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SHOULD MILD COGNITIVE IMPAIRMENT BE SUBTYPED?

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Abstract

Purpose of Review—To review evidence on the validity and utility of recent approaches to subtyping late-life mild cognitive impairment.

Recent Findings—There is growing evidence that amnestic mild cognitive impairment is associated with biomarkers for Alzheimer's disease, while non-amnestic mild cognitive impairment maps more closely to cerebrovascular disease. The former is more likely to progress to dementia than the latter. Mild impairment in multiple cognitive domains appears to represent a more advanced disease state than single-domain impairment, and is more likely to progress to dementia. The cognitive subtypes have imprecise boundaries and have limited ecological validity. Approaches to subtyping that also incorporate biomarkers increase diagnostic specificity and have greater predictive value. However these approaches have yet to be validated outside specialized memory clinic populations.

Summary—Mild cognitive impairment as currently defined is still etiologically and prognostically heterogeneous, particularly outside specialty clinical settings. The objective of further subtyping is to delineate subgroups that are more clinically homogeneous. The current cognitive subtypes have some validity and utility but additional approaches should be explored so as to enhance these properties.

Keywords

Amnestic MCI; non-amnestic MCI; single-domain MCI; multiple-domain MCI; Alzheimer's disease; cerebrovascular disease; biomarkers

INTRODUCTION

Mild cognitive impairment (MCI) is a cognitive state intermediate between normal cognitive aging and dementia [1]. The terms "intermediate" and "transitional" are not interchangeable, because MCI is not inevitably a prodromal or preclinical state of dementing disorders. Like dementia, MCI is a syndrome with one or more underlying causes. However, a substantial proportion of individuals with MCI progress to dementia (the proportion depending on the population and the setting), doing so at a higher rate than cognitively normal individuals [2*, 3*]. There is debate about how exactly MCI should be defined, and whether it medicalizes the normal aging process.

The term MCI was first used to refer to an early stage of the dementia of Alzheimer's disease (AD) (Stage 2–3 on the Global Deterioration Scale) [4]. It gained widespread use

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after the introduction of the Mayo Criteria [1] for Amnestic MCI, a syndrome including both *objective* and *subjective* evidence of memory loss, in the context of *essentially normal mental status* and *preserved functional independence*, and *not rising to the threshold of dementia*. Note that many authorities regard the above as guidelines for expert clinicians rather than as criteria to be operationally defined. The Amnestic MCI syndrome itself subsequently became a subtype of a broader concept of MCI, as defined by an International Working Group (IWG Criteria) [5*] to cover causes including but not limited to AD. Most studies today subtype MCI into **amnestic MCI (aMCI)** and **non-amnestic MCI (naMCI)** depending on whether or not memory is impaired; many also further subtype these two entities into **single-domain** and **multiple-domain** impairment, depending on how many cognitive domains are impaired. These four cognitive subtypes have dominated the literature in recent years. They appear particularly influential in the ongoing development of diagnostic criteria for neurocognitive disorders [http://www.dsm5.org], and for AD [http://www.alz.org/research/diagnostic_criteria/], and practice parameters for MCI [http://www.aan.com/go/practice/guidelines/projects/].

An editorial in this journal in 2008 [6] referred to the clinical and prognostic heterogeneity of the broad MCI concept as currently defined. The goal of subtyping MCI should be to reduce this heterogeneity, thus enhancing both validity and utility [7*]. The ideal MCI - and MCI subtype -definition should reflect an accurate statement about etiology or prognosis or both. Individuals we describe as having MCI (or an MCI subtype) should be identifiably different in appearance and behavior from those we do not call MCI (or other MCI subtypes), in distinctive ways that help us predict what will happen to them over time. Subtypes satisfying these conditions will facilitate research into etiology and treatment and help us provide patients with management options more specific to their conditions.

REVIEW

We will focus on the evidence for the amnestic/non-amnestic and the single-domain/ multiple approaches to subtyping MCI.

Concurrent Validity

The distinction between aMCI and naMCI is increasingly validated by evidence of associations with biological or disease markers and risk genes.

aMCI and AD biomarkers—aMCI consistently shows associations with biomarkers suggestive of, and assumed to be specific for, AD pathology. A detailed analysis of brain MRI measures among MCI subtypes and healthy control subjects demonstrated greater hippocampal atrophy in aMCI than naMCI [8**]. Two other MRI studies have found medial temporal atrophy to be greater in those with aMCI than naMCI and normal cognition [9, 10*], although differences were small and the MRI profiles overlapped in one study [10*]. In a magnetic resonance spectroscopy (MRS) study, which also reported reduced hippocampal volume in aMCI but not in naMCI, single-domain aMCI showed the greatest association with elevated markers of glial activation and membrane integrity [11]. In the realm of brain metabolism, a fluorodeoxyglucose positron emission tomography (FDG-PET) study showed a pattern of parietotemporal or hippocampal hypometabolism in 57% of aMCI (single-domain), compared to 35% of naMCI (single-domain), and 14% of naMCI (multiple-domain) patients [12*]. Another FDG-PET study showed greater medial temporal hypometabolism in aMCI than naMCI [13]. A PET study using Pittsburgh Compound B (PiB), an amyloid binding probe, found the majority (75% of 24) of aMCI patients were PiB-positive, compared to 0% of 6 patients with naMCI [14]. Similarly, although less dramatically, another study reported amyloid positivity in 58% of 19 patients with aMCI compared to 43% of 7 patients with naMCI [15**]. Here, all patients who progressed from

MCI to dementia during followup had aMCI and were PiB-positive. However, this first report of amyloid positivity in naMCI also clearly demonstrated that amyloid plaques in the brain do not map exclusively to the amnestic phenotype. A study of cerebrospinal fluid (CSF) AD markers revealed worse performance on tests of episodic memory and speed/attention associated with high total tau and low A-beta42 among all MCI patients [16]. However, this association did not hold when MCI patients were further subtyped as aMCI vs. naMCI. In another case-control study, aMCI cases had significantly lower CSF a-beta42 and higher tau than normal controls [17].

naMCI and vascular disease markers—Increasingly, studies are demonstrating associations between naMCI and cerebrovascular disease. Two studies from memory disorder clinics have shown naMCI to be associated, more often than aMCI, with vascular disease markers, e.g., of medial temporal atrophy only when combined with white matter hyperintensities [10*], of ischemic heart disease, TIA/stroke, higher ischemia score, and increased white matter lesions on MRI [18]. In population-based studies, history of stroke is associated more strongly with naMCI than aMCI [19*], and hypertension is associated with increased risk of incident naMCI but not aMCI [20*]. An MRI study showed aMCI (single-domain) had the lowest prevalence of cortical infarctions, while naMCI had significantly more concomitant vascular risk factors than aMCI [8**].

aMCI vs. naMCI and the *APOE*4* genotype—The E4 allele of the Apolipoprotein E (APOE) gene on chromosome 19 is a well-established risk factor for AD [21] as well as for heart disease [22]. In an MRI case-control study [8**], aMCI was associated with *APOE*4* genotype and hippocampal atrophy. Two population-based studies [19*, 23] found *APOE*4* was associated only with aMCI and not with naMCI. However, others have not found *APOE*4* associated with MCI subtype [10*].

Predictive validity

Regardless of the underlying pathology, MCI subtypes can be identified and followed over time to compare their rates of progression to dementia. In a recent meta-analytic review of progression rates across nine longitudinal studies, the estimated annual progression rate was higher for multiple-domain MCI (12.2%) and aMCI (11.7%) than for naMCI (4.1%) [2*]. That review included older studies conducted before the current MCI definitions and subtypes were proposed, with designs limited to imposing these categories on data not originally intended to capture them. Here, we will highlight more recent longitudinal studies.

aMCI vs. naMCI—Population birth cohorts [24, 25**, 26] have revealed substantially higher progression rates to dementia from aMCI than naMCI. In two population studies comparing outcomes of different definitions of MCI and MCI subtypes at the population level, the amnestic definitions showed greater progression than non-amnestic subtypes, although the majority of MCI cases remained stable [27*, 28].

Combining cognitive subtypes with biomarkers, a population-based cohort study demonstrated that a subtype defined by aMCI (multiple-domain) plus high CSF total tau was associated with progression to AD, while a subtype defined by naMCI (multiple-domain) plus vascular disease was associated with progression to mixed and vascular dementia. Thus, biomarkers may enhance the predictive value of the aMCI vs. naMCI distinction [25**].

Single-domain vs. multiple-domain MCI—Newer prospective studies show that multiple-domain MCI (particularly amnestic) confers greater risk of progression to dementia than single-domain, even when examining multiple definitions of MCI [27*, 28, 29, 30].

Conversely, those with single-domain aMCI and naMCI have a relatively high rate of reversion to normal cognition [30, 31, 32]. These findings may simply reflect a threshold/definitional effect, in that multi-domain impairment represents more advanced disease than single-domain impairment and is closer to the dementia threshold, i.e. the outcome of interest is very similar to the predictor. This notion is supported by the similarity of *APOE*4* frequency among single and multiple-domain subtypes of aMCI and naMCI [10*].

Ecological validity

Although the overall definition of MCI includes essentially preserved everyday functioning, some difficulty or increased effort in carrying out normal activities is integral to the presence of a subjective or informant's "complaint." Consistent evidence of differential functional difficulties across MCI cognitive subtypes would confer a measure of real-world ecological validity. In general, aMCI is associated with greater IADL deficits than naMCI [33, 34, 35], and difficulty managing money was the only deficit that appeared consistently different across studies [33, 34].

Other considerations

Two additional issues are relevant to validity.

Variable Definitions and Prevalence Estimates—In theory [7*], the boundaries or zones of rarity around a diagnostic entity should be sufficiently distinct that minor variations in diagnostic criteria should not lead to major variations in prevalence. The precise definitions of MCI and the current four cognitive subtypes remain somewhat fluid; recent studies have operationally defined each criterion in different ways (e.g., one memory test versus two), with different thresholds (e.g., memory test scores 1.0 versus 1.5 standard deviations below the relevant mean), and produced a wide range of prevalence estimates depending on the definition [23, 27*, 28, 30, 36]. Thus, even if the MCI subtypes reviewed here are conceptually sound, their precise definitions await further validation.

Study samples and sources—Research in specialty memory clinics involves willing research volunteers carefully screened for medical exclusionary criteria and with reliable and motivated surrogate "informants." In contrast, most normal or mildly impaired individuals in the community are not seeking care for cognitive difficulties and do not necessarily have knowledgeable informants; their impairment may be longstanding or transient and may be caused by a variety of conditions other than a progressive brain disease. Thus, MCI may be a more heterogeneous entity at the population level than in the specialty clinical setting, where it is likely to represent preclinical AD. Most biomarker studies of AD are out of necessity conducted using clinic samples, while most studies showing associations with cerebrovascular disease have been carried out in population-based cohorts. In fact, community-based autopsy studies have shown that mixed AD-cerebrovascular disease pathology is extremely common in older adults [37]. Additionally, rates of progression from MCI to dementia are consistently lower in community settings than in specialty clinical research programs, with the difference possibly accounted for by varying degrees of baseline functional impairment across settings [3*].

CONCLUSIONS

In their classic review, Kendell & Jablensky argued for the importance of distinguishing between **validity** and **utility** in psychiatric diagnosis [7*]. From their perspective, a diagnostic category is valid if *either* the category is defined as a syndrome separated from normality and neighboring syndromes by a zone of rarity; *or*, the category is defined as an entity with biological underpinnings that are distinct from other conditions with similar

syndromes. Since these requirements rarely prevail in psychiatric classification, our field generally focuses on the utility of diagnostic categories. Utility is present if a diagnostic grouping represents sufficient etiologic and prognostic homogeneity that assigning a patient this diagnosis has real implications for the probability of clinically relevant issues (e.g., treatment outcomes "and/or testable hypotheses about biological and social correlates"). Unlike validity, utility is dependent on context. In practical terms, this notion of utility encompasses what is usually referred to in the psychological literature as predictive validity.

The ultimate scientific purpose of first defining MCI, and then subtyping it, is to provide categories with both validity and utility. The original Mayo Criteria [1] focused on mild memory deficits and was clearly an "Alzheimer-centric" approach to identifying mild impairment, describing a syndrome that resembled dementia of AD in all aspects but severity. The IWG [5*] criteria expand the concept of MCI to include other cognitive domains, and therefore other causes. However, the amnestic vs. non-amnestic distinction still targets memory deficits by lumping all non-memory impairments together. aMCI is therefore still designed primarily to detect prodromal AD, and, when that is the goal, these subtype criteria provide broad utility and some validity. While the majority of published studies of MCI are focused on early detection and treatment of AD, there is an emerging literature on MCI in other brain disorders such as Parkinson's disease [38, 39]; Huntington's disease [40]; and cerebrovascular disease (Vascular Cognitive Impairment, VCI) [41, 42], in which the phenotype, associated features and outcome is not identical to MCI of AD (i.e., aMCI). Further, executive dysfunction may occur as early as memory dysfunction in AD [43], and memory loss can occur early in VCI. Thus, our current subtyping approach may be missing early cases of non-AD MCI, or over-applying assumptions of AD etiology.

Besides objective cognitive deficits, current MCI criteria also require subjective complaints or reports, which might also inform efforts at meaningful subtyping. For instance, a study of primary care patients divided subjective complaints into "worried" vs. "not worried" (despite noticing changes); the former predicted progression to dementia more strongly than the latter [44*]. Some authors conceptualize "subjective cognitive impairment" as the stage preceding objectively detectable mild cognitive impairment [45]. In a sense, clinicians implicitly subtype MCI on the basis of the patient's and families' complaints, in that those without concerns are unlikely to undergo evaluation and treatment. This might be an example of an approach where utility rather than validity is in play, but it might also be a reflection of disease stage or severity. The overall concept of MCI, as currently defined, remains "clinically and prognostically heterogeneous" [6]. Its value should be enhanced by empirically validating the overall and subtype definitions, based on demonstrated outcomes rather than solely on theory, and also by validating the definitions in populations outside the specialty clinical setting.

Looking ahead, the most fruitful approach may be to subtype MCI in different ways for different purposes. Thus, to enrich samples for likelihood of underlying AD pathology, or screen older adults for a disease-modifying therapy, or cross-validate a new AD biomarker, the amnestic vs. non-amnestic distinction may remain useful. To do the same for another disease, a different cognitive domain may be explored, e.g., mild executive function impairment to detect early frontotemporal lobar degeneration. Different cognitive subtypes may also be relevant to predicting difficulties in different everyday activities, such as managing finances or driving automobiles. Subtyping according to associated features, such as behavioral disturbances, may have utility for treatment and also help identify variations in underlying biology. Subtyping MCI by number of domains impaired, and/or by presence of subjective concern, may be useful in identifying disease stage, whether in relation to different biomarkers or to selecting the appropriate intervention at a given patient's stage. Subtyping MCI according to the presence of a biomarker or genotype may improves

predictive value and determine response to specific treatment modalities. When sufficient prospective data become available, the observed outcomes may permit us to identify the profiles of MCI subtypes that do and do not progress to dementia. Such profiles may require a more nuanced approach to subtyping or risk-stratification, including combinations of phenotypic, biomarker, and risk factor data. Eventually, we predict that it will become possible to subtype MCI according to its etiology, which will also indicate its prognosis and required treatment.

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KEY POINTS

1. The overall concept of mild cognitive impairment (MCI) remains clinically heterogeneous, and the purpose of subtyping it is to delineate subgroups that are homogeneous with respect to etiology and prognosis.
2. Currently MCI is subtyped on a cognitive basis as amnestic vs. non-amnestic and single domain vs. multidomain.
3. Amnestic MCI shows associations with Alzheimer's disease pathology, non-amnestic MCI is associated with cerebrovascular disease pathology, and multi-domain MCI suggests more advanced disease than single-domain MCI.
4. Incorporating biomarkers into subtyping may enhance diagnostic specificity and predictive value, but should be validated outside specialty clinic settings.
5. Eventually, MCI will be subtyped according to underlying etiology.