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Mild Cognitive Impairment: A Concept and Diagnostic Entity in Need of Input from Neuropsychology

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Abstract

This virtual issue consists of studies previously published in the *Journal of the International Neuropsychological Society* and selected on the basis of their content related to one of the most highly researched concepts in behavioral neurology and neuropsychology over the past decade: mild cognitive impairment (MCI). The reliance on cognitive screening measures, staging-based rating scales, and limited neuropsychological testing in diagnosing MCI across most research studies may miss individuals with subtle cognitive declines or mis-diagnose MCI in those who are otherwise cognitively normal on a broader neuropsychological battery of tests. The assembled articles highlight the perils of relying on these conventional criteria for MCI diagnosis and reveal how the reliability of diagnosis is improved when sound neuropsychological approaches are adopted. When these requirements are met, we illustrate with a second series of articles that neuropsychological measures associate strongly with biomarkers and often reflect pathology beyond or instead of typical AD distributions. The final set of articles reveal that people with MCI demonstrate mild but identifiable functional difficulties, and a challenge for neuropsychology is how to incorporate this information to better define MCI and distinguish it from early dementia. Neuropsychology is uniquely positioned to improve upon the state of the science in MCI research and practice by providing critically important empirical information on the specific cognitive domains affected by the predominant neurodegenerative disorders of late life as well as on the diagnostic decision-making strategies used in studies. When such efforts to more comprehensively assess neuropsychological functions are undertaken, better characterizations of spared and impaired cognitive and functional abilities result and lead to more convincing associations with other biomarkers as well as to prediction of clinical outcomes.

Keywords

Mild cognitive impairment; Alzheimer’s disease; Neuropsychology; Episodic memory; Semantic memory; Executive functions; Neuroimaging; Magnetic resonance imaging; Functional MRI;

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Diffusion tensor imaging; Cerebrospinal fluid; Biomarkers; Activities of daily living; Functional capacity

INTRODUCTION

Since the publication of criteria for mild cognitive impairment (MCI) by Petersen et al. (1999), there has been an exponential growth in publications focused on MCI (Geda & Nedelska, 2012), and it has become one the most highly studied topics in the fields of behavioral neurology and neuropsychology. Initially conceived as a means to describe the borderland between early and mild forms of memory impairment and dementia due to Alzheimer's disease (AD), it has undergone revisions to describe non-amnestic forms of cognitive impairment (Petersen & Morris, 2005) and to capture non-AD dementia prodromes (e.g., MCI in Parkinson's disease: Tröster, 2011; vascular cognitive impairment: Gorelick et al., 2011; non-amnestic MCI progressing to dementia with Lewy bodies: Ferman et al., 2013). It has also been revised to capitalize on the latest wave of research investigating the use of biomarkers to improve confidence in the diagnosis of MCI due to AD (Albert et al., 2011).

Despite this high volume of research on MCI over the past decade, the concept has been hampered by rather cursory nosologies (e.g., in "non-amnestic" MCI, is it disordered executive function, language, visuospatial skills?), and its operational definitions have been routinely mired in blunt assessment methods. Reliance on single impaired cognitive test scores, simple cognitive screening measures, and measures rating day-to-day function such as the Clinical Dementia Rating (CDR) scale have all likely contributed to inaccuracy and instability in diagnosis (see Smith & Bondi, 2013). Adding to the poor diagnostic reliability is poor consensus on a uniform set of criteria and MCI diagnosis based on few measures and excessive clinical judgment.

Commenting on the revised 2011 criteria for dementia due to AD, McKhann (2011) offered that "[t]here are no exact transition points that define when an individual has progressed from the MCI phase to the dementia phase. It is a question of clinical judgment." However, research consistently shows actuarial methods to be superior to clinical judgment, given the latter method's susceptibility to a host of errors, biases, and occasionally faulty assumptions (see Dawes, Faust, & Meehl, 1989). For example, Saxton et al. (2009) have shown that a neuropsychologically based algorithm for MCI diagnosis better predicted progression than a clinically based method that staged decline *via* the CDR and which produced more "false positive" diagnostic errors. Chang et al. (2011) have also found the CDR to be insensitive to severity of cortical thinning as well as impairments in activities of daily living (ADL) in those diagnosed with MCI. Still other studies have used clinical decision-making strategies that assign an individual's lower cognitive test score as out of proportion to their other cognitive scores or to their "expected" level based on educational or occupational attainments (e.g., Jicha et al., 2006). Unfortunately, this clinical judgment rests on a faulty assumption that an individual's abilities are roughly equivalent across cognitive domains, despite evidence that education or IQ explains negligible to modest variance on a variety of memory tests (Delis, Kramer, Kaplan, & Ober, 2000; Fastenau, Denburg, & Hufford, 1999; Heaton, Taylor, & Manly, 2003; Murayama et al., 2013).

Neuropsychology is uniquely positioned to improve upon this state of the science in MCI research and practice by providing critically important actuarial information on the specific cognitive domains affected by the predominant neurodegenerative disorders leading to dementia as well as on the diagnostic decision-making strategies used in studies. In many cases, neuropsychology provides some of the most valid and reliable distinctions by comparing the patterns and severities of neurocognitive impairment among the dementias (e.g., frontotemporal dementia: Rascovsky et al., 2011; vascular dementia: Gorelick et al., 2011; dementia with Lewy bodies: McKeith et al., 2005). Outlining the criteria for diagnosing vascular contributions to cognitive impairment and dementia, Gorelick et al. (2011) for example state the "diagnosis of dementia *must* be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions." [Italics added for emphasis]. Although recent revisions to the criteria for dementia in the DSM-5 (American Psychiatric Association, 2013) or by the NIA-AA (McKhann et al., 2011) encourage the use of neuropsychological assessments, many of these revisions fall short of requiring neuropsychological assessment in their diagnostic schema (e.g., McKhann et al., state that "…either a "bedside" mental status examination or neuropsychological testing…" is sufficient). Consequently, reliability and stability of MCI diagnosis is likely to be diminished when comprehensive neuropsychological assessment is not undertaken.

In this virtual issue, we sample some of the articles published in recent years by *JINS* that highlight the perils of relying on conventional criteria for MCI diagnosis and that reveal how the reliability of diagnosis is improved when sound neuropsychological approaches are adopted (Brooks, Iverson, Holdnack, & Feldman, 2008; Clark et al., 2013; Howieson et al., 2008; Libon et al., 2010). When these requirements are met, we illustrate with a second series of articles that neuropsychological measures associate strongly with neuroimaging and cerebrospinal (CSF) biomarkers in expected patterns and that often reflect pathology beyond or instead of typical AD distributions (Hantke et al., 2013; Nordlund et al., 2008; Stricker et al., 2013). Finally, when prerequisite conditions exist, people with MCI may demonstrate mild but identifiable functional difficulties, and a challenge for neuropsychology is how to incorporate this information to better define MCI and delineate it from early dementia (Aretouli, Okonkwo, Samek, & Brandt, 2011; Bangen et al., 2010; Okonkwo et al., 2008; Sherod et al., 2009).

Sound Neuropsychological Approaches Improve MCI Diagnosis

Many if not most MCI studies diagnose participants on the basis of a single impaired test score, the most prevalent of which is an impaired memory score. The Alzheimer's Disease Cooperative Studies group Vitamin E and donepezil trial (Petersen et al., 2005) and the Alzheimer's Disease Neuroimaging Initiative (www.adni-info.org) are but two large-scale examples that routinely use a single impaired memory test score (e.g., delayed recall of Story A of the Wechsler Memory Scale-Revised Logical Memory subtest) in diagnosis. In our first paper to be included in this virtual issue, Brooks et al. (2008) demonstrate that reliance on a single impaired memory test score can lead to over-interpretation of low memory scores and thus increase the likelihood of false-positive misclassification. In brief, Brooks et al. (2008) demonstrated with the Wechsler Memory Scale-III (Wechsler, 1997)

that 26% of the *standardization* sample of older adults obtained one or more age-adjusted standard scores at or below 1.5 *SD*s on the memory tests. A second paper in the series by Howieson et al. (2008) reveals that the common practice of relying on delayed recall of an episodic memory test may miss the earliest manifestations of an evolving dementia unless other neuropsychological functions are assessed. They revealed that not only does verbal episodic memory decline precede the diagnosis of MCI and dementia by at least several years, so too does change in semantic memory and visuospatial skills—and that the trajectory of declines are characterized by unique linear and nonlinear changes (see also Smith et al., 2007). Examination of within-person cognitive change, whether by the change point analyses used by Howieson et al., reliable change indices (e.g., Pedraza et al., 2007) or other methods, will have powerful possibilities to help determine whether change within the individual will better identify trajectories of decline rather than comparisons to group norms.

A third paper in this series by Libon et al. (2010) follows up on the notion that a comprehensive sampling of neuropsychological functions is necessary to better reveal the heterogeneity of cognitive impairments in MCI. In this article, Libon and colleagues employed the use of cluster analysis to statistically determine neuropsychological characterizations of MCI in a clinic-based sample of older adults. This technique provides an actuarial method of identifying homogenous subgroups with similar patterns of neuropsychological dysfunction, and they found evidence for *amnestic*, *dysexecutive*, and *mixed* (impaired memory and language) clusters of MCI participants. These authors have further shown that empirically derived MCI subtypes demonstrate dissociable profiles of forgetting, temporal gradients, interference, and errors (Eppig et al., 2012; Libon et al., 2011) that may also reflect distinct underlying neuropathologic substrates. In a fourth paper in this series by Clark et al. (2013) that also used cluster analysis in a community sample, they found that neuropsychological criteria for MCI diagnosis (see Jak, Bondi, et al., 2009) produced several distinct cognitive phenotypes (e.g., amnestic, dysexecutive) similar to that of the Libon et al. (2010) study, and with differing degrees of severity of cognitive impairment. Remarkably, when cluster analysis was applied to those who had been diagnosed with MCI based on conventional Petersen/Winblad (Petersen & Morris, 2005; Winblad et al., 2004) criteria (e.g., using a cutoff of 1.5 or more *SD*s below normative means on at least one measure), a large number of the MCI group performed within normal limits on more extensive and detailed cognitive testing. That is, when the group was diagnosed using Petersen/Winblad criteria it was composed of *amnestic* and *mixed* MCI subtypes as well as a third subtype that performed within normal limits across the neuropsychological measures. This *Cluster-Derived Normal* group included nearly half of the MCI sample and did not differ from a normal control group in terms of cognition or measures of cortical thickness in areas usually affected in MCI or AD. These results suggest a high susceptibility of the conventional diagnosis of MCI to false positive diagnostic errors, reinforcing the conclusions drawn by Brooks et al. (2008; see also Brooks, Iverson, & White, 2007). Further work profiling these potential false positive misclassifications on biomarkers and longtiduinal outcomes represent important next steps.

Neuropsychological Approaches to MCI Diagnosis Improve Biomarker Associations

As the above studies selected for this series suggest, when sound neuropsychological approaches to MCI diagnosis are met, significant improvements are made in characterizing the specific cognitive phenotypes of MCI. This offers the possibility that biomarkers may associate more strongly with phenotypes in expected patterns and may also reveal associations beyond or instead of typical AD pathophysiology (e.g., regions related to semantic memory activation and white matter integrity). Our fifth paper in this series by Nordlund et al. (2008) offers one example of the ways in which more comprehensive neuropsychological methods shed light on cerebrospinal fluid (CSF) biomarker associations. Here, they demonstrate that MCI participants diagnosed according to conventional Winblad et al. (2004) criteria have different neuropsychological profiles if sub-divided on the basis of normal *versus* abnormal levels of CSF AD biomarkers (low amyloid-β, high total tau concentrations, or both). Specifically, when MCI participants with normal CSF AD biomarkers are compared to healthy control participants, the neuropsychological differences on a vast array of neuropsychological tests of memory, speed and attention, language, executive and visuospatial functions are strikingly small despite their MCI diagnosis. However, those MCI patients with abnormal levels of CSF AD biomarkers showed significant neuropsychological impairments across the five cognitive domains when compared to control participants. This MCI group with abnormal CSF levels also showed impairments on episodic memory, naming, and speed/attention/executive functions (digit symbol, Trails A and B) relative to the MCI group with normal CSF levels.

A sixth paper in this series by Hantke et al. (2013) examined cognitively stable and declining groups of older adults to determine if baseline functional magnetic resonance imaging (fMRI) tasks of semantic (famous name discrimination) and episodic (name recognition) memory predicted cognitive outcomes 18 months later. They defined cognitive decline based on a comprehensive neuropsychological assessment at both time points and computed residualized change scores that adjusted for baseline performance, practice effects, and regression to the mean. Participants with standardized residuals of −1.0 or lower on one or more of the primary neuropsychological measures were assigned to the cognitively declining group; the remaining participants were classified as cognitively stable. With this rigorous approach to defining “decline,” they found that fMRI activation during a semantic memory task was more accurate in predicting future cognitive decline than activation during the episodic memory task, echoing the findings of Howieson et al. (2008) discussed in the prior section.

A seventh paper by Stricker et al. (2013) examined, *via* diffusion tensor imaging, whether decreased white matter integrity in MCI would persist when controlling for AD-signature cortical thinning. Instead of using conventional MCI diagnostic criteria, the authors applied neuropsychologically based MCI criteria using the more comprehensive scheme described by Jak, Bondi, et al. (2009). Controlling for cortical thickness, the authors found their MCI group showed decreased fractional anisotropy (FA) in parietal white matter and in white matter underlying the entorhinal and posterior cingulate cortices relative to the NC group. They further observed significant cognitive associations such that medial temporal FA was related to memory and parietal FA was related to executive functioning. Their results

provide support for the role of white matter integrity as an early biomarker for individuals at risk for AD and highlight that changes in white matter may be independent of gray matter changes.

Neuropsychological Approaches to MCI Diagnosis Associate with Functional Challenges

Although MCI diagnosis, outcome, and biomarker associations represent the foci of the vast majority of studies, a relatively neglected but important area of MCI research centers on the assessment and predictive utility of functional impairments. Many people with MCI often also demonstrate mild but identifiable functional difficulties. A challenge for neuropsychology is how to incorporate this functional information to better define MCI and distinguish it from early dementia. An eighth paper in this series by Aretouli et al. (2011) nicely illustrates this notion by revealing that progression from MCI to dementia over a 2-year period was best predicted by a combination of informant ratings of subtle functional impairments as well as lower baseline scores on episodic memory, category fluency, and constructional praxis. The ninth and tenth papers in the series from Daniel Marson's group focus specifically on two complex instrumental ADLs critical to independent functioning for older adults: financial capacity (Sherod et al., 2009) and medical decision-making capacity (Okonkwo et al., 2008). Marson (2001; Marson et al., 2000) constructed the Financial Capacity Instrument to directly assess the financial abilities of older adults and Sherod et al. (2009) administered it to normally aging, amnestic MCI, and AD groups. They demonstrated that, across the aging-MCI-AD continuum, the same cognitive functions (i.e., arithmetic skills, memory, and executive functions) were associated with both intact financial capacity in older controls and declining financial capacity in patients with MCI and AD. Okonkwo et al. (2008) revealed similar findings that medical decision-making capacity was predicted by short-term verbal memory and executive functions in patients with amnestic MCI. A final paper in this series by Bangen et al. (2010) examined whether the type of functional difficulty varies by MCI subtype and found participants with amnestic MCI demonstrated significant decrements in financial management, whereas those with non-amnestic MCI showed poorer performance in abilities related to health and safety. Logistic regression demonstrated that functional abilities accurately predicted MCI subtype.

Results from each of the studies in this latter section generally support the need for better delineation of specific functional declines in MCI. Given the implications of functional status for MCI diagnosis and treatment, the direct or actuarial assessment of functional abilities is recommended. Results further suggest performance-based ADL assessments may have utility in distinguishing MCI subtypes. Such integration of neuropsychological test performances alongside operationally defined measures of instrumental activities of daily living will ultimately more fully characterize the cognitive and functional difficulties that lead to dementia.

CONCLUSIONS AND FUTURE DIRECTIONS

The reliance on very limited cognitive testing and staging-based rating scales in most research studies of MCI, and recently also of preclinical AD studies (e.g., Vos et al., 2013), will potentially miss individuals with subtle cognitive declines or mis-diagnose MCI in those who are otherwise cognitively normal on a broader neuropsychological battery of

tests. The articles selected for this virtual issue make it clear that neuro-psychological measurement is key to the valid and reliable identification of persons that may be having subtle problems in living that are due to a range of pathologies and for which supportive interventions (e.g., see Greenaway, Duncan & Smith, 2013; Hampstead, Sathian, Bacon Moore, Nalisnick, & Stringer, 2008; Lubinsky, Rich, & Anderson, 2009) may be indicated. When such efforts to more comprehensively assess neuropsychological functions are undertaken, better characterizations of spared and impaired cognitive and functional abilities result and lead to more convincing associations with other biomarkers (Jak, Urban, et al., 2009; Nordlund et al., 2008) as well as to clinical outcomes (Hantke et al., 2013; Howieson et al., 2008).

Future directions for research in this area include comparing anatomical and functional neuroimaging biomarkers to the empirically derived MCI subtypes obtained by Libon et al. (2010) and Clark et al. (2013). For example, if it is determined that there are imaging-based regional distinctions between neuropsychologically derived MCI subtypes (e.g., see Delano-Wood et al., 2009), all of whom nevertheless progress to AD, then it could have major implications for MCI and possibly preclinical AD diagnostic and treatment efforts. The necessity of a comprehensive canvassing of cognitive domains with sensitive neuropsychological tests would be needed to identify other profiles of cognitive dysfunction leading to AD (e.g., difficulties in semantic memory, executive functions, visuospatial skills). This comprehensive neuropsychological assessment strategy would be especially important for efforts to characterize the “subtle cognitive declines” inherent in the criteria for detection of preclinical AD stagings (Sperling et al., 2011) or to derive quantitative MCI phenotypes for genetic or genome-wide association studies (Shen et al., 2013). Finally, empirical determinations of the composition of neuropsychological measures in diagnostic batteries, effects of the addition or subtraction of tests, gradations of test difficulty, and verbal-visual balances of items within cognitive domains would all be of interest for future study.

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