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CONTRIBUTIONS OF NEUROPSYCHOLOGY AND NEUROIMAGING TO UNDERSTANDING CLINICAL SUBTYPES OF MILD COGNITIVE IMPAIRMENT

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Abstract

The original conceptualization of mild cognitive impairment (MCI) was primarily as an amnestic disorder representing an intermediate stage between normal aging and Alzheimer's dementia (AD). More recently, broader conceptualizations of MCI have emerged that also encompass cognitive domains other than memory. These characterizations delineate clinical subtypes that commonly include amnestic and non-amnestic forms, and that involve single and multiple cognitive domains. With the advent of these broader classifications, more specific information is emerging regarding the neuropsychological presentation of individuals with MCI, risk for dementia associated with different subtypes of MCI, and neuropathologic substrates connected to the clinical subtypes. This review provides an overview of this burgeoning literature specific to clinical subtypes of MCI. Focus is primarily on neuropsychological and structural neuroimaging findings specific to clinical subtypes of MCI as well as the issue of daily functioning. Although investigations of non-amnestic subtypes using advanced neuroimaging techniques and clinical trials are quite limited, we briefly review these topics in MCI because these data provide a framework for future investigations specifically examining additional clinical subtypes of MCI. Finally, the review comments on select methodological issues involved in studying this heterogeneous population, and future directions to continue to improve our understanding of MCI and its clinical subtypes are offered.

I. Introduction

Mild cognitive impairment (MCI) is a clinical construct that describes individuals with mildly impaired performance on objective neuropsychological tests but relatively intact global cognition and daily functioning (Petersen *et al.*, 1999, 2001). MCI has been validated as qualitatively different from both normal aging and dementia (Petersen, 2004; Smith and Ivnik, 2003) and is a risk factor for the development of dementia. Because of its potential importance for early identification and intervention in those at risk for the development of dementia, the concept of MCI has received considerable research attention. However, the definition has evolved considerably over time. As originally proposed by Petersen and colleagues, MCI was characterized primarily as an amnestic disorder that represented an intermediate stage between normal aging and Alzheimer's dementia (AD) (Petersen *et al.*, 1999). More recently, broader conceptualizations of MCI have emerged that also encompass cognitive domains other than memory (Petersen and Morris, 2005; Petersen *et al.*, 2001). These characterizations delineate clinical subtypes that commonly include amnestic and non-amnestic forms, and that involve single and multiple cognitive domains (Manly *et al.*, 2005; Petersen and Morris, 2005; Petersen *et al.*, 2001; Tabert *et al.*, 2006) against the backdrop of intact daily functioning. With the

advent of these broader classifications schemes, more specific information is emerging regarding the neuropsychological presentation of individuals with MCI, risk for dementia associated with different subtypes of MCI, daily functioning, and neuropathologic substrates connected to the clinical subtypes. The aim of this review is to provide an overview of neuropsychological, neuroimaging, functional, and treatment findings specific to clinical subtypes of MCI. In addition, methodological issues involved in studying this heterogeneous population and future directions to continue to improve our understanding of MCI and its clinical subtypes will also be highlighted and discussed.

II. Neuropsychological Presentation

It is certainly of great interest to determine factors placing individuals at highest risk for development of dementia so as to target them for early intervention. To this end, a better understanding of who is at risk for developing MCI may be an important first step. Presently, there are limited data about risk factors that correspond to conversion from cognitively normal to specific clinical subtypes of MCI; although, the existing evidence suggests that advancing age and lower education levels do place individuals at higher risk for MCI (Kryscio *et al.*, 2006), particularly for non-amnestic subtypes (Bickel *et al.*, 2006; Fischer *et al.*, 2007). For example, individuals with less than 9 years of education have an increased likelihood of isolated language and visuospatial deficits, as well as multiple domain amnestic MCI, whereas higher education was associated with increased chance of having isolated memory and executive impairments (Manly *et al.*, 2005). The presence of the apolipoprotein epsilon 4 allele (APOE ε4) seems to more strongly influence transitions from normal cognition to amnestic MCI and influence conversion to multi-domain MCI to a lesser degree (Kryscio *et al.*, 2006).

More research attention has been paid to the neuropsychological presentation of MCI and use of neuropsychological testing to delineate distinct clinical subtypes (e.g., amnestic vs non-amnestic and single domain vs multiple domain). Even when stratified into clinical subtypes, MCI is still a heterogeneous concept. Complicating factors include widely differing neuropsychological tests and diagnostic criteria used across studies in arriving at the MCI classifications as well as inconsistency in how clinical subtypes are assigned. While Petersen advocated for four subtypes, including single and multiple domain amnestic MCI and single and multiple domain non-amnestic MCI, non-amnestic subtypes continue to receive less attention in the literature and multiple domain classifications often do not separate amnestic from non-amnestic presentations. Despite these challenges, some converging evidence about the presentation of distinct MCI subtypes is emerging.

Generally, multi-domain presentations seem to be more common than purely amnestic presentations (Alexopoulos *et al.*, 2006; Alladi *et al.*, 2006; Lopez *et al.*, 2003; Manly *et al.*, 2005; Rasquin *et al.*, 2005); although, some studies have identified single domains that are more common than multi-domains, and the non-amnestic type is as frequent as the amnestic (Busse *et al.*, 2006; Palmer *et al.*, 2008). Multi-domain MCI (mMCI) is the most common subtype in both stroke and memory clinic samples (Rasquin *et al.*, 2005). The prevalence of single domain amnestic MCI (aMCI) ranges from 0.5 to 8% (Bickel *et al.*, 2006; Das *et al.*, 2007; Di Carlo *et al.*, 2007; Jungwirth *et al.*, 2005; Lopez *et al.*, 2003), mMCI ranges from 0.5 to 16% (Bickel *et al.*, 2006; Busse *et al.*, 2003; Das *et al.*, 2007; Di Carlo *et al.*, 2007; Jungwirth *et al.*, 2005; Lopez *et al.*, 2003), and single domain non-amnestic MCI ranges from approximately 3 to 15% (Bickel *et al.*, 2006; Busse *et al.*, 2003; Di Carlo *et al.*, 2007). There is only limited information on prevalence rates of multi-domain non-amnestic MCI, in which one group has identified less than a 5% prevalence rate (Bickel *et al.*, 2006). In addition to vastly different methodological approaches to defining MCI, the prevalence rates also differ due to varying sample origins, with hospital samples having generally higher prevalence rates across subtypes than community samples (Bickel *et al.*, 2006; Busse *et al.*, 2003). Presence of

the APOE ε4 allele may also contribute to differing prevalence rates. Amnestic MCI presentations have a higher proportion of individuals with the apolipoprotein ε4 allele as compared to non-amnestic groups (Gabryelewicz *et al.*, 2007; Manly *et al.*, 2005; Whitwell *et al.*, 2007). Thus, if genetic risk is not determined, samples are likely to have differing proportions of individuals with the ε4 allele and, therefore, different prevalence rates.

Certainly the prevalence rates are impacted by the definition of MCI applied by each study. Basing amnestic subtype diagnoses on the presence of either verbal and/or visual memory deficits results in a larger proportion of individuals identified as amnestic MCI than just relying on verbal memory alone (Alladi *et al.*, 2006). Varying the cutoff score for defining impairment also alters diagnostic outcomes by up to 12%; use of a more stringent statistical cutoff for impairment (1.5–2.0 SD below normative expectations) increases positive predictive power compared to lower cut points (Busse *et al.*, 2003); although, a more liberal cutoff for impairment has been shown to have higher sensitivity and specificity for future development of dementia (Busse *et al.*, 2006). These sensitivity and specificity determinations are problematical; however, as they are based on a quite limited neuropsychological assessment.

Aside from the use in diagnosis and determination of objective cognitive deficits in MCI, additional neuropsychological findings may help differentiate MCI subtypes. Perhaps not surprisingly, Lopez and colleagues (2006) found that, compared to aMCI and normal cognition, mMCI was characterized by poorer language, psychomotor speed, fine motor control, and visuoconstructional functioning. What is of note is that, although the mMCI group had memory deficits, they were to a lesser degree than the deficits noted in the aMCI group (Lopez *et al.*, 2006). A substantial minority of the MCI cases did not have any memory impairment (Lopez *et al.*, 2006), further emphasizing that examining only amnestic subtypes fails to capture the full spectrum of possible cognitive declines associated with MCI.

Spatial navigation skills of those with multi-domain amnestic MCI tend to be more similar to spatial navigation skills of AD patients than to non-amnestic MCI subtype groups, with both the AD and multi-domain amnestic MCI groups impaired on virtually all portions of a spatial navigation task (Hort *et al.*, 2007). However, the multi-domain amnestic MCI group was generally more impaired than other groups across all neuropsychological tests, so it is not clear that these spatial navigation difficulties occurred in isolation from the other impaired functions. Visuospatial skills specific to facial emotional processing have also been found to be intact in those with single domain amnestic MCI but impaired in those with multi-domain amnestic MCI, particularly in facial affect discrimination (Teng *et al.*, 2007).

III. Stability of Diagnosis

Multiple studies indicate that not all individuals diagnosed with MCI will decline and progress to a dementia diagnosis. In fact, a proportion of individuals appear to “improve” over time such that, at follow up, those initially identified as MCI are later categorized as cognitively normal. Anywhere from 20 (Fischer *et al.*, 2007) to 40% (Bickel *et al.*, 2006) of those with MCI appear to revert to the normal range upon retesting. Single domain classifications appear particularly susceptible to this instability, with single domain non-amnestic subtype often exhibiting the least stability over time (Bickel *et al.*, 2006; Busse *et al.*, 2006; Fischer *et al.*, 2007; Jak *et al.*, 2007). For example, one study reported that 50% of those with single domain MCI were normal upon later retesting whereas only 12% of those with multi-domain MCI “recovered” (Bickel *et al.*, 2006). Additional sources of instability in the MCI diagnosis can manifest via individuals changing MCI subtypes over time. Approximately 6% of those with MCI at baseline changed subtypes at follow up (Fischer *et al.*, 2007; Jak *et al.*, 2007). In contrast, over a 3-year interval, Zanetti and colleagues (2006) identified a more anticipated

trajectory of their MCI cohort; all MCI subtypes either converted to dementia (about a quarter) or retained their MCI status (Zanetti *et al.*, 2006).

IV. Conversion to Dementia

Perhaps the largest amount of information exists on likelihood of conversion to dementia from various MCI clinical subtypes. Some evidence suggests that those with multi-domain amnestic MCI appear to be at greatest risk for future dementia (Di Carlo *et al.*, 2007; Palmer *et al.*, 2008; Tabert *et al.*, 2006), whereas others indicate that amnestic MCI places one at highest risk for conversion to dementia (Ravaglia *et al.*, 2006; Yaffe *et al.*, 2006). Amnestic MCI subtypes do seem to impart significant risk for future development of AD while multi-domain presentations may be more common in those who eventually develop vascular dementia (Fischer *et al.*, 2007; Rasquin *et al.*, 2005; Yaffe *et al.*, 2006; Zanetti *et al.*, 2006). Yaffe and colleagues (2006) found that, of those who progressed to AD, 76% were initially diagnosed with aMCI, 11% initially presented with single domain non-amnestic MCI, and 13% were initially identified as mMCI (Yaffe *et al.*, 2006). Conversely, of those who progressed to vascular dementia, 50% were initially diagnosed with aMCI, 8% had single domain non-amnestic MCI, and 42% had mMCI (Yaffe *et al.*, 2006). Rozzini and colleagues (2007) reported that, in a group of amnestic MCI individuals, poor global cognitive performance at baseline and worsening executive functioning, but not worsening memory performance, were associated with conversion to AD over a 1-year follow-up period. Those with non-amnestic multiple domain subtype appear more likely to convert to a non-AD dementia (Busse *et al.*, 2006), with the single domain non-amnestic MCI at particular risk to progress to a frontal dementia syndrome (Yaffe *et al.*, 2006). There are reports, however, in which detailed information about MCI subtypes does not add significant benefit in determining who may be at greatest risk for conversion to dementia (Maioli *et al.*, 2007; Ravaglia *et al.*, 2006; Rountree *et al.*, 2007).

V. MCI and Health Variables

Understanding any additional health factors that may be more prevalent in distinct MCI subtypes is also noteworthy as a way to further delineate risk profiles. For example, cardiovascular risk factors, presence of the apolipoprotein ε4 allele, mood symptoms, and parkinsonian symptoms have all been investigated in MCI subtypes. Recent research has shown that multi-domain or non-amnestic MCI subtypes may be more likely to have cardiovascular risk factors than either those with single domain amnestic presentations or those without MCI (Di Carlo *et al.*, 2007; Zanetti *et al.*, 2006). Mariani and colleagues (2007) found that those with single domain non-amnestic MCI had a higher frequency of ischemic heart disease, transient ischemic attack (TIA) or stroke, a higher Hachinski ischemic score, and more white-matter lesions on MRI compared to aMCI. Further, multi-domain and single domain amnestic subjects exhibited similar clinical characteristics; although, the multi-domain amnestic subtype did have a greater history of TIA/stroke (Mariani *et al.*, 2007). Amnestic MCI groups showed a higher prevalence of diabetes than controls whereas participants with non-amnestic MCI were more likely to have hypertension than were controls (Verghese *et al.*, 2008).

In contrast, Debette *et al.* (2007) found that white matter changes may play a role in cognitive decline in MCI as a whole, but they do not appear to be specific to either amnestic or non-amnestic clinical subtypes. Because their amnestic and non-amnestic characterizations were multi-domain, the authors found the rate of cognitive decline and the presence of periventricular hyperintensities was more prominent in those with baseline executive dysfunction (Debette *et al.*, 2007).

Mood symptoms also appear to be more common in those with multi-domain MCI relative to those with single domain amnestic presentations (Gabryelewicz *et al.*, 2007; Zanetti *et al.*,

2006). Additionally, higher depression ratings are linked to those whose cognitive symptoms progressed over the follow-up period (but not to the point of dementia) and to those who converted from MCI to dementia as compared to the stable group (Gabryelewicz *et al.*, 2007). Hallucinations and sleep disorders are more common in the non-amnestic than amnestic subtype (Rozzini *et al.*, 2008). Others have found, however, that mood symptoms are increased in MCI cohorts as compared to cognitively normal samples, but with no significant differences in mood symptoms emerging between specific MCI subtypes (Palmer *et al.*, 2007; Rozzini *et al.*, 2008).

Other health factors seem to be associated with MCI in general but are not necessarily specific to amnestic or non-amnestic presentations. For example, lower serum folate levels (Maioli *et al.*, 2007; Ravaglia *et al.*, 2006), history of atrial fibrillation (Ravaglia *et al.*, 2006), and higher serum HDL levels (Maioli *et al.*, 2007) contribute to increased likelihood of conversion from MCI to dementia, regardless of MCI subtype. Odor identification skills of MCI participants also fall in between those of AD and healthy control groups, and MCI subtypes did not differ on smell identification performances (Westervelt *et al.*, 2008).

Most conceptualizations of MCI exclude Parkinson's disease, given that the historical conceptualization has been of MCI as a precursor to Alzheimer's disease or other non-Parkinsonian dementias. In addition, the motor symptoms associated with Parkinson's disease often produce demonstrable changes in a person's activities of daily living (ADL), which confound its utility in the classification of MCI. Recently, however, there have been efforts to characterize the transitional period between normal cognitive function and dementia in Parkinson's disease (PD). The expanded clinical subtypes are particularly relevant to this effort given the difference in presentation between dementias of different origins. Data suggest that MCI in those with Parkinson's is predictive of future dementia in much the same way that it is for individuals with MCI without co-morbid PD. Non-amnestic subtypes are particularly prevalent in Parkinson's disease and the presence of MCI in individuals with Parkinson's disease does substantially raise one's risk of developing dementia as compared to those with PD and normal cognition (Janvin *et al.*, 2006). In contrast to AD, conclusions about amnestic subtypes of PD MCI are more difficult to draw given the low prevalence of this subtype. Boyle *et al.* (2005) found that those individuals with MCI had higher levels of parkinsonian symptoms (though not Parkinson's disease) than those who were cognitively normal. Verghese *et al.* (2008) found greater gait abnormalities in those with aMCI as compared to those with non-amnestic MCI or controls while others have noted that non-amnestic subtypes have higher rates of gait dysfunction than amnestic MCI (Boyle *et al.*, 2005). Those with mMCI may present with more extra-pyramidal features than those with aMCI (Zanetti *et al.*, 2006).

VI. Daily Functioning and MCI

Embedded in the controversy surrounding the establishment of specific diagnostic criteria for MCI, there is much debate regarding whether impairment in everyday activities should be included as a criterion. In its initial conceptualization, MCI guidelines required that functional abilities remain intact (Petersen *et al.*, 1999) as this specific criterion helped distinguish MCI from dementia. However, as Farias *et al.* (2006) note, cognitive and functional deterioration clearly occurs over the course of MCI since such change eventually leads to conversion to dementia for many individuals with MCI (e.g., Bruscoli and Lovestone, 2004; Petersen *et al.*, 1999). In light of this accumulating evidence, an international working group proposed modified criteria for MCI, which includes "preserved basic activities of daily living" and "minimal impairment in complex instrumental functions" (Winblad *et al.*, 2004, p. 243). Similarly, participants of the International Psychogeriatric Association Expert Conference on MCI did not require intact ADL/instrumental activities of daily living (IADL) as a criterion but, instead, defined MCI as "a syndrome defined as cognitive decline greater than expected

for an individual's age and education level but that does not interfere notably with activities of daily life" (Gauthier *et al.*, 2006, p. 1262).

Emerging information about the functional status of those with distinct clinical subtypes of MCI may shed additional light on the continuum of functional abilities spanning normal cognition to dementia. Supporting the notion that functional decline occurs on a continuum, several groups have reported that IADL decrements in MCI are intermediate to the subtle declines associated with normal aging and the frank impairments required for a dementia diagnosis (Farias *et al.*, 2006; Giovanetti *et al.*, 2008; Griffith *et al.*, 2003; Peres *et al.*, 2006).

Published reports comparing ADL and IADL performance between MCI individuals and their cognitively normal counterparts have demonstrated that those with MCI show greater IADL changes in areas including shopping, managing medications, and handling finances (Mariani *et al.*, 2008). In a study examining IADL performance across different MCI subtypes, Tam *et al.* (2007) reported that individuals with multiple domain MCI demonstrated impairment in IADL relative to both amnestic MCI participants and cognitively normal older adults. Corroborating this finding, Zanetti and colleagues (2006) demonstrated that individuals with multi-domain MCI performed more poorly on measures of ADL and IADL relative to amnestic MCI participants. In contrast, Farias and colleagues (2006) demonstrated that the MCI with memory impairment group showed somewhat more functional change relative to their MCI peers with no memory impairment and cognitively normal older adults. Similarly, Wadley and colleagues (2007) reported that amnestic, non-amnestic, and multiple domain MCI subgroups all demonstrated greater difficulty with IADL performance compared to the cognitively normal group. However, unlike the other two MCI groups, individuals with non-amnestic MCI did not differ from the cognitively normal participants in terms of IADL performance. Notably, at least one study (Boeve *et al.*, 2003) did not find differences between amnestic MCI individuals and cognitively normal older adults in terms of functional abilities. However, it should be noted that the MCI participants who were included in this study were characterized as MCI based, in part, on intact ADL.

Farias and colleagues (2006) administered self-report and informant-based versions of the Daily Function Questionnaire (DFQ) and calculated a difference score by subtracting patients' DFQ from informants' DFQ. DFQ difference scores, which indicate a lack of awareness of deficits, were greater in demented individuals relative to their cognitively normal counterparts and MCI subtype groups (i.e., MCI with memory impairment and MCI without memory impairment). However, the difference scores did not differ between MCI groups and cognitively normal older adults. Based on these findings, Farias and colleagues (2006) argued that individuals with MCI do not underestimate functional changes as is often the case for demented individuals.

What seems clear from the above discussion is that changes in ADL and IADL are not uncommon across the spectrum of MCI; although, it remains to be determined whether many of these changes would be conceptualized as frank "deficits" or "impairments." Comparing the ADL and IADL changes of MCI to overt dementia groups would be helpful in determining cutoff criteria for impairment, or administering performance-based ADL and IADL measures with normative reference standards would also help to delineate whether such changes represent impairment.

VII. Neuroimaging

A. Structural MRI

In determining the clinical viability of the various clinical subtypes, many would assert that different subtypes should have distinct neuropathology or different courses of change in brain

integrity. Certainly, structural neuroimaging provides a non-invasive way to begin to examine brain changes associated with MCI, and there is emerging evidence to support distinct neuropathological profiles in clinical subtypes of MCI. Whitwell *et al.* (2007) found that those with amnestic presentations (single or multiple domain) had greater gray matter atrophy in medial and inferior temporal lobes compared to controls. Those with multi-domain amnestic MCI additionally showed loss in posterior temporal lobe, parietal association cortex, posterior cingulate, anterior insula, and the medial frontal lobe, a pattern of atrophy similar to that found in AD (Whitwell *et al.*, 2007). In support of this finding, Seo and colleagues (2007) reported that those diagnosed with single domain amnestic MCI showed cortical thinning in left medial temporal lobe (MTL) only, whereas those identified as multi-domain amnestic MCI showed cortical thinning in the left MTL, precuneus, and anterior and inferior basal temporal, insular, and temporal association cortices. The precuneus atrophy may be responsible for additional cognitive impairments present in the multi-domain MCI subtype and may suggest that the multi-domain presentations are a progression from single domain presentations since the areas of thinning noted in the multi-domain subtype encompassed all those in the single domain subtype and the extent of MTL atrophy was greater in the multi-domain versus the single domain subtype (Seo *et al.*, 2007).

In contrast, Becker and colleagues (2006) did not support the multi-domain subtype as the more advanced, transitional state between normal cognition and AD. They found that hippocampal volumes in those with multi-domain MCI were not statistically different from those of controls, but were significantly larger than both the amnestic MCI and AD groups (Becker *et al.*, 2006).Bell McGinty and colleagues (2005) found that the amnestic MCI group had greater volume loss in left entorhinal cortex and inferior parietal lobe as compared with multi-domain MCI. However, the multi-domain MCI group may exhibit their neuropathological changes in other areas, namely by smaller right inferior frontal gyrus, right middle temporal gyrus, and bilateral superior temporal gyrus as compared to amnestic MCI (Becker *et al.*, 2006).

Although the data are conflicting as to whether multi-domain subtypes necessarily have more extensive brain changes than single domain subtypes, current research does support the idea that different clinical subtypes of MCI have distinct neuropathology. Taken together, the available evidence suggests that those individuals with a more focal memory presentation have greater involvement of mesial temporal structures while those with more widespread deficits had greater involvement of association areas. Distinct MCI subtypes may represent different etiological paths to dementia, but the small sample sizes available in most of the imaging studies to date make conclusions tentative at best.

Other advanced imaging techniques hold promise to further clarify the nature and extent of brain changes associated with distinct clinical MCI subtypes though, to date, use of techniques such as functional magnetic resonance imaging (FMRI) and diffusion tensor imaging (DTI) has focused globally on MCI or on amnestic MCI, without significant investigation of non-amnestic subtypes. An overview of the use of these imaging techniques in MCI is provided, nonetheless, as this preliminary work is an essential framework for future examinations of clinical MCI subtypes.

B. Diffusion Tensor Imaging

A growing body of research suggests that white matter pathology contributes to age-related cognitive impairment and possibly potentiates the development of dementia (Raz and Rodrigue, 2006; Sullivan and Pfefferbaum, 2006). Although studies have generally shown white matter changes to be accelerated and more severe in AD (Pfefferbaum *et al.*, 2000; Rose *et al.*, 2006; Takahashi *et al.*, 2002), to date, few studies have employed DTI to examine early white matter changes in older adults with MCI with exceptionally limited focus on DTI-derived white matter changes in specific MCI clinical subtypes. Several studies have shown reduced

fractional anisotropy (FA), a proxy of white matter integrity, in the posterior cingulum fibers, and this relationship seems to be stronger in the left versus right hemisphere (Fellgiebel *et al.*, 2005; Medina *et al.*, 2006; Rose *et al.*, 2006; Zhang *et al.*, 2007). Rose *et al.* (2006) demonstrated increased diffusivity in the entorhinal and parieto-occipital cortices, and decreased FA in the limbic parahippocampal white matter in patients with MCI. Moreover, Kantarci *et al.* (2005) was among the first to show that increased mean diffusivity of the hippocampus in amnestic MCI predicted future progression to dementia.

Several studies have shown decreased integrity in the posterior region of the corpus callosum (i.e., splenium) in those with MCI (Cho *et al.*, 2008; Delano-Wood *et al.*, 2007; Ukmar *et al.*, 2008), an area which is particularly sensitive to degenerative processes (Naggara *et al.*, 2006; Rose *et al.*, 2000; Takahashi *et al.*, 2002). Although some studies have shown changes in the frontal white matter of MCI patients (Bozzali *et al.*, 2002; Medina *et al.*, 2006; Naggara *et al.*, 2006), other studies have not identified any differences (Delano-Wood *et al.*, 2007; Head *et al.*, 2004; Medina *et al.*, 2006; Ukmar *et al.*, 2008). Although data are limited, results suggest a pattern of retrogenesis (Bartzokis, 2004), by which microstructural changes first occur in late-myelinating regions, spreading to early-myelinating regions only after the disease process has progressed beyond a particular threshold, which may initially manifest itself with the onset of MCI.

C. Functional MRI

Evidence to date indicates that functional brain decline precedes structural decline in prodromal dementia, including adults with MCI. Therefore, functional neuroimaging techniques may offer the unique ability to detect early functional brain changes in at-risk adults and identify the neurophysiological markers that best predict dementia conversion.

Given that AD neuropathology preferentially targets the MTL early in the course of the disease, thereby resulting in the hallmark episodic memory decline, and amnestic MCI is thought to represent prodromal AD, the majority of FMRI studies of MCI involve memory processing (particularly encoding) in amnestic samples. No known FMRI studies have been published focusing on other clinical subtypes of MCI. While several studies demonstrate increased blood oxygen level dependent (BOLD) response in the MTL (Dickerson *et al.*, 2004, 2005; Hamalainen *et al.*, 2007; Kircher *et al.*, 2007; Sperling, 2007), others report decreased MTL activity in MCI (Johnson *et al.*, 2006; Machulda *et al.*, 2003; Mandzia *et al.*, 2009). These discrepant findings have been interpreted as reflecting bimodal functional activity whereby less impaired MCI subjects show increased BOLD response in the hippocampus corresponding to a slight or moderate neuronal dysfunction, and more impaired MCI subjects demonstrate decreased BOLD response—similar to the levels observed in mild AD patients—as the cortical neuronal networks become more severely impaired with greater disease progression (Celone *et al.*, 2006; Dickerson *et al.*, 2004, 2005; Hamalainen *et al.*, 2007; Johnson *et al.*, 2006; Machulda *et al.*, 2003; Masdeu *et al.*, 2005; Petrella *et al.*, 2007a). However, this interpretation is primarily derived from cross-sectional studies and can only adequately be tested with longitudinal designs.

Few longitudinal FMRI studies of MCI have been reported. Although these studies are often limited by small sample sizes, they demonstrate promise for the use of FMRI to detect early AD. Those MCI patients who converted to AD showed a stronger relationship between brain activity in the left superior parietal lobe and the left precuneus during an angle discrimination task in the context of comparable performance (Vannini *et al.*, 2007). Similarly, despite equivalent memory performance, Dickerson *et al.* (2004) reported that MCI patients who subsequently declined during a 2.5-year follow-up period demonstrated increased right parahippocampal gyrus activity during picture encoding. In a more recent study, the same research group reported increased hippocampal activation predicted greater degree and rate of

cognitive decline during a 6-year follow-up period, even after controlling for baseline level of impairment (Miller *et al.*, 2008).

Mandzia *et al.* (2009) reported that MTL activation during recognition was positively correlated with behavioral performance. However, unlike their healthy peers, MCI adults did not show a strong relationship between MTL activity during picture encoding and subsequent retrieval success, highlighting the complexity of the relationship between BOLD signal and effectiveness of encoding strategies. In contrast, Johnson *et al.* (2006) found reduced BOLD signal change in the right hippocampus during picture encoding and in the posterior cingulate during recognition of learned items in an amnestic MCI group despite comparable performance to their healthy peers. However, when activation corresponding only to successfully learned words was examined, an increase in hippocampal activity was seen, suggesting that an increase in MTL activity may support successful memory encoding (Kircher *et al.*, 2007). Similarly, a positive correlation between extent of parahippocampal and hippocampal activation and memory performance was found in MCI but, in a paradoxical fashion, greater clinical impairment, was also associated with recruitment of a larger region of the right parahippocampal gyrus during encoding (Dickerson *et al.*, 2004). Data from Johnson *et al.* (2004) provided further evidence for hippocampal dysfunction in MCI, suggesting that adults with MCI do not habituate to increasingly familiar items in the same manner as healthy older adults who show expected reductions in BOLD response to repeated items over time.

Despite the prevalence of studies examining medial temporal cortex function supporting memory, other cortical areas have also been implicated in MCI. For example, a reduction in functional activity in the posterior cingulate cortex (PCC) during recognition and episodic retrieval of previously learned line drawings (Johnson *et al.*, 2006) and object working memory (Yetkin *et al.*, 2006), but not during self-appraisal (Ries *et al.*, 2007), has implicated this region in the memory retrieval difficulty seen in amnestic MCI. The degradation of PCC functioning in MCI is not surprising given that PET metabolic alterations in the temporoparietal cortices and in the posterior cingulate have been reported in MCI and AD (Desgranges *et al.*, 1998; Matsuda, 2001; Reiman *et al.*, 1996) as well as in nondemented young and middle-aged adults at genetic risk for AD (Petrella *et al.*, 2007b; Reiman *et al.*, 1996, 2004, 2005; Wolf *et al.*, 2003). Similarly, dedifferentiation in the retrosplenial cortex during the retrieval of recent versus remote autobiographical memories and during episodic versus semantic memory retrieval has been reported in amnestic MCI (Poettrich *et al.*, 2009), further implicating the medial posterior cortex in MCI. Additionally, the neural substrates of visual working memory (Yetkin *et al.*, 2006), self-appraisal (Ries *et al.*, 2007), and emotional working memory (Dohnel *et al.*, 2008) in MCI have also been examined, and generally implicate a greater number of cortical regions. However, results are varied and highlight the need for greater attention to other cognitive processes in MCI in order to more fully understand changes in cortical functioning that may signal impending cognitive decline.

VIII. Treatment

One motivation to better understand the heterogeneous concept of MCI and the risk it imparts for future development of dementia is to provide early interventions that could halt or at least slow progression of symptoms. To date, unfortunately, there are no FDA-approved therapies for MCI. Further, aMCI has received all the attention with regard to treatment trials with no trials investigating other distinct clinical subtypes of MCI. Of the existing treatment trials in MCI, most have used a “progression to AD” design with the focus on slowing cognitive decline and delaying conversion to AD. As a whole, the trials have been disappointing with one possible exception, the Alzheimer’s Disease Cooperative Study (ADCS)-sponsored trial (Petersen *et al.*, 2005) (see Table I).

The ADCS-sponsored study of Vitamin E and donepezil for MCI involved 769 subjects at 69 centers in the US and Canada over 3 years. There were three treatment arms: Vitamin E 2000 IU/day, donepezil 10 mg/day, and placebo. The primary trial endpoint was conversion to AD. Although conversion to AD favored donepezil at 1 year, there were no differences among groups with regard to conversion to AD at 3 years. However, possession of the APOE ε4 allele was noted to be associated with a threefold greater risk of conversion from aMCI to dementia and, thus, clearly an important predictor of progression. When the authors looked at the progression to AD for APOE ε4 positive participants by treatment group, they found that the effect of donepezil was greater in ε4 positive individuals and persisted for 2 years. While neither of the two active arms reduced the risk of progressing to AD over the entire 36 months, donepezil reduced the risk of progression to AD for the first 12 months in all subjects and up to 24 months in those who were positive for the APOE ε4 allele. No treatment effect was noted for Vitamin E.

Other treatment trials have been less promising for halting conversion from MCI to dementia over time. A large trial of rivastigmine, an acetylcholinesterase inhibitor, was a double blind, placebo-controlled trial of 1018 patients that had many of the same features as the ADCS trial, but was conducted in 14 countries using multiple languages and translations of the neuropsychological instruments (Feldman *et al.*, 2007). At baseline, arms were not well matched with regard to frequency of APOE ε4 genotype, which was 46% in the placebo arm but only 37% in the rivastigmine arm. The study also had a lower conversion rate than expected and had to be extended to 4 years; over that time, 21.4% of placebo treated, but only 17.3% of rivastigmine treated, subjects progressed to AD. Although rivastigmine was favored, the results were not statistically significant, and secondary assessments were also not significant. Investigation of the efficacy of another acetylcholinesterase inhibitor, galantamine, also failed to reveal a significant effect of galantamine on conversion to dementia in those with MCI in either of two trials (Winblad *et al.*, 2008).

Finally, another large randomized, placebo-controlled, double-blind study examined the ability of the COX 2 inhibitor, rofecoxib, to delay disease progression in 1457 aMCI subjects (Thal *et al.*, 2005). Once again, there was a lower than expected annual rate of conversion to AD. Conversion to AD actually favored placebo in this trial but the authors dismissed the significance of this finding because the secondary cognitive measures did not corroborate the primary outcome.

In hindsight, several important factors likely influenced the results of these studies, including, perhaps first and foremost, the variable rate of progression from aMCI to AD. Sources of this variability likely include subject heterogeneity, with regard to impairment level, culture, language, and APOE ε4 carrier status, in addition to even simple differences in implementation of enrollment criteria. MCI patients may show increased awareness of, or lower tolerability for, adverse events, resulting in higher discontinuation rates. Our current outcome measures may be insensitive; for example, the conversion design dichotomizes a continuous variable and most of the currently used efficacy measures follow an AD trial model of decline. Rather than decline, however, MCI patients may show improvement on cognitive measures, no matter which treatment group they are assigned to, because of at least some preservation in their ability to learn. Future MCI trials may benefit from less heterogeneous recruitment with stricter entry criteria and enriched populations, more sensitive cognitive and global outcome measures that reflect subtle impairments in complex activities, novel imaging outcomes, and longer trials.

IX. Conclusions

MCI remains a heterogeneous concept, though division of MCI into distinct clinical subtypes serves as a promising approach to better understanding MCI as a diagnostic entity and a risk

factor for future cognitive decline. Evidence to date suggests that multi-domain amnestic presentations are more prevalent than either single domain amnestic or multi-domain non-amnestic presentations, though relatively little attention has been paid to the latter subtype. Converging neuropsychological, daily functioning, and neuroimaging data suggest that multiple domain presentations may place one at highest risk for future development of dementia. The current literature also supports that knowledge of subtypes of MCI informs the risk for future development of different types of dementia.

Though knowledge of MCI subtypes appears helpful in predicting risk of conversion to dementia, there remains a significant minority of individuals with MCI, particularly single domain subtype that may revert to normal cognition when followed over time. This instability in diagnosis as well as the varying prevalence rates, rates of conversion to dementia, and general oft-conflicting results in the literature, are likely due to ongoing challenges in operationalizing the diagnostic criteria for MCI. The methods for documenting objective neuropsychological impairment tend to be a particularly variable and ill-defined aspect of the MCI diagnostic process across studies (Portet *et al.*, 2006). There is little consensus about what neuropsychological tests (or how many) should be used to document objective cognitive impairment, what level of performance is considered cognitively impaired, how diagnostic criteria for different clinical subtypes of MCI are applied, what constitutes intact daily functioning, or about whether or not functional abilities should be included in the diagnostic decision-making regarding MCI. As this review highlights, the variable results in the current MCI literature clearly illustrate the importance of (a) understanding the criteria used to identify cognitive impairment in making the MCI diagnosis, (b) the value of using comprehensive neuropsychological assessment when diagnosing MCI subtypes, and (c) point to the need for further exploration of MCI subtypes, particularly non-amnestic presentations. Investigations and interventions targeting only amnestic subtypes are potentially missing a sizable number of individuals at risk.

Neuroimaging holds promise as a technique to better understand differences between distinct MCI subtypes although all of the above-mentioned methodological challenges together with small sample sizes and very limited attention paid to non-amnestic subtypes make drawing firm conclusions from the existing imaging literature challenging. To date, data do seem to support distinct neuropathology in the different clinical subtypes of MCI. However, there is still much overlap in structural imaging profiles and conflicting evidence making conclusions tentative at best. Advanced imaging techniques, such as DTI and functional MRI hold promise for detecting microstructural white matter damage or altered activation patterns in older adults prior to the manifestation of the full dementia syndrome. This early identification would identify the group in whom targeted therapies will likely have the greatest clinical impact (see Fagan *et al.*, 2005, for discussion). Overall, results from recent DTI studies indicate that white matter changes are evident in at-risk older adults and further validate the use of DTI to capture subtle, early white matter changes before significant atrophy is present. However, to date, very few studies have employed DTI in older adults with MCI, and even fewer have investigated the relationship between clinical subtype of MCI and white matter integrity.

Similarly, although FMRI techniques may prove to be instrumental in the early detection of AD, interpretation of current findings in MCI is complicated by various methodological differences between studies. In general, functional changes in the MTL and posterior medial cortex appear to signal cognitive decline and dementia conversion. However, discrepant results across studies may be due to differences in diagnostic classification of MCI adults. Specifically, although the majority of studies reviewed classified their patients as amnestic MCI, it is likely that the patient sample represented a more heterogeneous group that may reflect different underlying neural pathology. This highlights the need for future research aimed at integrating

behavioral performance with measures of functional activity that directly compare different MCI subtypes with these sophisticated neuroimaging techniques.

Finally, results of intervention trials to halt the progression of MCI have generally been disappointing. Future trials are needed that address both amnestic and non-amnestic presentations, employ more stringent entry criteria, use more sensitive cognitive and global outcome measures that reflect subtle impairments in complex activities, and include novel imaging outcomes.

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TABLE I

Clinical Trials in aMCI

Agent	*N*	Duration	Endpoint	Outcome
Donepezil	269	24 weeks	Symptoms	Negative
Donepezil/Vitamin E	769	3 years	AD	Partially positive
Rofecoxib	1200	2–3 years	AD	Negative
Galantamine	995	2 years	CDR 1	Negative
	1062	2 years	CDR 1	Negative
Rivastigmine	1018	3–4 years	AD	Negative

AD, Alzheimer's disease; CDR, clinical dementia rating.