

# State of the science on mild cognitive impairment (MCI)

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Mild cognitive impairment (MCI) represents a transitional stage between healthy aging and dementia, and affects 10–15% of the population over the age of 65. The failure of drug trials in Alzheimer's disease (AD) treatment has shifted researchers' focus toward delaying progression from MCI to dementia, which would reduce the prevalence and costs of dementia profoundly. Diagnostic criteria for MCI increasingly emphasize the need for positive biomarkers to detect preclinical AD. The phenomenology of MCI comprises lower quality-of-life, greater symptoms of depression, and avoidant coping strategies including withdrawal from social engagement. Neurobiological features of MCI are hypoperfusion and hypometabolism in temporoparietal cortices, medial temporal lobe atrophy particularly in rhinal cortices, elevated tau and phosphorylated tau and decreased  $A\beta_{42}$  in cerebrospinal fluid, and brain  $A\beta_{42}$  deposition. Elevated tau can be identified in MCI, particularly in the entorhinal cortex, using positron emission tomography, and analysis of signal complexity using electroencephalography or magnetoencephalography holds promise as a biomarker. Assessment of MCI also relies on cognitive screening and neuropsychological assessment, but there is an urgent need for standardized cognitive tests to capitalize on recent discoveries in cognitive neuroscience that may lead to more sensitive measures of MCI. Cholinesterase inhibitors are frequently prescribed for MCI, despite the lack of evidence for their efficacy. Exercise and diet interventions hold promise for increasing reserve in MCI, and group psychoeducational programs teaching practical memory strategies appear effective. More work is needed to better understand the phenomenology and neurobiology of MCI, and how best to assess it and delay progression to dementia.

Received 6 February 2018; Accepted 28 August 2018; First published online 17 January 2019

**Key words:** Amyloid, biomarkers, exercise and diet interventions, memory strategy training, mild cognitive impairment, neuroimaging, neuropsychological assessment, tau.

## Introduction

A new case of dementia is diagnosed every 3 seconds, the equivalent of 9.9 million new cases globally in 2015.<sup>1</sup> The worldwide prevalence of dementia is expected to almost double every 20 years, from 46.8 million in 2015 to 131.5 million in 2050, with most of the increase occurring in low and middle income countries.<sup>1</sup> The combined cost of health care and loss of earnings due to dementia, already at \$81 billion (USD) per year, is predicted to rise to \$2 trillion by 2030.<sup>1</sup> Considering Alzheimer's disease (AD) in particular, no disease-modifying treatment exists, and clinical drug trials in the past decade have had a 99.6% failure rate.<sup>2,3</sup> One contributor to this high failure rate is the fact that brain pathology begins years before onset of objective cognitive symptoms and may be irreversible by the time of diagnosis.<sup>4</sup> These depressing statistics have led many investigators to

switch their focus toward delaying dementia in persons who are in preclinical phases of the disease. Economic analyses have concluded that a treatment introduced in 2025 that delays the onset of dementia by five years would reduce the prevalence and associated healthcare costs of dementia by approximately 40% over the following 25 years.<sup>5</sup>

Mild cognitive impairment (MCI) represents the preclinical, transitional stage between healthy aging and dementia and represents what researchers and clinicians view as a “window” in which it may be possible to intervene and delay progression to dementia. The goal of this article is to broadly cover the state of the current science on MCI, including its phenomenology and neurobiology, how MCI is screened for and assessed, and interventions designed to improve cognitive functioning in MCI, thereby delaying progression to dementia. To set the stage for these discussions, this article begins by describing the evolving operational definitions of MCI and its prevalence.

The notion of preclinical cognitive decline has existed for decades, and was variously termed, eg, “aging-associated cognitive decline”<sup>6</sup> and “cognitive impairment, no dementia.”<sup>7</sup>

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Another important conceptualization is the Clinical Dementia Rating (CDR) of 0.5, termed “questionable dementia.”<sup>8</sup> A CDR of 0.5 includes the following features, as judged by a clinician: (1) mild consistent forgetfulness; partial recollection of events; (2) fully oriented; (3) only doubtful or mild impairment, if any, in independent functioning; (4) no major influence on home life, hobbies, or intellectual interests; and (5) fully capable of basic activities of daily living. Researchers at Washington University in St. Louis, Missouri, in particular have advocated the use of the CDR, arguing that what others call MCI is in fact early-AD, and therefore there is no need to view MCI (or a CDR of 0.5) as a separate entity from AD.<sup>9</sup>

The term MCI was introduced in 1988,<sup>10</sup> but became common nomenclature when Ron Petersen and his colleagues at the Mayo Clinic in Rochester, Minnesota, developed the first clinical criteria for MCI in 1999.<sup>11</sup> The original Mayo criteria were the following: (1) memory complaint, preferably corroborated by an informant; (2) objective memory impairment for age and education; (3) largely normal general cognitive function; (4) essentially normal activities of daily living; and (5) not demented. Thus, the focus was very much on what is now called *amnestic* MCI, given the key criterion that memory, of all cognitive domains, must be impaired. Later, the Mayo group suggested different subtypes of MCI,<sup>12,13</sup> representing the factorial crossing of single-domain/multiple-domain and amnestic/nonamnestic. For example, someone with deficits in memory and 1 or more other cognitive domain (eg, language, executive functioning, visuospatial ability) would have multiple-domain amnestic MCI. Someone with solely an executive functioning impairment would have single-domain non-amnestic MCI, and is likely to be in the preclinical stages of a dementia other than AD (eg, frontotemporal dementia or vascular dementia).

The tide has swung even further away from memory impairment as a key feature of preclinical AD MCI. The recent guidelines put forth by the National Institute on Aging-Alzheimer’s Association (NIA-AA) workgroups distinguished between clinical criteria and research recommendations for “MCI due to AD.”<sup>14</sup> The clinical criteria are the following: (1) concern regarding a change in cognition, from the patient, an informant, or a skilled clinician; (2) impairment in one or more cognitive domain relative to a person’s age and educational attainment; (3) independence in functional abilities (although they may take more time or be performed less efficiently); and, (4) not demented. Thus, the main difference between the original and the newer clinical criteria is that individuals do not have to have memory impairment to meet criteria for MCI due to AD. The clinical diagnosis of MCI, these newer guidelines also state, should also involve a clinical evaluation to confirm a likely AD etiology of the individual’s cognitive impairment (eg, family history of AD, ruling out other possible

causes). Separate research recommendations for the diagnosis of MCI due to AD include biomarkers of A $\beta$  deposition and neuronal injury: individuals with positive tests of both biomarkers are considered to be highly likely to have MCI due to AD, individuals with positive tests on one biomarker are considered to have an intermediate likelihood of having MCI due to AD, and individuals for whom both biomarkers are negative are considered to have MCI, but unlikely due to AD.

Finally, in 2013, the American Psychiatric Association, in its *Diagnostic and Statistical Manual for Mental Disorders*, Fifth Edition,<sup>15</sup> developed the term *mild neurocognitive disorder* (mild NCD) to describe MCI. The clinical criteria for mild NCD include: (1) evidence of cognitive decline in one or more cognitive domains, obtained from reports from the client, an informant, or a clinician, or from objective testing; (2) preserved functional independence; (3) the cognitive impairments do not occur exclusively during episodes of delirium; (4) the cognitive deficits cannot be better explained by another condition (eg, depression); and (5) no dementia. These criteria, unlike those of the NIA-AA, are not specific to MCI due to preclinical AD, but rather include a second diagnostic step of determining the potential etiology of the cognitive deficits (eg, AD, frontotemporal dementia, vascular disease, traumatic brain injury, substance abuse). Despite these being the most recent criteria, the term MCI still dominates in research and clinical circles.

Prevalence estimates of MCI vary widely, with one review reporting prevalence as low as 3% to as high as 42% across 35 studies, varying across country of study origin, and as a function of the age range of study inclusion, with lower prevalence in studies that included younger participants.<sup>16,17</sup> Prevalence of MCI has also been reported to be higher in clinic-based than community-based samples.<sup>18,19</sup> Approximately 10–15% of people with amnestic MCI progress to AD each year, compared to 1–2% of the healthy older adult population.<sup>11,20</sup> It is thus imperative that we understand the phenomenology, neurobiology, and clinical characteristics of MCI, and how best to treat it, in efforts to improve functioning and delay progression to dementia.

### Phenomenology of MCI

The phenomenology of MCI has been examined using both quantitative and qualitative research methods. Studies using a quantitative approach, such as administering questionnaires to people with MCI and healthy older adults, have found reduced quality-of-life in individuals with MCI,<sup>21,22</sup> particularly when they are aware of their diagnosis.<sup>23</sup> Symptoms of depression, anxiety, hostility, and low morale have also been reported to be elevated in people with MCI compared to healthy

older adults.<sup>24</sup> Indeed, people with MCI experience depressive symptoms at approximately double the rate of healthy seniors,<sup>25,26</sup> with one of these studies finding that symptoms of depression, including those that met the cut-off for clinical significance, were elevated in individuals with amnesic, but not non-amnesic, MCI.<sup>26</sup> The authors argued that depression can result when memory difficulties interfere with the ability to perform instrumental activities of daily living, but it should be noted that such activities also rely on executive functions.<sup>27</sup>

A handful of qualitative studies have shared the lived experience of people with mild cognitive impairment. Roberts and Clare<sup>28</sup> used interpretative phenomenological analysis of interview data with 25 people who had been diagnosed with MCI, a method which interprets the meaning of the statements shared by participants. Their analysis identified 4 themes. The first theme reflected participants' appraisals of their cognition in the context of their perceived social network: individuals living alone identified retention of independence as being of high importance, in fear it might be taken away, while those who lived with others leaned on their partners to maintain their independence. The second theme reflected a normalization of participants' own memory problems, viewing them as a normal consequence of aging, with comments such as "All my friends forget things too." The third theme described participants' unwillingness to consider negative impact or outcomes as a result of their diagnoses. Participants often used humor to deflect the seriousness of their condition. The final theme reflected participants' lack of sophisticated knowledge about what MCI is and their concerns for the future. While these last two themes may seem to contradict each other, the frequent vacillation between memory concerns and minimization of the significance of their diagnosis is commonly observed in clinical practice, often times even in a single statement, eg, "I worry all the time I might become demented, but then again, all my friends forget things!"

Berg *et al.*<sup>29</sup> interviewed 17 individuals who maintained a diagnosis of MCI across 4 assessments over a 7-year period. The majority of them expressed wanting to spare their children of the experiences they had caring for their mothers with dementia. Another common theme, like the results of Roberts and Clare,<sup>28</sup> was attribution of the experienced memory difficulties to normal aging, a minimization which may also be a form of avoidant coping. Most participants expressed concerns for the future and the impending loss of capabilities and the impact that this will have on their participation in activities they find meaningful. Finally, participants reported avoidant coping behaviors, reducing stress by avoiding situations they thought they could not handle.

Avoidant coping was also a key observation of the qualitative study of 14 individuals with amnesic MCI

reported by Parikh *et al.*<sup>30</sup> These individuals reported withdrawing from the social activities they previously enjoyed to avoid embarrassment and frustration when their memory fails them in these settings. Social exclusion was also reported, such as being interrupted when they hesitate in conversations, and feeling that their friends no longer share information with them in the way they had previously.

In summary, this literature paints a picture of reduced quality of life, elevated symptoms of depression, and avoidant coping strategies such as minimizing the significance of one's diagnosis and withdrawing from leisure activities as key features of the phenomenology of MCI. Treating depression and not only encouraging, but facilitating, social engagement are important elements in the treatment of MCI, as discussed in the final section of this article, particularly given the identified role of depression and reduced social engagement as risk factors for dementia<sup>31,32</sup> and the influence of depression in the progression from MCI to dementia.<sup>33</sup>

### Neurobiology of MCI

All of the neuropathologies identified in MCI cohorts can also be found in seniors with intact cognition and in seniors with dementia, and typically fall in the intermediate stage in terms of severity.<sup>34</sup> These include atrophy of medial temporal lobe regions, particularly the hippocampus and entorhinal regions, and posterior cingulate cortex,<sup>35</sup> hypometabolism in temporoparietal and posterior cingulate cortices, as assessed by fluorodeoxyglucose positron emission tomography (FDG-PET);<sup>36</sup> and hypoperfusion of parietal cortices and the hippocampus as measured by single-photon emission computed tomography (SPECT).<sup>37</sup>

The other primary neurobiological markers of MCI pertain to the neuropathology of AD—amyloid plaques and neurofibrillary tangles. Evidence of amyloid accumulation in MCI (and AD) can be detected with positron emission tomography using the (11)C-labelled Pittsburgh Compound-B ((11)C-PIB) ligand. The great variability in how PIB scans are performed and interpreted has raised calls for greater standardization of this high cost procedure.<sup>38</sup> Amyloid beta ( $A\beta_{42}$ ) can be detected in the cerebrospinal fluid (CSF) at much lower cost, with lower CSF  $A\beta_{42}$  concentrations indicating higher levels of brain  $A\beta_{42}$  (ie, poorer clearance), whereas elevated CSF concentrations of total tau and phosphorylated tau indicate neuronal injury and predict progression from MCI to AD-related dementia. Both CSF  $A\beta_{42}$  and tau, as well as PET PIB, have better sensitivity than specificity,<sup>39,40</sup> suggesting that they are more useful in ruling out preclinical AD than in confirming it.

The epsilon 4 allele of the apolipoprotein gene (APOE-e4) confers a risk for MCI, as it does for AD.<sup>41</sup> Differences in gene expression in cortical brain regions

have been reported in MCI that are unique compared to healthy cohorts and those with AD.<sup>42</sup> These authors report an upregulation of genes associated with anabolic and biosynthetic pathways and mitochondrial energy generation. Upregulation of genes associated with synaptic transmission and plasticity was also identified in entorhinal cortex and hippocampus, but this was associated with poorer cognitive functioning as assessed with the Mini-Mental State Examination (MMSE).<sup>43</sup> This finding is reminiscent of previous reports of a “paradoxical” hyperactivation of the hippocampus during encoding in MCI, with greater hyperactivation associated with greater atrophy and cortical thinning in medial temporal lobe regions.<sup>44,45</sup> One interpretation of this apparent paradox is that it is the brain’s last ditch attempt to maintain functioning in the face of mounting neuropathology.

The elevated rates of depression in MCI deserve mentioning in the context of the neurobiology of MCI. There is much debate about the causal relationship between depression and MCI. As spelled out by Shahna-waz *et al.*,<sup>26</sup> 4 mechanisms of this relationship have been proposed: (1) the downstream consequences of depression (eg, elevated cortisol and its effects on the brain) may cause cognitive decline;<sup>46</sup> (2) depression may be an early outcome of MCI as individuals experience cognitive decline;<sup>47</sup> (3) an independent, third variable commonly comorbid with both conditions, such as vascular disease, may be causing both depression and cognitive decline;<sup>48</sup> and (4) medications for depression may exacerbate cognitive decline due to their anticholinergic effects.<sup>49</sup>

Emerging approaches in neuroimaging may prove useful for early detection of MCI. For example, altered synchronization of brain signals has been reported using magnetoencephalography (MEG)<sup>50</sup> and functional magnetic resonance imaging (fMRI).<sup>51</sup> Likewise, electroencephalography (EEG) and MEG studies have shown increased power in low frequencies (delta and theta bands) and decreased power in higher frequencies (alpha and beta bands) in people with MCI compared to controls,<sup>52</sup> suggesting a shift away from firing patterns required for complex cognitive processes, such as working memory and avoiding distraction, toward more basic processes such as orienting attention. Analyses of the complexity of EEG and MEG time-series data, such as entropy, typically show reduced signal complexity compared to healthy older adults,<sup>52,53</sup> suggesting that people with MCI have less complex (ie, more regular) neural dynamics, thus limiting the repertoire of brain states and restricting transitions between states.<sup>54</sup> Moreover, the synchrony of resting-state EEG oscillatory neural activity may be reduced in MCI,<sup>55</sup> restricting short-range and long-range communication.

A final neurobiological biomarker that is also not part of standard diagnostic practices, but has promise for the

future, is the structural and functional integrity of perirhinal cortex. Given that Alzheimer’s pathology begins in the transentorhinal cortex,<sup>56</sup> which corresponds to the medial perirhinal cortex,<sup>57</sup> it is not surprising that a hallmark feature of amnesic MCI is atrophy and thinning of the rhinal cortices (see Zhou *et al.*<sup>58</sup> for a review), combined with hippocampal atrophy that exceeds that seen in healthy aging (see Leal and Yassa<sup>59</sup> for a review). The volume of the anterolateral entorhinal cortex has recently been reported to correlate with performance on the Montreal Cognitive Assessment (MoCA),<sup>60</sup> a cognitive screening tool that is sensitive to MCI, in a group of healthy older adults, some of whom had failed the MoCA.<sup>61</sup> Perirhinal neurofibrillary tangle deposition in people with MCI has also been recently reported,<sup>62</sup> and in early AD, greater perirhinal atrophy is associated with greater tau deposition, whereas greater hippocampal atrophy is associated with greater amyloid deposition.<sup>63</sup> Thus, the deployment of high-resolution structural magnetic resonance imaging to assess the volume and cortical thickness of perirhinal cortices, and the combination of fMRI with clever tasks that drive perirhinal and lateral entorhinal processes, as discussed in the next section of this article, may be fruitful avenues for early detection of MCI.

### Assessment of MCI

The current clinical and research criteria for diagnosis of MCI were enumerated at the outset of this article. This section will comment on how those criteria are assessed. In clinical practice, and as per the research criteria for the assessment of MCI, neuroimaging is often performed. This can include SPECT and/or FDG-PET to verify hypoperfusion and glucose hypometabolism of temporoparietal cortices, respectively; structural MRI to identify medial temporal lobe atrophy; and CSF assays to verify elevated levels of tau and phosphorylated tau, all indicative of neuronal injury. Likewise, reduced CSF levels of A $\beta$ <sub>42</sub> (indicative of elevated brain levels of A $\beta$ <sub>42</sub>) or of A $\beta$ <sub>42</sub> deposition in the brain using PET imaging are increasingly common tests at least in better resourced communities to confirm MCI diagnosis. A recent international working group published guidelines for CSF biomarker in the diagnosis of MCI concluded that CSF biomarkers hold significant utility in predicting conversion to AD 3 years later, but the evidence was too limited to recommend any one CSF biomarker over another.<sup>64</sup> Finally, confirmation that a client carries 1 or 2  $\epsilon$ 4 alleles in the APOE gene increases confidence in the diagnosis of MCI due to AD.

Researchers are constantly aiming to identify lower cost, less invasive biomarkers of AD neuropathology in the preclinical phases of the disease. One group recently reported the utility of a blood plasma-based composite

biomarker of A $\beta$  deposition that fared very well against PIB-PET imaging and CSF A $\beta$ .<sup>65</sup> Thus, the notion that individuals can receive an early diagnosis in their family physician's office, and then be directed toward treatments that delay progression to dementia, is foreseeable.

In addressing the diagnostic criteria of cognitive impairment in clinical practice, it is not uncommon for physicians to rely solely on a cognitive screening measure such as the MMSE or the MoCA. The MMSE, however, lacks in sensitivity to detect MCI,<sup>60</sup> and the MoCA is insufficient to determine the specific cognitive domains affected in order to determine MCI subtype (although see Julayanont *et al*<sup>66</sup> for an approach that hopefully will be validated against a more extensive assessment). There are 3 versions of the MoCA, permitting re-assessment without undue influence of practice effects; however, the first version of the test was published by media outlets in January 2018, following the news that President Trump had passed it, and so clinicians are now recommended to avoid using this version in case their clients have become familiar with the test items.

A more comprehensive approach to cognitive assessment involves a neuropsychological assessment. Neuropsychologists typically administer a 90-minute to 3-hour assessment of cognitive functioning and factors that could influence performance (eg, mood, self-report of learning disabilities, other major medical conditions, sensory and language fluency limitations). The neuropsychological assessment typically includes measures of memory, executive functioning, attention, language, and visuospatial skills. In the diagnosis of MCI (and other conditions for that matter), it is important to find evidence of impairments across multiple tests within a cognitive domain, such as on multiple tests of episodic memory. This is because a surprisingly high percentage of healthy seniors will score below cut-off on at least 1 memory measure in a battery (eg, 38% scoring < 5th percentile in Brooks *et al*<sup>67</sup> and > 60% scoring < 10th percentile in Mistridis *et al*<sup>68</sup>), rendering the potential for misdiagnosis of MCI high if made on the basis of 1 failed test. Those examples also highlight the variability in the literature and in clinical practice in how a cognitive "impairment" is operationalized, with some using a cut-off of 1.5 standard deviations (SD) below the age- (and education-, where available) corrected normative data (<7th percentile), and others using a less stringent -1.0 SD cut-off (<16th percentile). This inconsistency in diagnostic practice contributes to the variability in not only prevalence and incidence rates of MCI, but also in its prognostic patterns.

Failing to take a clients' medical and psychosocial history into account in differential diagnosis can likewise lead to misclassification of MCI; for example, if a client reports that his memory difficulties emerged following open-heart surgery, but have not continued to decline,

memory impairment secondary to hippocampal damage due to anoxia could be mistaken for preclinical dementia. Issues such as these likely contribute to the sometimes high rates of "reversion to normal" when people previously diagnosed with MCI are tested later and score within normal ranges (for a meta-analysis, see Malek-Ahmadi<sup>69</sup>).

Another contentious aspect about the assessment of MCI has been the criterion regarding subjective concern. The unreliable nature of memory concerns in MCI that was mentioned in a previous section of this article has been validated by studies reporting poor associations between the degree of subjective memory concerns and actual memory performance in MCI<sup>70</sup> (see Roberts *et al*<sup>71</sup> for an earlier review), most typically reflecting an underestimation of the magnitude of actual impairment.<sup>72</sup> This has led many investigators to question the reliability of the *patients'* concerns about their memory (versus the concerns of a family member and/or healthcare professional) as a core clinical criterion for MCI. Yet, it should be noted that the impetus for including in the diagnostic criteria a concern that one's memory (or other cognitive domain) is becoming worse was to distinguish a probable neurodegenerative process from a non-degenerative process.

A final point about the cognitive assessment of MCI relates to the assessment tools used in neuropsychology, which have a rich history, with most developed or at least rooted in early efforts to understand brain-behavior relationships. New versions of tests are frequently released, but the tests remain essentially the same. One implication of the relative rigidity of neuropsychological practices is that assessment tends not to capitalize on recent advances in our understanding of the neurobiology of conditions, including MCI. Given that the earliest neuropathological changes in MCI occur in the perirhinal cortex, as mentioned in the previous section of this article, cognitive tests that tap into perirhinal functioning may prove to be particularly sensitive to MCI. The perirhinal cortex and lateral entorhinal cortex have been discovered to mediate complex object discrimination,<sup>73-75</sup> whereas spatial information is processed by an alternate medial temporal lobe route involving the parahippocampal gyrus and medial entorhinal cortex.<sup>76</sup> Indeed, compared to their healthy counterparts, people with aMCI report problems with "object memory," forgetting what things are called, what they watched on television, to do things that are right in front of them, but share similar complaints with healthy seniors about "spatial memory," such as where they put things or recognizing places.<sup>77,78</sup> The perirhinal cortex has also been implicated in the mnemonic process of familiarity—the gut sense that you have experienced something before but you fail to remember the original context of the event.<sup>79-81</sup>

This literature would suggest that tests of complex object discrimination (and memory for objects when they have to be distinguished from highly similar lures) and tests of familiarity may be particularly sensitive to MCI. Indeed, MoCA performance was more strongly associated with the ability to select a studied item over a highly similar lure item for objects than scenes in the study by Fidalgo *et al.*,<sup>82</sup> and people with MCI have greater difficulty identifying objects when they are presented in an overlapping line-drawn display.<sup>83</sup> The literature on whether familiarity is spared or impaired is split, with approximately half of the studies finding spared familiarity in MCI (eg, <sup>84,85</sup>) and the other half finding familiarity deficits in MCI (eg, <sup>86,87</sup>). This author believes this confusion can be attributed to how familiarity is typically assessed experimentally, pitting it against recollection (the ability to recall a prior event and its context), and advocates for more novel approaches to assess familiarity free from the influence of recollection. Indeed, one study in this vein had older adults who were either carriers or noncarriers of APOE  $\epsilon$ 4 study faces against a red or blue background.<sup>88</sup> Later, they performed a yes/no recognition task of the studied faces intermixed with new faces, and then for faces deemed “old” (studied), indicated if it was studied with a red or blue background. The two groups did not differ in the ability to recognize a studied face and remember its context (recollection), but  $\epsilon$ 4 carriers were less likely to recognize a studied face but not remember its studied context (familiarity).

Despite all of the neurobiological reasons to think that complex object discrimination or familiarity may be exquisitely sensitive to MCI, standardized tests of these abilities have not been developed. It is high time that the assessment of MCI (and other neurological disorders) catches up with state of neuroscience research findings.

### Treatment of MCI

Given that MCI, particularly in its amnesic form, is often a precursor to AD, it is not surprising that most (70%) physicians report prescribing cholinesterase inhibitors “off-label” at least sometimes in this cohort, and 39% reported prescribing memantine.<sup>89</sup> These prescribing practices occur despite the continued lack of high-quality evidence for their efficacy in MCI,<sup>16</sup> perhaps because physicians suspect that their patients might have progressed to the early stages of AD.<sup>89</sup> Likewise, there is insufficient evidence to support treatment of MCI with alternate agents such as the nicotine patch or vitamin E.<sup>16</sup> Physicians are recommended to wean their patients off other medications that may impair cognition, and to treat other modifiable risk factors that may be contributing to cognitive impairment, including mood disorders.<sup>16</sup>

Given that there are no disease-modifying agents for MCI, and that the symptomatic treatments for AD lack efficacy in MCI, what can be done for people in this precarious state? The approaches described in the remainder of this section are not cures, and no one holds the belief that these measures will have direct effects on the neuropathological changes occurring in MCI, but there is still reason to think that they may delay progression to dementia. This thought rests on the fact that to progress to dementia one has to have cognitive deficits that are severe enough to interfere significantly with everyday functioning. Thus, if we can raise an individual’s level of cognitive functioning, that person will have to experience a greater degree of cognitive decline before progressing to dementia, which will essentially buy him or her more time in relatively good cognitive health. This idea is a corollary of the notion of reserve<sup>90</sup> that has been offered to explain the discrepancy between the degree of neuropathology and one’s level of cognitive functioning. Research has identified several early-life and mid-life factors, such as educational and occupational attainment, that increase reserve and permit individuals to tolerate higher levels of neuropathology yet maintain their cognitive functioning.<sup>90</sup> Reserve can be neural, for example by fostering richer neural connections, or cognitive, allowing individuals to approach tasks in new ways.<sup>90</sup> The approaches described below are efforts to enhance neural and/or cognitive reserve.

Physical exercise interventions have shown small but significant neural and cognitive benefits for cognition in people with MCI (for a meta-analysis, see Ströhle *et al.*<sup>91</sup>). For example, Baker *et al.*<sup>92</sup> randomized 33 people with amnesic MCI to either aerobic training or a stretching control group 4 times a week over 6 months. In addition to the expected effects on cardiorespiratory fitness, aerobic training was associated with improved attention and executive functioning. However, the association between improvements in cardiorespiratory functioning (VO<sub>2</sub> peak) and these cognitive measures was larger for women than men. Aerobic exercise also had greater benefits for glucoregulatory function and plasma brain derived neurotrophic factor in women than men. These sex-specific improvements occurred despite the fact that both groups enjoyed comparable improvements in cardiorespiratory fitness. Similar reports of greater benefits of exercise, and physical activity more generally, in women than men have been reported in other meta-analytic and epidemiological studies<sup>93,94</sup> and may be explained by the fact that the women in these studies tend to be less fit overall (body fat, lipid profiles, cortisol levels) at baseline, and thus have more room for improvement.

Adherence to Mediterranean-style dietary patterns has been associated with a reduced risk of MCI and AD in

epidemiological studies.<sup>95</sup> Few diet intervention studies in MCI populations have been published to date, but so far their results are promising. For example, Bayer-Carter *et al*<sup>96</sup> randomized 49 healthy older adults and 29 adults with amnesic MCI to either a high-saturated fat/high glycemic index (HIGH) diet or a low-saturated fat/low glycemic index (LOW) diet for four weeks. In the MCI group, compared to the HIGH diet, the LOW diet resulted in increased CSF A $\beta$  levels (indicative of improved brain clearance); increased CSF insulin concentrations; and decreased plasma lipids, insulin, and CSF F2-isoprostane concentrations. The beneficial effects of the LOW diet on CSF A $\beta$  were later found to be potentiated in individuals who reported engaging in more high intensity physical activity,<sup>97</sup> hinting at the likely additive or synergistic effects of multicomponent approaches to healthy lifestyle interventions to increase reserve in people with MCI.

Another approach to increase reserve and everyday functioning in people with MCI is group psychosocial education. These interventions typically teach people practical, everyday memory strategies such as mental imagery and semantic processing to improve encoding of information; teach people about the effects of lifestyle factors such as exercise, diet, and cognitive and social engagement on memory and facilitate adoption of healthier lifestyles; and address coping strategies such as relaxation and preparing for the future.<sup>98–102</sup> These studies have reported some improvements on objective tests of memory and other cognitive abilities<sup>98–101</sup> and improvements in subjective memory,<sup>98,99,102</sup> but due to variations in the quality of these studies (eg, use of an active control group, selection of appropriate outcome measures), the most recent MCI guidelines suggest that clinicians may (versus should) recommend such programs.<sup>16</sup> More large-scale trials are needed with proper controls to identify the most effective group intervention approaches for MCI.

The MCI guidelines<sup>16</sup> also highlight the need to educate patients and families about MCI, and suggest that clinicians should counsel patients and families. This type of counseling is common in some of these programs (eg,<sup>102</sup>), but in response to an identified need for more, accessible information, the current author and her colleagues wrote a book in lay language about what MCI is, how it is diagnosed, and how it can be managed.<sup>103</sup>

In addition to these more comprehensive intervention approaches, a number of investigators are discovering the best approaches to memory interventions for MCI. For example, it has been repeatedly shown that people with MCI learn new information best if they are prevented from making errors while learning.<sup>104–106</sup> Efforts to train working memory using adaptive approaches, meaning that the task becomes more

difficult as individuals improve on the task, have shown improvements in working memory, but limited generalization to other cognitive domains.<sup>107,108</sup> Likewise, trials of memory recollection training have shown limited generalization.<sup>109,110</sup> These latter efforts indicate that restorative approaches, attempting to retrain specific cognitive processes, may be less effective cognitive rehabilitation approaches than compensatory approaches such as memory strategy training.

## Conclusions

A massive amount of research has focused on honing the clinical criteria for MCI, and on gaining a better understanding of its prevalence and prognosis, its phenomenology and neurobiology, and how best to assess and treat MCI in efforts to delay progression to dementia. In fact, the number of articles that have been indexed in PubMed that can be found with the search term “mild cognitive impairment” since the term was introduced by Reisberg *et al*<sup>10</sup> until the end of 2016 exceeds 12,000, the vast majority of which (>94%) have appeared since the beginning of the 21st century.<sup>111</sup> Yet, consensus still needs to be achieved concerning the clinical (and research) criteria for MCI and how to operationalize those criteria, and we still have a long way to go to better understand what it is like to live with MCI. As neuroimaging, genetic (and epigenetic), and molecular techniques advance, we will certainly learn much more about how MCI manifests in the brain. Academic neuropsychologists look forward to the day when standardized assessment tools catch up to the state of the neuroscience to develop new, validated behavioral or neurofunctional tests that prove more sensitive to the very early stages of MCI. And we all anticipate new treatments, pharmacological or otherwise, that improve prognosis of MCI and reduce prevalence of dementia.

## Disclosures

Nicole Anderson receives royalties from Oxford University Press.

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