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Neuropsychological assessment in collaborative Parkinson's disease research:

A proposal from the National Institute of Neurological Disorders and Stroke Morris K. Udall Centers of Excellence for Parkinson's Disease Research at the University of Pennsylvania and the University of Washington

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Abstract

Cognitive impairment (CI) and behavioral disturbances can be the earliest symptoms of Parkinson's disease (PD), ultimately afflict the vast majority of PD patients, and increase caregiver burden. Our two Morris K. Udall Centers of Excellence for Parkinson's Disease Research were supported by the National Institute of Neurological Disorders and Stroke (NINDS) to recommend a comprehensive yet practical approach to cognitive and behavioral assessment to fuel collaborative research. We recommend a step-wise approach with two levels of standardized evaluation to establish a common battery, as well as an alternative testing recommendation for severely impaired subjects, and review supplemental tests that may be useful in specific research settings. Our flexible approach may be applied to studies with varying emphasis on cognition and

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behavior, does not place undue burden on participants or resources, and has a high degree of compatibility with existing test batteries to promote collaboration.

INTRODUCTION

Cognitive and behavioral impairments are key features of Alzheimer's diseases, as recently highlighted by the *National Alzheimer's Project Act* [1] and the *Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention* [2], and are increasingly recognized in other types of neurodegenerative disease. Indeed, non-motor symptoms are prevalent in Parkinson's disease (PD) and contribute substantially to its morbidity and mortality. Up to 80% of patients with PD will eventually develop dementia, and cognitive impairment (CI) in the absence of dementia can be the earliest symptom of PD [3–5]. Similarly, behavioral complications–including psychosis, apathy, depression, and anxiety–commonly are associated with PD [6]. Together, cognitive and behavioral disturbances in PD account for increasing disability and caregiver burden as the disease progresses [7–9].

Given the range of deleterious effects from cognitive and behavioral impairments and increased emphasis on the neuropsychiatric features of PD, there is a compelling need for a standard approach to neuropsychiatric assessment in collaborative PD research. However, the lack of a common core assessment battery, such as that used in Alzheimer's Disease Centers (ADCs)[10], limits comparisons across studies. In addition, some instruments traditionally used in PD are insensitive to the earliest cognitive changes. For example, the Mini-Mental State Examination (MMSE), which has been widely used in dementia evaluation, may not be the optimal tool for assessment of general cognition in PD [11]. Although a number of different cognitive batteries have been used among large clinical investigations of PD (Table 1), a broad consensus has not emerged for the use of any particular set of tests [10, 12–15].

The University of Pennsylvania and the University of Washington Udall Centers both have a primary focus on cognitive and behavioral aspects of this disease, yet have been limited in our ability to collaborate more closely with each other, as well as other groups with a similar research focus, because of incompatibilities in cognitive and behavioral assessments [16]. The NINDS recently sponsored our efforts to develop a cross-institutional collaborative approach to the assessment of cognition and behavior in research subjects with PD.

PENN-UW CONSENSUS PROCESS

A working group comprising scientists and clinicians at our Udall Centers was convened and met on a regular basis by teleconference. A review of neuropsychological batteries previously used in studies of cognition in PD or national programs (Table 1) was undertaken. We considered each test's psychometric properties, research and clinical utility, inclusion in previous and ongoing batteries, measurement of important aspects of CI in PD, and testing burden on both patients and research staff with the goal of assembling a relatively comprehensive but efficient approach to cognitive and behavioral testing for varying research contexts.

The resulting recommendations follow a step-wise approach with two Levels, as well as Supplemental Testing that may be applicable for more detailed testing in particular research settings (Figure and Table 2); we also include an Alternative Testing recommendation for severely impaired subjects. Level I contains two brief screening tests of global cognition and behavior recommended for all subjects with PD. Level II is a battery of domain-specific cognitive tests and secondary assessment of behavior and psychiatric functioning, as they may impact cognition, and is recommended for PD subjects participating in research focused

on cognition and behavior. We also stress the value of study-specific supplemental testing and include multiple examples that may have value in PD research. These recommendations were submitted for comments from a range of stakeholders including Udall Center personnel, representatives of the NINDS CDE process, and experts in PD and cognition. Their feedback was incorporated into the final recommendations.

We deliberately selected assessments from other published batteries to maximize common assessments for subjects with neurodegenerative diseases. The NINDS has recently published the CDE for PD and included a recommended list of cognitive and behavioral measures [14]. The cognitive measures from the CDE focused on general cognition, and as such, are not intended to focus on domain-specific assessments. Our current proposal is designed to complement and build upon the efforts of the CDE by adding a focus on domain-specific cognitive assessments in Level II. The Montréal Cognitive Assessment (MoCA) [17], recommended for Level I screening, was included among the recommended scales of the CDE, and five of the remaining ten general cognitive scales are also included in our list of supplemental tests, thus permitting sites historically using these alternate global assessments to continue to use those measures. For behavioral evaluation, all of our recommended or supplemental tests are included in the CDE for psychiatric symptoms. Importantly, our approach is compatible with the cognitive domains and behaviors recommended by the Movement Disorders Society's diagnostic criteria for dementia associated with PD [18, 19]. Our recommendations also contain many of the same tests in the battery from the recently-closed PD-DOC and the Parkinson's Progression Markers Initiative [14, 15]. Similarly, there is broad compatibility between the approach recommended here and the Uniform Data Set used by the ADCs [10]. In contrast to the diagnostic guidelines set forth by the Movement Disorers Society Task Force recommendations, we sought to restrict our Level II assessment to a battery that could be completed in its entirety without undue burden in a research setting. Future efforts should emphasize harmonization among researchers interested in cognition and behavior in neurodegenerative disorders. Our step-wise approach with study-specific supplementation is sufficiently flexible to accommodate such collaborations. Ultimately, our proposal is intended as a first step toward a process of broader consensus.

RECOMMENDED TESTING

Level I. Screening

Level I is intended for global assessment of cognition and behavior with minimal burden on subjects or Center resources, and is recommended for all PD subjects, even for studies without a focus on cognition or behavior because of the pervasive nature of these deficits in patients with PD. For this level, we recommend the MoCA (cognition) and the Neuropsychiatric Inventory (NPI) [20] (behavior). The MoCA is a 30-point screening instrument originally designed to detect mild CI. It possesses adequate psychometric properties for the detection of CI and measures a broad spectrum of cognitive abilities that are relevant to PD. Several studies have shown that the MoCA demonstrates improved sensitivity over other general screening measures in PD patients [11, 17, 21–23] and the Parkinson Study Group Cognitive/Psychiatric Working Group has recommended the MoCA for use in PD populations over multiple alternate screening tools [24]. We note, however, that although the MoCA has good psychometric properties, this instrument alone is not sufficient to diagnose CI or dementia in patients with PD [25]. The NPI is a rater-administered, informant-based neuropsychiatric inventory that surveys a range of behavioral disturbances and is widely used by the PD research community. The NPI has been used in epidemiologic and treatment studies in both demented and non-demented patients with PD [6], although it has never been validated for any individual psychiatric disorder in PD. These measures are brief, can be administered by a range of study personnel, and require minimal

effort from patients, caregivers, and investigators However, they are not comprehensive instruments, and we encourage the use of more domain-specific measures (described in Level II) for centers with a specific focus on cognition. See Appendix for detailed characteristics of these tests.

Level II. Standard Battery

The Level II tests were chosen as the recommended standard battery for all PD subjects who are enrolled in cognitive or behavioral research protocols at our Centers. Level II testing may also be valuable for subjects who score below 26 on the MoCA, even if enrolled in a study that is not focused on cognition or behavior, in order to define better their cognitive profile. We stress that the choice of tests in Level II reflects a balance between comprehensiveness and efficiency, informed by our experience, as we strive to develop an acceptable common battery to fuel collaboration.

The nine recommended cognitive tests in Level II (Table 2) build on Level I by adding assessment of premorbid abilities and four basic cognitive domains: frontal-executive skills, memory, visual spatial abilities, and language. This battery forms the foundation for broad neuropsychological characterization. Given the high frequency of depression in PD [26], we also recommend additional characterization of mood symptoms with the Geriatric Depression Scale, 15-item version (GDS-15) [26, 27]. See Appendix for detailed characteristics of these tests.

Supplemental Testing

The testing proposed in Levels I and II establishes a step-wise common battery but clearly is not exhaustive and cannot meet the needs of all studies focused on cognition and behavior in PD. For this reason we underscore the importance of study-specific supplemental testing that may be used when research aims or clinical needs require more detailed assessment of cognitive and behavioral functions. Indeed, the supplemental tests listed in Table 2 are examples of some tests that can address more detailed cognitive features outside the scope of the Level II standard battery. However, we do not recommend that supplemental tests be administered routinely unless they for a study-specific research need, nor do we recommend that these tests be administered in their entirety or as a stand-alone battery. See Appendix for more information.

Alternative testing for severely impaired subjects

Alternative testing is recommended for subjects who, according to the best clinical judgment of the study investigators, are not capable of completing Level II testing. As a group, these individuals are difficult to evaluate, largely due to floor effects on cognitive testing. In addition to the MoCA and the NPI, we recommend the Mattis Dementia Rating Scale-2 (DRS-2) [28] as an appropriate tool to rate the level of impairment across domains in participants with substantial impairments. Some severely impaired subjects will not be able even to complete the DRS-2; however, there is the capacity to examine subscale performance in the sections that an individual is able to complete. We considered recommending additional tests designed specifically for severely impaired subjects, but rejected this approach because outcomes on these tests are difficult to compare with results from less impaired subjects.

DISCUSSION

The primary motivation for this common approach is to harmonize cognitive and behavioral characterization of subjects with PD across the clinical research programs of our two Udall

Centers and with our colleagues at other institutions to thereby promote data sharing and propel collaborative research.

Despite the advantages of promoting cross-site collaborative research, a common cognitive and behavioral approach also has limitations. On the one hand, it may require more time than some researchers think necessary to address specific research questions. Conversely, it may not cover all the specific functions of interest for some research groups. Furthermore, a common battery may exclude or place at a lower priority certain instruments favored by some researchers. We have attempted to minimize these limitations with our step-wise approach that has brief global assessments in Level I, focuses on a limited number of domain-specific assessments in Level II, and is expandable through study-specific supplemental testing.

Due to the motor impairment in PD, there is appropriate concern about the utilization of paper-and-pencil tasks that include motor and/or timed components. In the current approach, we attempted to minimize the use of such tests; however, certain tasks (including Trail Making) are validated and frequently used in this population. Nevertheless, for domains in which paper-and-pencil tasks are utilized, we also included tasks without a motor component. In addition, tasks such as Trail Making can be evaluated with regard to motor speed (Trails A) versus complex divided attention (Trails B), and scores can be adjusted accordingly. In addition, motor symptoms can be taken into account both at the level of clinical assessment and at the point of statistical analyses. Finally, depending upon the goals of the study or extent of motor impairment, inclusion of supplemental tests that have a non-motor component (e.g., Stroop) may be appropriate and useful in helping to determine whether motor or CIs are more prominent.

In conclusion, we recommend a step-wise approach to the cognitive and behavioral characterization of PD subjects to fuel collaborative research. Our approach allows an appropriately broad and harmonized assessment of cognition and behavior that is not overly burdensome to participants, and can be tailored to specific research interests. This approach already is promoting greater collaboration between our Udall Centers and our colleagues at other sites. Finally, our proposed battery was design to be compatible with other national research programs focused on neurodegenerative diseases and cognition, and potentially may be extended to clinical and health effectiveness research into brain aging, as proposed by the *National Alzheimer's Project Act* [1] and the *Alzheimer's Disease Research Summit 2012: Path to Treatment and Prevention* [2].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix: Detailed Review Of Assessments

LEVEL I

General Cognitive Screening

Montréal Cognitive Assessment (MoCA)—The MoCA is a 30-point cognitive screening instrument, originally designed to detect mild cognitive impairments. This test briefly assesses orientation, attention and concentration, memory, language, abstract verbal reasoning, and visual spatial skills. The MoCA contains items that are similar to several of the tests described in the Level II battery; however, MoCA items are less demanding and form the basis for a general assessment, but are inadequate to evaluate domain-specific functioning.

Test characteristics: The MoCA has good test-retest and inter-rater reliability, as well as good construct validity when correlated with a complete neuropsychological battery in PD patients [1]. The test protocol, administration instructions, validation data, and references are readily accessible on the website http://www.mocatest.org/, and are available for clinical and non-profit research use without cost.

Administration time: 5–10 minutes

Alternate forms: No

Normative data: Validation data and recommended cutoff scores are published on the MoCA website.

Inclusion in major PD-related studies: Parkinson's Progression Markers Initiative (PPMI), National Institute of Neurological Disorders and Stroke Common Data Elements (NINDS-CDE).

Utility for PD: Several studies have shown that the MoCA demonstrates improved sensitivity over other general screening measures in PD patients [2–6], and the Parkinson Study Group Cognitive/Psychiatric Working Group has recommended the MoCA for use in PD populations over multiple alternate screening tools [7]. It should be noted, however, that although the MoCA has good psychometric properties, this instrument alone is not considered sufficient to diagnose cognitive impairment or dementia in patients with PD [8].

Behavior

Neuropsychiatric Inventory (NPI)—The NPI is a rater-administered, informant-based neuropsychiatric inventory that broadly assesses ten neuropsychiatric domains: delusions, hallucinations, dysphoria, agitation/aggression, apathy, euphoria, anxiety, disinhibition, irritability/lability, and aberrant motor behavior [9]. Each domain is rated for severity (3-point scale) and frequency (4-point scale) of symptoms, with a single score that considers both aspects.

Test characteristics: Good content and concurrent validity, test-retest reliability, inter-rater reliability, and internal consistency have been reported [9]. Characteristics are further described on the NPI website (http://npitest.net/about-npi.html).

Administration time: 5–20 minutes, depending upon the extent of the neuropsychiatric symptoms reported by the caregiver.

Alternate forms: Although the NPI is typically administered by a clinician to an informant, there also is a self-completed version of the NPI called the NPI-Q, (also informant-based) [10], as well as a version designed for administration by nursing home personnel (NPI-NH) [11].

Normative data: Normative data do not appear to be available at this time.

Inclusion in major PD-related studies: Parkinson's Disease Data Organizing Center (PD-DOC), National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS).

Utility for PD: The NPI has been widely used in epidemiologic and treatment studies in both demented and non-demented patients with PD [12], although it has never been validated for any individual psychiatric disorder in PD.

LEVEL II

Premorbid Abilities

Inclusion of a measure that provides an estimate of premorbid cognitive abilities facilitates evaluation of changes associated with neurodegenerative disease [13–15]. Research participants vary in their innate abilities and lifetime experiences; comparison of individual test results with an individual's likely peak cognitive abilities should provide a better estimate of decline from previous functioning. For example, when an individual is highly educated, an average performance on a given test may represent a decline from prior abilities. Conversely, a person with lower lifetime educational opportunities may appear to be impaired on cognitive testing in the absence of a true decline. In particular, assessment of

subtle cognitive impairments requires increased sensitivity to individual changes in cognition.

Shipley Institute of Living Scale-2, Vocabulary—The Shipley Institute of Living Scale-2, Vocabulary [16] is a 40-item test of vocabulary knowledge in which a target word is presented along with four possible synonyms. Because vocabulary knowledge tends to be relatively stable into the eighth decade of life [17], it can serve as a surrogate for premorbid cognitive abilities [14,15].

Test characteristics: The Shipley has good test-retest reliability and internal consistency, and concurrent validity has been demonstrated consistently by moderate to high correlations with both intelligence batteries and achievement tests [16].

Administration time: Typically 5–10 minutes; however, this measure is self-paced and can take longer.

Alternate forms: No; however, for the purposes of obtaining a premorbid estimate of intellectual functioning, this measure can be administered at baseline only for longitudinal studies.

Normative data: Age-based normative data are available in the Shipley-2 manual [16].

Inclusion in major PD-related studies: None

Utility for PD: Although the Shipley has not been specifically validated for use in PD populations, vocabulary scores have been widely administered to older adults as a measure of crystallized ability [18]. The Shipley is considerably briefer than full intelligence batteries and is self-administered; therefore, it is generally well-tolerated in aging and brain-injured populations [19].

Frontal-Executive

Attention, concentration, and working memory are supported primarily by the frontal lobes and frontal pathways [20–22]. Simple attention does not frequently appear to be compromised pervasively in patients with PD; however, more complex aspects of attention and working memory, including divided attention, planning, response inhibition, working memory, mental flexibility, and abstract reasoning commonly are impaired [23–26]. For basic assessment of patients with PD, we recommend measures that entail both motor and auditory complex sequencing, working memory, and processing speed. If additional focus on higher executive functions, such as abstract reasoning, is desired, supplemental executive tests (described later) may be added.

The Trail Making Test–Parts A and B—The Trail Making Test [20–22] is a commonly used neuropsychological instrument with demonstrated clinical and research utility that measures attentional speed, sequencing, visual search, and mental flexibility [27]. Part A assesses simple graphomotor sequencing of numbered circles. Part B, a test of divided attention, assesses complex graphomotor sequencing of alternating numbers and letters.

Test characteristics: The Trail Making Test is established as a highly sensitive test for brain damage [22]. Trails B is correlated with other tests of executive function [22] and has been associated with activation of the left dorsolateral prefrontal cortex, prefrontal gyrus, cingulate gyrus, and medial frontal gyrus [28]. High inter-rater reliability is reported [22], as well as relative insensitivity to practice effects [27].

Administration time: 4–12 minutes

Alternate forms: No

Normative data: The Trailmaking Test has been the focus of many normative studies [21,22]. We recommend use of the Mayo Older Adult Normative Studies (MOANS) [29,39], which are psychometrically sound and facilitate comparison across a number of neuropsychological instruments.

Inclusion in major PD-related studies: NACC UDS

Utility for PD: In patients with PD, few studies report impairments on Trails A, whereas Trails B is typically impaired [24–26, 31]. McDowd and colleagues recently observed that non-demented patients with PD performed better than patients with Alzheimer's disease, but worse than healthy older adults, on both Trails A and B [32]. Because this test has a strong motor and timed component, evaluation of Trails B alone may not provide an accurate portrayal of visuospatial working memory in patients with PD. Rather, subtracting Trails A from Trails B or statistically controlling for motor impairment may provide a better indication of complex visual attention.

Digit Symbol-Coding—Digit Symbol-Coding (from the Wechsler Adult Intelligence Scale®, 3rd edition [WAIS®–III] [33])[a] is a measure of graphomotor working memory and processing speed. For this test, subjects are shown a key that consists of unique digit-symbol pairs and then complete a matrix consisting of numbered boxes paired with empty boxes in which they are asked to write the corresponding symbol.

Test characteristics: High test-retest and inter-rater reliability, as well as good construct validity, have been reported for Digit Symbol-Coding [34].

Administration time: 3 minutes

Alternate forms: No.

Normative data: The WAIS-III Manual provides age-adjusted normative data.

Inclusion in major PD-related studies: PD-DOC, PPMI

Utility in PD: Non-demented patients with PD have been shown to perform better than patients with AD but worse than healthy older adults on this task [32]. Significant associations between performance on Digit Symbol and CSF levels of Brain-Derived Neurotrophic Factor (BDNF), $A\beta_{42}$ and $A\beta_{42}$/total tau (t-tau) have been observed in non-demented patients with PD [35]. A variation of this test has been used to investigate the effects of therapeutic interventions [36], predict driving abilities [37], and characterize the effects of depression on bradyphrenia [38] in patients with PD.

Letter-Number Sequencing—Letter-Number Sequencing (LNS; from theWAIS®–III and the Wechsler Memory Scale®—Third Edition [WMS®–III]) is a measure of auditory working memory and processing speed. For this test, the subject hears a combination of

[a]The Wechsler Adult Intelligence Scale and the Wechsler Memory Scale are currently in their 4th Edition (published 2008 and 2009, respectively). Given that the WAIS-III and WMS-III have been in use since 1998, use of these scales may facilitate consistency across sites.

single-digit numbers and letters and is asked to repeat the numbers in ascending order followed by the letters in alphabetical order.

Test characteristics: No significant practice effects are reported with LNS in middle- to older-aged adults, suggesting that this measure can be readministered effectively in a longitudinal sample [39]. Good inter-rater reliability, as well as good construct validity, have also been reported for LNS [34].

Administration time: 5 minutes

Alternate forms: No

Normative data: The WAIS-III Manual provides age-adjusted normative data.

Inclusion in major PD-related studies: PD-DOC, PPMI

Utility in PD: Functional magnetic residence imaging (fMRI) suggests that LNS is sensitive to age-related changes in cognition. Emery and colleagues [40] recently reported that older adults demonstrated more extensive activation in the bilateral prefrontal cortical working memory network than younger adults when completing this task, relative to a memory maintenance task. Although this test has not been used extensively in the investigation of PD, our clinical experience suggests that LNS likely has great potential with this population, and psychometric studies suggest that it is sensitive to the effects of the catechol-O-methyltransferase (COMT) valine-158, methionine polymorphism (val(158)met) and tolcapone [41].

Memory

PD-associated memory performance deficits have been attributed largely to dysfunction of the fronto-striatal pathways resulting from characteristic dopamine loss in the basal ganglia [42–45]. Conventionally, it was postulated that the resulting dysexecutive syndrome primarily interfered with the ability to recall information on demand (free recall), while generally sparing recognition ability [44, 46, 47]. More recently, however, disruptions in both encoding [42,48] and recognition [47, 49–51] have been demonstrated in PD patients with and without dementia. Patterns of responding (impaired organizational strategies and positive response bias) again suggest that these deficits are primarily related to frontal-executive dysfunction rather than memory loss mediated by the temporal lobes [47, 49, 52]. However, PD has also been associated with temporal and parietal hypoperfusion and atrophy [53–59], and some PDD patients also have neuropathologic changes consistent with AD [31, 60, 61]. As a result, some individuals with PD may present with AD-like memory impairments that are independent of executive dysfunction [48]. In addition, memory performance pattern may be dependent upon initial motor symptom presentation and/or early laterality of motor symptoms [62, 63]. Given the scope of memory problems potentially associated with PD, utilization of a task that provides clues as to the origin of the memory dysfunction (encoding, retention, retrieval) is essential for PD-related cognitive research.

Hopkins Verbal Learning Test-Revised—The Hopkins Verbal Learning Test-Revised (HVLT-R) [64] is a 12-item list-learning task that permits examination of learning, free recall, and recognition. Because the words are selected from three semantic categories, higher-order organizational strategies that require effective executive functioning can be evaluated. In addition, learning slope and cumulative word learning can be assessed by comparing scores across the three learning trials. The initial encoding trials are followed by

free recall delay and recognition trials, which help to clarify whether the memory problems are associated with encoding or retrieval processes.

Test characteristics: Good alternate forms and test-retest reliability have been established [64–66]. The HVLT-R also has good convergent validity with similar measures, including the California Verbal Learning Test (CVLT) [67, 68], yet the shorter administration time increases the likelihood that it will be well-tolerated by patients. It is thus frequently used in elderly populations [68].

Administration time: 7–10 minutes, excluding a 20–25 minute delay.

Alternate forms: Six parallel forms are available.

Normative data: Normative studies have been completed in older adults [64, 69, 70].

Inclusion in major PD-related studies: PD-DOC, PPMI

Utility in PD: List-learning test performance correlates with motor symptoms, processing speed, independent activities of daily living, mood, and executive functions in PD [71–74], and is a strong predictor of functional outcome in older adults [75]. Specifically, the HVLT-R discriminates between PD and AD [76], and can be used to identify subsets of PD patients with different memory profiles [48].

Visual Spatial

Visuospatial dysfunction, which may be among the first cognitive changes noticed in PD [59, 77], is predictive of both cognitive decline and eventual dementia [78, 79]. The neuroanatomic substrate of defective visuospatial processing in PD is not well understood, but is hypothesized to result from asymmetric dopamine loss in the right basal ganglia [80], deficits in the dorsolateral prefrontal pathways with resulting structural and functional changes in the parietal lobes [81, 82], disruptions in the fronto-striatal loop [83], or other neuropathologic changes in the temporal, parietal, and/or occipital lobes [84]. Spatial processing and concept formation are difficult to assess in patients with PD, however, given the motor component often required to complete spatial tasks. In addition, impaired executive processes may contribute to visuomotor dysfunction and make it difficult to assess pure spatial performance [85, 86]. In order to address both of these issues, we include two visuospatial measures with varying levels of motor and frontal-executive demand.

Judgment of Line Orientation—The Judgment of Line Orientation (JoLO) [87] is considered to be a more “pure” visual-perceptual task that has a minimal motor component and does not require substantial higher-order organizational abilities [88]. The test asks the subject to match pairs of angled lines to a display array of lines.

Test characteristics: Venderploeg et al. [89] found the 15-item short form method (which involves doubling the short form score) to be a well-tolerated, valid, and reliable method of test administration. High test-retest reliability and an absence of practice effects in both PD patients and controls have been demonstrated [88]. Good construct validity has also been established with the JoLO [90]; performance on this task correlates with tests that require visual perception and spatial updating [91].

Administration time: 5–10 minutes

Alternate forms: Yes. To reduce subject fatigue, we recommend using a 15-item short form, in which either the odd or even numbers are given; these can be administered as parallel forms [89].

Normative data: MOANS age-based normative data are available and recommended to facilitate comparison across tests [92].

Inclusion in major PD-related studies: PD-DOC, PPMI

Utility in PD: Both global score and detailed error classification [93] can be useful in discriminating between patients with PD, AD, and normal controls. For example, individuals with PD may demonstrate specific error profiles (e.g., fewer "simple" errors and more complex intraquadratic errors), relative to controls and patients with AD [88, 94].

Clock Drawing Test.[b]—The Clock Drawing Test (CDT) [22] is a brief, well-tolerated measure that is used to assess visuospatial and executive difficulties in which participants are asked to draw a clock to command [95, 96]. We recommend extracting the CDT from the MoCA for this task.

Test characteristics: The CDT has good interrater and test-retest reliability, as well as good concurrent validity with the MMSE and executive function measures [96–99].

Administration time: Given as part of the MoCA (see above).

Alternate forms: No

Normative data: Limited age-based normative data are available for the CDT using the 10-point scoring system [100]; however, cut-off scores rather than means are frequently used [22].

Inclusion in major PD-related studies: PPMI, NINDS-CDE (as part of the MoCA)

Utility for PD: Individuals with PD may be more likely to perform poorly on complex visuo-construction tasks that require executive organizational skills. The CDT appears to be sensitive to cognitive changes associated with PD and can discriminate between MCI due to AD and PD [101]. It has also been shown to be sensitive to changes associated with treatment in PD medication trials [102, 103]. Scoring required for the MoCA is relatively simple; however, other more detailed scoring techniques exist and may be helpful in further discriminating PD from controls and other neurodegenerative diseases (*e.g.*, patients with PD are more likely to make stimulus-bound errors than patients with AD) [97]. We thus recommend that the ten-point scoring system be used for patients with PD [98, 99].

Language

Although language dysfunction is not typically identified as a core clinical feature of PD, deficits in both verbal fluency and naming have been reported even early in the disease process [104–107]. Language deficits may be a consequence of the dysexecutive syndrome commonly associated with PD [108–111] or secondary to impaired speech production

[b]Many neuropsychological tests measure multiple cognitive domains. For example, the CDT measures both spatial functioning and executive skills, while verbal fluency (particularly phonemic fluency) can reflect language ability and/or executive functions. We thus recommend evaluating performance across tasks in relation to performance on other tasks to determine whether individual performance is related to primary deficits in one or more areas of cognition.

resulting from motor dysfunction and bradykinesia [112]. Others have suggested a specific disruption of the semantic networks that leads to language impairment [107]. Thus, pure language impairment may be present in PD (although to a lesser degree than other deficits); alternatively, compromised language performance may reflect deficits in other cognitive domains [26]. In either case, neuropsychological characterization of PD would be incomplete without language assessment. For this reason, we recommend assessing both confrontation naming (a more "pure" test of anomia) and verbal fluency (which has a strong executive component).

Short Boston Naming Test—One of the most commonly used visual confrontation naming measures is the Boston Naming Test (BNT) [113], in which the subject is shown a picture of an object and is asked to provide the name of that object. We are recommending the use of an abbreviated form of the BNT (Short BNT) to ameliorate frustration and fatigue often observed in patients with lower levels of education, lower intellectual levels, or severe cognitive impairments [114, 115].

Test characteristics: The BNT has sound psychometric properties, including adequate test-retest reliability [116] and concurrent validity [117] as well as clinical utility in discriminating different forms of dementia [118]. The current version of the BNT contains a 15-item form validated by Mack and colleagues [119, 120].

Administration time: 5 minutes

Alternate Forms: Yes [114, 115, 119, 120]

Normative data: Multiple normative studies are available for verbal fluency measures [21, 22].

Administration time: 5 minutes

Inclusion in major PD-related studies: PD-DOC, NACC UDS

Utility in PD: There is evidence that naming is impaired in patients with PD both with and without dementia [59, 106]; however, nonspecific effects may contribute to anomia, which is common to many neurodegenerative diseases and traumatic brain injury [20, 121].

Verbal fluency skills depend heavily on retrieval strategies (e.g., clustering words by sound or meaning and switching to a new clustering strategy when the current strategy is exhausted), knowledge of semantic relationships, and long-term memory for words [32]. They have been used to assess semantic processing, word knowledge, and executive functions [32]. The overall pattern of test results (as well as the relative impairment on semantic vs. phonemic fluency) determines whether impaired verbal fluency represents a primary language or executive deficit. Verbal fluency tasks have been used in the study of PD to assess the therapeutic effects of cognitive training, rasagiline [122], duodenal levodopa administration, and deep brain stimulation [123], as well as the correlates of gender, laterality of motor impairment, and freezing of gait [124].

Phonemic verbal fluency—We recommend FAS [20–22] as the standard phonemic verbal fluency task. Respondents are instructed to freely generate as many words as possible in 60 seconds that begin with a specified letter.

Test characteristics: Phonemic verbal fluency tests have been shown to exhibit adequate internal consistency and test-retest reliability in healthy adults [125] and good inter-rater and test-retest reliability in patients with multiple sclerosis [126]. It is likely that phonemic verbal fluency performance is affected by age and education but not by gender [20].

Administration time: 4 minutes

Alternate forms: Other letter combinations (e.g., CFL) have been validated; however, raw scores on these different forms may not be equivalent. We note that Ruff et al. suggest that z-scores and percentiles may be equivalent for the FAS and CFL versions of phonemic verbal fluency [125].

Normative data: Many normative studies are available for verbal fluency measures [21, 22].

Inclusion in major PD-related studies: PD-DOC, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonsism (DATATOP).

Utility in PD: Phonemic verbal fluency activates the left inferior and middle frontal cortices, anterior cingulate cortex, putamen, thalamus and cerebellum [127]. Interestingly, right cerebellar lesions impair phonemic verbal fluency and, to a lesser extent, semantic verbal fluency, corroborating a role for lateralized posterior involvement in verbal fluency [128]. Patients having undergone pallidotomy performed worse on phonemic verbal fluency relative to baseline evaluation, especially if lesions were mostly in the internal pallidal segment rather than the external pallidal segment or internal capsule [122].

Semantic verbal fluency—We recommend using the category of “animals” as the standard semantic verbal fluency task. Respondents are asked to produce as many animal names as possible in 1 minute.

Test characteristics: Semantic verbal fluency test-retest reliability is adequate, and performance appears to be influenced by age, education, and IQ but not by gender [20, 129]. Performance on semantic verbal fluency appears to be sensitive to the presence of dementia [20].

Administration time: 2 minutes

Alternate forms: Other semantic categories have been validated; however, these are not considered to be equivalent measures.

Normative data: Many normative studies are available for verbal fluency measures [21, 22].

Inclusion in major PD-related studies: PD-DOC, PPMI, DATATOP, NACC UDS

Utility in PD: There are conflicting reports concerning the relative impairment of semantic and phonemic fluency in PD patients as compared to controls and other dementia types [130]; however, semantic verbal fluency may be more strongly associated with dementia in PD patients [131]. COMT val(158)met status appears to modulate left inferior frontal gyrus activation during a semantic verbal fluency task [132].

Behavioral

Given the high frequency of depression in PD [133], we recommend that the Level II evaluation include a measure specifically to assess mood *in addition to* the NPI.

Geriatric Depression Scale –15 item (GDS-15)—The GDS-15 is a 15-item, self-administered instrument that is widely used in depression, including in patients with PD [134, 135]. Each item is scored as a 0 or 1, with higher scores indicating increasing depression severity. The GDS-15 does not include a suicide item, but is brief and easy for patients to use, as it utilizes a "yes/no" format. The GDS has fewer physical symptoms than most depression rating scales, so it is less subject to symptom overlap in PD patients.

Test characteristics: The GDS-15 has good sensitivity and specificity for detecting depression in older adults, and correlates highly with scores on other depression measures [136]. Moderate internal consistency retest reliability has been reported [137].

Alternate forms: No

Normative data: Normative data do not appear to be available at this time.

Inclusion in major PD-related studies: PD-DOC, PPMI, NACC UDS

Utility for PD: The GDS also has good sensitivity and predictive value in PD [133]. It performs well in patients with mild-moderate cognitive impairment and is entirely in the public domain. A cutoff score of 5 has been recommended in PD to indicate clinically significant depressive symptoms [138, 139].

SUPPLEMENTAL TESTS

Additional measures may be appropriate for more detailed evaluation of specific cognitive and behavioral domains in patients with PD. These measures may be added to the core Level II battery as required for study aims and/or more detailed clinical assessments. Given that these are supplemental measures to be added at the discretion of the clinician and/or study site, we have not described these measures in the same detail as the tests above. The reader interested in descriptions and test characteristics is referred to MD Lezak, DB Howieson, and DW Loring, Neuropsychological Assessment (Fourth Edition), New York: Oxford University Press, 2004 [20], and to E Strauss, EMS Sherman, and O Spreen, A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary (Third Edition), New York: Oxford University Press, 2006) [22].

General cognitive function

Included in the Supplemental tests are a number of measures of general cognitive abilities that may be administered in addition to the MoCA due to their frequency of use in both older and PD populations: the Mattis Dementia Rating Scale-2 (DRS-2) [140], the Mini-Mental State Exam (MMSE) [141], Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) [142], Scales of Outcomes of Parkinson's Disease–Cognition (SCOPA-cog) [143], and the Parkinson's Disease Cognitive Rating Scale (PD-CRS) [144]. However, these measures may not be as sensitive to PD-related changes in global functioning as the MoCA, and thus are not recommended as substitutes [2, 7].

Frontal-Executive

Given the frequency of dysfunction reported in PD patients in the areas of attention, concentration, working memory, and executive abilities, more comprehensive exploration of

these cognitive domains may be a primary focus of PD-related neuropsychological research. Thus, the inclusion of additional measures to determine complex scanning and visual tracking and processing speed (Target Cancellation [20], Symbol Search [WAIS-III]), sustained and selective attention (Stroop test [22]), working memory/mental control (Digit Span [WAIS-III]), planning and complex executive functions (Tower of London [145], Wisconsin Card Sorting Test [146]), or verbal reasoning and concept formation abilities (Similarities [WAIS-III]) may be appropriate.

Memory

More detailed memory assessment may be undertaken when research aims call for comparison of list-learning performance and story recall (Logical Memory [WMS-III]), examination of proactive and retroactive interference effects (California Verbal Learning Test-II [CVLT-II] [147] or Rey Auditory Verbal Learning Test [RAVLT] [148]), performance following semantic cues (CVLT-II), visual memory (Visual Reproduction [WMS-III], Benton Visual Retention Test [BVRT] [149]), and comparison of right- vs. left-sided recognition performance (Recognition Memory Test [150]).

Visual Spatial

If more in-depth assessment of visuospatial functioning is desired, the Rey Complex Figure Test [151] requires a higher level of visual organization (as well as memory and executive components), Block Design (WAIS-III) may provide more information concerning conceptual-spatial processing, and the Hooper Visual Organization Test [152] offers a measure of visual integration that separates the perceptual spatial component from motor abilities. For dementia-specific research, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [153] construction tasks and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [154] complex figure and line orientation subtests may be appropriate, particularly for more impaired groups.

Language

For additional language measures, the Narrative Writing Sample ("cookie theft" from the Boston Diagnostic Aphasia Examination) [155] can provide insight into changes in semantic processing, perceptual abilities, and motor problems (micrographia). Alternate semantic fluency tasks, including fruits and vegetables and/or supermarket items, may provide supplementary information concerning semantic strategies.

Behavior

Depending upon study goals, more in-depth assessment of mood and behavior also may be warranted. The Hamilton Depression Scale (HAM-D) [156], Beck Depression Inventory-II (BDI-II) [157], Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), part I [158], Starkstein Apathy Scale [159], or the Hospital Anxiety and Depression Scale (HADS) [160] may be added to the Level II behavior assessments for this purpose.

QUALITY CONTROL

For all levels of assessment, appropriate measures to ensure quality control are strongly recommended. While the MoCA may be administered by a range of study personnel, domain-specific cognitive tests should be administered by trained psychometrists with regular performance review and ongoing auditing of assessment procedures. In addition to quality standards for test administration procedures, careful control of testing conditions should be undertaken. For example, given the potential for fluctuations in cognition in

participants with Lewy Body disease, documentation of the current cognitive state of the participant should be made at each study visit. Further, although testing participants with PD while on medication is preferred, thorough documentation of medication dose, timing, and those not on medication should be undertaken. For longitudinal studies, careful review of prior test conditions (on/off medication, cognitive fluctuation status) will permit reassessment under similar conditions.

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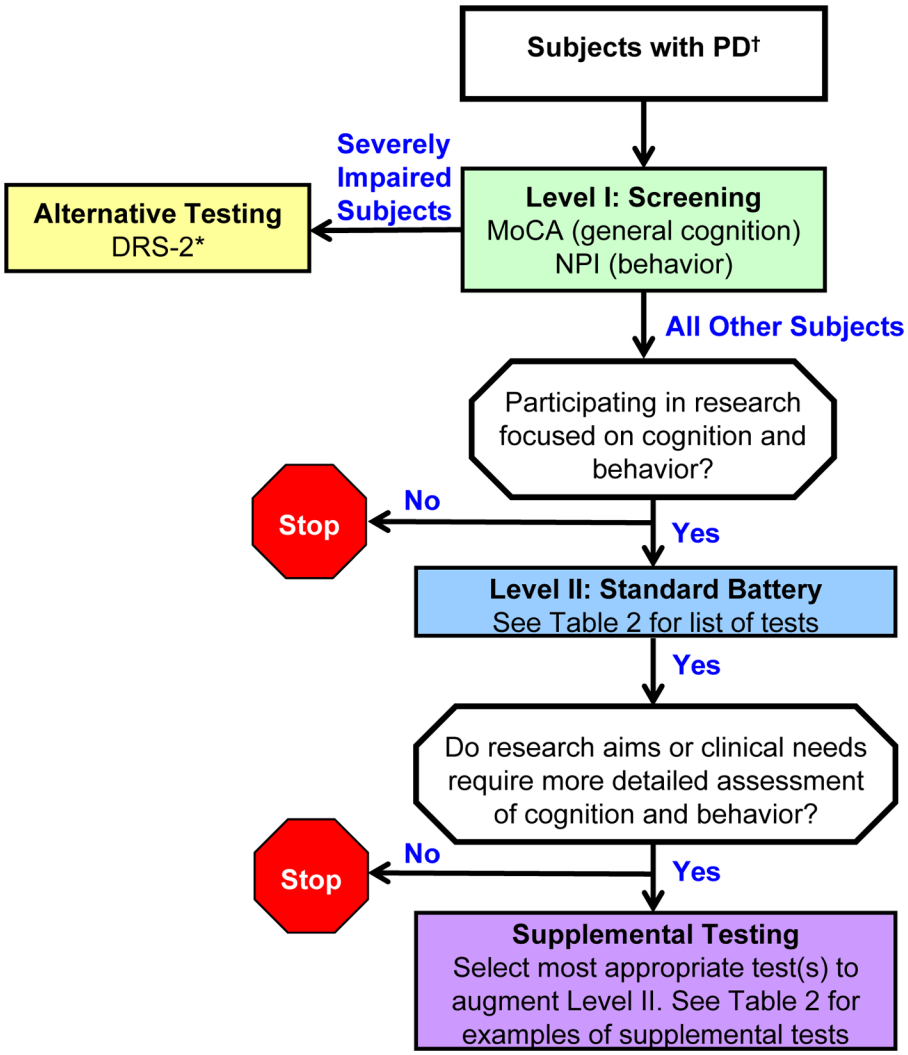

Figure. Penn-UW recommendations for cognitive and behavioral testing of PD subjects

Our recommended strategy for assessing cognition and behavior are shown. Refer to Table 2 for the test battery recommended for Level II and for examples of additional tests to consider for Supplemental Testing. ***Abbreviations.*** MoCA: Montréal Cognitive Assessment. NPI: Neuropsychiatric Inventory. DRS-2: Mattis Dementia Rating Scale-2.

†Meet United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria [30].

*While patients may not be able to complete the DRS-2, there is the capacity to examine subscale performances in the sections that they are able to complete.

Table 1

Comparison of Penn-UW Battery with Major Studies of Parkinson's Disease or National Programs

		TEST	DATATOP	PD-DOC	PPMI	NINDS CDE	NACC UDS	Penn-UW	
								Level I	Level II
GENERAL COGNITION		Clinical Dementia Rating					X		
		Mattis Dementia Rating Scale-2				X			
		Mini–Mental State Exam	X	X		X	X		
		Montréal Cognitive Assessment			X	X		X	
PREMORBID FUNCTION		Shipley Institute of Living Scale-2, Vocabulary							X
DOMAIN-SPECIFIC COGNITION	**Frontal-Executive**	Digit Span	X				X		
		Letter-Number Sequencing		X	X				X
		Odd Man Out	X						
		Symbol-Digit Modalities	X		X				
		Digit symbol–Coding					X		X
		Trail Making					X		X
	Memory	Hopkins Verbal Learning Test– Revised		X	X				X
		Logical Memory					X		
		Selective Reminding Test	X						
	Visual Spatial	Clock Drawing Test			X	X			X
		Judgment of Line Orientation		X	X				X
		New Dot	X						
	Language	Phonemic Verbal Fluency	X	X					X
		Semantic Verbal Fluency	X	X	X		X		X
		Short Boston Naming		X			X		X
BEHAVIOR/AFFECT		Geriatric Depression Scale, 15-Item		X	X		X		X
		Hamilton Depression Scale	X						
		MDS-UPDRS, Part I			X				
		Neuropsychiatric Inventory		X			X	X	
		QUIP (Weintraub et al)			X				

	TEST	DATATOP	PD-DOC	PPMI	NINDS CDE	NACC UDS	Penn-UW	
							Level I	Level II
	State-Trait Anxiety Inventory			X				

Abbreviations. DATATOP: Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonsism; PD-DOC: Parkinson's Disease Data Organizing Center; PPMI: Parkinson's Progression Markers Initiative; NINDS-CDE: National Institute of Neurological Disorders and Stroke Common Data Elements; NACC UDS: National Alzheimer's Coordinating Center Uniform Data Set. QUIP: Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

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Table 2

Penn-UW Recommended Screening and Standard Battery with Examples of Supplemental Tests

LEVEL I: SCREENING						
General Cognition	**Premorbid**	**Frontal- Executive**	**Memory**	**Visual Spatial**	**Language**	**Behavior**
Montréal Cognitive Assessment (MoCA)						Neuropsychiatric Inventory (NPI)
LEVEL II: STANDARD BATTERY						
General Cognition	**Premorbid**	**Frontal-Executive**	**Memory**	**Visual Spatial**	**Language**	**Behavior**
	Shipley Institute of Living Scale-2, Vocabulary	Trail Making Test	Hopkins Verbal Learning Test-Revised (HVLT-R)	Judgment of Line Orientation (JoLO)	Short Boston Naming Test	Geriatric Depression Scale-15 item (GDS-15)
		Digit Symbol-Coding[1]		Clock Drawing[2]	Phonemic verbal fluency (FAS)	
		Letter-Number Sequencing[1]			Semantic verbal fluency (Animals)	
EXAMPLES of SUPPLEMENTAL TESTS						
General Cognition	**Premorbid**	**Frontal-Executive**	**Memory**	**Visual Spatial**	**Language**	**Behavior**
Mattis Dementia Rating Scale-2 (DRS-2) *		Target Cancellation	Logical Memory[3]	Rey Complex Figure Test	Narrative Writing Sample[6]	Hamilton Depression Scale (HAM-D)
Mini Mental State Exam (MMSE)		Symbol Search[1]	California Verbal Learning Test (CVLT)	Block Design[1]	Semantic verbal fluency (fruits, vegetables, super-market items)	Beck Depression Inventory-II (BDI-II)
AD Assessment Scale, Cognitive (ADAS-Cog)		Stroop (Golden version)	Rey Auditory Verbal Learning Test (RAVLT)	Hooper Visual Organization Test		MDS-sponsored revision of Unified PD Rating Scale (MDS-UPDRS), part 1
Scales of Outcomes of PD Cognition (SCOPA-cog)		Digit Span[1]	Visual Reproduction[3]	Complex Figure and Line Orientation[4]		Starkstein Apathy Scale
PD Cognitive Rating Scale (PD-CRS)		Tower of London	Benton Visual Retention Test (BVRT)	Constructional Praxis[5]		
		Wisconsin Card Sort Test	Recognition Memory Test (RMT)			Hospital Anxiety and Depression Scale (HADS)
		Similarites[1]				

[1]From Wechsler Adult Intelligence Scale-III.

[2] From Wechsler Memory Scale-III.

[3] Extracted from MoCA; additional scoring required.

[4] From Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

[5] From Consortium to Establish a Registry for AD (CERAD) battery.

[6] From Boston Diagnostic Aphasia Examination (BDAE).

[*] Also recommended for severely impaired individuals; see Figure legend.