As the experimenter moved the vertical mark toward the opposite side of the line, participants indicated when the mark reached the perceived center of the line. Each trial started at different sides of center and at different distances resulting in five trials that started to the right of center and five trials that started to the left of center. The distance between the perceived center and the actual center was the dependent variable. The average absolute value of distance from the actual center was taken for the 10 trials with lower numbers indicating less variation and better performance.

The Visual Dependence task. The Visual Dependence task (Azulay, Mesure, Amblard, & Pouget, 2002; Danta & Hilton, 1975; Davidsdottir et al., 2008) measures visual dependence without motor demands. Participants viewed a computerized rotating white rod on a black screen presented at an angle (five tilted upward to the right and five tilted upward to the left). The researcher manually rotated the rod from a separate station. The participant was asked to indicate when the rod reached a horizontal position. Scoring was based on how close to horizontal each trial was (dependent variable). The average of 10 trials was used for analysis with lower numbers indicating better performance.

The Delayed condition for the Rey Auditory Verbal Learning Test (RAVLT). The RAVLT-delay (Rey, 1964) measures delayed memory. Participants were given a list of 15 words read in a monotone voice with even spacing. Participants were asked to repeat as many words as they remember from the list in any order. This was repeated 5 times. Then, there was an interference recall wherein the participants were read a new list of words in a monotone voice, then asked to repeat the words in any order. After approximately 20 minutes of neuropsychological testing, the participants were asked to recall the original list (with no additional prompting). The score was the total number of correctly recalled words in the delay portion only with lower scores indicating poorer performance.

Results

The data were examined in three main ways. First, HC and PD participants were compared to one another to evaluate group performance. Second, test performance was evaluated for each PD participant to examine variability within the group. Finally, subtyping of deficits was established to identify cognitive decline based on anterior and posterior deficits. As the data reflect the results of an ongoing study on PD and cognition, some participants were not administered all tests.

Group Performance

Independent groups t-tests with a Bonferroni correction of .008 (.05/6) was used to examine group (i.e. HC and PD) differences on the six anterior- and six posterior-type assessments. As illustrated in Table 1, the HC group significantly outperformed the PD group on most tasks including anterior-based tasks of Stroop word and color-word, FAS, switching, Trails A, and Trails B. The PD group also performed significantly more poorly on the posterior-based

tasks of Line Bisection and RAVLT-delay. See Table 1 for the t-test results, means, and SDs of each group.

Individual Performance

Individual PD performance was evaluated to examine within group variability and sensitivity of tests to PD performance. To examine individual performance, means and SDs were calculated for HC participants for each test. PD scores were then converted to z-scores by using the means and SDs of the HC group for each test. For purposes of this project, a deficit was identified as a score that fell at least 1.5 SD below the HC mean for a particular test. The number and percentage of PD participants who exhibited a deficit for the anterior and posterior-type tests according to the 1.5 SD and 2 SD criteria is shown in Table 2. As illustrated, PD participants showed the largest percentage of deficits on Trails A (55.88% and 50% respectively) and the least on semantic fluency (12.50% and 0% respectively). Table 3 shows individual PD performance for each test. Noted deficits and their severity (1.5 SD or 2.0 SD below the HC mean) are provided. Number of deficits on tests ranged from four (switching, cube copy, and semantic fluency) to 19 (Trails A) deficits. Individual performance ranged from zero deficits (five participants) to 10 deficits (one participant).

Subtyping of Cognitive Deficit

As explained above, we examined PD participants whose z-score fell at least 1.5 SD below the HC group mean as well as a stricter cut-off of at least 2 SD below the HC mean on any given task. For both sets of criteria, participants who had two or more deficits in a single domain (anterior, posterior) were categorized as being deficient in that domain. This subtyping resulted in the establishment of four groups: anterior deficit only, posterior deficit only, anterior and posterior deficit (both), and no deficit in either domain (neither). This categorization for 1.5 SD

below showed nine individuals with anterior deficit only, one individual with posterior deficit only, 10 individuals with anterior and posterior deficits (both), and 14 participants with neither deficit. When the cut-off was increased to the more strict 2 SD below the mean, four participants categorized as both moved to the frontal only category, four from the frontal only and one from the both categories moved to neither. This change in categorization maintained the 9 individuals with anterior deficit only and one individual with posterior deficit only, however, individuals categorized as being deficient in both fell to five, and neither deficit increased to 19 (see Table 4).

Discussion

Comparison of PD and HC Performance

The first hypothesis stated that PD participants would show more cognitive deficits than HC participants. As predicted, the non-demented PD participants in this study performed significantly more poorly than the HC participants on several measures of cognition, including all anterior-based tests (Stroop word, Stroop color-word, FAS, switching, Trails A, and Trails B) and two posterior-based tests (Line Bisection and RAVLT delayed recall). These results are in line with previous studies which have found that anterior deficits as opposed to posterior deficits are more commonly observed in PD (Janvin et al., 2002; Miller et al., 2013; Williams-Gray et al., 2007, 2009). Contrary to research by Williams-Gray et al. (2009), semantic fluency did not appear to be a strong indicator of posterior cognitive deficits in this PD population, as no significant difference in performance was observed on this measure between PD and HC participants. This may be due to the fact that these PD participants were extremely high functioning whereas Williams-Gray et al. included participants who were high functioning, but they also included participants who exhibited early signs of dementia.

The current project directly compared PD performance to that obtained by age and education matched control participants from the greater Boston area. The majority of researchers who study PD-MCI, however, compared their obtained PD group data to published normative data. This remains the case even when a control group was included as a part of the research study (Williams-Gray et al., 2007, 2009). The control group comparison method was chosen over the use of published norms in order to minimize demographic differences that might skew the data. Published normative data are often inconsistent when accounting for demographic variables such as education. Our PD sample was highly educated, ranging from 13 years (one participant) to 21 years (two participants) of education with a mean of 17.09 years. Our matched controls had a range of 14 years (two participants) to 21 years (two participants) of education with a mean of 17.30 years. Less well-matched normative data may have indicated less cognitive impairment in our PD group thereby masking changes in cognition.

Subtyping Cognitive Deficits

The second hypothesis stated that PD participants would fall into one of four cognitive groups: anterior deficit only, posterior deficit only, both deficit, and neither deficit. As demonstrated by the data, the numbers of PD participants that were categorized in the groups changed as a function of the criteria adopted for inclusion as explained below. As predicted, PD participants exhibited more cognitive deficits on anterior-based tasks when compared to posterior-based tasks. These results were consistent with the literature on cognitive performance in PD participants (Aarsland et al, 2011; Williams-Gray et al., 2009).

As indicated above, only one participant was categorized solely in the posterior deficit group. Based on research by Williams-Gray and colleagues (2009), deficits on posterior-based tasks are predictive of the development of dementia whereas anterior-based deficits are not. It is

worth noting that this participant had a disease duration of 3 years and was 54- years-old at the time of testing. This participant fell 2 SD below HC on the posterior-based tests of Cube Copy and Line Bisection. No anterior-based tests indicated deficits.

A total of four participants showed no cognitive deficits on any task (one additional person had no deficits but only participated in 11 out of the 12 cognitive tests). The remaining participants showed some cognitive deficit on at least one measure of cognition in either domain. This was expected as some degree of cognitive impairment is associated with PD.

Categorization of MCI

There are no set diagnostic criteria for MCI in PD. The Movement Disorder Society recently assembled a task force to clarify MCI in PD, but used various ways to establish a diagnosis. These guidelines suggested that multiple domains be assessed with many neuropsychological measures, but did not come to a consensus as to which measures to use and urged additional research to determine these measures. To diagnose MCI, they suggested that a deficit should be found on at least two tests within a single domain. Determining a cognitive deficit on a test had various options. A deficit could be determined if the patient scored between 1 and 2 SD below matched normative data. If available, a significant decline on serial cognitive testing or estimated premorbid abilities could be considered a cognitive deficit in the corresponding domain (e.g. executive function, visuospatial abilities). Finally, if a patient had undergone neuropsychological testing previously, reported a change in cognition, and fell at least 1 SD below previously tested abilities, a score of less than 1 SD below published norms was sufficient to determine a deficit on that task (Litvan et al., 2012).

Determining a deficit within a domain varies among researchers. Some studies have emphasized the need to show a deficit on two tests within a single domain (Foltynie et al., 2004,

Petrova et al. 2012; Williams-Gray at al., 2007, 2009). Dalrymple-Alford et al. (2011) proposed that one deficit across two domains (e.g. one anterior test and one posterior test) was sufficient for the categorization of MCI in PD. Janvin and colleagues (2002) accepted only one neuropsychological test deficit as long as the patient scored at least 2 SD below the mean. Researchers in Taiwan (Yu et al., 2012) considered a domain impaired if the participant scored 1.5 SD below normative data on a minimum of one test within that domain. With so many variations, it is clear that more research is needed to establish reliable and valid guidelines.

MCI was evaluated using cut-off values of 1.5 SD below the HC participants' mean and 2 SD below the HC participants' mean with two deficits in a single domain (anterior or posterior) constituting a deficit in that domain. When 1.5 SD below the HC participants' mean was used, nine PD participants were categorized as having anterior deficits, one PD participant was categorized as having posterior deficits, 10 PD participants were categorized as having both deficits, and 14 PD participants were categorized as having neither deficit. When the more strict cut-off of 2 SDs was used, anterior and posterior grouping remained the same (nine and one respectively), but the PD participants classified as both deficits was decreased to five and neither deficit increased to 19.

The type and number of neuropsychological tests used to determine this subtyping is needed in future research. Many of the investigations into PD-MCI have used various neuropsychological tests. Other research into PD-MCI has used unbalanced numbers of tests between domains. Dalrymple-Alford et al. (2011) used 12 anterior-based cognitive tests and eight posterior-based tasks. Sollinger, Goldstein, Lah, Levey, & Factor (2010) used seven anterior-based cognitive tests and four posterior-based cognitive tests.

Besides the unbalanced nature of the cognitive domains, different researchers use different batteries of tests. Some common anterior-based tasks that show deficits in PD are Tower of London (Liepelt-Scarfone et al., 2011; Muslimović, 2005; Williams-Gray, 2009), Trails A and B (Dalrymple-Alford et al., 2011; Liepelt-Sacrfone et al., 2011; Miller et al., 2013; Muslimović at al., 2005; Sollinger et al., 2010), Stroop Color-Word (Dalrymple-Alford et al., 2011; Miller et al., 2013; Muslimović et al., 2005;) and verbal fluency (Dalymple-Alford et al., 2011; Miller et al., 2013; Sollinger et al., 2010). Posterior-based cognitive tasks are generally less agreed upon among researchers. Many investigators focus on memory impairment, but visuospatial tests may be more indicative of posterior deficits. Some tests that have shown deficits among PD patients are Judgment of Line Orientation (Dalrymple-Alford, 2011; Levin et al., 1991; Muslimović et al., 2005; Sollinger et al., 2010;), MMSE Pentagon copy (Miller et al., 2013; Sollinger et al., 2010; Williams-Gray et al., 2009); semantic fluency (Miller et al., 2013; Sollinger et al., 2010; Williams-Gray et al., 2009), and Mental Rotation (Amick, Schendan, Ganis, & Cronin-Golomb. 2006; Levin et al., 1991).

Limitations

One of the biggest limitations of this study was that it was a cross-sectional study, which allowed for only a single investigation of our PD population. Future research on this topic will need to involve longitudinal data that will allow researchers to investigate the cognitive changes in PD participants over many years over the course of the disease. First, a conclusive determination of MCI in PD should be determined to streamline future investigations. Second, it is imperative that researchers assess the best measures of cognition in various domains that are sensitive to PD without being influenced by a motor component that might negatively impact PD scores. Most of the tests used in the current study did not contain a motor component, but for

some, it was unavoidable (i.e. Trails A & B). Third, a longitudinal study including newly diagnosed PD participants that spans a minimum of 10 years would show a range of cognitive outcomes and shed light on the idea of cognitive domain classification. This would help show cognitive decline of people who do and do no go on to develop PD-D and if cognitive decline in a specific domain (posterior cortices) is indicative of PD-D. Also, this research could investigate how MCI progresses or stagnates in the PD population and if it is, indeed, a transitory state to PD-D or simply a function of PD.

Another limitation of this study was the fact that our PD population was very high functioning. Many researchers study PD participants with a range of cognitive function including mild or moderate dementia (Dalrymple-Alford et al., 2011; Foltynie et al., 2004; Williams-Gray et al., 2007, 2009; Petrova et al., 2012). The data from this research were part of a larger study that required high functioning PD participants. This resulted in some data that were inconsistent with previous findings. Generally, disease duration is considered to be a major risk factor of declining cognition in PD up to and including dementia. Our PD sample, however, did not include any participants whose MMSE scores indicated possible dementia and there were no exclusion criteria for disease duration. As a result, our participants with higher disease duration (10 or more years) exhibited better or equal cognitive results when compared to PD participants with shorter disease durations. Aarsland and Kurz (2010) stated that 75% of PD patients with a diagnosis of more than 10 years will develop dementia, however, our participants that fell into that group were high functioning.

Conclusions

Because the present study was not longitudinal in nature, conclusions about PD-D cannot be made. However, it is apparent that based on the MCI criteria used, non-demented PD

participants can be classified into anterior and/or posterior cognitive deficit subtypes. This appears to be possible at various stages of PD including newly diagnosed, high functioning, and mildly impaired.

Overall, research into PD-D is highly variable and subject to limitations such as a participant's inability to continue with research for reasons of motor impairment, dementia resulting in the inability to complete a neuropsychological battery, and even death. Because of these factors, a large pool of participants is needed. It is important to test newly diagnosed PD participants to obtain a baseline score on neuropsychological tests to better understand the course of the disease. Finally, by continuing the research for 10 or more years, the progression to dementia in PDs may be better understood resulting in more precise risk factors being identified. Through continued research, better understanding of PD, and its progression to dementia will aid in the care of the patients. As the baby boom generation continues to age, it is quite possible that we will see an increase in instances of PD. While this increased population will result in the need for more care, it will also increase the pool of possible research participants as well as generate more interest in PD.

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Table 1: Comparison of HC and PD Cognitive Performance. Mean (SD) total score unless indicated otherwise

Test Name	PD (n)	HC (n)	PD Mean (SD)	HC Mean (SD)	95% Confidence Interval	PD-HC significant difference (1-tailed)	Effect Size η2
Anterior-type tests							
Stroop Word score	34	27	32.09 (9.30)	42.11 (8.97)	[12.11, 27.02]	.001*	0.22
Stroop Color-Word score	34	27	85.88 (12.59)	105.44 (16.52)	[5.30, 14.75]	.001*	0.11
D-KEFS FAS	34	27	39.79 (7.55)	54.85 (12.00)	[9.71, 20.40]	.001*	0.20
D-KEFS Switching	17	22	12.94 (3.11)	14.77 (2.83)	[-.10, 3.76]	.032*	0.02
Trails A completion time	34	27	35.11 (10.33)	24.48 (5.17)	[-14.72, -6.56]	.001*	0.23
Trails B completion time	34	27	90.71 (42.98)	54.09 (15.16)	[-52.62, -20.64]	.001*	0.33
Posterior-type tests							
mMMSE Cube Copy	34	27	5.85 (1.40)	6.41 (0.97)	[-.05, 1.16]	0.365	0.05
mMMSE Pentagon Copy	29	25	6.90 (.90)	7.04 (0.68)	[-.30, .58]	0.258	0.12
D-KEFS Semantic Fluency	32	27	22.03 (5.55)	23.85 (5.80)	[-1.14, 4.79]	0.112	0.01
Visual Dependence	34	27	0.51 (0.52)	0.35 (0.26)	[-.37, .04]	0.061	0.00
Line Bisection	34	27	-0.10 (0.77)	0.55 (0.70)	[-.51, .03]	.001*	0.01
RAVLT Delayed recall	17	22	7.24 (3.73)	10.41 (3.53)	[.81, 5.54]	.005*	0.08

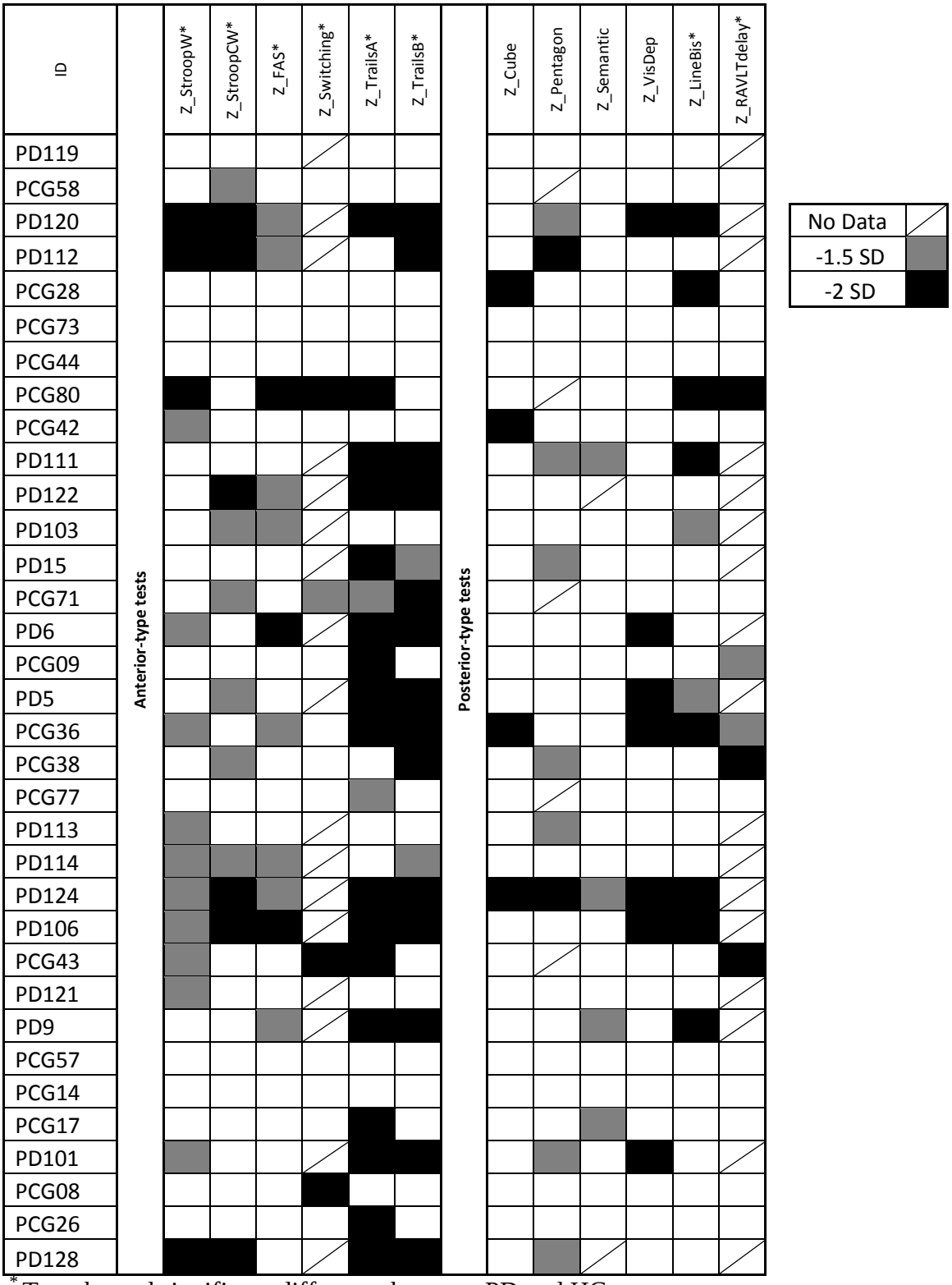
* Indicates significant difference at $\alpha = .05$between HC and PD groups

Table 2: Test performance across PD participants

Test Name	Total PD	Total Deficits at -1.5 SD	Percentage	Total Deficits at -2 SD	Percentage
Anterior-type tests					
Stroop Word	34	14	41.18	4	11.76
Stroop Color-Word	34	12	35.29	6	17.65
FAS	34	11	32.35	3	8.82
Switching	17	4	23.53	3	17.65
Trails A	34	19	55.88	17	50.00
Trails B	34	16	47.06	14	41.18
Posterior-type tests					
Cube Copy	34	4	11.76	4	11.76
Pentagon Copy	29	9	31.03	2	6.90
Semantic Fluency	32	4	12.05	0	0.00
Visual Dependence	34	7	20.59	7	20.59
Line Bisection	34	10	29.41	8	23.53
RAVLY-delay	17	5	29.41	3	17.65

Test Name	Total PD	Total Deficits at -1.5 SD	Percentage	Total Deficits at -2 SD	Percentage
Anterior-type tests					
Stroop Word	34	14	41.18	4	11.76
Stroop Color-Word	34	12	35.29	6	17.65
FAS	34	11	32.35	3	8.82
Switching	17	4	23.53	3	17.65
Trails A	34	19	55.88	17	50.00
Trails B	34	16	47.06	14	41.18
Posterior-type tests					
Cube Copy	34	4	11.76	4	11.76
Pentagon Copy	29	9	31.03	2	6.90
Semantic Fluency	32	4	12.05	0	0.00
Visual Dependence	34	7	20.59	7	20.59
Line Bisection	34	10	29.41	8	23.53
RAVLY-delay	17	5	29.41	3	17.65

Table 3: Individual PD Performance



* Test showed significant difference between PD and HC

Table 4: Type of cognitive deficit

Criteria	Anterior	Posterior	Both Deficits	Neither
PD -1.5 SD	9	1	10	14
PD -2 SD	9	1	5	19

PD participant's whose z-score fell at least 1.5 SD below the HC group mean and 2 SD below the HC mean on any given task.

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