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REVIEW

Evolution of Diagnostic Criteria and Assessments for Parkinson's Disease Mild Cognitive Impairment

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ABSTRACT: Mild cognitive impairment has gained recognition as a construct and a potential prodromal stage to dementia in both Alzheimer's disease and Parkinson's disease (PD). Although mild cognitive impairment has been recognized in the Alzheimer's disease field, it is a relatively more recent topic of interest in PD. Recent advances include the development of diagnostic criteria for PD mild cognitive impairment to provide more uniform definitions for clinical and research use. Studies reveal that mild cognitive impairment in PD is frequent, but also heterogeneous, with variable clinical presentations, differences in its progression to dementia, and likely differences in underlying pathophysiology. Application of the International Parkinson and Movement Disorder Society PD Mild Cognitive Impairment Task Force diagnostic criteria has provided insights regarding cognitive measures, functional assessments, and other key topics that may require additional refinement. Furthermore, it is important to consider definitions of PD mild cognitive impairment in the landscape of other related Lewy body disorders, such as dementia with Lewy bodies, and in the context of prodromal and early-stage PD. This article examines the evolution of mild cognitive impairment in concept and definition, particularly in PD, but also in related disorders such as Alzheimer's disease and dementia with Lewy bodies; the development and application of International Parkinson and Movement Disorder Society PD Mild Cognitive Impairment diagnostic criteria; and insights and future directions for the field of PD mild cognitive impairment. © 2018 International Parkinson and Movement Disorder Society

Key Words: biomarkers; dementia; diagnostic criteria; mild cognitive impairment; neuropsychological

Cognitive impairment is an important focus for clinical care, research, and education in Parkinson's disease (PD). Our understanding of the clinical diversity, underlying neurobiological mechanisms, and potential therapeutic strategies for PD mild cognitive impairment (PD-MCI) and dementia (PDD) has grown in recent years. However, in contrast to amnestic mild cognitive impairment (MCI) as a prodrome to Alzheimer's disease (AD), the construct of PD-MCI is a relative newcomer to the field with developments in diagnostic criteria, biomarker research programs, and treatment trials. This review will highlight the evolution of MCI in PD as well as other disorders, such as AD and dementia with Lewy bodies (DLB), the development of the International Parkinson and Movement Disorder Society (MDS) PD-MCI Task Force diagnostic criteria and learning points from its application and validation, and future directions for PD-MCI.

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MCI: Initial Concepts and Evolving Definitions in AD

The concept of MCI refers to a syndrome representing a stage between normal aging and dementia. MCI

was initially used to describe amnestic deficits that would precede AD.[1] Thereafter, MCI was recognized to be heterogeneous, with amnestic and nonamnestic deficits, and with MCI patients evolving not only to AD, but also having other etiologies (e.g., degenerative, vascular, and psychiatric).[2] Initial MCI criteria, used for many years, required: subjective patient complaint of cognitive decline, preferably corroborated; minimal impact on functioning; and evidence of cognitive abnormalities not due simply to age, that could be based on clinician judgment, although formal neuropsychological testing is recommended.[3,4]

The concept of preclinical AD has emerged because of discovery of biomarkers associated with AD neuropathology and application of biomarkers for diagnostic purposes.[5] For example, high tau levels and low beta-amyloid (Aβ) levels, and their ratio, found in cerebrospinal fluid (CSF), as well as increased amyloid on brain PET, are excellent predictors of underlying AD neuropathology. Of note, clinical, biomarker, and pathological correlations provide evidence of abnormalities in these biomarkers preceding AD diagnosis and even in elderly with normal cognition.[6,7] These advances introduced the concept of diagnosing AD in vivo using biomarkers and at preclinical stages.[5] With these advances, AD criteria have undergone revision. The National Institute on Aging (NIA) committee to redefine AD criteria[5,8] proposed criteria that incorporate clinical phenotype and presence of positive biomarkers (i.e., CSF Aβ and tau, Aβ on PET imaging, brain atrophy on MRI, or hypometabolism on fluorodeoxyglucose PET). The AD spectrum is divided into clinical AD (i.e., the clinical phenotype of AD, encompassing both prodromal and dementia stages), preclinical AD (i.e., preclinical phenotype but positive AD biomarkers), and asymptomatic at risk for AD (i.e., cognitively normal and biomarker patterns insufficient to meet AD definitions).[5] Concomitantly, an Alzheimer's Association (AA) committee revised diagnostic criteria for "MCI due to AD"[9] and a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) Neurocognitive Disorders Work Group also revised definitions.[8,10] The NIA-AA revised criteria for MCI attributed to AD incorporate clinical and research categories, with the latter category encompassing differing levels of certainty depending on the presence and nature of the biomarker.

MCI in PD: A History of Its Development in Concept and Criteria

Diagnostic Criteria for PDD and PD-MCI

The statement by James Parkinson in 1817 that the "senses and intellect were uninjured" in the disease may have influenced many in their historical views of PD symptomatology. Initially, the study of cognition in PD mostly focused on characterizing the dementia present at advanced PD stages, its associated neurochemical and pathological changes, and in differentiating dementia in PD from AD.[11-14] This led to the concept and definition of PDD, including clinical diagnostic criteria by the MDS Task Force for PDD.[15] These criteria provide a framework for defining a dementia syndrome in PD that does not require memory impairment (in contrast to AD criteria) and recognizes important associated clinical and behavioral features (e.g., apathy, psychosis, and excessive sleepiness) in PD. Subsequently, the MDS Task Force proposed practical guidelines for diagnosing PDD using a two-level schema (Level I: abbreviated testing and Level II: more comprehensive testing).[16] The MDS PDD criteria have now been utilized as inclusion criteria in clinical trials.[17]

Recognition of cognitive deficits in nondemented PD increased over the years.[18] These deficits mostly affected executive and visuospatial functions, rather than memory disturbances typically found in MCI in AD, and commonly preceded the development of PDD. This led to the consideration of a predementia or MCI state in PD, drawing from the MCI/AD field.[19] Initially, MCI in PD was defined using MCI criteria recognized in the AD field[2,3] or assorted criteria with differing numbers of tests per cognitive domain, types and numbers of cognitive domains, and test cut-off scores.[20-23]

It soon became clear that the definition of MCI in PD (increasingly becoming known as "PD-MCI") required standardization. Key issues included the lack of definition uniformity, challenges in interpreting and comparing studies, differences in PD populations assessed, and a need to differentiate MCI in PD from MCI in AD. The MDS formed a Task Force on PD-MCI to first review the literature, which determined a prevalence rate of ~25%, and subsequently develop diagnostic criteria. The MDS PD-MCI criteria are rooted in concepts of MCI/AD and earlier definitions,[7] but modified to address specific PD concerns and be consistent with the MDS PDD criteria including two levels of certainty depending on the number and extent of cognitive tests used.[24] Both levels have been validated and predict conversion to PDD.[25-27]

MDS PD-MCI Diagnostic Criteria: Application and Key Points

To date, the MDS PD-MCI criteria have been applied in multiple clinical and research settings, ranging from single- to multi-site cohorts, international consortium validation efforts, and inclusion criteria for treatment trials.[26-41] Both Level I and Level II categories have been examined; some studies, however,

have modified the original definitions (e.g., calling limited neuropsychological batteries as "modified Level II" rather than Level I). These studies provide a working knowledge of operationalizing the criteria, including types of cognitive tests, cut-off scores for impaired cognitive performance, subtype classification, and types of functional assessments. In addition, our knowledge has grown about clinical, pathological, and biomarker aspects of PD-MCI. PD-MCI is recognized as heterogeneous in its clinical phenotype, progression rates to PDD, underlying pathophysiological processes or associated genotypes, and biomarkers. This section will discuss recent applications of the MDS PD-MCI diagnostic criteria and highlight several key topics relevant to defining PD-MCI.

Application of MDS PD-MCI Level I and II Criteria

Studies have investigated MDS PD-MCI Level I criteria, using either an abbreviated neuropsychological assessment or a scale of global cognitive abilities validated for use in PD,[26,37-40,42-45] or Level II criteria using a comprehensive neuropsychological assessment that includes at least two tests within each of the five cognitive domains. Level I criteria were proposed as acknowledgement that comprehensive testing may not always be possible. Though practical in clinical settings, however, Level I criteria do not permit subtyping PD-MCI cognitive domains.

Studies utilizing the Level I criteria reveal that PD-MCI is frequent, ranging from 9% to 47% of PD cohorts.[37-39,46] Frequencies, however, vary based on neuropsychological tests used, cut-offs for determining impairment, consideration of premorbid functioning, and PD populations studied. Studies applying MDS PD-MCI Level II criteria also reveal that PD-MCI is frequent, ranging from 20% to 65% of PD cohorts,[23,28-33,35-37] rates comparable with studies predating MDS PD-MCI criteria. Several studies have explored the effects of using different cut-off scores for determining impairment (e.g., –1, –1.5, –2 standard deviations [SDs] below normative data); the frequency of classifying PD patients as having MCI increases with a more liberal –1 SD, whereas there is greater sensitivity for PD-MCI using a –2 SD cut-off.[31,36] One notable, consistent finding that emerged from Level II testing is an increased frequency of multiple domain impairment, occurring in some combination in 65% to 93% of PD-MCI patients.[27,29,31,35-37] A large, international consortium pooling data for 467 PD patients demonstrated the predictive validity of Level II criteria for PDD.[27] Overall, these studies demonstrate successful application of Level II classification of PD-MCI, characterization of its frequency and subtypes, and support for increased likelihood of PDD development. Several outstanding issues remain, including optimal cut-off scores for defining impairment, the disproportionate frequency of multiple- versus single-domain impairment, and difficulty discerning cognitive domain subtypes.

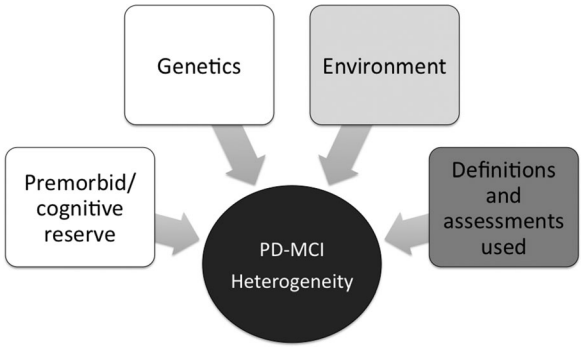

FIG. 1. Factors influencing the heterogeneity of PD-MCI. Intrinsic features include genetics, premorbid functioning/cognitive reserve, and extrinsic features, including the environment and definitions used for PD-MCI.

Key Topics in Defining PD-MCI

Cognitive Subtyping in PD-MCI: Changes in Definitions and Insights Into Heterogeneity

The profile of cognitive deficits in PD-MCI is heterogeneous, regardless of definitions and tests used,[36,47,48] in terms of which domains are affected, in what combination (e.g., up to 20 combinations have been reported),[49] and how they may evolve within individuals (Fig. 1). Delineation of PD-MCI cognitive subtypes is pertinent given that they may variably predict cognitive decline, map onto different pathophysiological substrates, and potentially require different therapeutic interventions.

The characterization of PD-MCI cognitive subtypes is still evolving conceptually. Previously, cognitive deficits in PD had been classified as being subcortical (e.g., psychomotor, executive, and working memory deficits),[50] though cortical deficits can occur too (e.g., visuospatial, memory, and language deficits).[20,37,51] Choice of classification criteria, however, drives cognitive subtyping outcomes. Use of modified Petersen's MCI criteria or other definitions[24] defined nonamnestic and amnestic subtypes with single- or multiple-domain impairments.[23,52] Such amnestic-centric classifications stemming from the AD field did not capture the heterogeneity of PD cognitive deficits. Therefore, the MDS PD-MCI Level II categorization allowed for subtyping all five cognitive domains (attention/working memory, executive, memory, visuospatial, and language). Application of the MDS PD-MCI criteria has led to epidemiological changes in the relative prevalence of single- versus multiple-domain impairment, with increased reports of the latter,[35-37,51] potentially driven by criteria used for diagnosing domain impairment.[48]

Cognitive subtyping may provide insights regarding the underlying pathophysiology of PD-MCI and conversion to PDD. In PD, nonamnestic multiple-domain MCI may be associated with axial dysfunction, gait instability,[3] and older age, whereas female sex and lower global cognition have been associated with amnestic multidomain MCI. In contrast, disease duration, levodopa dose, motor severity, mood, and quality of life are not consistently related to PD-MCI subtype.[47,48,53] The longitudinal CamPaIGN study provides a strong argument for cognitive subtyping, though it predated PD-MCI criteria.[54,55] Distinct cognitive subtypes emerged as a frontostriatal/executive function profile and posterior cortical dysfunction profile (i.e., language and visuospatial deficits), the latter of which at baseline predicted global cognitive decline and markedly increased odds for developing dementia within 5 years of PD diagnosis.[55] MDS PD-MCI subtyping may provide enhanced predictive potential, but longitudinal prospective studies are presently lacking. Neuroimaging, pharmacological, and genotyping studies suggest that neural substrates may differ among different PD-MCI cognitive subtypes.[54-57] The divergent cognitive profiles reported in the CamPaIGN study and others support a dual hypothesis of PD cognitive impairment: (1) Executive-attention deficits, which are frontostriatal based and contingent on dopamine depletion interacting with *COMT* genotype (2) posterior cortical deficits, which are associated with AD pathology (Aβ), nondopaminergic neurotransmitters (e.g., cholinergic), and *APOE* E4 genotype.[55,58]

Cognitive Measurements: Tests, Cutoffs, and Controversies

Cognitive tests provide objective measures of cognition in PD and are essential parts of both PD-MCI and PDD diagnostic criteria. Several issues, however, require consideration when applying cognitive testing in PD. Clinimetric properties of assessment scales, including measures of reliability and validity, frequently vary across different cognitive tests and may limit their utility.[59] Many tests used in PD have not undergone clinimetric evaluation in this population and lack adequate normative data for PD performance, which can lessen confidence in their interpretation in PD patients. Use of individual tests versus fixed batteries can influence interpretation and diagnostic utility.[60] Tests frequently measure several cognitive domains, which makes it difficult to get a pure measure of one particular cognitive domain. Careful thought is needed when developing a cognitive battery for PD-MCI to avoid imbalance in the coverage of domains.[61]

Measurement of cognition is strongly influenced by individual patient variables and interactions of these variables with disease-related effects. Factors including age, premorbid function, educational background, and cognitive reserve can affect performance. Inclusion of estimates of premorbid functioning can influence cognitive classification and therefore the proportion of people categorized as PD-MCI.[37] Some of these effects are well known (e.g., educational effects on IQ testing); however, others, such as cognitive reserve, are not fully understood and often difficult to measure. Cognitive assessment in PD can be confounded by factors such as motor function, motor fluctuations (ON/OFF), neuropsychiatric symptoms, fatigue/somnolence, pain, and medications (e.g., anticholinergics), which can compromise performance on cognitive tasks with substantial motor components, that are timed, or which require verbal input.

Interindividual variability may be accentuated in PD. Even in healthy individuals, within-person (across-session) SD averages around 50% of the between-person SD for a variety of different cognitive variables.[62] Cognitive fluctuations, which are common in PDD and DLB, may also occur in PD-MCI patients and lead to greater variability in cognitive performance. One-time assessments may not be accurate for diagnostic classification or measuring change. It may be important to demonstrate MCI on consecutive assessments over time, thereby indicating a degree of stability to the PD-MCI diagnosis; one should be cautious about a one-time diagnosis that could be attributed to other factors (e.g., medication effects such as from anticholinergics or dopamine agonists, or other confounders such as excessive sleepiness, depression, apathy, etc.). Different cognitive tests may be associated with more or less interindividual variability, which may explain the widely divergent paths that PD-MCI can take over time.[26,29,63-65] Additionally, many cognitive tests are subject to learning effects, thus impacting serial measurements and potentially affecting outcomes in clinical trials.

Functional Assessment in PD-MCI

Significant functional decline resulting from cognitive impairment remains a primary feature in differentiating dementia from MCI.[15] However, all MCI criteria lack specification on how to document the absence of marked functional decline. Impairment in activities of daily living related to cognition are recognized in nondemented PD[66-68] and may even precede PD diagnosis by up to 7 years.[69] Functional assessment in PD is further complicated by the need to distinguish impairments attributed to cognitive versus motor deficits.

Several methods of functional assessment exist, including self-report, informant-based, and performance-based scales, each with varying utility in PD. Self-reported cognitive functional measures reveal significant discordance

between patient report and objective evaluation, and may not be ideal in PD. For example, overestimation of medication management abilities has been reported to occur in 80% of patients.[70] The Pill Questionnaire, in which patients are asked to describe their medication regimen, has been suggested in PD,[16] but only detected 52% of those with functional impairments and missed those with milder cognitive symptoms.[71] Two brief PD-specific questionnaire-based cognitive functional scales, the Penn Daily Assessment Questionnaire (PDAQ) and the Parkinson's Disease-Cognitive Functional Rating Scale (PD-CFRS), have been developed. The PDAQ demonstrates good psychometric properties and can reliably detect any cognitive impairment and PDD.[72,73] The PD-CFRS also demonstrates strong psychometric and discriminative properties for PD cognitively normal versus noncognitively normal.[74] Informant-based scales such as these may be subject to bias from caregiver burden, mood, or familiarity with a patient's actual daily activities.[75,76] Performance-based assessments using role playing to demonstrate activities of daily living avoid these biases and allow for assessment of motor effects and targeted interventions for observed impairments. Numerous performance-based assessments exist, though few have been investigated in PD. PD-MCI patients exhibited lower scores on performance-based measures of medication management and financial management compared to healthy older adults.[67] The Performance Assessment of Self-Care Skills[77] was more strongly correlated with cognitive testing results than motor testing in PD.[66] The Multiple Object Test[78] distinguished normal cognition from PDD and PD-MCI from PDD, but could not discriminate normal cognition from PD-MCI.[79] The UCSD Performance-Based Skills Assessment[80] reliably detected any cognitive impairment and PDD and strongly correlated with measures of global cognition, as well as the PDAQ and PD-CFRS.[81] Combining practical questionnaire-based scales with objective performance-based assessments may be needed for cognitive functional assessment in PD-MCI.

PD-MCI Within the Landscapes of Early and Prodromal PD and DLB

Although PD-MCI may represent a stage within PD or a prodrome to PDD, it is important to understand how this construct also fits within other contexts. Studies of early, de novo PD cohorts demonstrate that MCI is common,[26,38,46,82] and cognitive changes may also occur in prodromal PD, an entity with recently proposed clinical and research criteria.[83,84] Cognitive dysfunction in premotor PD has been demonstrated in leucine-rich repeat kinase 2 (LRRK2) carriers, hyposmic individuals, those with reduced dopamine transporter binding or rapid eye movement (REM) sleep behavior disorder, and first-degree relatives of PD patients.[82,85-88] Several biomarkers and algorithms incorporating demographics, PD characteristics, genetics, and imaging have been proposed to predict cognitive impairment in PD;[89,90] however, none is presently sufficiently robust to be used clinically or in therapeutic trials. Identification of diagnostic biomarkers for PD-MCI, or PDD, may be challenging because there are various reasons for cognitive disturbances in PD. Biomarkers may need to include those associated with AD as well.[91,92] Because the cognitive deficits in PD are frequent, can impact patients quality of life, and can be objectively measured, cognitive testing should be part of the standard clinical evaluation of PD with baseline and serial assessments and be an outcome measure in all intervention research studies.

Another challenge is determining how PD-MCI fits in with DLB. Whereas the MDS PD-MCI criteria focus on clinically diagnosed PD, it is recognized that the chronology of cognitive and motor symptom onset can be historically vague in some individuals. Furthermore, the concept of MCI as prodromal DLB has gained support from longitudinal and biomarker studies. Clinical diagnostic criteria for DLB[93] require a dementia syndrome. Therefore, they inherently exclude prodromal presentations of DLB, which include: mild cognitive impairment (DLB-MCI), delirium onset (DLB-DEL), which may be spontaneous or provoked, or psychiatric disorder onset (DLB-psych), presenting as late-onset affective disorder or psychosis, often treatment refractory and potentially exhibiting severe antipsychotic sensitivity.[94]

Two large retrospective studies of MCI clinics suggest that one person develops DLB for every 3 to 5 cases eventually diagnosed with AD.[95,96] Nonamnestic MCI profiles are most predictive of DLB, with prominent visuospatial impairments and preserved episodic memory. Although nonamnestic MCI is 10 times more likely to progress to clinically probable DLB than AD,[96] progression of MCI to DLB does not always depend on the absence of early memory impairment/amnesia.[97] In addition, the presence of one or more core clinical features of DLB, particularly REM sleep behavior disorder, cognitive fluctuations, and mild parkinsonism, is strongly associated with an increased probability of conversion to DLB. Hallucinations and delirium at the MCI stage may suggest DLB rather than AD,[98] as may olfactory dysfunction, constipation, and increased salivation, though these can also suggest PD.[99]

Moving forward, formal consensus criteria for the diagnosis of MCI in DLB are required. Fulfilling a standard MCI definition and having one or more DLB features or biomarkers present may be essential components. This is broadly the approach taken in DSM-5, in which mild neurocognitive disorder with Lewy bodies can be diagnosed as either possible or probable

depending on the number and type of DLB type features present.[100] The performance of indicative biomarkers of DLB (e.g., dopamine transporter imaging, metaiodobenzylguanidine scintigraphy, and polysomnography) at the MCI stage will need to be established. Structural MRI, quantitative EEG, perfusion scanning, CSF markers, and peripheral nerve biopsy may prove important in identifying MCI-DLB. Clear distinction also needs to be made between MCI-DLB and PD-MCI. MCI-DLB can be diagnosed in the presence of mild, or no, spontaneous parkinsonism, whereas PD-MCI can only be diagnosed in the context of established PD. People presenting with simultaneous onset of MCI and parkinsonism might initially be given a prodromal Lewy body disorder diagnosis until a predominantly motor or predominantly cognitive route of progression, though in the revised PD criteria, dementia at onset is no longer exclusionary.[101]

Future of PD-MCI

Although MCI has become increasingly recognized in PD, its usefulness as a concept has been debated, particularly given its clinical heterogeneity, variable progression to PDD, and lack of symptomatic or disease-modifying therapeutics. However, greater awareness of PD-MCI can lead to appropriate counseling for patients and caregivers regarding symptoms, prognosis, and planning. Moreover, it can lead to increased research efforts regarding its pathophysiology, associated biomarkers, progression, and potential interventions for symptomatic treatment or for preventing cognitive decline.

PD-MCI criteria represent a necessary first step toward a uniform diagnosis in the field, for research trials, and across multiple sites. Diagnostic challenges, however, may reflect not only operational and interpretive aspects of the criteria, but also the inherent clinical heterogeneity of PD-MCI. Future studies and modified diagnostic criteria may need to incorporate biomarkers that reflect the heterogeneity of PD-MCI. Moreover, as longitudinal studies in PD and AD indicate, MCI can follow a number of courses, including persistent MCI, progression to dementia, and even reversion to normal cognition. Determining the earliest phase of MCI represents another challenge and a potential period for interventions to improve cognitive reserve, protect cognitive status, or prevent cognitive decline. The future may bring about a concept of "pre-PD-MCI" for PD patients with cognitive complaints, but not meeting PD-MCI criteria, and which potentially may incorporate positive biomarkers such as in MCI-AD criteria.[9] Here, cognitive characterization would be recommended when PD patients are first diagnosed, or even in the prodromal PD stage. Future studies should determine whether pre-PD-MCI converts into PD-MCI and, subsequently, PDD (Fig. 2). Last, regulatory paths for therapeutic development and approval are needed for PD-MCI. Diagnostic criteria for PD-MCI represent an important tool for the research setting, though future developments may elucidate optimal cognitive and functional measurements and incorporate imaging, fluid, or other biomarkers in diagnosis, progression, and monitoring of therapeutic effects. ■

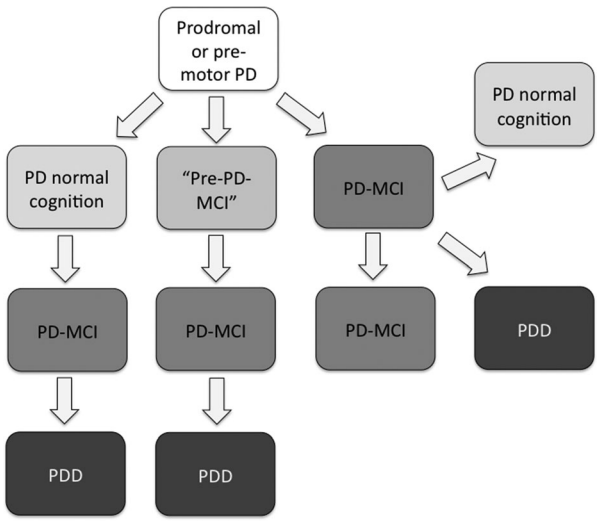

FIG. 2. Potential trajectories and changes in cognition within PD over time.

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