Mild cognitive impairment: an update in Parkinson’s disease and lessons learned from Alzheimer’s disease

Jennifer G Goldman*,1, Neelum T Aggarwal2 & Cynthia D Schroeder3

Practice points

- Cognitive deficits are frequent in Parkinson’s disease (PD) and encompass a broad spectrum of clinical features and severity. Patients may have difficulty with attention, working memory, executive function, psychomotor speed, visuospatial abilities, language and memory domains, individually or in combination.
- It is important for clinicians to inquire about cognitive changes or problems, even early in the course of PD and even when symptoms are at mild stages.
- Mild cognitive impairment (MCI) has gained recognition as a construct, an early stage of cognitive decline and a risk factor for developing dementia in PD.
- Recent advances in our understanding of PD-MCI, its variable clinical presentations and differences in progression to dementia, however, suggest that PD-MCI may not be a single, uniform entity. Differences in underlying neurobiological substrates, neuropathology, genetics, among other factors, may contribute to the clinical variability of PD-MCI.
- Research studies have investigated biomarkers such as cerebrospinal fluid markers, neuroimaging studies and genetics that may be associated with PD cognitive impairment and could potentially be used for diagnosis, prognosis or early detection of cognitive decline.
- Compared to the field of MCI and Alzheimer’s disease (AD), PD-MCI is a ‘relative newcomer’ with more recent advances in diagnostic criteria, biomarker studies and therapeutic trials.
- Many lessons can be learned from the MCI-AD field including the evolution of MCI definitions over the years, clinical trials that now incorporate biomarkers and genetics in the study design and emerging therapeutic strategies targeting specific biological mechanisms, novel compounds and delivery systems, and earlier stages of cognitive impairment with potential disease-modifying or prevention trials.

Cognitive dysfunction is an important focus of research in Parkinson’s disease (PD) and Alzheimer’s disease (AD). While the concept of amnestic mild cognitive impairment (MCI) as a prodrome to AD has been recognized for many years, the construct of MCI in PD is a relative newcomer with recent development of diagnostic criteria, biomarker research programs and treatment trials. Controversies and challenges, however, regarding PD-MCI’s definition, application, heterogeneity and different trajectories have arisen. This review will highlight current research advances and challenges in PD-MCI. Furthermore, lessons from the AD field, which has witnessed an evolution in MCI/AD definitions, relevant advances in biomarker research and development of disease-modifying and targeted therapeutic trials will be discussed.

*Author for correspondence: Tel.: +1 312 563 2900; Fax: +1 312 563 2024; Jennifer_Goldman@rush.edu
While the presence of cognitive deficits in Parkinson’s disease (PD) has been recognized for many years, it is only more recently that mild cognitive impairment in PD (PD-MCI) has emerged as a concept and distinct entity, with epidemiological studies, proposed diagnostic criteria and symptomatic treatment trials. PD-MCI may represent an early stage of cognitive decline and a risk factor for developing dementia [1,2], and thus, an intermediate state between normal cognition and dementia, similar to amnestic MCI in the context of developing Alzheimer’s disease (AD). Recent advances in our understanding of PD-MCI, however, suggest that PD-MCI is rather heterogeneous with different clinical phenotypes, rates of progression and perhaps underlying mechanisms. In 2012, a Movement Disorder Society (MDS) Task Force proposed diagnostic criteria for PD-MCI in order to harmonize disparate definitions of PD-MCI across multiple clinical and research sites and to identify PD-MCI cohorts for future therapeutic trials (Figure 1) [3]. The MDS PD-MCI criteria have now been applied in clinical and research settings, including international validation efforts and recent treatment trials, but unresolved issues and areas for further study remain [4]. This review will discuss recent findings related to PD-MCI, highlighting its heterogeneity and challenges, discussing several debates and unmet needs regarding PD-MCI, and exploring lessons that can be learned from the MCI-AD field.

PD-MCI: a heterogeneous construct

• Frequent & identifiable

MCI in nondemented PD is frequent, affecting 25–50% [5–10]. While estimates vary across studies depending on the PD population (e.g., clinic or community-based, incident or prevalent PD), presence/absence of co-morbid neuropsychiatric disorders (e.g., depression, anxiety, apathy, sleep), severity of motor problems, potential effects of PD-related and other medications and methodological issues (e.g., diagnostic criteria, cognitive assessments, definitions of impairment), which will be further discussed below, they are fairly consistent across these studies and definitions. PD-MCI has gained attention as an identifiable cognitive category within the PD cognitive spectrum, a common problem and a state distinct from dementia. However, PD-MCI has emerged as a more heterogeneous entity in its clinical phenotype, timing, progression, and pathology, perhaps even beyond what might be expected by differences in PD-MCI definitions across studies.

• Clinical phenotypes & definitions

Cognitive dysfunction in PD-MCI encompasses a broad spectrum of clinical deficits and severity with impairment in attention, working memory, executive function, psychomotor speed, visuospatial abilities, language and memory domains, individually or in combination. In older PD studies using modified Petersen’s MCI criteria or other definitions, cognitive phenotypes were frequently categorized as nonamnestic and amnestic cognitive domains affected and as single and multiple-domain impairment [11]. Instead of classifying PD-MCI as nonamnestic or amnestic type, the MDS PD-MCI criteria recommended specification of the affected domain(s) in order to examine potential differences among cognitive domain subtypes and since episodic memory function, albeit impaired at times in PD, was not the main hallmark as found in AD. Subtype designation of PD-MCI nonamnestic deficits thereby captures individual domains (e.g., attention/working memory vs executive function vs language vs visuospatial function). Moreover, these proposed subtype distinctions may facilitate investigations of whether different types of cognitive impairment differ in their progression rates and neurochemical or neuropathological substrates.

Clinical phenotypes of PD-MCI, in studies of incident and prevalence cohorts and pre- and post-MDS PD-MCI criteria, are highlighted below and in Table 1 [5,7,8,10,12–23]. Newly diagnosed PD patients across different studies demonstrate deficits in executive function, attention, psychomotor speed and visuospatial skills, as well as memory, in some studies [5,10,17,24]. In one study of incident PD cases, PD-MCI as defined by MDS criteria level II (comprehensive neuropsychological battery), occurred in 42.5% with memory deficits in 15.1% [17]. In studies of prevalent, nondemented PD cohorts prior to MDS PD-MCI criteria, similar cognitive profiles occur with greater nonamnestic subtypes, but predominantly as single domain impairment [7–9,14,15,25]. Recent studies applying MDS PD-MCI level II criteria demonstrate that PD-MCI remains frequent, ranging from 35 to 65% of PD cohorts [13,15,18,26–28]. Several studies categorize the PD-MCI cohorts as having single domain and multiple domain
Figure 1. The interface of different Parkinson’s disease-mild cognitive impairment criteria. PD-MCI, diagnostic flowchart adapted from MDS task force criteria for diagnosis of PD-MCI and Petersen’s amnestic/nonamnestic mild cognitive impairment criteria MDS PD-MCI criteria features in solid dark gray; MCI criteria features (Petersen) in gray striped pattern; overlap of both of these criteria features in light gray.

MCI: Mild cognitive impairment; MDS: Movement Disorder Society; NC: Normal cognition; PD: Parkinson’s disease.

Impairment

Neuropsychological impairment found?

Level I: Global cognitive abilities scale or limited battery of neuropsychological tests with impairment on ≥2 tests

Level II: Two tests in each of 5 cognitive domains (attention/working memory, executive, language, memory, visuospatial) with impairment on ≥2 tests (either as two impaired tests in one cognitive domain or one impaired test in two different cognitive domains), defined as 1–2 SD below norms, or significant decline on serial cognitive testing or significant decline from estimated premorbid levels

No impairment

PD Patients

Decline in cognitive abilities over time reported by patient or informant, or observed by clinician, but deficits do not impede functional independence

Patient has other condition explaining cognitive impairment (e.g., co-morbidity, stroke, delirium, head trauma, severe psychiatric illness) or meets dementia criteria

No

Excluded from MCI criteria

Yes

Overlap of criteria

MDS PD-MCI criteria

MCI criteria (Petersen)

Impairment

How many affected domains?

1

Memory domain affected?

Yes

No

PD-MCI single-domain amnestic

PD-MCI single-domain nonamnestic (specify which domains)

PD-MCI multiple-domain amnestic (specify which domains)

PD-MCI multiple-domain nonamnestic (specify which domains)

Memory domain affected?

Yes

No

Patient does not meet criteria for PD-MCI, patient classified as PD-NC

>1

Yes

No

PD-MCI single-domain amnestic

PD-MCI single-domain nonamnestic (specify which domains)

PD-MCI multiple-domain amnestic (specify which domains)

PD-MCI multiple-domain nonamnestic (specify which domains)

Excluded from MCI criteria

PD-MCI diagnostic flowchart adapted from MDS task force criteria for diagnosis of PD-MCI and Petersen’s amnestic/nonamnestic mild cognitive impairment criteria. MDS PD-MCI criteria features in solid dark gray; MCI criteria features (Petersen) in gray striped pattern; overlap of both of these criteria features in light gray.

impairment, but details regarding individual cognitive domain subtypes are limited. One consistent, notable finding across recent studies utilizing the MDS PD-MCI level II criteria is an increased frequency of multiple domain impairment. PD-MCI multiple domain impairment occurred in 90, 93, 91.2 and 65% of PD-MCI, compared with single domain impairment in 5, 7, 8.5 to 35%, respectively, a feature that may relate to criteria requirements of impairment in at least one test in two or more cognitive domains [13,15,18,26]. Another schema for categorizing PD cognitive impairment has emerged from the CamPaIGN study with two distinct phenotypes: frontostriatal/executive function deficits and posterior cortical dysfunction (i.e., impaired language/semantic fluency and visuospatial orientation/pentagon copying) [2,29]. Executive deficits may primarily relate to disrupted dopaminergic frontostriatal networks, whereas posterior cortical impairment reflects nondopaminergic dysfunction, cortical Lewy body deposition and/or AD-type pathology [30]. Different neurochemical and neuropathological predispositions may underlie not only the cognitive phenotype in early PD, but also their rates of progression and conversion to dementia. This cognitive categorization of ‘frontostriatal’
<table>
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<tr>
<th>Population/sample size</th>
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</tr>
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<tbody>
<tr>
<td>Prevalent, community, n = 103</td>
<td>≥2 SD below normative data on ≥1 test</td>
<td>General: MMSE, DRS; attention/executive function: Stroop Color Word Test; memory: BVRT; visuospatial/constructive skills: JLO</td>
<td>55%</td>
<td>57.1%/42.8%</td>
<td>Janvin et al. (2003)</td>
<td>[6]</td>
</tr>
<tr>
<td>Incident, community, n = 159</td>
<td>MMSE ≥24 and impairment on pattern recognition memory test or Tower of London task</td>
<td>General: MMSE, NART; frontal lobe: phonemic fluency, semantic fluency; CANTAB modified Tower of London; temporal lobe: CANTAB pattern recognition memory task; frontal/temporal: CANTAB spatial recognition memory task</td>
<td>36%</td>
<td>58%/42%</td>
<td>Foltynie et al. (2004) (CamPaIGN)</td>
<td>[5]</td>
</tr>
<tr>
<td>Incident, community, n = 115</td>
<td>≥2 SD below normative data on ≥3 tests</td>
<td>General: MMSE, DART; attention: Digit Span Forward and Backward, TMT-B, Stroop Color Word Test Part C; executive function: modified WCST, COWAT, semantic fluency, WAIS-III Similarities, Tower of London-Drexel Test; language: BNT; memory: RAVLT trials (delayed free recall), recognition, RBMT Logical Memory Test immediate (delayed recall); WMS-III Face recognition immediate (delayed recognition); Visual Association Test; Psychomotor speed: WAIS-R Digit Symbol test, TMT-A, Stroop Color Word Test (Parts A/B); visuospatial/constructive skills: JLO, Groningen Intelligence Test spatial test, Clock Drawing Test</td>
<td>23.5%</td>
<td>Not specified</td>
<td>Muslimovic et al. (2005)</td>
<td>[10]</td>
</tr>
<tr>
<td>Prevalent, clinic, n = 86</td>
<td>≥1.5 SD below normative data on ≥1 domain</td>
<td>Attention: digits forward and backward; executive function: TMT-B, Stroop; language: COWAT, semantic fluency; memory: RAVLT learning, delayed recall; visuomotor processing speed: TMT-A (TMT-B); visuospatial (motor/nonmotor): JLO, clock drawing test</td>
<td>21%</td>
<td>67%/33%</td>
<td>Caviness et al. (2007)</td>
<td>[8]</td>
</tr>
<tr>
<td>Incident, community, n = 196</td>
<td>&gt;1.5 SD below normative data in &gt;1 domain</td>
<td>General: MMSE, IQCODE; attention/executive function: serial 7s from MMSE, semantic fluency, Stroop; memory: CVLT-II immediate recall, short- and long-delay recall; visuospatial: VOSP silhouettes</td>
<td>18.9%</td>
<td>86.5%/13.5%</td>
<td>Aarsland et al. (2009) (ParkWest)</td>
<td>[12]</td>
</tr>
</tbody>
</table>

BNT: Boston naming test; BVRT: Benton visual retention test; CANTAB: Cambridge neuropsychological test automated battery; CDR: Cognitive drug research; CERAD: Consortium to establish a registry for Alzheimer’s disease; COWAT: Control word association test; CVLT: California verbal learning test; DART: National adult reading test, Dutch version; D-KEFS: Delis-Kaplan executive function system; DRS: Dementia rating scale; FCSRT: Free and cued selective reminding test; HVLT: Hopkins verbal learning test; IQ-CODE: Informant questionnaire on cognitive decline in the elderly; JLO: Judgment of orientation test; MCI: Mild cognitive impairment; MMSE: Mini-mental state exam; MoCA: Montreal cognitive assessment; NAI: Nueemberger alternans test; NART: National adult reading test; NIH: Neurobehavioral signs and symptoms Abbreviated Inventory; PD: Parkinson’s disease; PD-CRS: Parkinson’s disease cognitive rating scale; RAVLT: Rey auditory verbal learning test; RBMT: Rivermead behavioral memory test; RCF: Rey complex figure test; SD: Standard deviation; SRT: Selective reminding test; TAP: Test for attentional performance; VOSP: Visual object space perception test; WAIS: Wechsler adult intelligence scale; WCST: Wisconsin card sorting test; WMS: Wechsler memory scale; WTAR: Wechsler test of adult reading.
### Table 1. Cross-sectional studies of mild cognitive impairment in Parkinson’s disease cohorts (cont.).

<table>
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<tr>
<th>Population/sample size</th>
<th>MCI criteria</th>
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<tr>
<td>Incident and prevalent, community and clinic, multi-center, n = 1346</td>
<td>≥1.5 SD below norms on ≥1 domain</td>
<td>Attention/executive function: DRS attention/initiation, Stroop Color Word Test, phonemic fluency, semantic fluency, Tower of London, PD-CRS subtests (attention)/Serial 7s from MMSE, CDR Digit Vigilance and simple/choice reaction time, Digit Span, Cancellation test, Similarities, Corsi block span, TMT-A (executive function); memory: CVLT-II (immediate recall short- and long-delay recall), DRS memory, CDR delayed word recognition, SRT (immediate delayed recall recognition), HVLT (immediate delayed recall), PD-CRS (immediate and delayed recall), RAVLT (immediate and delayed recall, verbal)/BVRT, CANTAB pattern and spatial recognition memory, CDR delayed picture recognition, RCF recall (visual); visuospatial: Benton test matching, DRS construction, Intersecting Pentagons, JLO, RCF, PD-CRS Clock Copy, VOSP cube and silhouettes</td>
<td>25.8%</td>
<td>76.1%/23.9%</td>
<td>Aarsland et al. (2010)</td>
<td>[7]</td>
</tr>
<tr>
<td>Prevalent, retrospective clinic, n = 72</td>
<td>Petersen criteria, SD cutoff not specified, deficits on ≥2 tests/domain</td>
<td>Attention: Digit Span Forwards, TMT-A; executive function: TMT-B, ‘WORLD’ backwards from MMSE; language: BNT, phonemic fluency, semantic fluency; memory: CERAD or HVLT-R, 3–item recall from MMSE; visuospatial: Intersecting Pentagons, JLO</td>
<td>52.8%</td>
<td>60.5%/39.5%</td>
<td>Sollinger et al. (2010)</td>
<td>[15]</td>
</tr>
<tr>
<td>Prevalent, clinic, n = 143 (n = 119, nondemented PD)</td>
<td>≥1.5 SD below normative data on 2 tests in ≥1 one domain, or ≥1.5 SD or ≥2 SD below normative data for 1 test (multiple cutoffs and combinations explored)</td>
<td>Attention: Stroop Color Word Test, Digit span Forward and Backward, Digit Ordering, Map Search, TMT-A; executive function: action verb fluency, verbal fluency (letter, category), category switch from D-KEFS, Stroop Interference, TMT-B; memory: CVLT-II acquisition, short delay, long delay, RCF short delay, long delay; visuospatial: RCF copy, JLO, Fragmented Letters</td>
<td>30% (for ≥1.5 SD below normative data on 2 tests/domain)</td>
<td>53%/47%</td>
<td>Dalrymple-Alford et al. (2011)</td>
<td>[19]</td>
</tr>
</tbody>
</table>

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PD: Parkinson’s disease; PD-CRS, Parkinson’s disease cognitive rating scale; RAVLT, Rey auditory verbal learning test; BVRT, Benton visual retention test; CVLT: California verbal learning test; CANTAB: Cambridge neuropsychological test automated battery; CDR: Cognitive drug research; CERAD: Consortium to establish a registry for Alzheimer’s disease; COWAT: Control word association test; CVLT: California verbal learning test; DART: National adult reading test, Dutch version; D-KEFS: Delis-Kaplan executive function system; DRS: Dementia rating scale; FCSRT: Free and cued selective reminding test; HVLT: Hopkins verbal learning test; IQ-CODE: Informant questionnaire on cognitive decline in the elderly; JLO: Judgment of line orientation test; MCI: Mild cognitive impairment; MMSE: Mini-mental state exam; MoCA: Montreal cognitive assessment; NAI: Nuernberger alterinventar; NART: National adult reading test; NBI: Neurobehavioral signs and symptoms Abbreviated Inventory; PD: Parkinson’s disease; PD-CRS; Parkinson’s disease cognitive rating scale; RAVLT: Rey auditory verbal learning test; RCF: Rey complex figure test; RBMT: Rivermead behavioral memory test; SRT: Selective reminding test; SD: Standard deviation; TAP: Test for attentional performance; VOSP: Visual object space perception test; WAIS: Wechsler adult intelligence scale; WMS: Wechsler memory scale; WCST: Wisconsin card sorting test.
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<tr>
<td>Prevalent, clinic, n = 107</td>
<td>≥1 SD, ≥1.5 SD, or ≥2 SD below normative data on one test/domain or ≥1 SD, ≥1.5 SD, or ≥2 SD below normative data on ≥2 tests/domain (multiple cutoffs and combinations explored)</td>
<td>Attention: TAP (Alertness, Go-Nogo subtests); executive function: Tower of London, TMT-B, NAI, Digit Span Forward and Backward; memory: CERAD word list memory, delayed recall, recognition, Logical Memory I and II; psychomotor speed and naming ability: TMT-A, BNT, CERAD semantic fluency; praxis and visual function: CERAD line drawings, object decision of VOSP</td>
<td>9.9–92.1% (depending on definition used)</td>
<td>25.8–100%/0–74.2% (depending on definition used)</td>
<td>Liepelt-Scarfone et al. (2011)</td>
<td>[23]</td>
</tr>
<tr>
<td>Prevalent, clinic, n = 61</td>
<td>≥1.5 SD below normative data in ≥1 one domain</td>
<td>General: MMSE, NART; executive function: TMT-B; language: semantic fluency, phonemic fluency; memory: Logical Memory; psychomotor speed: TMT-A; working memory: Digit Span total</td>
<td>62%</td>
<td>37.7%/24.6%</td>
<td>Naismith et al. (2011)</td>
<td>[20,21]</td>
</tr>
<tr>
<td>Prevalent, clinic, n = 40</td>
<td>≥1.5 SD below standardized mean (or scaled score ≤6 or percentile range ≤10) on two tests in the same domain</td>
<td>General: DRS–2, MMSE; attention/executive function: Stroop Color Word Test, TMT-B, semantic fluency, phonemic fluency; memory: RAVLT lists, immediate and delayed recall, recognition; visuospatial: RCF copy, Block design (WAIS-III); Bell test</td>
<td>45%</td>
<td>61.1%/38.9%</td>
<td>Villeneuve et al. (2011)</td>
<td>[21]</td>
</tr>
<tr>
<td>Prevalent, clinic, n = 350</td>
<td>≥1.5 SD below normative data in ≥1 one domain</td>
<td>General: MMSE; attention/executive function: Digit Span Forward and Backward, Symbol Digit Modalities Test, semantic fluency; language: BNT, Similarities; memory: CERAD word list learning and delayed recall; visuospatial: intersecting pentagons, JLO</td>
<td>36.6%</td>
<td>67%/33%</td>
<td>Goldman et al. (2012)</td>
<td>[14]</td>
</tr>
<tr>
<td>Prevalent, clinic, n = 80</td>
<td>≥1.5 SD below normative data in ≥1 one domain</td>
<td>General: MMSE; attention: Digit Span; executive function: Stroop Color Word Test; memory: RAVLT immediate recall, delayed recall; visuospatial: Clock Drawing Test</td>
<td>60%</td>
<td>58.3%/41.7%</td>
<td>Wu et al. (2012)</td>
<td>[22]</td>
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**PD cohorts with MDS PD-MCI Level II criteria (with modifications as noted)**

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<tr>
<td>Prevalent, clinic, n = 104</td>
<td>≥1.5 SD below normative data</td>
<td>General: MMSE; attention/working memory: TMT, Digit cancellation, Digit Span Forwards and Backwards, Stroop, Corsi test; executive function: Phonemic fluency, FAB, Clock Drawing Test; language: Similarities, semantic fluency; memory: RAVLT immediate and delayed recall, RCF immediate recall; visuospatial: Clock Drawing Copy Test, RCF copy</td>
<td>33%</td>
<td>Not specified</td>
<td>Biundo et al. (2013)</td>
<td>[24]</td>
</tr>
</tbody>
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**Abbreviations:** BNT: Boston naming test; BVRT: Benton visual retention test; CVLT: California verbal learning test; CANTAB: Cambridge neuropsychological test automated battery; CDR: Cognitive drug research; CERAD: Consortium to establish a registry for Alzheimer’s disease; CONAT: Control word association test; CVL: California verbal learning test; DART: Delis-Kaplan executive function system; DRS: Dementia rating scale; F:CSRT: Free and cued selective reminding test; HVLT: Hopkins’ verbal learning test; IQ:CODE: Informant questionnaire on cognitive decline in the elderly; JLO: Judgment of line orientation test; MCI: Mild cognitive impairment; MMSE: Mini-mental state exam; MoCA: Montreal cognitive assessment; NAI: Nuernberger altersinventar; NART: National adult reading test; NB: Neurobehavioral signs and symptoms Abbreviated Inventory; PD: Parkinson’s disease; PD-CRS: Parkinson’s disease cognitive rating scale; RAVLT: Rey auditory verbal learning test; RCF: Rey complex figure test; RBMT: Rivermead behavioral memory test; SRT: Selective reminding test; SD: Standard deviation; TAP: Test for attentional performance; VOSP: Visual object space perception test; WMS: Wechsler adult intelligence scale; WMS: Wechsler memory scale; WPAR: Wechsler test of adult reading; WCST: Wisconsin card sorting test.
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<th>Study (year)</th>
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<tr>
<td>Incident, clinic, n = 123</td>
<td>≥1.5 SD below normative data</td>
<td>General: MMSE, DART; attention: Digit Symbol Test, TMT-A; executive function: Modified WCST, COWAT; language: BNT, WAIS-III Similarities; memory: RAVLT, RBMT Logical Memory subtest; visuospatial: Clock Drawing Test, JLO</td>
<td>35%</td>
<td>35%/65%</td>
<td>Broeders et al. (2013)</td>
<td>[26]</td>
</tr>
<tr>
<td>Prevalent, clinic, n = 76</td>
<td>≥2 SD (also 1–2.5) below normative data</td>
<td>General: MMSE; attention/working memory: Digit Span Forwards, LNS, SDMT, TMT-A; executive function: Clock Drawing Test, COWAT, Digit Span Backwards, Progressive Matrices, TMT-B; language: BNT, semantic fluency, WAIS-III Similarities; memory: CERAD word list learning, delayed recall, and recognition, Logical Memory I and II, FCSRT, Figural Memory; visuospatial: Clock Copying Test, Intersecting Pentagons, JLO</td>
<td>62% (for ≥2 SD below normative data)</td>
<td>8.5%/91.5%</td>
<td>Goldman et al. (2013)</td>
<td>[13]</td>
</tr>
<tr>
<td>Prevalent, clinic, multicenter, n = 139</td>
<td>≥1.5 SD below normative data</td>
<td>General: MMSE, MoCA, NBI, WTAR; attention: LNS, DKEFS Color Word Interference Color Naming test; executive function: Visual Verbal Test, TMT B-A; language: Naming, MoCA sentence subsets; memory: CANTAB Pattern Recognition Memory, Spatial Recognition Memory, Paired Associates Learning; visuospatial: JLO, RCF copy</td>
<td>33%</td>
<td>7%/93%</td>
<td>Marras et al. (2013)</td>
<td>[15]</td>
</tr>
<tr>
<td>Incident, community, n = 219</td>
<td>≥1.5 SD (also 1–2) below norm in ≥1 domain</td>
<td>General: MMSE, MoCA; attention: CDR Power of Attention score; executive function: Modified Tower of London task, phonemic fluency, semantic fluency; language: Naming, MoCA sentence subsets; memory: CANTAB Pattern Recognition Memory, Spatial Recognition Memory, Paired Associates Learning; visuospatial: JLO, Cube Copy</td>
<td>42.5%</td>
<td>Not specified</td>
<td>Yamall et al. (2013) (ICICLE)</td>
<td>[17]</td>
</tr>
<tr>
<td>Prevalent, multicenter, clinic, n = 142</td>
<td>≥1.5 SD below norm in ≥1 test</td>
<td>General: MMSE, MoCA, DRS–2, Shipley–2; attention/working memory: Digit Symbol subtest, LNS, Digit Span, TMT; executive function: Clock Drawing Test, phonemic fluency; language: semantic fluency, BNT; memory: HVLT-R, Logical Memory; visuospatial: JLO, Cube Copy</td>
<td>67%</td>
<td>5%/95%</td>
<td>Cholerton et al. (2014)</td>
<td>[18]</td>
</tr>
</tbody>
</table>

BNT: Boston naming test; BVRT: Benton visual retention test; CVLT: California verbal learning test; CANTAB: Cambridge neuropsychological test automated battery; CDR: Cognitive drug research; CERAD: Consortium to establish a registry for Alzheimer’s disease; COWAT: Control word association test; CVLT: California verbal learning test; DART: National adult reading test, Dutch version; D-KEFS: Delis-Kaplan executive function system; DRS: Dementia rating scale; FCSRT: Free and cued selective reminding test; HVLT: Hopkins verbal learning test; IQ-CODE: Informant questionnaire on cognitive decline in the elderly; JLO: Judgment of line orientation test; MCI: Mild cognitive impairment; MMSE: Mini-mental state exam; MoCA: Montreal cognitive assessment; NAI: Nuernberger altersinventar; NART: National adult reading test; NB: Neuropsychological signs and symptoms Abbreviated Inventory; PD: Parkinson’s disease; PD-CRS: Parkinson’s disease cognitive rating scale; RAVLT: Rey auditory verbal learning test; RCF: Rey complex figure test; RBMT: Rivermead behavioral memory test; SRT: Selective reminding test; SD: Standard deviation; TAP: Test for attentional performance; VOSP: Visual objects space perception test; WAIS: Wechsler adult intelligence scale; WMS: Wechsler memory scale; WTA: Wechsler test of adult reading; WCST: Wisconsin card sorting test.
versus ‘posterior cortical’ deficits is reminiscent to some degree of the nonamnestic and amnestic categorization. Along with the aforementioned challenges in parsing out individual subtypes of single domain PD-MCI and identifying sufficient subject numbers per subtype, further research is needed regarding optimal definitions of PD-MCI subtypes and whether subtyping by individual cognitive domains will be a fruitful concept.

• Timing
Besides its clinical spectrum, PD-MCI also can be thought of in terms of its time course and relationship to motor symptom onset and PD diagnosis. Cognitive impairment in PD is no longer just a late-stage phenomenon but rather it can occur in incident PD with reports of PD-MCI in 20–40% [5,10,12,17]. Although these studies vary in definitions of PD cognitive impairment or PD-MCI used, it is apparent that cognitive dysfunction can be a symptom in PD early on and even prior to initiation of dopaminergic therapy. Furthermore, these studies support the importance of asking PD patients and caregivers about cognitive symptoms even at this early disease stage.

The presence of cognitive deficits in de novo, untreated PD patients leads to several questions including: how early in the course of PD can cognitive deficits occur, are they present in premotor PD, is their presence related to dopaminergic deficiency (and perhaps improved by dopaminergic treatments) or related to other neurochemical, neuropathological or clinical issues (e.g., depression, anxiety, sleep disturbances), and is there a distinction between early cognitive deficits in PD or in dementia with Lewy bodies (DLB)? Indeed, there is increasing evidence for cognitive deficits in ‘premotor’ PD (e.g., persons who do not have motor features characteristic of diagnosable PD but who may have nonmotor features affecting smell, bowel function, mood or sleep), ‘preclinical’ PD (e.g., persons who may not have any clinical features but have abnormalities on neuroimaging measures such as [18F]-fluorodopa PET or dopamine transporter [DAT] SPECT imaging), or in cohorts ‘at risk’ or relatives of PD patients, who also may be at genetic risk [31]. Rapid eye movement behavior disorder (RBD) is associated with cognitive deficits in executive function, memory and visuospatial abilities and the development of synucleinopathies such as PD or DLB by 5 or more years [34], and about half of ‘idiopathic’ RBD patients will develop a synucleinopathy after 12 years [35]. The Parkinson Associated Risk Study found that healthy relatives of PD patients with hyposmia and decreased DAT uptake on imaging scans had worse scores on verbal fluency, attention/executive function and processing speed [36]. While a primary inclusion criterion of the MDS PD-MCI is the presence of clinically diagnosed PD, there is a current movement in the PD field to redefine the criteria for PD [37]. Indeed, studies of these premotor or ‘at-risk’ cohorts challenge our notions of when PD actually begins and at what stage MCI may occur within the PD diagnostic spectrum.

Another challenge in defining PD-MCI is determining how this construct fits in with DLB. Whether PD dementia and DLB are the same disorder has been debated over the years [37,38]. In the development of the MDS PD-MCI criteria, the task force recognized this issue, particularly since the onset of cognitive symptoms relative to motor symptoms can be historically vague, and in some cases, occur concurrently. The PD-MCI criteria focus on clinically diagnosed PD but acknowledge the challenge of differentiating PD-MCI from incipient DLB. Indeed, the concept of MCI as prodromal DLB has gained attention and support from studies documenting the progression of nonamnestic MCI to DLB and other non-AD dementias as well as clinicopathological correlates of MCI in longitudinally followed cohorts [11,39]. Nonamnestic MCI subjects, compared with those with amnestic MCI, had a 10-fold greater likelihood to develop probable DLB; these subjects initially manifested greater attention and/or visuospatial impairment (88%) than memory deficits (25%) as well as RBD, daytime sleepiness and fluctuations [40]. Clinical features found in other MCI cases later confirmed by autopsy to have DLB [41]. Further studies regarding MCI as prodromal DLB, including clinical features, biomarkers and pathological correlates, may be needed to determine the timing, phenotype, definitions and context of MCI in parkinsonian/synuclein disorders.

• Progression, stability or reversion
Emerging data from longitudinal studies of PD-MCI shed light on the progression of PD-MCI and its conversion to PD dementia, but also raise questions regarding whether PD-MCI subtypes differ in their course and whether all
PD-MCI progresses to dementia. In a study of prevalent PD subjects, 18/29 (62%) of those with PD-MCI who completed follow-up at 4 years converted to PD dementia, whereas dementia ensued in only 6/30 (20%) with intact cognition at baseline; although a small sample with a limited neuropsychological battery, the study suggested that single domain nonamnestic MCI, along with higher depression scores, were associated with dementia conversion, whereas predominant amnestic deficits and multiple domains were not [1]. The CamPaIGN study provides over a decade of follow-up of incident PD persons and suggests divergent patterns of PD-MCI [2,29,22]. At 3–5 years follow-up, 13/126 (10%) converted to dementia and an additional 57% had cognitive impairment, mainly frontostriatal deficits [2]. Multiple factors predicted global cognitive decline at 5 years including: age ≥72 years (Odds ratio [OR]: 4.81; 95% CI: 1.14–20.23), decreased semantic fluency (OR: 6.89; 95% CI: 1.30–36.55), impaired copy of intersecting pentagons (OR: 2.78; 95% CI: 1.001–7.73), non-tremor dominant motor phenotype (OR: 3.93; 95% CI: 0.79–19.57) and a genetic variant in the MAPT gene (H1/H1 genotype) (OR: 12.14; 95% CI: 1.26 = 117.36). Older age along with the impaired posterior cortical cognitive function (i.e., semantic fluency and intersecting pentagons) had a combined OR of 88 for developing dementia within the first 5 years of PD diagnosis [29]. This study suggests that not all cognitive impaired PD patients will necessarily develop dementia and proposes that PD patients with greater posterior cortical phenotypes, but not those with greater frontostriatal-based/executive dysfunction, develop dementia at follow-up. Moreover, a functional polymorphism in the dopamine-regulating enzyme COMT was associated with executive dysfunction but not dementia, whereas the MAPT and APOE4 polymorphisms were strongly associated with earlier dementia in this cohort [29,29,42].

Other longitudinal studies of PD cohorts, particularly those using MDS PD-MCI diagnostic criteria, are in early stages but provide some estimates of PD-MCI progression. In a community-based incident PD cohort in Sweden, 37/134 (27%) of PD patients developed dementia over 5 years of follow-up [43]. Of the 49 PD patients diagnosed as MCI, 25/49 (50%) developed dementia in this timeframe. Presence of MCI and older age predicted dementia, and baseline scores on episodic memory, semantic fluency, mental flexibility and visuospatial function tests were worse in those PD-MCI who converted to dementia, compared with those who did not. A follow-up study of the incident Norwegian ParkWest PD cohort at 1 year and 3 year supports that PD patients with MCI at baseline were more likely to progress to dementia, with 27% of the initial group subsequently diagnosed with PD dementia [44]; similar findings were found in a Netherlands study with increasing rates of PD-MCI and of those with baseline PD-MCI, dementia at 3-year and 5-year follow-up [26]. These studies, however, also demonstrate a high rate of attrition at follow-up and thereby, an important challenge of conducting longitudinal studies.

PD-MCI may also be an unstable state with reversion to normal cognitive status at follow-up in some studies. In the Swedish study, 6 (11%) patients with PD-MCI at baseline reverting to normal cognition, and 10 patients fluctuated between MCI and normal cognition [43]. Both the Dutch and Norwegian studies also demonstrate that some PD-MCI patients at follow-up revert to normal cognition, though with longer follow-up, may ultimately have MCI or dementia. In the ParkWest study, at 1-year follow-up approximately 20% of PD-MCI had normal cognition; however, among those patients with MCI at baseline and 1-year follow-up, only 9% reverted to normal cognition at 3 years. Thus, PD-MCI status may fluctuate, and there may be other contributing factors to consider, such as cognitive test performance, co-morbid non-motor features, medication use, underlying neuropathology or other biomarkers.

- Biomarkers & neuropathology

There is a growing interest in identifying biomarkers such as cerebrospinal fluid (CSF), genetics, neuroimaging, among others to characterize PD-MCI and its underlying neuroanatomical, neurochemical or neuropathological substrates and that may predict conversion to dementia. While the MDS PD-MCI criteria do not incorporate biomarkers into current definitions, there may be lessons to be learned from the MCI/AD field (as discussed below) with the inclusion of biomarkers in recent revisions of MCI research criteria and their use in AD prevention trials [45].

Proposed CSF biomarkers for PD cognitive decline include several previously associated with AD pathology but also others. Decreased CSF-αβ 1–42 levels are thought to reflect...
amyloid deposition in the brain, and increased tau or phosphorylated tau (p-tau) CSF levels, increased neuronal death. Several PD studies reveal decreased CSF-αβ 1–42 in cognitively impaired PD patients compared with healthy controls [46–48]. Lower αβ 1–42 levels correlated with semantic fluency [47] and a more rapid cognitive decline from baseline to 1-year follow-up [48]. Levels of tau and p-tau have been variable with some, but not all, studies reporting increased CSF levels in PD dementia; in one study, elevated tau also correlated with impaired naming and memory performance [49]. Newly diagnosed PD patients had decreased CSF-αβ levels, though not as reduced as in AD, and levels were significantly associated with memory impairment but not with attention/executive or visuospatial dysfunction; CSF total tau or p-tau impairment but not with attention/executive or visuospatial dysfunction; CSF total tau or p-tau levels neither differed between PD patients and controls, nor correlated with cognitive measures [49]. In another incident PD study, CSF-αβ correlated with pattern recognition memory and Montreal Cognitive Assessment (MoCA) scores, with lower levels in PD-MCI patients [57]. These CSF markers may reflect pathological processes of PD cognitive impairment, including possible co-morbid AD and thereby, generate new avenues for diagnostic and prognostic biomarkers and intervention targets.

Several genetic biomarkers have been explored in PD cognitive impairment. As previously mentioned, data from the CamPaIGN study suggest a genotype-phenotype dissociation regarding risk of PD dementia, increased with tau-related MAPT gene polymorphisms and posterior cortical deficits, but not COMT polymorphisms and frontal-executive type deficits [2,30]. Others have described similar associations between the MAPT H1 polymorphism and PD dementia [50] as well as an effect on parietal activation in spatial rotation tasks in early PD [51]. Although APOE ε4 is a strong risk factor for AD, conflicting results have been found in PD dementia [52]. Other genetic mutations associated with PD dementia, more rapid cognitive decline and greater neuropsychiatric features include those related to alpha-synuclein triplication and carriers of mutations in the GBA gene, encoding the lysosomal enzyme glucocerebrosidase [42,53]. In the CamPaIGN cohort, GBA mutations occurred in 3.5%, and GBA carriers exhibited greater risk for progression to dementia (hazard ratio 5.7) and worse motor function (hazard ratio 4.2). The relationship between cognitive dysfunction and mutations in LRRK2, a common genetic and sporadic cause of PD, has been variable with mixed study results, some revealing lower executive function or Mini-Mental State Examination scores [54–56]. Future studies including well-defined PD-MCI cohorts and longitudinal follow-up will be needed to establish links between genotype and dementia risk as well as the possibility of incorporating genotype in clinical trials and study design.

Structural and metabolic neuroimaging offer other opportunities to study biomarker correlates of PD-MCI [57,58]. Gray matter atrophy on brain MRI has been variably found in PD-MCI, depending on the cohort studied (incident vs prevalent), PD-MCI definitions and MRI analyses (voxel-based morphometry [VBM], cortical thickness, others). PD-MCI patients, defined using Petersen criteria, had reduced gray matter in the left frontal and bilateral temporal lobe regions, compared with PD without MCI; however, these differences did not remain significant after corrections for multiple comparisons and patient groups were small in size [59]. Other studies reveal that PD-MCI patients exhibit anterior caudate atrophy and posterior ventricular enlargement on MRI [60], and compared with healthy controls, multiple areas of reduced gray matter such as frontal, temporal (including the hippocampus), parietal and pre/post central gyri; however, compared with cognitively normal PD patients, PD-MCI patients have not always demonstrated statistically significant differences in gray matter atrophy [61]. In a comparison of PD patients with amnestic MCI (n = 41) to amnestic MCI patients (without PD, n = 78), the PD group had decreased gray matter in the right temporal and anterior prefrontal areas compared with amnestic MCI (without PD); when multiple domains were affected in PD-MCI, regional atrophy was more extensive [62]. Several studies have focused on MRI correlates of PD-MCI in the incident PD cohorts. Two VBM studies of de novo PD patients, however, did not reveal differences in gray matter atrophy in PD-MCI patients compared with PD without MCI or healthy controls [17,63], though PD-MCI patients drawn from a large, de novo cohort revealed cortical thinning in temporal, parietal, frontal and occipital areas compared with healthy controls, and in the right inferior temporal region compared with cognitively normal PD patients [64]. Metabolic studies of PD-MCI reveal abnormalities in posterior cortical regions, similar to
regions frequently abnormal in PD dementia patients and AD. PD-MCI patients with multiple domains impaired had decreased glucose metabolism on 18F-fluorodeoxyglucose (FDG) PET scans in prefrontal and parietal regions, while PD-MCI patients with single domain impairment had a similar pattern but to a lesser degree [65]. A PD-MCI cohort (of whom 11 had an isolated memory deficit and 4, a mild deficit in verbal fluency) demonstrated parietal, temporal and occipital hypoperfusion compared with cognitively intact PD [66]. Interestingly, the PD-MCI had greater hypoperfusion in parieto-occipital regions compared with the amnestic MCI patients (without PD), whereas the amnestic MCI patients had greater hypoperfusion in medial temporal lobe regions, thereby, perhaps suggesting different underlying neural substrates and neuropathologies. These neuroimaging studies support regional gray matter atrophy patterns or altered metabolism in PD-MCI, with notable abnormalities in posterior cortical areas that may potentially reflect shared substrates with PD dementia and in some cases, AD.

To date, few studies describe the neuropathology of PD-MCI. Adler et al. report on 8 PD-MCI cases (of 80 PD cases), of whom 4 had amnestic single domain MCI, 3 nonamnestic single domain MCI (executive dysfunction) and 1 nonamnestic multiple domain MCI (executive/visuospatial dysfunction); the neuropathologies of the PD-MCI cases were heterogeneous with varying Lewy body distributions and in 50%, moderate neuritic plaque pathology (though only 2 met AD criteria), and cerebrovascular pathology in 3 cases [67]. Jellinger also reported a mix of Lewy bodies, AD pathology and cerebral amyloid angiopathy in 8 PD-MCI autopsy cases with amnestic and nonamnestic deficits [68]. Future clinico-pathological studies will be needed to examine the underlying neuropathology of PD-MCI and its relationship to MCI subtype.

**PD-MCI: theory, practice & debated issues**

### Conceptual usefulness

Whether PD-MCI represents a useful concept has been debated in the field [38,69]. Recognition of mild cognitive deficits in PD has brought increased awareness, education and research to an important and previously under-recognized area of PD patient care. The emergence of PD-MCI as a diagnostic entity provides a framework for investigating its clinical features and pathophysiology and for identifying patients for clinical research trials for symptomatic therapies, and ultimately, disease-modifying or preventive agents. Greater awareness of PD-MCI lead to appropriate counseling for patients and caregivers, validation of symptoms that are sometimes ‘dismissed’ or attributed to aging, and discussions regarding safety, driving and care planning. However, there are several concerns with the concept and diagnosis of PD-MCI. As previously discussed, PD-MCI is a heterogeneous condition, with different phenotypes and progression, and not necessarily a prodrome to dementia. In some cases, PD-MCI may be a static entity without further decline, a ‘short-term’ event with reversion to normal cognition, or a marker of impending dementia. How this information is conveyed to patients and caregivers in clinical settings and applied in research settings with symptomatic and disease-modifying treatment trials and selected target patients will need to be sorted out for the concept of PD-MCI to be successfully utilized in the field.

### Diagnostic challenges

The diagnosis of PD-MCI rests upon the concept that MCI, in general and in PD, refers to a clinical syndrome of cognitive impairment in the absence of dementia. However, many different definitions have been used over the years and thereby, influence our understanding of PD-MCI. The MDS PD-MCI criteria provide an important initial step toward a uniform diagnosis across multiple sites. Even with these criteria as a framework, there is latitude in interpretation and application with different neuropsychological tests, cut off scores and levels of assessment used.

There are a number of challenges in diagnosing PD-MCI clinically. First, one needs to identify that a decline in cognitive abilities has occurred. Estimates of cognitive impairment by patients and their caregivers vary in their reliability, due to either over or under reporting [8,20,70] or to difficulty separating cognitive from motor problems, and information from several sources (e.g., patient, caregiver and clinician) may be needed. PD-MCI studies vary in how preservation of activities of daily living is evaluated, and this issue is further compounded by difficulty in distinguishing cognitive and motor effects. Other motor and nonmotor features of PD may affect cognitive
function and thereby, the diagnosis of PD-MCI. Cognitive performance may differ in ‘on’ versus ‘off’ motor states \[71,72\], and neuropsychological tests with timed components or significant motor demands may be difficult for PD patients. Nonmotor features such as depression, anxiety, apathy, psychosis, fatigue and sleep disturbances are common in PD, particularly alongside impaired cognition or dementia \[73,74\]. Lastly, there are unresolved methodological issues regarding choices for global screening tests, neuropsychological test batteries and cutoffs of 1–2 standard deviation (SD) below normative data. Different research groups have interpreted these elements of the MDS PD-MCI criteria differently. To date, there is no agreement regarding

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Core clinical criteria met</th>
<th>Likelihood of biomarker probability of AD etiology</th>
<th>Likelihood of Aβ presence (PET or CSF)</th>
<th>Likelihood of neuronal injury evidence (CSF tau, FDG-PET, structural MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD by clinical criteria</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>AD core clinical criteria: cognitive or behavioral symptoms that: interfere with ability to function at work or at usual activities; represent a decline from previous levels of functioning; are not explained by delirium or major psychiatric disorder; cognitive impairment is detected and diagnosed (history, objective assessment); involve at least 2 domains (impaired ability to acquire and remember new information; reasoning and handling of complex tasks or poor judgment; visuospatial abilities; language functions; or changes in personality, behavior, or comportment; insidious onset; amnestic presentation (most common), nonamnestic presentation; absence of concomitant substantial cerebrovascular disease, features of other dementias (DLB, PPA) or other neurological or medical disorders or medications that could substantially affect cognition</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>AD by biomarker criteria</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Probable AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>Yes</td>
<td>Uninformative</td>
<td>Unavailable, indeterminant or conflicting</td>
<td>Untested, indeterminant or conflicting</td>
</tr>
<tr>
<td>Evidence of AD pathophysiological process</td>
<td>Yes</td>
<td>Intermediate/intermediate high</td>
<td>Unavailable/indeterminant positive/positive/intermediate positive</td>
<td>Positive unavailable/indeterminant positive</td>
</tr>
<tr>
<td><strong>Possible AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>Atypical course or etiologically mixed presentation</td>
<td>Uninformative</td>
<td>Unavailable, indeterminant or conflicting</td>
<td>Untested, indeterminant or conflicting</td>
</tr>
<tr>
<td>Evidence of AD pathophysiological process</td>
<td>No, but meets non-AD dementia criteria (e.g., DLB, FTD)</td>
<td>High but does not exclude alternative etiology</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Unlikely AD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical criteria</td>
<td>No, or sufficient evidence for alternative diagnosis (e.g., HIV dementia, HD)</td>
<td>Low</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Evidence of AD pathophysiological process</td>
<td>No</td>
<td>Low</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>MCI by clinical criteria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCI core clinical criteria: concern regarding a change in cognition, impairment in one or more cognitive domains, preservation of independence in functional abilities, not demented; objective evidence of cognitive decline, preferably on cognitive testing, scores typically 1–15 SD below norms; episodic memory impairment, though other domains may be impaired</td>
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</tr>
<tr>
<td><strong>MCI due to AD by biomarker criteria</strong></td>
<td></td>
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<tr>
<td>High likelihood</td>
<td>Yes</td>
<td>High</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Intermediate likelihood</td>
<td>Yes</td>
<td>Intermediate</td>
<td>Positive or untested</td>
<td>Positive</td>
</tr>
<tr>
<td>No likelihood</td>
<td>Yes</td>
<td>Low</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Aβ: Amyloid-beta; AD: Alzheimer’s disease; CSF: Cerebrospinal fluid; DLB: Dementia with Lewy bodies; FDG: 18fluorodeoxyglucose; FTD: Frontotemporal dementia; HD: Huntington’s disease; MRI: Magnetic resonance imaging; PET: Positron emission tomography; PPA: Primary progressive aphasia.

Data taken from \[45,89\].
the ideal neuropsychological battery, given the plethora of tests available to evaluate global and individual cognitive functions, the best sources of normative data, handling of normative scores and best cutoff scores to use, though data are emerging [11,28,75]. Cutoff scores used to define impairment can greatly influence frequency estimates of PD-MCI. Sensitivity and specificity of PD-MCI by MDS PD-MCI level II criteria varied depending on whether 1, 1.5, 2 and 2.5 SD cutoffs below norms were used in one study, with the best sensitivity (85.4%) and specificity (78.6%) measures achieved using a cutoff of 2 SD below norms; other cutoff scores compromised either specificity (21.4% for 1 SD below norms and 60.7% for 1.5 SD below norms) or sensitivity (58.3% for 2.5 SD below norms) [13]. Validation of the MDS PD-MCI criteria including efforts of a large international consortium may help elucidate these operationalization issues in defining PD-MCI, particularly across cognitive test batteries and diverse PD populations.

Table 3. Examples of preclinical and preventive Alzheimer’s disease trials incorporating biomarkers in the study design.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Biomarker</th>
<th>Intervention</th>
<th>Aim</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE e4 treatment trial</td>
<td>Persons who are homozygous for APOE e4 alleles</td>
<td>APOE e4</td>
<td>Antiamyloid medication</td>
<td>Prevent or delay the emergence of AD symptoms in persons at high risk for developing AD</td>
<td>[108]</td>
</tr>
<tr>
<td>Alzheimer prevention initiative</td>
<td>Large extended Columbian family with rare presenilin (PS1) gene mutation</td>
<td>PS1 mutation</td>
<td>Crenezumab</td>
<td>Study whether a monoclonal antibody targeting Aβ precursor protein can delay the onset of AD</td>
<td>[109]</td>
</tr>
<tr>
<td>Dominantly inherited Alzheimer network</td>
<td>Persons who have a known genetic mutation that causes autosomal dominant AD or have parent, sibling with a known genetic mutation</td>
<td>PS1, PS2 or APP mutation</td>
<td>Solanezumab, gantenerumab, beta-secretase inhibitor</td>
<td>Examine and compare the safety, side effects and effect on imaging and biomarkers of three investigational drugs</td>
<td>[110]</td>
</tr>
<tr>
<td>Antiamyloid treatment of asymptomatic AD (A4 ADCS- NIA, Lilly)</td>
<td>Healthy population sample with positive amyloid imaging on PET scan</td>
<td>Positive amyloid imaging</td>
<td>Solanezumab</td>
<td>Evaluate whether early treatment will slow down memory loss and cognitive decline and delay the progression of AD-related brain injury on imaging</td>
<td>[111]</td>
</tr>
<tr>
<td>A4 sub-study: LEARN (ADCS- NIA Alzheimer’s Association)</td>
<td>Older individuals who have negative amyloid imaging on PET scans performed in A4 study</td>
<td>Negative amyloid imaging</td>
<td>None</td>
<td>Longitudinal natural history study of cognitive function outcomes in amyloid PET negative individuals from A4 study, examining differences in rates of clinical decline</td>
<td>[112]</td>
</tr>
<tr>
<td>Takeda/Zinfandel Trial (TOMMOROW)</td>
<td>Healthy population sample genetic risk of developing AD</td>
<td>APOE and TOMM40</td>
<td>Pioglitazone</td>
<td>Study a new investigational risk algorithm to predict the genetic risk for developing MCI and test the safety and effectiveness of an investigational medication in delaying MCI due to AD</td>
<td>[113]</td>
</tr>
</tbody>
</table>

Aβ: Amyloid-beta; AD: Alzheimer’s disease; MCI: Mild cognitive impairment; MRI: Magnetic resonance imaging.
been found to progress to different types of dementia syndromes, with amnestic MCI representing a potential precursor to AD, while nonamnestic MCI subtypes may progress to other forms of dementia [24,78]. These MCI studies paved the way for many of the early studies of cognitive impairment in nondemented PD, application of MCI definitions in PD cohorts, and subsequently, the generation of MCI as a construct in PD.

The MCI-AD field has also faced its own issues regarding variable prevalence estimates, conversion rates and heterogeneity, and these shared challenges may offer insights and support to the PD field. Prevalence estimates of MCI and its subtypes vary with respect to which diagnostic criteria were employed or what type of patient population was examined, similar to our recent experiences in the field of PD-MCI [79,80]. In addition, reversion rates of MCI to normal cognitive functioning have been reported, varying widely from 15% over a 3.6-year follow-up to 34% with 1.5-year follow-up [81–83]. These observations underscore the challenges encountered in accurately characterizing and diagnosing MCI and support the view that clinical classification of MCI should be considered a heterogeneous and potentially unstable diagnostic entity, in both AD and PD [84].

At present, there are no widely accepted screening tests for MCI. In the MCI-AD field, there have been efforts to develop tests and batteries (e.g., MMSE enriched with delayed recall items, or the MoCA) that can be validated against the clinical diagnosis of MCI or predictively against the development of dementia [85,86] as well as computerized cognitive assessment systems (e.g., CogState) that can discriminate MCI from cognitively healthy individuals and can be used to screen community-dwelling individuals or implemented in large scale clinical trials for AD prevention [87]. In PD-MCI, similar challenges are faced, and efforts to determine the optimal cognitive batteries or tests that discriminate PD-MCI from PD patients with intact cognition or dementia and mode of administration for clinical trials are underway [28,75].

**Incorporating biomarkers & genetics into clinical criteria & research study design**

With advances in clinical and pathophysiological relationships over the years, the diagnostic definitions of AD and MCI have been refined to incorporate biomarkers. In 2011, consensus reports from National Institute on Aging (NIA) and the Alzheimer’s Association (AA) working groups described MCI-AD as three contiguous disease phases: the ‘AD pathophysiological process’, ‘MCI due to AD’ and ‘clinical AD dementia’ in an effort not only to assist physicians in diagnoses, but also to provide a platform for developing primary prevention therapies (Table 2) [45,88,89]. The modified definitions include biomarkers that reflect the underlying neurodegenerative processes [90,91], spanning those with potential for identifying early and subtle but measureable signs (e.g., decreased CSF-αβ42, increased total tau or p-tau levels) and later stage evidence (e.g., MRI-derived hippocampal and entorhinal cortex atrophy, reduced glucose metabolism in temporoparietal and posterior cingulate cortices) [92,93].

Other studies focus on the role of genetics such as dominantly inherited mutations for early-onset AD (APP, PSEN1 and PSEN2) and susceptibility factors for late-onset AD (APOE gene polymorphism, APOE ε4) [94–96]. Current clinical trials have now incorporated family history and genetic criteria into the study design to enrich the studies with persons at risk for development of cognitive decline, MCI and AD. Thus, the application of genetics and biomarkers in therapeutic trials is a growing research area, which in due time and with research advances, may also emerge in the PD field.

**Emerging therapeutic strategies in MCI & AD research**

Conventional therapies to treat AD, such as cholinesterase inhibitors and NMDA receptor antagonists, have not produced a disease-modifying effect or impacted the progression of AD over a prolonged period of time. Lessons to be learned from the MCI-AD field include the development of novel therapies targeting pathophysiological mechanisms (e.g., amyloid cascade, tau production and processing or specific biological mechanisms related to inflammation, insulin, cholesterol, etc.) [97–98]. The amyloid hypothesis also has evolved in AD, from its initial focus on contributions of plaques in disease development to using specific soluble plaque components (oligomers, monomers) as potential drug targets. The latest antiamyloid strategies focus on facilitating amyloid’s clearance, inhibiting its production, or preventing its aggregation [99]. Metabolic factors influencing brain glucose utilization and insulin-like growth factor resistance also may play a role in cognitive function [100–102], and clinical trials of novel compounds such as intranasal insulin in MCI and AD are underway. In addition, clinical...
trials with immunotherapy (e.g., intravenous immunoglobulin-G) and anti-amyloid antibodies (e.g., bapineuzumab, solanezumab) have been, and continue to be cautiously tested in patients, with lessons to be learned regarding safety issues, heightened immune responses and optimal doses and delivery [103–107].

Recent clinical trials now focus on the preclinical stages of AD with the aim of preventing cognitive decline or AD and implementing aggressive treatment at earlier stages. Biomarker profiles play an important role in guiding study design, selecting target populations and identifying drug interventions for several large-scale trials in persons at risk for developing AD (Table 3) [108–113]. Furthermore, studying disease mechanisms, biomarkers and therapies longitudinally, across preclinical phases to dementia, can inform the timelines and benchmarks of progression needed for trials and identify those persons who are the most likely to decline and thereby, potentially benefit from early therapeutic intervention, prior to substantial synaptic loss and neurodegeneration. Thus, strategic use of biomarkers and sensitive cognitive tests in prevention trials, whether for cognitive decline in AD or PD, may help provide the necessary evidence of efficacy to support future drug approval. The MCI-AD field has set forth informative examples for the MCI-PD field regarding the direct application of biomarker and genetic information in clinical trial design; development of novel therapeutic targets based on advances in neuroscience, animal models, neuroimaging and molecular studies; and early identification of those at highest risk of cognitive decline.

Conclusion & future perspective

Whether in PD or AD, the construct of MCI has taken hold over the years and has been defined, and redefined, and will likely continue to evolve as research advances. In both fields, research devoted to identifying persons at the earliest stage of cognitive symptoms has gained attention. Improved therapeutic interventions are still needed for symptomatic benefit and disease-modification. Discovery of biomarkers that reflect disease progression and underlying pathologies associated with cognitive impairment may provide a path toward early detection of persons at high risk for cognitive decline and thereby, prevention and/or early intervention. However, these advances, whether for PD or AD, do not come without some risks and limitations as studies will need to reconcile the potentially negative aspects of early diagnosis, the risk–benefit ratios of various therapeutics, and accessibility of biomarker testing and clinical resources, counseling and therapies once available. While MCI in PD is a relatively newer concept compared with MCI due to AD, lessons highlighted in this review may be shared by both neurologically disorders and individually or collectively, advance our understanding of neurodegenerative processes and treatment interventions for both.

Author disclosures

JG Goldman: Consultancies: Acadia, Advisory Boards: Acadia, Pfizer, Teva, Employment: Rush University Medical Center, Honoraria: Movement Disorders Society, American Academy of Neurology, Michael J. Fox Foundation, Grants: NIH, Michael J. Fox Foundation, Parkinson’s Disease Foundation, Rush University, Teva (study site-PI), Biotta (study site-PI). NT Aggarwal: Consultancies: Medical Consultant – Illinois Institute of Continuing Legal Education (ICLE), Advisory Boards: Lilly Alzheimer’s Disease Environment Evolution (ADEE) Working Group, MERCK, Employment: Rush University Medical Center, Honoraria: Preventative Cardiologist Nursing Association, Grants: NIH/NIA, PCORI, Eli Lilly (study site), Lundbeck (study site). CD Schroeder: Employment: Rush University Medical Center, Governors State University, Grants: NIH T32AG000269–15. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.
REVIEW
Goldman, Aggarwal & Schroeder


• Review of studies of MCI studies in PD which led to the development of the PD-MCI diagnostic criteria.


• Longitudinal study of incident PD patients from the CamPaIGN study that includes 10-year follow-up data and demonstrates baseline clinical and genetic variables that may predict poor outcomes.


37 Berg D, Postuma RB, Bloem B et al. Time to redefine PD? Introductory statement of the MDS Task Force on the definition of
Mild cognitive impairment: an update in Parkinson's Disease & lessons learned from Alzheimer's Disease

**Review article that generates discussion on reconsidering defining PD along with various challenges and controversies.**


**Revised recommendations for diagnosis of MCI due to Alzheimer's disease (AD).**


**Revised recommendations for diagnostic guidelines including use of clinical and biomarker information for AD.**


**Revised recommendations for diagnostic guidelines including use of clinical and biomarker information for AD.**


106 Dodel R, Balakrishnan K, Keyvani K et al. Naturally occurring autoantibodies against beta-amyloid: investigating their role in transgenic animal and *in vitro* models of


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