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**SHORT REVIEW**

# A Précis of Recent Advances in the Neuropsychology of Mild Cognitive Impairment(s) in Parkinson's Disease and a Proposal of Preliminary Research Criteria

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**Abstract**

Cognitive changes of Parkinson's disease (PD) manifest earlier and are more heterogeneous than previously appreciated. Approximately one-third of patients have at least mild cognitive changes at PD diagnosis, and subtle changes might be appreciable among those at risk for PD. Executive dysfunction is the most common cognitive change, but other phenotypes exist. Pathobiologic and potential prognostic differences among cognitive phenotypes remain poorly understood. Progress in the neuropsychology, epidemiology and pathobiology of mild cognitive impairment (MCI) in PD is hampered by lack of diagnostic criteria. This study proposes preliminary research criteria for two categories of PD non-dementia cognitive impairment. (*JINS*, 2011, *17*, 393–406)

**Keywords:** Lewy body disease, Dementia, Memory disorders, Executive function, Attention, Biological markers

## INTRODUCTION

Neuropsychological measures alone generally fail to distinguish Parkinson's disease dementia (PDD) from dementia with Lewy bodies (DLB) (Metzler-Baddeley, 2007; Tröster, 2008), though subtle qualitative differences between the two conditions occasionally emerge (Filoteo et al., 2009). PDD and dementia with Lewy bodies (DLB), both synucleinopathies, might be distinct entities or one whose clinical manifestations vary simply as a function of the temporal and spatial distribution of the same neuropathologic features. Decade-long debate about the distinction between PDD and DLB has become more subdued (Aarsland, Londos, & Ballard, 2009; McKeith, 2009). Instead, among recent emphases in neurobehavioral PD research are the identification of mild cognitive deficits in PD, detection of cognitive deficits in newly diagnosed PD, and prediction of PDD (Marder, 2010). It is these recent emphases on milder cognitive impairment and their potential neuropathologic, neuroimaging, and genetic correlates that are the subject of this short review. There is need to review and clarify criteria for mild cognitive impairment (MCI) in PD, and this study offers preliminary research criteria for consideration and empirical evaluation.

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## NEUROPSYCHOLOGICAL DYSFUNCTION IN EARLY PD AND IN THOSE AT RISK FOR PD: A SHIFT IN PERSPECTIVE

That neuropsychological declines accompany PD without dementia has been appreciated for some time. Studies in the 1980s and 1990s, though informing of the typical or "average" frontal-subcortical pattern of PD cognitive impairment, included patients with normal and mildly impaired cognition in PD groups without dementia, and confused early and mild disease (Levin & Katzen, 1995), thus potentially underestimating the extent of dysfunction and obscuring cognitive heterogeneity. Especially in the last 5 years there has been a shift in perspective, such that studies have attempted to isolate subgroups of PD with and without cognitive dysfunction (Figure 1) and to define the types of deficits observed.

Recent studies have attempted to elucidate extent and nature of cognitive impairments at or near the time of PD diagnosis. Three studies have shown that approximately one third of patients with PD have cognitive decrements on formal neuropsychological testing already at or near the time

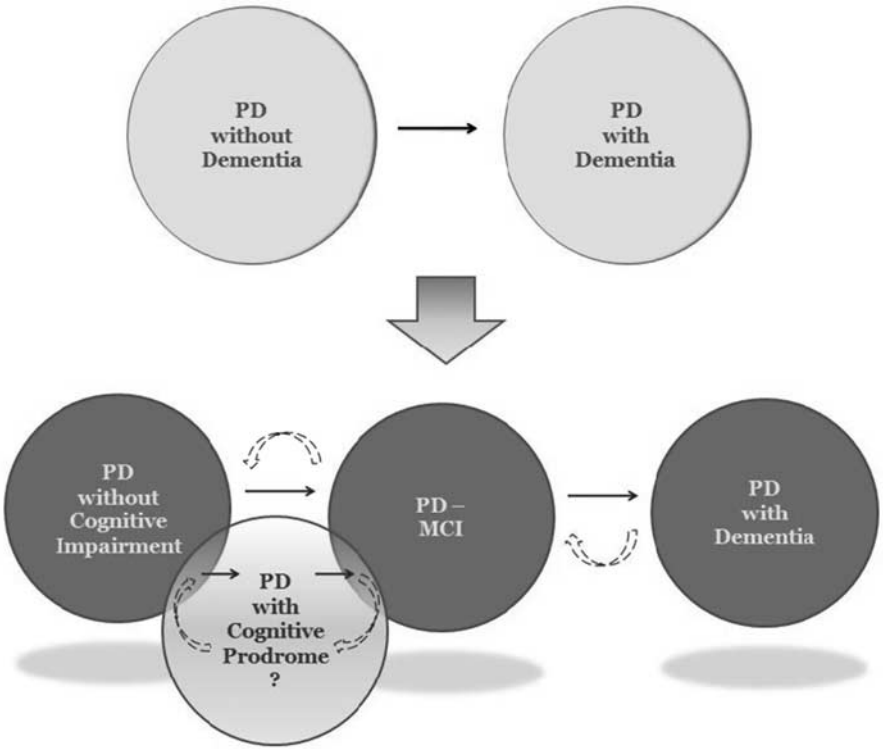


**Fig. 1.** Schematic of shift in the conceptualization of Parkinson's disease (PD) without dementia and its progression to dementia.

of PD diagnosis, even though they used a variety of tests and impairment criteria. In the CamPaIGN cohort (Foltynie, Brayne, Robbins, & Barker, 2004) it was found that 36% of 159 newly diagnosed PD patients (mean age = 70.6 years; mean age at diagnosis = 70.3 years; mean UPDRS motor score = 26/108) had cognitive impairment defined by one or more of: MMSE (<24/30), CANTAB modified Tower of London (ToL; <8/14) and pattern recognition (PRM; <16/24). Among those persons with MMSE ≥ 24 who completed both other tasks ($n = 134$), 10% were impaired on the ToL only, 9% were impaired on PRM only, and 12% were impaired on both tasks (31% overall, non-dementia impairment rate).

A study of 115 newly diagnosed PD patients with MMSE ≥ 24 (mean age = 66.2 years; mean disease duration 18.8 months; mean UPDRS motor score = 17), used a wide-ranging neuropsychological test battery (Muslimovic, Post, Speelman, & Schmand, 2005). By defining impairment as a score ≥2 *SD* below age appropriate norms, 24% of patients were impaired on at least three tests, and 39% were impaired on at least two tests (100% of patients had impairments on one or more tests). Most common were impairments on tests of attention and executive functions, consistent with the report that executive dysfunction (defined by poor performance on letter, category, and/or alternating verbal fluency) are common (41%) in PD (Kulisevsky, Pagonabarraga, Pascual-Sedano, Garcia-Sanchez, & Gironell, 2008). Another study (Elgh et al., 2009) evaluated eight domains of cognition and defined impairment in a domain as more than 50% of single test results in a domain being ≥1.5 *SD* below normative means. Among 88 patients (MMSE ≥ 24; mean age = 68.1 years; mean UPDRS motor score 24; disease duration and age at diagnosis not provided), 30% had impairments in one or more domains of cognition. Overall, although studies have defined cognitive impairments on the basis of different tests and cutoff scores in PD patients near time of diagnosis, they have yielded fairly comparable estimates of the prevalence of cognitive changes.

Findings of cognitive changes near the time of PD diagnosis raise the question whether subtle cognitive decrements occur before PD diagnosis. One study examined cognition in persons defined as "at risk" for PD (Hawkins et al., 2010). Using a sample of persons 50 years or older who did or did not have a first degree relative with PD, groups without and with hyposmia, a common finding in early PD, were identified. Ninety-eight hyposmic and 50 normosmic subjects underwent dopamine transporter (DAT) scanning and neuropsychological evaluation. All 17 patients with DAT abnormalities were hyposmic (and, thus, 17/98 hyposmic patients had DAT abnormalities). Hyposmic subjects with DAT abnormalities (presumably at greatest risk for PD) performed significantly more poorly on tests of processing speed (WAIS-III) and executive functions (Trailmaking, semantic and letter verbal fluency) than hyposmic subjects without DAT abnormalities. In contrast, groups with and without DAT abnormalities did *not* differ on measures of verbal and visual memory, naming, and visuospatial reasoning and construction.

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## MILD COGNITIVE IMPAIRMENT IN PD

Instead of studying cognitive impairment in early PD (near time of diagnosis), other studies have attempted to define the domains of cognition compromised in mild cognitive impairment. Attempts to apply the concept of mild cognitive impairment (MCI) from Alzheimer's disease (AD) research to PD, although complicated by methodological and conceptual challenges (Dubois, 2007; Fernandez, Crucian, Okun, Price, & Bowers, 2005; Tröster, 2008), have borne fruit by highlighting heterogeneity of pre-PDD cognitive impairment. These studies are based on the idea that MCI is not a disease state but a syndrome and have generally followed recent classification schemes of MCI (i.e., amnestic *vs.* non-amnestic and single domain *vs.* multiple domain). Studies have shown a prevalence of MCI in PD of approximately 15–62% (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009; Caviness et al., 2007; Hoops et al., 2009; Janvin, Larsen, Aarsland, & Hugdahl, 2006; Mamikonyan et al., 2009; Naismith, Pereira, Shine, & Lewis, 2010; Sollinger, Goldstein, Lah, Levey, & Factor, 2010; Song, Kim, Jeong, Song, & Lee, 2008).

The wide prevalence range likely reflects differences in MCI definition and sample characteristics (see Table 1). The highest rates are reported by studies that used either clinician consensus or impairment on a single test to define MCI. The lowest rate was reported when a 2 *SD* below the mean score cutoff was used. Most common are estimates of approximately 30% and generally, single domain MCI is more common than multiple domain MCI and non-amnestic MCI is more common than amnestic MCI. One study found that amnestic MCI is more common when single and multiple domain estimates are combined (Aarsland et al., 2010). In a retrospective study of eight patients with autopsy verified Lewy body disease (7 with clinical DLB), five initially had non-amnestic MCI (Molano et al., 2010). Early detection of non-amnestic MCI is important given preliminary evidence that atomoxetine, a selective norepinephrine reuptake inhibitor (Marsh, Biglan, Gerstenhaber, & Williams, 2009; Weintraub et al., 2010) and cognitive rehabilitation might alleviate executive or cognitive dysfunction in PD (Sammer, Reuter, Hullmann, Kaps, & Vaitl, 2006; Sinforiani, Banchieri, Zucchella, Pacchetti, & Sandrini, 2004).

## PROGRESSION OF EARLY AND MILD COGNITIVE IMPAIRMENT IN PD

Studies of the progression of cognitive impairment in PD without dementia have generally found modest to small declines over relatively short re-test intervals. A meta-analysis of 25 longitudinal studies of 901 patients (average disease duration approximately 8 years; mean follow-up 29 months) observed the largest declines (albeit of small effect sizes, not exceeding d = .40) among eight domains in overall level of cognition, visuoconstruction, and memory (Muslimovic, Schmand, Speelman, & De Haan, 2007), and these declines were generally associated with advancing age and lower education. Similarly, when examining change among individual patients rather than groups, patients re-evaluated after approximately 18 months tended to rarely (<10%) show gains or declines exceeding reliable change indices corrected for practice effect in fluency, naming, memory, visuoperceptual, and executive function tests (Tröster, Woods, & Morgan, 2007).

What is less well studied is how cognitive deficits progress in newly or recently diagnosed patients. One study compared neuropsychological performance in newly diagnosed patients and patients with established PD (average disease duration 6.5 years) over approximately 3 years (Muslimovic, Post, Speelman, De Haan, & Schmand, 2009). The newly diagnosed patients demonstrated declines especially in attention and psychomotor speed (Trailmaking A and B) and impairments on Trailmaking Part B were noted in 21% at 3-year follow-up compared to 11% at baseline. The established patients too showed declines in attention and psychomotor speed, but also on constructional tasks. The newly diagnosed patients showed a greater decrease than healthy controls on 20 of 27 measures, and 48% evidenced changes in a multivariate measure exceeding the 5th percentile in controls (a similar analysis showed that 50% of established PD showed declines). Of the newly diagnosed patients, 8.5% were demented at follow-up, either by neuropsychological test criteria or neurologist diagnosis. This dementia incidence is similar to that (10%) observed among recently diagnosed patients after 3.5-year follow-up in the Cambridge cohort (Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007).

## NEUROCOGNITIVE PREDICTORS OF DEMENTIA

The majority of prospective and retrospective studies demonstrate the importance of frontal/executive dysfunction in the prediction of dementia in PD. Predictive tasks include: Lurian tasks (Piccirilli, D'Alessandro, Finali, Piccinin, & Agostini, 1989), Raven Matrices (Reid et al., 1996), perseverative errors on the Wisconsin Card Sorting Test (Woods & Tröster, 2003), letter verbal fluency (Mahieux et al., 1998), identification of similarities and differences on the Dementia Rating Scale (Jacobs et al., 1995), and the Stroop interference task (Janvin, Aarsland, & Larsen, 2005; Mahieux et al., 1998). Tests on which performance is thought to be primarily mediated by more posterior brain regions, however, also may have predictive value and include tests of memory (Jacobs et al., 1995; Reid et al., 1996; Woods & Tröster, 2003), semantic verbal fluency (Jacobs et al., 1995; Williams-Gray et al., 2007), and visual attention, perception, and/or construction (Mahieux et al., 1998; Williams-Gray et al., 2007). Only one study examined MCI in the prediction of dementia, and in that study, single domain *non-amnestic* MCI and multiple domain MCI were associated with dementia after 4-year follow-up (Janvin et al., 2006). Specifically, 59 patients (85%) completed 4-year follow-up, including 29 (76%) of those with MCI at baseline and 30 (88%) of those cognitively intact at baseline. By follow-up 62% of those with baseline MCI had dementia, whereas only 20% of those intact at baseline had developed dementia 4 years later. Significantly

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**Table 1.** Studies of mild cognitive impairment (MCI) subtypes and prevalence in Parkinson's disease (PD) (studies using only cognitive screening instruments or not explicitly defining MCI criteria were excluded)

| Study | Sample size | Clinical/community sample/mean age (years)/disease duration (years)/ UPDRS Motor (/108) | Cognitive domains assessed/tests used to define MCI | MCI criteria | MCI types and prevalence (% of all patients) (sum of MCI subtype percentages and total percentage may not be equivalent given rounding) |
|---|---|---|---|---|---|
| Aarsland et al., 2009 | 196 drug-naïve PD; 201 healthy controls | Community<br>67.6/2.3/22.8 | 3<br>Verbal memory: CVLT-II total immediate, short- and long-delay free recall<br>Visuospatial: Visual Object and Space Perception Silhouettes<br>Attention/Executive: Semantic verbal fluency, Serial 7s, Stroop (Color, Word, and Color-Word) | Subjective cognitive complaint not required<br>Patients with dementia excluded<br>At least 1.5 *SD* below domain composite mean score of control group on one or more domains | 19% MCI<br>12% non-amnestic single domain<br>5% amnestic single domain<br>1% non-amnestic multiple domain<br>2% amnestic multiple domain |
| Aarsland et al., 2010 | 1,346 PD; 8-center study | Mixed: four centers with clinical samples; four centers with community samples<br>67.5/6.1/21.6 | 3 (at least 2 per subject)<br>Attention/Executive<br>Visuospatial (assessed in 1,141)<br>Memory (verbal and/or visual)<br>Tests differed by center (some used only extended screening tests). Exact scores used from each test not specified. | Subjective cognitive complaint not required<br>Patients with dementia excluded<br>At least 1.5 *SD* below domain composite mean score of control or normative sample on one or more domains | 26% MCI<br>11% non-amnestic single domain<br>9% amnestic single domain<br>1% non-amnestic multiple domain<br>5% amnestic multiple domain |
| Caviness et al., 2007 | 86 PD (15 with PDD) | Clinical/brain bank<br>Cognitively normal: 7 5.2/5.4/17.5<br>PD-MCI: 74.6/9.2/24.9<br>PDD: 79.9/16.8/36.1 | 5<br>Executive: Stroop; Trailmaking<br>Language: Letter and semantic verbal fluency<br>Attention: Digit span forward and backward<br>Memory: Auditory Verbal Learning Test<br>Visuospatial: Clock drawing, Judgment of Line Orientation | Subjective cognitive complaint<br>No significant functional decline<br>"Consistent pattern of impaired performance on neuropsychological measures that load on that cognitive domain" | 21% MCI (of 86 including 15 PDD)<br>42% MCI if 1.5 *SD* on single test criterion was used<br>9% non-amnestic single domain<br>5% amnestic single domain<br>5% non-amnestic multiple domain<br>2% amnestic multiple domain |

*(Continued)*

**Table 1.** Continued

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|---|---|---|---|---|---|
| Hoops et al., 2009 | 132 PD (17 with PDD) | Clinical; 2-center study<br>Cognitively intact: 63.9/5.5/NA<br>PD-MCI and PDD: 68.1/8.2/NA | 4<br>Memory: Hopkins Verbal Learning Test immediate recall or recognition discrimination<br>Executive: Tower of London total moves or total correct, Stroop Color-Word, Verbal fluency<br>Attention: Digit span backward<br>Visuospatial: Montreal Cognitive Assessment (MOCA) cube copying | Subjective cognitive complaint<br>Preserved instrumental activities of daily living<br>Score at least 1.5 *SD* below normative mean on "tests" within a cognitive domain ($\leq$4 on digit span backward; $\leq$2/5 on cube copy) | 17% MCI |
| Janvin et al., 2006 | 72 PD, 38 healthy controls | Community<br>MCI amnestic: 71.5/10.6/NA<br>MCI single domain, non-amnestic: 73.4/11.4/NA<br>MCI multiple domains: 74.8/11.6/NA<br>Cognitively intact: 68.1/12.2/NA | 3<br>Memory: Benton Visual Retention Test multiple choice version<br>Visuospatial: Judgment of Line Orientation<br>Executive/Attention: Stroop (all three cards given, but Color-Word was used to define MCI) | Subjective cognitive complaint<br>Patients with dementia (functional impairment) excluded<br>Single test score at least 1.5 *SD* below control group mean | 53% MCI<br>24% non-amnestic single domain<br>8% amnestic single domain<br>21% multiple domain |
| Mamikonyan et al., 2009 | 106 PD | Clinic<br>64.6/6.5/NA | 3<br>Memory: Hopkins Verbal Learning Test (immediate recall, percent retained, recognition discrimination)<br>Attention: Digit span forward and backward<br>Executive: Tower of London, Stroop Color-Word, Semantic verbal fluency | Subjective cognitive complaint not required<br>Patients with dementia excluded<br>Score at least 1.5 *SD* below normative mean on 2/3 memory and executive function scores; below age cutoff on either digit span forward or backward for attention | 29% MCI<br>18% single domain<br>11% multiple domain |

*(Continued)*

**Table 1.** Continued

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|---|---|---|---|---|---|
| Naismith et al., 2010 | 61 PD | Clinic<br>64.5/6.2/36.3 | 5<br>Working memory: Digit Span total score<br>Psychomotor Speed: Trailmaking Part A<br>Verbal learning and memory: Wechsler Memory Scale –III Logical Memory<br>Language: Letter and semantic verbal fluency<br>Executive: Trailmaking Part B | Consensus between neuropsychologist and neurologist<br>At least 1.5 *SD* below *National Adult Reading Test- predicted IQ* (Nelson & Willison, 1991) in at least one domain | 62% MCI<br>37% single domain<br>25% multiple domain |
| Sollinger et al., 2010 | 72 PD | Clinic<br>Cognitively intact: 63.7/5.8/NA<br>PD-MCI: 66.0/8.7/NA | 5<br>Visuospatial: Judgment of Line Orientation, intersecting pentagon copy from MMSE<br>Language: Boston Naming Test, semantic and letter verbal fluency<br>Attention: Digit span forward, Trailmaking Part A<br>Memory: CERAD word list or Hopkins Verbal Learning Test—Revised, three-item recall from MMSE<br>Executive: Trailmaking Part B, spelling "WORLD" backward | Consensus of two neuropsychologists<br>Subjective cognitive complaint (patient or informant)<br>No functional (instrumental activities of daily living) decline<br>No test cutoff score: used clinical judgment about whether performance was deficient given estimated premorbid abilities | 53% MCI<br>19% Non-amnestic single domain<br>13% Amnestic single domain<br>8% Non-amnestic multiple domain<br>13% Amnestic multiple domain |
| Song et al., 2008 | 126 PD (51 with PDD), 33 healthy controls<br>PD-MCI: 64.9/4.8/11.2 | | 6<br>Attention: Digit span, letter cancellation<br>Language "and related function": spontaneous speech, comprehension, repetition, naming, Boston Naming Test, reading writing, calculation, finger naming, right-left orientation, body part identification, praxis | No dementia per DSM-IV<br>No history or symptoms of memory impairment<br>No cognitive dysfunction with functional impairment<br>Scores on one or more tests at least 2 *SD* below control group mean | 15% MCI |

*(Continued )*

**Table 1.** Continued

| | |
|---|---|
| | Visuospatial: intersecting pentagons, copy of Rey-Osterrieth complex figure |
| | Verbal memory: three words, Hopkins Verbal Learning Test (immediate and delayed recall and recognition) |
| | Visual memory: immediate and delayed recall and recognition of complex figure |
| | Executive: motor impersistence, contrasting programs, go-no go, fist-edge-palm, alternating hand movements, alternating squares and triangles, Luria loop, letter and semantic verbal fluency, Stroop color reading and word reading |

CERAD = Consortium to Establish a registry for Alzheimer's Disease; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MCI = mild cognitive impairment; MMSE = Mini Mental State Exam; NA = not available; PDD = Parkinson's disease dementia.

higher proportions of those with single domain, non-amnestic MCI (69%) or multiple domain MCI (63%) than those with single domain amnestic MCI (40%) developed dementia.

In the CamPaIGN cohort, decline in cognition (MMSE score) by 3.5 year follow-up was associated with "below average performance" on executive function tests (ToL), semantic fluency, visuoconstructional skill (pentagon copy) and spatial recognition memory (SRM) at baseline, though most strongly associated with poor fluency and pentagon copy independent of age (Williams-Gray et al., 2007). The latter were also predictors of dementia at 5-year follow-up (Williams-Gray et al., 2009).

## NEUROPATHOLOGIC CORRELATES OF COGNITIVE IMPAIRMENT AND PROGRESSION IN PD

The prospective Sydney Multicenter Study of PD (Halliday & McCann, 2010) identified three cognitive phenotypes of patients: (1) a group with early, prominent dementia and akinetic-rigid PD (corresponding clinically to DLB); (2) a group of older (greater than 70 years) PD patients developing dementia in 3–10 years (corresponding clinically to PDD) who have widespread alpha-synuclein pathology; and (3) a younger PD group (disease onset before 70 years) who may remain cognitively intact for some time (dementia occurs late in the disease, after 10 to 15 years) and who have a cell-loss dominant pathology with lesser alpha-synuclein deposition. Congruently, another study reported that PD patients developing dementia late in the disease (after approximately 10 years) had less cortical alpha-synuclein pathology (and fewer plaques) but greater cholinergic abnormalities than those developing dementia early on, whose pathology resembled that of DLB (Ballard et al., 2006). How these differences in progression to dementia are related to various cognitive phenotypes in early PD and PD-MCI remains unknown.

By the time of clinical PD diagnosis (usually at Braak stage III or IV, when Lewy bodies and neurites extend to midbrain, including the substantia nigra, basal forebrain, transentorhinal cortex and the hippocampal CA2 cell field) (Braak et al., 2003) cognitive impairments may be detectable in some patients even on cognitive screening instruments (Braak, Rub, Jansen Steur, Del Tredici, & de Vos, 2005). Once MCI is apparent, pathology is likely heterogeneous. An autopsy series of eight persons with PD-MCI (heterogeneous in cognitive domains affected), found highly variable pathology (Adler et al., 2010): five of the eight cases had limbic and/or neocortical Lewy bodies, while three had only brainstem Lewy bodies. Only three cases had no neuritic plaques. Two cases (both with amnestic MCI) met neuropathologic criteria for AD. Concomitant cerebrovascular pathology was observed in three cases.

Amyloid-beta pathology biomarkers associated with AD and amnestic MCI [especially reductions in cerebrospinal fluid (CSF) Aβ-42] may be evident in PD (Alves et al., 2010) and PD-MCI (Montine et al., 2010), and associated with more rapid cognitive decline (Siderowf et al., 2010), processing

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speed and semantic verbal fluency (Leverenz et al., 2010), and memory deficits in early, untreated patients (Alves et al., 2010). Unfortunately amyloid imaging (PIB binding) has generally not been informative in PD (see below). CSF markers of Tau in early PD appear unremarkable and unrelated to cognitive status (Alves et al., 2010).

## NEUROIMAGING CORRELATES OF COGNITIVE IMPAIRMENT IN PD

Cholinergic abnormalities have been implicated in the neurobehavioral changes in PDD (Mattila et al., 2001) and PD-MCI (Choi et al., 2011) and functional imaging studies are beginning to yield corroborating evidence in this regard. Cortical acetylcholinesterase (AChE) activity has been imaged in vivo using [11C] methyl-4-piperidinyl propionate (PMP) or [11C] methyl-4-piperidyl acetate (MP4A). Decreased PMP activity has been associated with depression (Bohnen et al., 2007) and working memory and executive deficits in PD and PDD (Bohnen et al., 2006). Cross-sectional studies of small samples agree that MP4A binding reductions, especially in posterior brain regions, occur in PD without dementia and are less pronounced than in PDD (Klein et al., 2010; Shimada et al., 2009). These findings' importance in elucidating a biologic basis of *specific* cognitive impairments in early PD or PD-MCI, and their progression to PDD, is difficult to define given the very small sample sizes. Furthermore, the PD patients without dementia in one study already had marked cognitive impairments, having scored $\geq 2$ *SD* below normative means on list learning and verbal fluency tasks (Klein et al., 2010) and in the other study no cholinergic abnormality differences were found between early ($\leq 3$ years) and advanced ($>3$ years) disease duration) PD groups (Shimada et al., 2009).

SPECT has also implicated posterior (parietal and occipital) resting state metabolic abnormalities in PD with amnestic MCI (Nobili et al., 2009), and multiple (but not single) domain MCI was related to prefrontal and parietal glucose hypometabolism in comparison to PD without cognitive impairment (Huang et al., 2008). Similarly, CDR-defined PD-MCI has been associated with posterior, especially parieto-temporal glucose hypometabolism in comparison to PD without cognitive impairment (Hosokai et al., 2009).

Dopaminergic augmentation has no profound impact on cognition in PD, but very specific aspects of cognition may be impacted transiently, especially during the early stages of the disease (Owen, Iddon, Hodges, Summers, & Robbins, 1997; Owen et al., 1995) and correlated with functional imaging (Cools, Stefanova, Barker, Robbins, & Owen, 2002). Caudate dopaminergic abnormalities have been related especially to executive dysfunction in newly diagnosed PD patients (Nobili et al., 2010).

Measurement of amyloid load by [11C] PIB PET imaging has revealed that only a minority of PDD patients (16–33%) has increased PIB uptake (Edison et al., 2008; Maetzler et al., 2009). These and other studies (Foster et al., 2010; Gomperts et al., 2008; Jokinen et al., 2010) have failed to reveal PIB binding abnormalities in PD patients without dementia, though parietal PIB uptake has been associated with visuospatial test performance (Gomperts et al., 2008). The contradiction with CSF biomarker findings might reflect that patients in the CSF biomarker studies were probably more heterogeneous in severity of cognitive impairment than in the imaging studies.

## COGNITION IN EARLY PD AND GENETICS

Studies examining the role of genetic risk factors for AD in PDD (e.g., apolipoprotein E4) have yielded inconclusive findings (Huang, Chen, Kaufer, Troster, & Poole, 2006) and the association of the *H1/H1* haplotype of the microtubule associated protein (*MAP*) gene encoding for tau protein (a component of neurofibrillary tangles) with PDD (Goris et al., 2007; Williams-Gray et al., 2009), awaits independent replication.

Studies of neurobehavioral correlates of genetic polymorphisms implicated in other disorders, for example, brain derived neurotrophic factor (*BDNF*) (Foltynie et al., 2005), cathechol-O-methyl-transferase (*COMT*) (Foltynie et al., 2004; Williams-Gray et al., 2009; Williams-Gray, Hampshire, Barker, & Owen, 2008) have not been replicated (Hoogland et al., 2010) or yielded inconsistent results. Studies of polymorphisms and mutations associated with familial PD, namely in leucine-rich repeat kinase 2 (*LRRK2*) (Healy et al., 2008) and parkin *(PARK2)* (Lohmann et al., 2009), and in glucocerebrosidase (*GBA*) (Alcalay et al., 2010) which has been associated with DLB, have yielded negative findings. Future studies using a variety of sensitive neuropsychological measures in large samples are much needed.

## MILD COGNITIVE IMPAIRMENT: PRELIMINARY RESEARCH CRITERIA

Given the variety of definitions of MCI to date, and the importance of this construct in detecting (and potentially treating) pre-PDD, uniform criteria are needed. The criteria proposed here are preliminary and offered for empirical evaluation. A two tier approach to "MCI" definition in PD is suggested. The first category is a general PD-MCI category in which cognitive impairment is evident in PD without dementia, but an etiologic attribution is not required. That is, the impairment may be related to PD or possibly attributed to other conditions such as depression or co-existing vascular impairment, or be of a qualitative pattern that suggests the possibility of another condition (e.g., early AD or DLB). The term "possible MCI" is not chosen here as such a term might convey uncertainty about the presence rather than etiology of MCI. The possibility of moving into and out of this category is illustrated in Figure 1, with possible change in diagnostic classification over time perhaps related to measurement error, etiology of MCI, co-morbidities such as REM sleep behavior disorder (Gagnon et al., 2009), and treatment effects. In the second category, MCI is confidently attributed to PD. Consequently this clinical entity is referred to as PCI or

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**Table 2.** Criteria for Parkinson's disease with mild cognitive impairment (PD-MCI)

1. Diagnosis of PD according to UK Parkinson Disease Society Brain Bank Criteria
2. Subjective cognitive complaint by patient or informant familiar with patient, or inference of cognitive impairment by a treating physician or allied health professional who is familiar with the patient
3. Cognitive decline or deficit occurs at time of or after development of motor symptoms
4. No impairment in instrumental activities of living attributable to neurocognitive factors (though tasks may take extra effort)
5. At least one of:
   a. A current deficit (1–2 *SD*) below age appropriate means) on a test or cognitive domain composite score OR
   b. A decline of at least 1 *SD* (or beyond the 90% confidence interval of a reliable change score) relative to prior quantitative testing on a test or cognitive domain composite score OR
   c. A score at least 1.5 *SD* below quantitative premorbid estimates

   In one domain of cognition as evidenced by primary scores on two or more tests in a single domain OR at least one abnormal primary test score in at least two domains of cognition
   i. Attention/working memory
   ii. Episodic memory
   iii. Executive function
   iv. Visuoperceptual, spatial and constructional function
   v. Language/praxis

   If a composite score is used for any domain, care is taken to ensure that constituent tests have similar score distributions in the normal population
6. Deficit is not present exclusively during episodes of major depression, altered awareness or psychosis
7. PD-MCI subcategorization can be made only if all five cognitive domains were assessed – otherwise, or when impairment is inferred solely on the basis of a multi-domain cognitive screening instrument validated for use in PD, list as PD-MCI-unspecified. If subcategorized
   a. Specify single (including domain affected) *vs*. multiple domain
   b. If multiple domain, specify amnestic, executive, or mixed when both memory and executive functions are among those impaired

Parkinson Cognitive Impairment, rather than by the more ambiguous "probable" PD-MCI. The label PCI makes clear the need to distinguish general MCI (often associated with AD and theoretically present in, but independent of PD) from PCI. The diagnostic criteria for the two categories are presented in Tables 2 and 3.

The criteria attempt to be congruent with the DSM-V draft criteria for Mild Neurocognitive Disorder (Jeste et al., 2010) and current PDD criteria (Emre et al., 2007). It is beyond the scope of a brief review to provide a detailed rationale for each aspect of the research criteria, and (as is the case for any set of research diagnostic criteria) clinical judgment will be required in arriving at a diagnosis. Subjective complaint of cognitive problems is required. Mild impairments in cognition do not appear to preclude valid self-report of disability (Brown, MacCarthy, Jahanshahi, & Marsden, 1989), although PD patients might be biased to reporting memory problems as their first cognitive complaint (Noe et al., 2004). An absence of significant compromise in instrumental activities of daily living (iADL) should be queried over a broad range of iADLs because MCI in different domains may impact different aspects of iADL (Bangen et al., 2010). Impairments or declines on multiple neuropsychological or cognitive tests are recommended because this enhances diagnostic reliability, especially in non-amnestic MCI (Jak et al., 2009). Furthermore, if the base rate of having at least one impaired score ($-2$ *SD*) in two different cognitive domains is approximately 5% in healthy elderly (Palmer, Boone, Lesser, & Wohl, 1998), one assumes that this approach is adequately conservative in PD, where a neurologic diagnosis already exists and the *a priori* probability of cognitive impairment is probably greater. A rigid use of a cutoff of $\geq 1.5$ *SD* below means might be eschewed for that same reason. Consistent with DSM draft criteria, perhaps more relaxed criteria (1–2 *SD* below means) can be used. The possibility of defining PD-MCI on the basis of declines from premorbid levels of cognitive function [or when prior testing is available, preferably using reliable change index scores (Tröster et al., 2007)] is consistent with DSM-V draft criteria and perhaps alleviates the problem of not detecting MCI in high functioning persons $\geq 0.5$ *SD* above the mean who would need to show declines in excess of 2 *SD* to meet definitions based on a 1.5 *SD* cutoff. Table 4 provides a list of preferred tests for establishing PD-MCI or PCI, though this list is intended to be neither prescriptive nor exhaustive and will no doubt change as new or existing tests receive greater validation for use in PD.

## SUMMARY

Cognitive impairment is heterogeneous and present in approximately 30% of persons at time of PD diagnosis and subtle declines may be evident in at-risk populations. Attention and executive deficits, likely related to dopaminergic abnormalities, are among the most common cognitive changes in early PD and they typically progress slowly over time. Progression to dementia is highly variable and at least three possible phenotypes have been identified, with those showing earlier and more rapid dementia development neuropathologically resembling DLB, and those developing dementia late (more than 10 years after diagnosis) having more cell loss, less alpha-synuclein deposition, and greater

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**Table 3.** Criteria for Parkinson cognitive impairment (PCI)

1. Diagnosis of PD according to UK Parkinson Disease Society Brain Bank criteria
2. Subjective cognitive complaint by patient or informant familiar with patient, or inference of cognitive impairment by a treating physician or allied health professional who is familiar with the patient
3. No impairment in instrumental activities of daily living attributable to cognitive dysfunction (though tasks may take extra effort)
4. No evidence of dementia within 12 months of, or preceding, development of motor symptoms and does not meet clinical diagnostic criteria for a dementia (e.g., PDD, DLB, AD, Vascular, FTD)
5. Cognitive deficits/decline are not solely evident during episodes of major depression, altered awareness, or psychosis
6. Cognitive deficits/declines are not solely attributable to medications
7. Cognitive deficits/declines are not solely attributable to excessive daytime sleepiness, sleep disorder, or autonomic dysfunction
8. At least one of:
   a. A current deficit (1-2 *SD*) below age appropriate means) on a test or cognitive domain composite score OR
   b. A decline of at least 1 *SD* (or beyond the 90% confidence interval of a reliable change score) on a test or cognitive domain composite score relative to prior quantitative testing OR
   c. A score at least 1.5 *SD* below quantitative premorbid estimates

   In one domain of cognition as evidenced by primary scores on two or more tests in a single domain OR at least one abnormal primary test score in at least two domains of cognition
   i. Attention/working memory
   ii. Episodic memory
   iii. Executive function
   iv. Visuoperceptual, spatial and constructional function
   v. Language/praxis

   If a composite score is used for any domain, care is taken to ensure that constituent tests have similar score distributions in the normal population
9. PCI subcategory must be specified and all five cognitive domains must have been assessed neuropsychologically (i.e., a multi-domain screening test validated for PD is sufficient in making a diagnosis of PD-MCI specified or unspecified, but *not* PCI)
   a. Specify single (including domain affected) vs. multiple domain
   b. If multiple domain, specify amnestic, executive, or mixed when both memory and executive functions are among those impaired

cholinergic abnormalities. Point prevalence of MCI is approximately 25–30%, though MCI identification is challenging in the absence of diagnostic criteria. Whether subtypes of MCI have prognostic significance remains unclear, as is the neurobiological basis of the various subtypes. Pathology of MCI is heterogeneous. While AD pathology exists in a minority of PD patients, and CSF biomarkers of amyloid abnormalities may herald cognitive decline, these

**Table 4.** Recommended tests for use in PD-MCI and PCI research

Tests should be selected so as to be age, education, gender, culturally, and linguistically appropriate, with due attention to: test-retest reliability, availability of Reliable Change Index scores, availability of normative data, known score distribution in the normal population, and empirically supported use in PD

1. Cognitive screening : Parkinson's Disease Cognitive Rating Scale (PD-CRS) (Pagonabarraga et al., 2008), Mattis Dementia Rating Scale (DRS) (Mattis, 2001), Scales for Outcomes of Parkinson's Disease—Cognition (SCOPA-COG) (Marinus et al., 2003), Parkinson Neuropsychometric Dementia Assessment (PANDA) (Kalbe et al., 2008), Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005)
2. Attention/Working memory/processing speed: Symbol Digit Modalities Test (Smith, 1982), digit span backward (with or without digit span forward) and spatial span backward (with or without spatial span forward) (Wechsler, 1997), Stroop task (various versions) (Golden & Freshwater, 2002; Trenerry, Crosson, DeBoe, & Leber, 1989), Digit ordering (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991)
3. Episodic memory: Hopkins Verbal Learning Test—revised (HVLT-R) (Brandt & Benedict, 2001), California Verbal Learning Test (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000), Selective Reminding Test (Buschke, 1973), Auditory Verbal Learning Test (Schmidt, 1996), Benton Visual Retention Test (Sivan, 1991), Wechsler Memory Scale Logical Memory and Faces (Wechsler, 1997), CANTAB Pattern and Spatial Recognition (Robbins et al., 1994), Brief Visuospatial Memory Test—revised (BVMT-R) (Benedict, 1997)
4. Executive function: Trailmaking test (Reitan & Wolfson, 1985), Wisconsin Card Sorting Test (various versions) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), Tower Test (various versions) (Delis, Kaplan, & Kramer, 2001; Robbins et al., 1994), Verbal fluency tests [letter, category, alternating/switching, action (Delis et al., 2001; Piatt, Fields, Paolo, Koller, & Tröster, 1999)]; no more than one can be used to support existence of executive dysfunction in PD-MCI or PCI), WAIS (Wechsler Adult Intelligence Scale) Matrix Reasoning or Similarities (Wechsler, 2008) ; Raven's Progressive Matrices (Raven, Raven, & Court, 2003)
5. Visuospatial and perceptual: Judgment of Line Orientation (Benton, Varney, & Hamsher, 1978), Clock Drawing (various versions) (Goodglass & Kaplan, 1983), Hooper Visual Organization Test (Hooper, 1983)
6. Language: Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) (short-forms acceptable if empirically validated for use in PD), Token test or Sentence repetition (Benton, Hamsher, & Sivan, 1994), WAIS Vocabulary (Wechsler, 2008)

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markers may not reflect cerebral plaque formation given that brain imaging has not linked amyloid deposition to cognitive deficits. Similarly, the finding of increased dementia risk conferred by the H1/H1 haplotype of the MAP gene encoding for tau remains to be replicated. Recent imaging implicates especially posterior resting and glucose metabolic and cholinergic deficits in dementia and amnestic and multiple-domain MCI in PD, but the predictive utilities of these measures is unknown. Similarly, although impairment on neuropsychological tests sensitive to posterior cerebral dysfunction might increase risk of cognitive decline and dementia, it is unclear if superimposition of "posterior" upon "anterior" or executive deficits is an artifact of the very definition of dementia (involving impairment of multiple cognitive domains) or a bias in studying patients developing more pronounced cognitive impairments relatively soon after PD diagnosis. Better understanding of the evolution of PDD will benefit from use of consistent MCI criteria and preliminary research criteria were provided in this study. Early identification of cognitive changes, especially those amenable to treatment, may reduce morbidity and enhance quality of life.

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## REFERENCES

Aarsland, D., Bronnick, K., Larsen, J.P., Tysnes, O.B., & Alves, G. (2009). Cognitive impairment in incident, untreated Parkinson disease: The Norwegian ParkWest study. *Neurology*, *72*, 1121–1126. doi:01.wnl.0000338632.00552.cb [pii] 10.1212/01.wnl.0000338632.00552.cb

Aarsland, D., Bronnick, K., Williams-Gray, C., Weintraub, D., Marder, K., Kulisevsky, J., … Emre, M. (2010). Mild cognitive impairment in Parkinson disease: A multicenter pooled analysis. *Neurology*, *75*, 1062–1069. doi:75/12/1062 [pii] 10.1212/WNL.0b013e3181f39d0e

Aarsland, D., Londos, E., & Ballard, C. (2009). Parkinson's disease dementia and dementia with Lewy bodies: Different aspects of one entity. *International Psychogeriatrics*, *21*, 216–219. doi:S1041610208008612 [pii] 10.1017/S1041610208008612

Adler, C.H., Caviness, J.N., Sabbagh, M.N., Shill, H.A., Connor, D.J., Sue, L., … Beach, T.G. (2010). Heterogeneous neuropathological findings in Parkinson's disease with mild cognitive impairment. *Acta Neuropathologica*, *120*, 827–828. doi:10.1007/s00401-010-0744-4

Alcalay, R.N., Mejia-Santana, H., Tang, M.X., Rakitin, B., Rosado, L., Ross, B., … Caccappolo, E. (2010). Self-report of cognitive impairment and mini-mental state examination performance in PRKN, LRRK2, and GBA carriers with early onset Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, *32*, 775–779. doi:919484122 [pii] 10.1080/13803390903521018

Alves, G., Bronnick, K., Aarsland, D., Blennow, K., Zetterberg, H., Ballard, C., … Mulugeta, E. (2010). CSF amyloid-beta and tau proteins, and cognitive performance, in early and untreated Parkinson's disease: The Norwegian ParkWest study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *81*, 1080–1086. doi:jnnp.2009.199950 [pii] 10.1136/jnnp.2009.199950

Ballard, C., Ziabreva, I., Perry, R., Larsen, J.P., O'Brien, J., McKeith, I., … Aarsland, D. (2006). Differences in neuropathologic characteristics across the Lewy body dementia spectrum. *Neurology*, *67*, 1931–1934.

Bangen, K.J., Jak, A.J., Schiehser, D.M., Delano-Wood, L., Tuminello, E., Han, S.D., … Bondi, M.W. (2010). Complex activities of daily living vary by mild cognitive impairment subtype. *Journal of the International Neuropsychological Society*, *16*, 630–639. doi:S1355617710000330 [pii] 10.1017/S1355617710000330

Benedict, R.H. (1997). *Brief Visuospatial Memory Test – revised: Professional manual*. Lutz, FL: Psychological Assessment Resources.

Benton, A.L., Hamsher, K., & Sivan, A.B. (1994). *Multilingual aphasia examination* (3rd ed.). Iowa City: AJA Associates.

Benton, A.L., Varney, N.R., & Hamsher, K.D. (1978). Visuospatial judgment. A clinical test. *Archives of Neurology*, *35*, 364–367.

Bohnen, N.I., Kaufer, D.I., Hendrickson, R., Constantine, G.M., Mathis, C.A., & Moore, R.Y. (2007). Cortical cholinergic denervation is associated with depressive symptoms in Parkinson's disease and parkinsonian dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *78*, 641–643.

Bohnen, N.I., Kaufer, D.I., Hendrickson, R., Ivanco, L.S., Lopresti, B.J., Constantine, G.M., … Dekosky, S.T. (2006). Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. *Journal of Neurology*, *253*, 242–247.

Braak, H., Rub, U., Jansen Steur, E.N., Del Tredici, K., & de Vos, R.A. (2005). Cognitive status correlates with neuropathologic stage in Parkinson disease. *Neurology*, *64*, 1404–1410.

Braak, H., Tredici, K.D., Rüb, U., de Vos, R.A., Jansen Steur, E.N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging*, *24*, 197–211.

Brandt, J., & Benedict, R.H. (2001). *The Hopkins Verbal Learning Test – Revised*. Lutz, FL: Psychological Assessment Resources.

Brown, R.G., MacCarthy, B., Jahanshahi, M., & Marsden, C.D. (1989). Accuracy of self-reported disability in patients with parkinsonism. *Archives of Neurology*, *46*, 955–959.

Buschke, H. (1973). Selective reminding for analysis of memory and learning. *Journal of Verbal Learning and Verbal Behavior*, *12*, 543–550.

Caviness, J.N., Driver-Dunckley, E., Connor, D.J., Sabbagh, M.N., Hentz, J.G., Noble, B., … Adler, C.H. (2007). Defining mild cognitive impairment in Parkinson's disease. *Movement Disorders*, *22*, 1272–1277.

Choi, S.H., Jung, T.M., Lee, J.E., Lee, S.K., Sohn, Y.H., & Lee, P.H. (2011). Volumetric analysis of the substantia innominata in patients with Parkinson's disease according to cognitive status. *Neurobiology of Aging*. doi:S0197-4580(10)00498-7 [pii] 10.1016/j.neurobiolaging.2010.11.015

Cools, R., Stefanova, E., Barker, R.A., Robbins, T.W., & Owen, A.M. (2002). Dopaminergic modulation of high-level cognition in Parkinson's disease: The role of the prefrontal cortex revealed by PET. *Brain*, *125*, 584–594.

Cooper, J.A., Sagar, H.J., Jordan, N., Harvey, N.S., & Sullivan, E.V. (1991). Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain*, *114*, 2095–2122.

Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio: The Psychological Corporation.

Delis, D.C., Kramer, J.H., Kaplan, E., & Ober, B.A. (2000). *California Verbal Learning Test – adult version* (2nd ed.). San Antonio: The Psychological Corporation.

Dubois, B. (2007). Is PD-MCI a useful concept? *Movement Disorders*, *22*, 1215–1216.

Edison, P., Rowe, C.C., Rinne, J.O., Ng, S., Ahmed, I., Kemppainen, N., … Brooks, D.J. (2008). Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*, 1331–1338. doi:jnnp.2007.127878 [pii] 10.1136/jnnp.2007.127878

Elgh, E., Domellof, M., Linder, J., Edstrom, M., Stenlund, H., & Forsgren, L. (2009). Cognitive function in early Parkinson's disease: A population-based study. *European Journal of Neurology*, *16*, 1278–1284. doi:ENE2707 [pii] 10.1111/j.1468-1331.2009.02707.x

Emre, M., Aarsland, D., Brown, R., Burn, D.J., Duyckaerts, C., Mizuno, Y., … Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders*, *22*, 1689–1707.

Fernandez, H.H., Crucian, G.P., Okun, M.S., Price, C.C., & Bowers, D. (2005). Mild cognitive impairment in Parkinson's disease: The challenge and the promise. *Neuropsychiatric Disease and Treatment*, *1*, 37–50.

Filoteo, J.V., Salmon, D.P., Schiehser, D.M., Kane, A.E., Hamilton, J.M., Rilling, L.M., … Galasko, D.R. (2009). Verbal learning and memory in patients with dementia with Lewy bodies or Parkinson's disease with dementia. *Journal of Clinical and Experimental Neuropsychology*, *31*, 823–834. doi:908749749 [pii] 10.1080/13803390802572401

Foltynie, T., Brayne, C.E., Robbins, T.W., & Barker, R.A. (2004). The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain*, *127*, 550–560.

Foltynie, T., Goldberg, T.E., Lewis, S.G., Blackwell, A.D., Kolachana, B.S., Weinberger, D.R., … Barker, R.A. (2004). Planning ability in Parkinson's disease is influenced by the COMT val158met polymorphism. *Movement Disorders*, *19*, 885–891.

Foltynie, T., Lewis, S.G., Goldberg, T.E., Blackwell, A.D., Kolachana, B.S., Weinberger, D.R., … Barker, R.A. (2005). The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. *Journal of Neurology*, *252*, 833–838.

Foster, E.R., Campbell, M.C., Burack, M.A., Hartlein, J., Flores, H.P., Cairns, N.J., … Perlmutter, J.S. (2010). Amyloid imaging of Lewy body-associated disorders. *Movement Disorders*, *25*, 2516–2523. doi:10.1002/mds.23393

Gagnon, J.F., Vendette, M., Postuma, R.B., Desjardins, C., Massicotte-Marquez, J., Panisset, M., & Montplaisir, J. (2009). Mild cognitive impairment in rapid eye movement sleep behavior disorder and Parkinson's disease. *Annals of Neurology*, *66*, 39–47. doi:10.1002/ana.21680

Golden, C.J., & Freshwater, S.M. (2002). *Stroop Color and Word Test: A manual for clinical and experimental uses*. Wood Dale, IL: Stoelting.

Gomperts, S.N., Rentz, D.M., Moran, E., Becker, J.A., Locascio, J.J., Klunk, W.E., … Johnson, K.A. (2008). Imaging amyloid deposition in Lewy body diseases. *Neurology*, *71*, 903–910. doi:71/12/903 [pii] 10.1212/01.wnl.0000326146.60732.d6

Goodglass, H., & Kaplan, E. (1983). *The assessment of aphasia and related disorders* (2nd ed.). Boston: Lea & Febiger.

Goris, A., Williams-Gray, C.H., Clark, G.R., Foltynie, T., Lewis, S.J., Brown, J., … Sawcer, S.J. (2007). Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. *Annals of Neurology*, *62*, 145–153. doi:10.1002/ana.21192

Halliday, G.M., & McCann, H. (2010). The progression of pathology in Parkinson's disease. *Annals of the New York Academy of Sciences*, *1184*, 188–195. doi:NYAS5118 [pii] 10.1111/j.1749-6632.2009.05118.x

Hawkins, K., Jennings, D., Marek, K., Siderowf, A., & Stern, M., PARS Study Investigators (2010). Cognitive deficits associated with dopamine transporter loss in the pre-motor subjects in the PARS cohort. *Movement Disorders*, *25*(Suppl. 3), S690–S691.

Healy, D.G., Falchi, M., O'Sullivan, S.S., Bonifati, V., Durr, A., Bressman, S., … Wood, N.W. (2008). Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: A case-control study. *Lancet Neurology*, *7*, 583–590. doi:S1474-4422(08)70117-0 [pii] 10.1016/S1474-4422(08)70117-0

Heaton, R.K., Chelune, G.J., Talley, J.L., Kay, G.G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test Manual*. Odessa: Psychological Assessment Resources.

Hoogland, J., de Bie, R.M., Williams-Gray, C.H., Muslimovic, D., Schmand, B., & Post, B. (2010). Catechol-O-methyltransferase val158met and cognitive function in Parkinson's disease. *Movement Disorders*, *25*, 2550–2554. doi:10.1002/mds.23319

Hooper, H.E. (1983). *Hooper Visual Organization Test*. Los Angeles, CA: Western Psychological Services.

Hoops, S., Nazem, S., Siderowf, A.D., Duda, J.E., Xie, S.X., Stern, M.B., & Weintraub, D. (2009). Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. *Neurology*, *73*, 1738–1745. doi:73/21/1738 [pii] 10.1212/WNL.0b013e3181c34b47

Hosokai, Y., Nishio, Y., Hirayama, K., Takeda, A., Ishioka, T., Sawada, Y., … Mori, E. (2009). Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. *Movement Disorders*, *24*, 854–862. doi:10.1002/mds.22444

Huang, C., Mattis, P., Perrine, K., Brown, N., Dhawan, V., & Eidelberg, D. (2008). Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease. *Neurology*, *70*, 1470–1477. doi:01.wnl.0000304050.05332.9c [pii] 10.1212/01.wnl.0000304050.05332.9c

Huang, X., Chen, P., Kaufer, D.I., Troster, A.I., & Poole, C. (2006). Apolipoprotein E and dementia in Parkinson disease: A meta-analysis. *Archives of Neurology*, *63*, 189–193.

Jacobs, D.M., Marder, K., Cote, L.J., Sano, M., Stern, Y., & Mayeux, R. (1995). Neuropsychological characteristics of preclinical dementia in Parkinson's disease. *Neurology*, *45*, 1691–1696.

Jak, A.J., Bondi, M.W., Delano-Wood, L., Wierenga, C., Corey-Bloom, J., Salmon, D.P., & Delis, D.C. (2009). Quantification of five neuropsychological approaches to defining mild cognitive impairment. *American Journal of Geriatric Psychiatry*, *17*, 368–375. doi:10.1097/JGP.0b013e31819431d5 00019442-200905000-00004 [pii]

Janvin, C.C., Aarsland, D., & Larsen, J.P. (2005). Cognitive predictors of dementia in Parkinson's disease: A community-based, 4-year longitudinal study. *Journal of Geriatric Psychiatry and Neurology*, *18*, 149–154.

Janvin, C.C., Larsen, J.P., Aarsland, D., & Hugdahl, K. (2006). Subtypes of mild cognitive impairment in Parkinson's disease: Progression to dementia. *Movement Disorders*, *21*, 1343–1349.

Jeste, D., Blacker, D., Blazer, D., Ganguli, M., Grant, I., Paulsen, J., … Sachdev, S. (2010). Neurocognitive disorders: A proposal from the DSM-5 Neurocognitive Disorders Work Group. Retrieved from http://www.dsm5.org/Proposed%20Revision%20Attachments/APA%20Neurocognitive%20Disorders%20Proposal%20for%20DSM-5.pdf

Jokinen, P., Scheinin, N., Aalto, S., Nagren, K., Savisto, N., Parkkola, R., … Rinne, J.O. (2010). [(11)C]PIB-, [(18)F]FDG-PET and MRI imaging in patients with Parkinson's disease with and without dementia. *Parkinsonism and Related Disorders*, *16*, 666–670. doi:S1353-8020(10)00219-1 [pii] 10.1016/j.parkreldis.2010.08.021

Kalbe, E., Calabrese, P., Kohn, N., Hilker, R., Riedel, O., Wittchen, H.U., … Kessler, J. (2008). Screening for cognitive deficits in Parkinson's disease with the Parkinson neuropsychometric dementia assessment (PANDA) instrument. *Parkinsonism and Related Disorders*, *14*, 93–101. doi:S1353-8020(07)00103-4 [pii] 10.1016/j.parkreldis.2007.06.008

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test*. Philadelphia: Lea & Febiger.

Klein, J.C., Eggers, C., Kalbe, E., Weisenbach, S., Hohmann, C., Vollmar, S., … Hilker, R. (2010). Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. *Neurology*, *74*, 885–892. doi:WNL.0b013e3181d55f61 [pii] 10.1212/WNL.0b013e3181d55f61

Kulisevsky, J., Pagonabarraga, J., Pascual-Sedano, B., Garcia-Sanchez, C., & Gironell, A. (2008). Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. *Movement Disorders*, *23*, 1889–1896. doi:10.1002/mds.22246

Leverenz, J.B., Stennis Watson, G., Shofer, J., Zabetian, C.P., Zhang, J., & Montine, T.J. (2010). Cerebrospinal fluid biomarkers and cognitive performance in non-demented patients with Parkinson's disease. *Parkinsonism and Related Disorders*. doi:S1353-8020(10)00250-6 [pii] 10.1016/j.parkreldis.2010.10.003

Levin, B.E., & Katzen, H.L. (1995). Early cognitive changes and nondementing behavioral abnormalities in Parkinson's disease. In W.J. Weiner & A.E. Lang (Eds.),, *Advances in neurology: Behavioral neurology of movement disorders* (*Vol. 65*, pp. 85–95). New York: Raven Press.

Lohmann, E., Thobois, S., Lesage, S., Broussolle, E., du Montcel, S.T., Ribeiro, M.J., & Brice, A. … (2009). A multidisciplinary study of patients with early-onset PD with and without parkin mutations. *Neurology*, *72*, 110–116. doi:01.wnl.0000327098.86861.d4 [pii] 10.1212/01.wnl.0000327098.86861.d4

Maetzler, W., Liepelt, I., Reimold, M., Reischl, G., Solbach, C., Becker, C., … Berg, D. (2009). Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. *Neurobiology of Disease*, *34*, 107–112. doi:S0969-9961(08)00319-7 [pii] 10.1016/j.nbd.2008.12.008

Mahieux, F., Fenelon, G., Flahault, A., Manifacier, M.J., Michelet, D., & Boller, F. (1998). Neuropsychological prediction of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *64*, 178–183.

Mamikonyan, E., Moberg, P.J., Siderowf, A., Duda, J.E., Have, T.T., Hurtig, H.I., … Weintraub, D. (2009). Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) scores. *Parkinsonism and Related Disorders*, *15*, 226–231. doi:S1353-8020(08)00163-6 [pii] 10.1016/j.parkreldis.2008.05.006

Marder, K. (2010). Cognitive impairment and dementia in Parkinson's disease. *Movement Disorders*, *25*(Suppl. 1), S110–S116. doi:10.1002/mds.22787

Marinus, J., Visser, M., Verwey, N.A., Verhey, F.R., Middelkoop, H.A., Stiggelbout, A.M., & van Hilten, J.J. (2003). Assessment of cognition in Parkinson's disease. *Neurology*, *61*, 1222–1228.

Marsh, L., Biglan, K., Gerstenhaber, M., & Williams, J.R. (2009). Atomoxetine for the treatment of executive dysfunction in Parkinson's disease: A pilot open-label study. *Movement Disorders*, *24*, 277–282. doi:10.1002/mds.22307

Mattila, P.M., Roytta, M., Lonnberg, P., Marjamaki, P., Helenius, H., & Rinne, J.O. (2001). Choline acetytransferase activity and striatal dopamine receptors in Parkinson's disease in relation to cognitive impairment. *Acta Neuropathologica*, *102*, 160–166.

Mattis, S. (2001). *Dementia Rating Scale-2*. Lutz, FL: Psychological Assessment Resources.

McKeith, I.G. (2009). Commentary: DLB and PDD: the same or different? Is there a debate? *International Psychogeriatrics*, *21*, 220–224. doi:S1041610208008624 [pii] 10.1017/S1041610208008624

Metzler-Baddeley, C. (2007). A review of cognitive impairments in dementia with Lewy bodies relative to Alzheimer's disease and Parkinson's disease with dementia. *Cortex*, *43*, 583–600.

Molano, J., Boeve, B., Ferman, T., Smith, G., Parisi, J., Dickson, D., … Petersen, R. (2010). Mild cognitive impairment associated with limbic and neocortical Lewy body disease: A clinicopathological study. *Brain*, *133*, 540–556. doi:awp280 [pii] 10.1093/brain/awp280

Montine, T.J., Shi, M., Quinn, J.F., Peskind, E.R., Craft, S., Ginghina, C., … Zhang, J. (2010). CSF Abeta(42) and tau in Parkinson's disease with cognitive impairment. *Movement Disorders*. doi:10.1002/mds.23287

Muslimovic, D., Post, B., Speelman, J.D., De Haan, R.J., & Schmand, B. (2009). Cognitive decline in Parkinson's disease: A prospective longitudinal study. *Journal of the International Neuropsychological Society*, *15*, 426–437. doi:S1355617709090614 [pii] 10.1017/S1355617709090614

Muslimovic, D., Post, B., Speelman, J.D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*, *65*, 1239–1245.

Muslimovic, D., Schmand, B., Speelman, J.D., & De Haan, R.J. (2007). Course of cognitive decline in Parkinson's disease: A meta-analysis. *Journal of the International Neuropsychological Society*, *13*, 920–932.

Naismith, S.L., Pereira, M., Shine, J.M., & Lewis, S.J. (2010). How well do caregivers detect mild cognitive change in Parkinson's disease? *Movement Disorders*. doi:10.1002/mds.23331

Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*, 695–699. doi:JGS53221 [pii] 10.1111/j.1532-5415.2005.53221.x

Nelson, H.E., & Willison, J. (1991). *National Adult Reading Test (NART): Test manual* (2nd ed.). Windsor, UK: NFER-Nelson.

Nobili, F., Abbruzzese, G., Morbelli, S., Marchese, R., Girtler, N., Dessi, B., … Rodriguez, G. (2009). Amnestic mild cognitive impairment in Parkinson's disease: A brain perfusion SPECT study. *Movement Disorders*, *24*, 414–421. doi:10.1002/mds.22381

Nobili, F., Campus, C., Arnaldi, D., De Carli, F., Cabassi, G., Brugnolo, A., … Rodriguez, G. (2010). Cognitive-nigrostriatal relationships in de novo, drug-naive Parkinson's disease patients: A [I-123]FP-CIT SPECT study. *Movement Disorders*, *25*, 35–43. doi:10.1002/mds.22899

Noe, E., Marder, K., Bell, K.L., Jacobs, D.M., Manly, J.J., & Stern, Y. (2004). Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. *Movement Disorders*, *19*, 60–67.

Owen, A.M., Iddon, J.L., Hodges, J.R., Summers, B.A., & Robbins, T.W. (1997). Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia*, *35*, 519–532.

Owen, A.M., Sahakian, B.J., Hodges, J.R., Summers, B.A., Polkey, C.E., & Robbins, T.W. (1995). Dopamine-dependent fronto-striatal planning deficits in early Parkinson's disease. *Neuropsychology*, *9*, 126–140.

Pagonabarraga, J., Kulisevsky, J., Llebaria, G., Garcia-Sanchez, C., Pascual-Sedano, B., & Gironell, A. (2008). Parkinson's disease-cognitive rating scale: A new cognitive scale specific for Parkinson's disease. *Movement Disorders*, *23*, 998–1005. doi:10.1002/mds.22007

Palmer, B.W., Boone, K.B., Lesser, I.M., & Wohl, M.A. (1998). Base rates of "impaired" neuropsychological test performance among healthy older adults. *Archives of Clinical Neuropsychology*, *13*, 503–511. doi:S0887617797000371 [pii]

Piatt, A.L., Fields, J.A., Paolo, A.M., Koller, W.C., & Tröster, A.I. (1999). Lexical, semantic, and action verbal fluency in Parkinson's disease with and without dementia. *Journal of Clinical and Experimental Neuropsychology*, *21*, 435–443.

Piccirilli, M., D'Alessandro, P., Finali, G., Piccinin, G.L., & Agostini, L. (1989). Frontal lobe dysfunction in Parkinson's disease: Prognostic value for dementia? *European Neurology*, *29*, 71–76.

Raven, J., Raven, J.C., & Court, J.H. (2003). *Manual for Raven's Progressive Matrices and Vocabulary Scales*. San Antonio, TX: The Psychological Corporation.

Reid, W.G., Hely, M.A., Morris, J.G., Broe, G.A., Adena, M., Sullivan, D.J., & Williamson, P.M. (1996). A longitudinal study of Parkinson's disease: Clinical and neuropsychological correlates of dementia. *Journal of Clinical Neuroscience*, *3*, 327–333.

Reitan, R.M., & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery*. Tucson: Neuropsychology Press.

Robbins, T.W., James, M., Owen, A.M., Sahakian, B.J., McInnes, L., & Rabbitt, P. (1994). Cambridge Neuropsychological Test Automated Battery (CANTAB): A factor analytic study of a large sample of normal elderly volunteers. *Dementia*, *5*, 266–281.

Sammer, G., Reuter, I., Hullmann, K., Kaps, M., & Vaitl, D. (2006). Training of executive functions in Parkinson's disease. *Journal of the Neurological Sciences*, *248*, 115–119. doi:S0022-510X(06)00224-3 [pii] 10.1016/j.jns.2006.05.028

Schmidt, M. (1996). *Rey Auditory and Verbal Learning Test: A handbook*. Los Angeles, CA: Western Psychological Services.

Shimada, H., Hirano, S., Shinotoh, H., Aotsuka, A., Sato, K., Tanaka, N., … Irie, T. (2009). Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET. *Neurology*, *73*, 273–278. doi:WNL.0b013e3181ab2b58 [pii] 10.1212/WNL.0b013e3181ab2b58

Siderowf, A., Xie, S.X., Hurtig, H., Weintraub, D., Duda, J., Chen-Plotkin, A., … Clark, C. (2010). CSF amyloid {beta} 1-42 predicts cognitive decline in Parkinson disease. *Neurology*, *75*, 1055–1061. doi:WNL.0b013e3181f39a78 [pii] 10.1212/WNL.0b013e3181f39a78

Sinforiani, E., Banchieri, L., Zucchella, C., Pacchetti, C., & Sandrini, G. (2004). Cognitive rehabilitation in Parkinson's disease. *Archives of Gerontology and Geriatrics. Supplement,*387–391.

Sivan, A.B. (1991). *Benton Viusal Retention Test* (5th ed.). San Antonio, TX: The Psychological Corporation.

Smith, A. (1982). *Symbol Digit Modalities Test*. Los Angeles: Western Psychological Services.

Sollinger, A.B., Goldstein, F.C., Lah, J.J., Levey, A.I., & Factor, S.A. (2010). Mild cognitive impairment in Parkinson's disease: Subtypes and motor characteristics. *Parkinsonism and Related Disorders*, *16*, 177–180. doi:S1353-8020(09)00274-0 [pii] 10.1016/j.parkreldis.2009.11.002

Song, I.U., Kim, J.S., Jeong, D.S., Song, H.J., & Lee, K.S. (2008). Early neuropsychological detection and the characteristics of Parkinson's disease associated with mild dementia. *Parkinsonism and Related Disorders*, *14*, 558–562. doi:S1353-8020(08)00027-8 [pii] 10.1016/j.parkreldis.2008.01.007

Trenerry, M., Crosson, B., DeBoe, J., & Leber, W. (1989). *Stroop Neuropsychological Screening Test*. Lutz, FL: Psychological Assessment Resources.

Tröster, A.I. (2008). Neuropsychological characteristics of dementia with Lewy bodies and Parkinson's disease with dementia: Differentiation, early detection, and implications for "mild cognitive impairment" and biomarkers. *Neuropsychology Review*, *18*, 103–119. doi:10.1007/s11065-008-9055-0

Tröster, A.I., Woods, S.P., & Morgan, E.E. (2007). Assessing cognitive change in Parkinson's disease: Development of practice effect-corrected reliable change indices. *Archives of Clinical Neuropsychology*, *22*, 711–718.

Wechsler, D. (1997). *Wechsler Memory Scale* (3rd ed.). San Antonio: The Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale (WAIS-IV)* (4th ed.). San Antonio, TX: The Psyhcological Corporation.

Weintraub, D., Mavandadi, S., Mamikonyan, E., Siderowf, A.D., Duda, J.E., Hurtig, H.I., & Stern, M.B. … (2010). Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology*, *75*, 448–455. doi:75/5/448 [pii] 10.1212/WNL.0b013e3181ebdd79

Williams-Gray, C.H., Evans, J.R., Goris, A., Foltynie, T., Ban, M., Robbins, T.W., … Barker, R.A. (2009). The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*, *132*, 2958–2969. doi:awp245 [pii] 10.1093/brain/awp245

Williams-Gray, C.H., Foltynie, T., Brayne, C.E., Robbins, T.W., & Barker, R.A. (2007). Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. *Brain*, *130*, 1787–1798.

Williams-Gray, C.H., Hampshire, A., Barker, R.A., & Owen, A.M. (2008). Attentional control in Parkinson's disease is dependent on COMT val 158 met genotype. *Brain*, *131*, 397–408. doi:awm313 [pii] 10.1093/brain/awm313

Woods, S.P., & Tröster, A.I. (2003). Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. *Journal of the International Neuropsychological Society*, *9*, 17–24.