Differentiating Mild Cognitive Impairment and Cognitive Changes of Normal Aging

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Introduction

Normal Cognitive Aging

As people live longer, scientists are given greater opportunity to improve their knowledge of the structure and function of the aging brain. In the United States, the current life expectancy at birth is 76 years for men and 81 years for women, and approximately 13% of US citizens are 65 years and older [1–3]. The US Census Bureau's projections estimate that about one in five citizens will be seniors by the year 2030 and the oldest old (85 years and older) is the fastest-growing segment of the population. Given these statistics, there is a great need for clinical services and research focusing on normal and pathological cognitive aging.

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It is generally accepted that some degree of cognitive decline associated with aging is inevitable, with a great deal of variability as to when these changes begin [4]. Interindividual variation in cognitive performance in areas such as memory and fluid intelligence increases with age. Thus, with advancing age, there becomes an increase in the proportion of elderly persons who show normative age-associated cognitive decline [5–8]. It can become difficult to parse out "normal" cognitive aging versus pathological cognitive decline in the absence of neuropsychological testing with normative comparison data.

Some aspects of cognition remain relatively intact with normal aging, including implicit memory, vocabulary, and storage of general knowledge [5, 8, 9]. The cognitive decline that typically accompanies normal cognitive aging involves decreased efficiency in information processing in several areas, including speed of processing, reaction time, working memory capacity, short-term memory, executive control (e.g., inhibitory functions), and verbal fluency [5, 10–12]. Visuoperception, visuoconstruction, and spatial orientation also decline with age [13, 14].

Slowed processing speed is a key cognitive change in the aging brain. It has been widely found, for example, that visual-motor tracking, sequencing, and set-shifting slow with age [15–17]. Reduced processing speed is suspected of mediating cognitive efficiency by restricting the speed at which cognitive processes can be executed

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[9, 11, 18, 19]. Reduced processing can also affect the quality and accuracy of performance due to the decreased quantity of information processed that is necessary for completion of the task [19]. Further, products of earlier processing may be lost by the time later processing occurs, rendering integration of relevant information difficult or impossible. The consequences of reduced processing include decreased working memory capacity because less information can be processed within a given time, as well as impaired higher-order cognitive functions such as abstraction or elaboration, because the relevant information is no longer available in working memory or storage [19].

Age-related changes in working memory are likely due to reduced inhibitory mechanisms of selective attention [20]. That is, older adults show decreased ability to effectively suppress the processing of irrelevant, or marginally relevant, stimuli and thoughts. This leads to a generalized attentional dysregulation that is also thought to account for age-related deficits in various aspects of executive performance, including shifting cognitive set, suppressing responses, and response competition [9]. Cognitive aging is also associated with poorer effortful or controlled processing, while automatic processing remains relatively intact [21]. Older adults retain relatively good memory for "gist" or familiar stimuli, while source memory and recollection of contextual details decline [12].

Normal age-related changes in language function include increased inefficiency in phonological retrieval, resulting in word-finding difficulties that are often referred to as the "tip of the tongue" phenomenon [22]. The literature shows that confrontation naming performance declines with age, with the rate of decline accelerating in older age groups [23–25]. Semantic fluency or the ability to retrieve words associated with a particular category under time constraints also declines with age, as does lexical fluency (i.e., the ability to rapidly retrieve words from declarative memory that begins with a particular letter or sound) [26]. However, it is suspected that the age-related decline in verbal fluency is at least partly due to the substantial contributions of auditory attention and verbal memory abilities to the tasks, rather than simply a primary degradation of semantic or lexical networks [27].

Structural Brain Changes

Numerous changes in brain structure accompany normal aging, including volumetric shrinkage, decreased white matter density, loss of dopaminergic receptors, and the emergence of neurofibrillary plaques and tangles. The greatest degree of cortical thinning and volumetric brain shrinkage across the lifespan occurs in the hippocampus, caudate, cerebellum, and calcarine (i.e., occipital) and prefrontal areas [28, 29]. Ventricular volume also increases in old age [30]. Decreases in white matter density and other white matter abnormalities are particularly evident in the frontal and occipital regions of the brain [31, 32]. White matter changes may be the primary culprit for age-related cognitive slowing, as white matter's main function is to facilitate transmission of signals to and from different areas of the brain via myelinated axons. As myelin integrity degrades with age, so does the speed of cognitive processing. Together with findings on cortical volume and thinning, studies on age-associated white matter changes point to significant alterations in frontal networks [31, 32].

Loss of dopaminergic receptors occurs with age and is thought to contribute to the attentional dysregulation, executive dysfunction, and difficulty with contextual processing that accompanies normal cognitive aging [33–35]. It has been proposed that context processing involves using internally represented task-relevant information in a way that influences processing in the pathways responsible for task performance [36]. For example, performance on the Stroop task is dependent upon the ability to use the context of task instructions (i.e., inhibit reading color-named words while saying the printed ink color) in order to maintain attention toward ink color rather than the printed word. Braver and Barch (2002) postulated that contextual representations are affiliated with the dorsolateral prefrontal

cortex and are regulated by dopamine projections to this area. The mechanism of context processing subserves cognitive functions such as attention, working memory, and inhibition by affecting the selection, maintenance, and suppression of information relevant (or irrelevant) to the task, accounting for the decline in these abilities with age [36].

An autopsy study on clinically nondemented oldest old (age ≥ 85 at death; $n = 9$) found neurofibrillary tangles (NFTs) in one or more limbic regions in all study participants [37]. The most affected regions included the entorhinal cortex, amygdala, subiculum, CA1 field of the hippocampus, and inferior temporal regions. Midfrontal, orbitofrontal, and parietal regions were less affected, and occipital regions were minimally affected in clinically nondemented persons. Senile plaque (SP) formation also was observed in this group and was found to affect all brain regions equally, with the exception of relative sparing of the occipital cortex. Participants who were clinically nondemented at death showed significantly less NFTs and SPs than participants with mild cognitive impairment (MCI) and dementia. Pathological lesion density was significantly related to cognitive status. However, two of nine participants who were nondemented in the few months prior to death met *pathological* criteria for Alzheimer's disease, suggesting individual variability in the relationship between brain pathology and cognitive presentation. One explanation for this variability is the notion of cognitive reserve, a hypothesized degree of protection against disease or injury whereby one is behaviorally unaffected by pathology sufficient to cause dementia in someone with less cognitive reserve. The construct of cognitive reserve is discussed more fully elsewhere in this volume (see Chap. 2).

Functional imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow for the examination of blood flow and oxygenation to particular brain structures, in participants as they engage in cognitive tasks. Comparisons of older and younger adults reveal an increase in bilateral activation with age, whereby tasks associated with focal, unilateral activation in younger adults (e.g., verbal memory) become associated with bilateral activation in older adults [38, 39]. Further, bilateral activation in older adults is associated with *better* performance on cognitive tasks, including working memory, semantic learning, and perception [40–43]. This suggests that the older brain engages in more widely distributed compensatory processing by activating the contralateral hemisphere to achieve greater cognitive benefits [9].

Theories of Aging

In a process termed "dedifferentiation," sensory function (i.e., visual acuity and audition) has been shown to predict performance on a wide range of cognitive tasks in older, but not younger, adults [44, 45]. It has been proposed that abilities that are relatively independent earlier in life, such as sensory ability and cognition, become more interrelated with old age. Functionally, this can be thought of as a decrease in neural specificity, whereby regions that respond selectively in younger adults change to respond to a wider array of inputs in older adults. Similarly, in older adults, increased prefrontal activation is associated with decreased parahippocampal activation and hippocampal volume shrinkage [46, 47]. Whereas activation in the parahippocampal regions is associated with learning new material in younger and middle-aged adults, increased prefrontal activation is instead observed in older adults, suggesting greater frontal activity may be a compensatory mechanism for decreased mesiotemporal activation [9, 46].

Salthouse proposed the processing-speed theory of cognitive aging, which assumes that a wide range of cognitive task performances are limited by the imposed constraints on the speed of processing [19]. Slow processing speed dampens cognition in two ways: (1) cognitive operations are executed too slowly to be successfully completed in the available time and (2) the amount of simultaneously available information, necessary for higher-level processing, is reduced,

as early processing is no longer available when new processing occurs. Complex operations are most affected by slow processing speed since they are dependent on the products of simpler (and earlier) operations, and often, the accuracy of performance is dependent on the number of operations that can be carried out in a given time period (e.g., associations, rehearsals). The amount of simultaneously available information may also be reduced due to disruptions in the synchronization of neural signals and activation patterns [19].

The *scaffolding theory* of aging and cognition proposes that structural brain changes associated with aging are accompanied by effort on the part of neural networks to maintain homeostatic cognitive functioning in the face of these changes [9]. This leads to changes in brain function through "strengthening of existing connections, formation of new connections, and disuse of connections that have become weak or faulty" (p. 175). Scaffolding is described as the brain's "normal response to challenge" (p. 183), and the theory can be used to explain the process of acquiring a novel skill. The initially engaged neural networks shift from broad and dispersed to a specific and honed circuit of neural regions. While the more specific regions assume dominant control over functions, the initial broad networks continue to be minimally active, suggesting that they remain available for compensatory processing [46]. In the aging brain, scaffolding is thought to maintain healthy cognitive function in the face of neural degradation. These circuits can provide supplementary, complementary, or alternative ways to complete a cognitive task and are thought to reside largely within the prefrontal cortex, consistent with findings on overactivation of frontal networks with age [9]. Scaffolded networks, however, are less efficient and more prone to error than honed circuits, which are highly functionally interconnected. According to scaffolding theory, this results in the observable and measurable cognitive decline seen in older adults. The need for compensatory scaffolding exceeds the available networks, resulting in a more profound decline in functioning in the oldest old.

Individual Factors in Cognitive Aging

Given the considerable variation in cognitive performance in older persons, particularly in the oldest old, examination of individual difference factors related to the cognitive aging process is warranted [5, 6]. Factors shown to contribute to cognitive reserve or to be related to cognitive decline in clinical studies include education, occupational complexity, physical health, and diet [48]. It is suspected that cognitive reserve is represented biologically by a number of processes, including (1) richer interconnectivity and organization of neural circuits; (2) alterations in synaptic efficiency, marked by changes in neurotransmitter release, receptor density, and receptor affinity; (3) and changes in intracellular signaling pathways [48].

Physical health status is arguably one of the more important factors to consider when predicting performances on cognitive assessment in noncognitively impaired elderly. Clinical and subclinical medical disorders have been found to be better predictors of neuropsychological performance than chronological age, and these disorders include hypertension, hypercholesterolemia, obesity, and white matter lesions [49]. Cardiac arrhythmias [50], sensory loss [51], pulmonary function [52], and other measures of biological age [53] have also been associated with poorer cognitive functioning.

Higher education has been associated with preserved cognitive performance over time (i.e., less decline) in aging adults [54, 55], though not all research has supported this outcome [56]. Occupational complexity is shown to be related to relatively better cognitive functioning with age, above and beyond the benefits afforded by higher levels of education [57]. More specifically, cognitive ability in older adults was found to be related to the degree of complexity of one's work with people but not to occupational complexity with data or things [57]. In particular, participants who held jobs with high complexity of work with people demonstrated better cognitive performance on measures of verbal skills, spatial skills, and processing speed than participants with low occupational complexity with people.

No differences in memory performances were found. The cognitive benefit received from high occupational complexity ceased following retirement, suggesting that once these occupational skills are no longer being practiced, they fail to retain their effectiveness in bolstering cognitive ability.

Mild Cognitive Impairment

Defining Mild Cognitive Impairment

Neuropsychological referrals are often made on the basis of a patient's or their family's perceived (i.e., subjective) report of a decline in cognitive ability. An integral part of the neuropsychologist's role is to determine whether a patient's complaints or their family's observations of cognitive decline are due to the normal cognitive aging process or if they instead represent an objective impairment in cognitive functioning relative to the patient's same-age peers. The construct of MCI represents a decline in cognitive performance greater than would be expected for the person's age but not sufficient to meet criteria for a diagnosis of dementia [58]. Petersen described MCI as interposed between normal cognitive changes associated with aging and the very early stages of a dementing process [59]. It is therefore conceptualized as a pathological condition and not merely a manifestation of the normal aging process. Incidence and prevalence rates vary as a consequence of study details, including diagnostic criteria, assessment procedures, and sample characteristics (e.g., community versus clinic, age, education, gender, race, health comorbidities). Within the general population, prevalence rates have been found to range from 1% to 35% [60, 61].

The original criteria for MCI proposed by Petersen et al. [58] are as follows:

1. Presence of a memory complaint
2. Normal activities of daily living
3. Normal general cognitive function
4. Abnormal memory for age
5. Not demented

These criteria are particularly useful for patients who have impairment in the memory domain but intact cognitive performance and functioning in all other domains. Such patients would be labeled as having amnesic MCI (a-MCI). Revised criteria were proposed by a multidisciplinary, international group of experts, in light of the heterogeneity of MCI clinical presentations reflected in the literature [62]. For example, some patients have a primary impairment in the memory domain only, whereas others have memory impairment in addition to other domain impairment(s). Still others have impairments in single or multiple nonmemory cognitive domains. These heterogenous clinical presentations may have multiple etiologies, including degenerative, vascular, metabolic, traumatic, psychiatric, etc. [59, 62].

The most updated clinical diagnostic criteria for MCI are recommended by the National Institute on Aging and Alzheimer's Association workgroup [63]. The diagnostic criteria for MCI in a clinical setting are as follows:

1. Concern regarding change in cognition: There is evidence of concern for change in the patient's cognitive status as compared to his/her previous level. This concern may be on the part of the patient, an informant who knows the patient well, or from a skilled clinician who has observed the patient.
2. Impairment in one or more cognitive domains: There is evidence of lower performance in one or more cognitive domains that is greater than what would be expected for the patient's age and educational background. Impairment may be in a variety of domains, including memory, attention, language, executive function, and visuospatial skills.
3. Preservation of independence in functional abilities: The patient generally maintains his/her independence of function in daily life without considerable aids or assistance. However, patients may have mild problems performing complex functional tasks (e.g., paying bills, preparing meals, shopping), whereby they may be less efficient, take more time, and make more errors than in the past.

4. Not demented: These cognitive changes are sufficiently mild so that there is no evidence of significant impairment in social or occupational functioning. A diagnosis of MCI requires evidence of intraindividual change. If the patient has been evaluated only once, change will be inferred from the history and/or evidence that cognitive performance is impaired beyond what is expected for that patient. Practical application of these criteria will be considered below in the Assessment section.

Subtypes

We have already mentioned *single-domain amnesic MCI* (*a-MCI*), which is a useful category for patients who have impairment in memory but intact cognitive performance in all other domains and in daily functioning. As research on MCI has advanced to include cognitive impairment in domains other than memory, several other subtypes of MCI have been proposed [59]. Some patients display impairment in a single nonmemory cognitive domain (e.g., executive function) but perform normally in other domains, including memory. These patients would be given labels of single-domain non-amnesic MCI (na-MCI). Still other patients present with impairments in multiple domains while continuing to display relatively intact activities of daily living (ADLs) and general cognitive functioning; these patients would be classified generally as having multiple-domain MCI. More specifically, in the event that a deficit in memory is present, a patient is given a diagnosis of multiple-domain MCI with amnesia (md-MCI + a); if memory impairment is not evident, then a diagnosis of multiple-domain MCI without amnesia (md-MCI-a) is appropriate.

Etiology and Prognosis

In addition to different subtypes, there also are multiple etiologies for MCI. Petersen suggested four main etiologies: (1) degenerative (e.g., Alzheimer's disease), (2) vascular (e.g., cerebrovascular disease), (3) psychiatric (e.g., depression), and (4) traumatic (e.g., head injury) [59]. Of course, a host of other potential etiologies should always be considered in the differential diagnosis, including medication side effects and other toxic factors, metabolic factors (e.g., thyroid dysfunction, vitamin B12 deficiency), or infection. Particular subtypes of MCI are reported to be more commonly associated with certain etiologies. For example, patients with a-MCI are more likely to convert to Alzheimer's disease than patients with na-MCI [58, 64–66]. An impairment in episodic memory, i.e., the ability to learn and retain new information, is most commonly seen in MCI patients who later convert to Alzheimer's disease [63]. Additionally, a longitudinal decline in cognition provides additional evidence for a likely etiology of Alzheimer's disease [63]. Those with impairments in nonmemory domains such as executive function and visuospatial skills may be more likely to convert to dementia with Lewy bodies [59]. Persons with na-MCI in one study were least likely to convert to any form of dementia [63].

Follow-up data from the initial Petersen et al. study on MCI using patients (N = 220) from the Mayo Alzheimer's Disease Center/Alzheimer's Disease Patient Registry (ADC/ADPR) demonstrated a rate of progression from MCI to dementia of 12% per year [58, 59]. At a 6-year follow-up, approximately 80% of MCI patients in the same study were reported to have progressed to dementia. Other studies have found conversion rates of 10–19% per year from MCI to Alzheimer's disease [65, 67]. In comparison, 1–2% of the general population develop Alzheimer's disease per year, providing evidence that MCI places one at increased risk for future dementia above the rate that is expected for a person's age [58]. Persons diagnosed with a-MCI were found in one study to have a fourfold greater risk than noncognitively impaired individuals to develop Alzheimer's disease over a 2-year follow-up period [68]. When considering a general diagnosis of MCI (i.e., not taking into account subtype), patients are found to have a three times greater risk of developing Alzheimer's disease (average follow-up of 4.5 years) [69].

At the same time, however, many persons with MCI remain stable with this diagnosis or revert to normal. For example, in a clinical sample, 41% remained stable over an average 3.5-year follow-up, and 17% returned to normal cognitive status [70]. These data suggest that for some patients, MCI represents an intermediate point on the continuum from normal cognition to dementia, while for others, MCI is a transient period of cognitive decline that resolves with time. The latter may be seen in patients with reversible causes of cognitive dysfunction, such as metabolic abnormalities or substance use. Those with na-MCI are most likely to revert to normal or improve their cognitive status over time [64].

Pathophysiology and Neurodiagnostic Findings

Neuroimaging data lends further support for MCI as a unique diagnostic entity, separate from both normal cognitive functioning and dementia states. Retention of Pittsburgh compound B (PIB), used to image beta-amyloid plaques in neuronal tissue, has been examined using positron emission tomography (PET) in persons with normal cognition, MCI, and Alzheimer's disease (AD) [71]. In their study, Forsberg et al. found that PIB retention in MCI patients is higher than that of normal controls but lower than in AD patients. Additionally, the MCI patients who converted to AD within the 2–16-month follow-up period had higher mean PIB retention than the MCI patients who remained stable during follow-up periods. Magnetic resonance imaging (MRI) has been used to examine trajectories of volumetric brain loss in a healthy aging sample over a 15-year period [30]. Ventricular expansion was found to be faster in persons developing MCI years prior to the emergence of clinical symptoms. An increasingly rapid expansion occurred approximately 2 years prior to the clinical diagnosis of MCI.

Neuroimaging studies show that subjects who progressed to AD within an 18-month follow-up period had greater volume loss than a stable MCI group and a control group in areas consistent with volume loss in AD (i.e., medial and inferior temporal lobes, temporoparietal neocortex, posterior and anterior cingulate, precuneus, and frontal lobes) [72]. Autopsy studies reveal that subjects who died with a classification of a-MCI showed the early pathologic changes seen in subjects diagnosed with AD prior to death with greater density of temporal lobe neurofibrillary tangles [73–75]. Annual increase in ventricular volume as assessed by serial MRI has revealed the greatest volume increase in AD subjects, followed by an intermediate increase in a-MCI subjects, and the smallest change in cognitive normals. Further, a-MCI and AD subjects with APOE-ε4 genotype show the greatest increase in ventricular volume. These findings also correlate clinically with concurrent change in cognitive and functional status [76]. Specific and distinguishing MRI abnormalities also have been identified in MCI subjects who ultimately convert to AD, vascular dementia, and Lewy body dementia, lending support for MCI as a prodrome to multiple dementing processes [77].

Assessment

Referrals

Referrals for neuropsychological evaluation when MCI is a diagnostic consideration may come from a variety of sources. Neurologists are likely to be one of the most common referral sources, along with primary care physicians, psychiatrists, and self-referral (initiated either by the patient or a family member). One study of male patients with MCI receiving care at a Veterans Affairs hospital found that, generally, either patients or their families prompted the consultation for memory loss [78]. In many cases, patients may be seen first by neurologists who then provide a neuropsychological referral for a more comprehensive cognitive evaluation. Most typical referral questions from other medical professionals in the context of an evaluation for MCI will pertain to differential diagnosis and etiology. Typical differentials will include normal cognitive aging versus MCI versus dementia, as well as

Table 28.1 MCI differential diagnosis

Normal cognitive aging
Dementia (e.g., Alzheimer's, vascular, frontotemporal dementia, Parkinson's plus syndromes)
Depression/"pseudodementia"
Delirium
Other potentially reversible causes for cognitive dysfunction (e.g., metabolic abnormalities, substance use, obstructive sleep apnea, concussion)

depression or "pseudodementia" versus MCI or dementia. Etiology of cognitive impairment also is a common referring question and usually involves a question of Alzheimer's disease pathology versus other causes such as vascular cognitive impairment, frontotemporal dementia, a Parkinson's plus syndrome (e.g., Lewy body dementia, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration), or metabolic causes. Table 28.1 shows a list of common differential diagnoses for MCI. There are other associated issues that may be relevant to referring physicians, such as beginning an appropriate cognitive-enhancing medication or psychotropic drugs for treatment of mood disorders. The neuropsychological evaluation is often requested to serve as a baseline for subsequent serial evaluations in order to track the trajectory of cognitive decline or improvement following treatment. Assessment of functional independence may be requested based on cognitive testing, such as whether the patient is completely independent or requires in-home assistance as part of their daily functioning. Cognitive testing may also help form an opinion as to whether the patient may require a formal driving evaluation. Assessment of driving abilities is detailed elsewhere in this volume (see Chap. 15).

Clinical Interview

An important component of the clinical interview when assessing patients with MCI involves obtaining an accurate picture of the emergence of cognitive symptoms and any functional difficulties. For this reason, it is ideal to have a collateral informant present at the interview to provide his or her insight into the patient's behaviors and functional status. The informant is typically a spouse, child, sibling, or other close family member or friend who is knowledgeable about the patient's history and can provide information about changes in cognitive and functional status.

One of the diagnostic criteria of MCI is the presence of a subjective cognitive complaint. Patient complaints may be corroborated by the collateral informant, whereas in some cases, the friend or family member's report is the only evidence for subjective cognitive change. This may occur in cases where the patient has little to no insight into their cognitive changes. It is important to obtain a thorough history of the emergence of cognitive symptoms, including examples of cognitive problems the patient is experiencing in everyday life. For example, the early and prominent emergence of language symptoms may be indicative of a primarily aphasic dementing process, whereas early memory difficulties may signal mesial temporal lobe involvement, the area initially and primarily affected in Alzheimer's disease. Evaluating functional abilities also is essential when considering a diagnosis of MCI. Functional independence is the key factor in the differential diagnosis of MCI or early dementia. Patients with MCI are considered to have intact basic activities of daily living (ADLs), with predominantly intact instrumental ADLs. An assessment of functioning should include questions about the patient's ability to care for his or her basic needs, such as hygiene, dressing, and feeding oneself, as well as his or her more instrumental needs, such as making and keeping appointments, financial management, driving abilities, and medication management.

The patient and his or her informant should also be questioned about changes in behavior or personality, which are often early indicators of a primarily behavioral dementing process, such as frontotemporal dementia. Behaviors to consider include those indicative of apathy, disinhibition, perseveration, or behaviors that are out of the ordinary for the person. In addition, irritability often accompanies symptoms of cognitive decline. Patients should be questioned about

emotional symptoms and psychiatric history to assess for the presence or increase in symptoms of depression, anxiety, or other salient psychological problems. This is particularly important because approximately 35–75% of patients with MCI endorse at least one neuropsychiatric symptom at a prevalence rate that is higher than same-age non-MCI peers [79–82]. The most commonly endorsed symptoms include depression/dysphoria, apathy, anxiety, and agitation [83, 84]. Commonly reported symptoms of depression in MCI include poor concentration, inner tension, pessimistic thoughts, lassitude, reduced sleep, thoughts of death, inability to feel, and reduced appetite [85]. There is some evidence for higher rates of depression in a-MCI versus na-MCI and in multiple-domain MCI versus single-domain MCI patients [79, 83]. Given evidence for elevated rates of mood symptoms in persons with MCI, it is imperative that patients are screened for clinical and subclinical symptoms of depression, anxiety, apathy, and irritability.

The clinician should obtain a thorough medical history and assessment of the patient's current health status. Results should be obtained from any completed neurodiagnostic studies (e.g., MRI, CT, EEG) for consideration in the differential diagnosis. Evaluating the presence of vascular risk factors such as hypertension, hypercholesterolemia, and diabetes is essential when considering etiology of cognitive decline. An assessment of the patient's sleep quality is important, including whether he or she has been diagnosed with sleep apnea, which has known effects on executive cognitive functioning, vigilance, and memory [86, 87]. A review of the patient's current and recent medications is also critical in order to consider medication-induced cognitive changes. It is important to obtain not only a list of the patient's medications but also a careful chronology of when each potentially psychoactive medication was introduced in relation to the chronology of cognitive symptom emergence. A review of the patient's use of recreational substances is necessary to rule out preventable causes for cognitive changes. Finally, family history of dementia should be assessed, including approximate age of onset of cognitive difficulties in family members.

Functional Impairment

In assessing whether ability to carry out activities of daily living (ADLs) is essentially normal (a diagnostic criterion for MCI), a thorough history from the patient (and ideally an informant) should be obtained. Self-report or clinician-administered ADL scales can also be employed but do not replace a careful detailed interview, since many of the ADL scales do not pick up on subtle changes in functioning. Petersen noted that minor inconveniences in a patient's daily functioning may be present, but they are not sufficient in severity to constitute a major disability in functioning [59]. Patients with MCI tend to report some degree of decline in their ability to handle daily tasks, whereby they feel they are more forgetful, are less able to multitask, and have difficulties with planning and organization [88]. These inefficiencies can manifest in a variety of ways, such as problems remembering where one has placed objects, forgetting new names, difficulty completing two tasks at once, and trouble remembering shopping items, recalling conversations, or prioritizing tasks by importance. It is often the ability to learn, retain new information, and perform higher-order executive skills that is dampened in persons with MCI, resulting in somewhat less efficient daily functioning [88–90]. Persons with MCI tend to make errors in performing tasks accurately and efficiently while still remaining able to complete tasks [91]. This is in contrast to dementia patients, who tend to also make these errors in addition to omitting major portions of tasks.

Poorer memory performance on cognitive testing has been found to predict future difficulties in financial management in patients with MCI, and impaired memory and psychomotor speed are the cognitive domains most strongly related to functional abilities [92]. Other research suggests that attention and executive functioning, but not memory, are associated with difficulties

managing multiple-step financial tasks, such as bill payment and preparation and management of bank statements [93]. Persons with MCI tend to show subtle functional declines in driving abilities when compared to noncognitively impaired persons, though their overall performances are not at the level of frank driving impairments [94]. Instead, they are less likely than their cognitively normal peers to perform certain driving routines seamlessly (e.g., left-hand turns, maintaining lane control), and their performances are more often rated as "less than optimal." Although some dampening in functioning is observed in MCI patients, it is much less severe than the functional decline seen in patients with dementia. MCI patients tend to perform functionally on a level intermediate between persons with normal cognition and dementia patients [91]. MCI patients are still able to function independently, albeit perhaps less efficiently and with the use of compensatory strategies.

Cognitive Impairment

Criteria for diagnosing MCI include not only self- or family report of cognitive decline but also objective measurements of deficits in cognitive functioning. An exact cutoff for what constitutes "mild" impairment has not been set in stone, but traditionally, a cutoff score of 1.5 SD below age norms has been used based on Petersen et al.'s original study [58]. In that study, the MCI group performed, on average, 1.5 SD below age-matched controls. However, Petersen emphasizes that this was not intended to serve as a cutoff score and that it is ultimately left up to clinician judgment whether or not a patient displays objective memory impairment relative to his or her baseline [59]. The most recent consensus criteria note that scores on cognitive tests for patients with MCI are typically 1–1.5 SD below the mean for age- and education-matched peers on culturally appropriate normative data [63]. It is emphasized that these ranges are to be used as guidelines and not cutoff scores.

Selecting neuropsychological instruments for evaluating MCI should include an evaluation of the patient's performance in all major cognitive domains (i.e., memory, attention, processing speed, language, executive functioning, visuospatial skills, motor functioning) in order to ensure a comprehensive assessment. Typically, a dementia screening measure is also administered and ideally an estimate of premorbid functioning (e.g., word reading). A comprehensive assessment approach that employs detailed neuropsychological assessment is advocated to improve the reliability and stability of the MCI diagnosis [95]. Although all major neurocognitive domains should be validly sampled, it is of particular importance to obtain multiple measures of memory, as this domain is typically the presenting subjective complaint and is essential for differential diagnosis. Because there are multiple possible etiologies of MCI, it would be inappropriate to focus only on memory testing and a global screening measure. Assessment of other areas, including executive, attentional, and motor abilities in assessing for a vascular etiology, as well as visuospatial functioning in assessing for Lewy body pathology, allows for the most comprehensive approach to determining etiology, a common referral question. Careful examination of memory profile patterns is also helpful in this regard. Given that a significant proportion of MCI patients present with neuropsychiatric symptoms, it is important to also include self-report measures of mood functioning, such as assessments of depression and anxiety symptoms. Table 28.2 provides a sample test battery for a comprehensive neuropsychological evaluation when MCI is considered in the differential diagnosis. Other measures and test batteries may be chosen, but the guiding principles of test selection should be comprehensive sampling of cognitive domains, appropriate norms for age and other patient demographic factors, and wide range of measurement between the floor and ceiling captured by the measures, and whenever possible, measures with alternate forms for retesting over time should be used.

Table 28.2 Sample core neuropsychological battery for assessment in MCI

Mini-Mental State Exam [96]
Repeatable Battery for the Assessment of Neuropsychological Status [97]
Wechsler Adult Intelligence Scale IV [98] or Wechsler Abbreviated Scale of Intelligence [99]
Wide Range Achievement Test 4 (Reading subtest) [100]
Trail Making Test A and B [101]
Stroop Color-Word Test [102]
California Verbal Learning Test II [103] or Hopkins Verbal Learning Test—Revised [104]
Rey Complex Figure Test [105, 106] or Brief Visuospatial Memory Test—Revised [107]
Wechsler Memory Scale III (Logical Memory) [108]
Boston Naming Test [109]
Controlled Oral Word Association [110] and Semantic Fluency (i.e., Animal Fluency) [111]
Wisconsin Card Sorting Test [112]
Clock Drawing and Copy [113]
Finger-Tapping Test [114]
Grooved Pegboard [115]
Geriatric Depression Scale [116] *or* Beck Depression Inventory, Second Edition [117]
State-Trait Anxiety Inventory [118]

Common Neurocognitive Deficits

The most common neuropsychological impairment seen in MCI patients who ultimately convert to Alzheimer's disease is a decline in episodic learning and memory early in the disease process [119, 120]. This is thought to be consistent with early involvement of structures in the medial temporal lobes (e.g., hippocampus, entorhinal cortex) in the progression to Alzheimer's disease (AD). Memory profile patterns in a-MCI tend to display reduced learning, rapid forgetting, poor recognition discrimination, and elevated intrusion errors [119, 121].

In terms of overall cognitive profiles, MCI patients have been found to show clearly defined memory impairments with only mild impairments in other domains, such as executive functioning [122, 123]. While a-MCI patients may show some difficulty in planning and problem-solving, md-MCI patients show the most severe impairments [124]. It is unclear whether md-MCI patients' cognitive profiles are more impaired due to different disease etiologies (e.g., vascular) or whether differences are due to md-MCI patients being further along in the disease process.

Although visual confrontation naming impairment is a hallmark symptom of AD, patients with a-MCI have not been found to differ from controls on such tasks, suggesting that the breakdown in semantic knowledge does not typically occur at the MCI stage [125]. At the same time, however, MCI patients have been shown to have poorer performance than controls on tasks of semantic memory, receive less benefit than controls when semantically cued on memory tasks, and use less semantic clustering strategies on verbal learning tasks [69, 126, 127]. It may be the case that these deficits in semantically related learning are due at least in part to dampened executive functioning processes that affect categorization or semantic organization [128].

In the attention domain, MCI patients who ultimately convert to AD demonstrate poorer immediate serial recall and divided attention than their MCI counterparts who remain cognitively stable [129]. This subgroup demonstrates the early stages of attentional impairment seen in AD, suggesting that such attentional impairments slowly decline over the course of the disease.

Vascular MCI has been less extensively studied in the research literature, though data suggest that patients with vascular disease or significant vascular risk factors demonstrate poorer attention, executive function, visuospatial performance, and slower processing speed than patients without vascular risk factors [130, 131].

Diagnosing MCI Subtypes

Once a diagnosis of MCI is established based on diagnostic criteria, selecting an MCI subtype is based on the results of the neurocognitive profile. In amnesic MCI (a-MCI), there is a single deficit in the learning and memory domain with

preserved cognitive functioning in all other domains. Other patients have impaired learning and memory in addition to impairment in another domain (oftentimes, executive functioning, but any other domain is possible), and these patients would receive a diagnosis of multiple-domain amnesic MCI (md-MCI + a). Patients who have a single nonmemory domain impairment (again, often executive dysfunction or attention/processing speed) are given the diagnosis of non-amnesic MCI (na-MCI). A subset of patients demonstrates impairment in two or more nonmemory domains and would be diagnosed with multiple-domain non-amnesic MCI (md-MCI-a).

Feedback and Recommendations

When reporting a diagnosis of MCI to a patient and possibly his or her family members, it is important that the clinician clearly explain the nature of the MCI diagnosis. Important information to highlight includes the degree of cognitive impairment associated with the diagnosis (i.e., greater than normal for the patient's age but not severe enough to warrant a diagnosis of dementia). Equally important to convey sensitively is the patient's increased risk for converting to dementia in the future, particularly for patients given an amnesic MCI diagnosis (single or multiple domain), which has the greatest association with future conversion to dementia, typically Alzheimer's disease [64, 68]. Patients should be made aware of their particular areas of difficulty (e.g., memory, executive functioning) and the real-world implications for these deficits. At the same time, cognitive and other personal strengths should be highlighted in the context of developing compensatory strategies for dealing with objective cognitive deficits and the functional difficulties that often accompany such deficits. If a-MCI is diagnosed, given its heightened association with a progression to Alzheimer's dementia, retesting may be recommended in 1 year. For other types of MCI, it may be more appropriate to recommend retesting as clinically warranted, if further cognitive changes are suspected by the patient, family, or referring clinician.

Useful information for clinicians disclosing an MCI diagnosis, including the meaning and impact for the patient, can be gleaned from a unique analysis of qualitative interview data from a small clinical sample of MCI patients ($N = 12$, diagnosed 3–6 months prior) [132]. The authors examined patient's experiences of living with and making sense of an MCI diagnosis. Interestingly, over 40% ($n = 5$) of their sample used positively valenced words to depict their emotional reactions to the diagnosis. Narrative accounts typically revealed satisfaction in finding professional validation for their subjective symptoms, as well as relief associated with a negative dementia diagnosis. Given evidence that MCI often is a precursor for dementia, this raises the issue of whether patients with MCI are adequately explained their increased risk of developing dementia in the future. Only 2 of 12 participants expressed a negative reaction to their diagnosis, and this occurred in the context of a perceived looming dementia diagnosis. Several participants did mention awareness of the possibility of further decline in cognitive status, often in the context of being unsure whether a decline would occur. Oftentimes, a current state of relief occurred simultaneously with tension surrounding an uncertain dementia prognosis. Around half of the participants related MCI as part of the normal aging process. Taken together, these findings suggest that there are varying interpretations of an MCI diagnosis, which the investigators pointed out have the potential to impact health behaviors, including returning for follow-up cognitive testing or planning for future states of decisional incapacity.

Recommendations for patients diagnosed with MCI may include follow-up with the patient's neurologist or psychiatrist to discuss potentially beginning a trial of anti-dementia medication, such as an acetylcholinesterase inhibitor. If the patient does not already have established medical care within these specialties,

an appropriate referral should be made, particularly if baseline neurodiagnostic studies (e.g., MRI, EEG) have not yet been completed. Management of risk factors associated with cognitive decline, such as medical comorbidities (e.g., vascular risk factors such as hypertension, diabetes, hyperlipidemia, sleep apnea, metabolic levels), should be recommended. Similarly, patients should be encouraged to participate in a physician-approved exercise regimen and maintain a healthful diet. Numerous studies have documented improvements among MCI participants in terms of cognitive abilities (particularly executive functioning), as well as decreased levels of pro-inflammatory cytokines and other neurodegenerative biomarkers. Moreover, research indicates that consumption of a healthy diet, including a Mediterranean-based diet, may prevent initial development of MCI symptoms and may also prevent conversion of MCI to AD [133–135]. Given that mood factors can exacerbate symptoms of cognitive impairment, appropriate monitoring of depression, anxiety, or other psychological factors is necessary. In some cases, a psychiatric or psychotherapy referral is warranted to assist in managing symptoms pharmacologically or cognitively/behaviorally. Patients should be encouraged to remain cognitively and socially active and to continue to complete daily tasks as independently as possible.

In terms of functional abilities, it is important for patients and their families to continuously monitor functional status, particularly with regard to potentially dangerous tasks such as driving. A change in functional status may be the simplest way for families of patients with MCI to recognize advancing cognitive decline, and they should be encouraged to assist the patient in monitoring instrumental activities of daily living (IADLs) such as financial management, driving, medication management, and higher-level organizational abilities. A decline in the ability to manage and perform IADLs is likely to represent a concordant decline in cognitive status and may alert the patient and family that neuropsychological reevaluation is warranted to assess for progression to a dementia syndrome.

With regard to neuropsychological retesting, it is difficult to establish a universally appropriate time for follow-up evaluation. Whereas a significant proportion of MCI patients will ultimately convert to dementia, many will also remain stable with the diagnosis or will revert to normal, depending on etiology. In those patients who ultimately receive a dementia diagnosis, the course of cognitive decline may be quite variable, with some patients remaining in the MCI category for years after initial evaluation and others converting to dementia rather rapidly. Patients present for their initial neuropsychological evaluation at various points on the continuum, further complicating an estimate for possible dementia conversion. Two points of reference can be helpful in determining a follow-up evaluation: (1) the severity and number of domains impaired and (2) the patient's functional status. It is likely that patients with relatively more severe cognitive impairments are further along in their disease progression and patients with multiple impaired domains may reach a dementia diagnosis sooner. Similarly, patients who show relatively greater impairment in daily functioning may be closer to a dementia diagnosis. Perhaps the safest benchmark for retesting is a 1-year follow-up period, in conjunction with the recommendation that the patient return for testing earlier should he or she (or family members) notice a significant decline in cognitive ability or functional status prior to the 1-year mark.

In conclusion, accurate clinical discrimination between normal cognitive aging and MCI is an important diagnostic challenge. This discrimination will become increasingly critical as new interventions are developed to target the very earliest manifestations of incipient brain disease.

Clinical Pearls

- A significant proportion of MCI patients will ultimately convert to dementia, although many will remain stable or will revert to normal, depending on the etiology of the cognitive disturbance.
- The most recent consensus criteria indicate MCI is associated with cognitive test scores that are typically 1–1.5 SD below the mean for age- and education-matched peers; it is emphasized that these ranges are to be used as guidelines, *not cutoff scores*.
- Although memory complaints of some kind are typically the most common presenting reason for evaluation, it is important to carefully assess the nature of the complaint since other aspects of cognition may actually underlie the perceived deficit.
- Assessment of mood/personality functioning is critical since subjective memory complaints tend to be more strongly correlated with negative affect than with objective memory performance.
- In addition to taking a general medical history, be sure to inquire about pain, sleep, and substance use in the context of the cognitive complaints.
- Assessing impact on activities of daily living (ADLs) requires careful clinical judgment. Be certain to clarify how ADLs are impaired by *cognitive* factors as opposed to physical or emotional factors. Ask the collateral source if the patient would still be *capable* of performing activities (e.g., driving, managing finances) that other family members are conducting.
- Memory complaints such as forgetting what you went into a room for or difficulty recalling names are common in older adults and may not be clinically significant. However, collateral reports suggesting repetitive speech/questioning or trouble navigating a familiar environment are more likely to be clinically relevant.
- The examiner should get the patient's consent to obtain collateral information from a well-known source. The congruence, or lack thereof, between patient self-report and collateral report is clinically informative in terms of lack of insight/awareness of deficits or a tendency to amplify complaints

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