Can the *DSM-5* framework enhance the diagnosis of MCI?

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ABSTRACT

As the field of mild cognitive impairment moves forward and various expert groups come together to update the diagnostic criteria, the framework adopted by the *DSM-5* deserves consideration as a model. This framework could help disentangle cause from consequence, maximize internal consistency, and minimize redundancy and ambiguity. It could make the diagnostic criteria easier for both clinicians and researchers to implement, thus enhancing reliability of diagnosis. It could help maintain conceptual rigor by distinguishing among core diagnostic features (inclusion as well as exclusion criteria), subtypes, specifiers, associated features, and risk factors. Each level of classification, subtyping, and specification should delineate an increasingly homogeneous subgroup with an enhanced likelihood of having common underpinnings and prognosis. New knowledge could be systematically incorporated into this framework. This approach could improve the predictive value and thus the utility of the overall diagnosis. *Neurology*® 2013;81:2045-2050

GLOSSARY

AD = Alzheimer disease; **CIND** = cognitive impairment, no dementia; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; **MCI** = mild cognitive impairment; **NCD** = neurocognitive disorder; **NIA-AA** = National Institute on Aging-Alzheimer's Association; **PD** = Parkinson disease.

The current concept of mild cognitive impairment (MCI) has been the focus of many concerted efforts to develop diagnostic criteria for both clinical and research purposes.¹⁻³ While their substantive content has remained fairly constant, different approaches to diagnosis have introduced new refinements and also some unintended consequences. The recently introduced 5th edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*⁴ has been the object of heated discussions, both of the entities listed as disorders and of the terminology used to describe them. Less attention has been paid to the *DSM-5*-wide diagnostic structure that frames the diagnostic criteria for all mental disorders. This commentary examines the potential benefits of a *DSM-5*-like approach to reframing the MCI criteria.

The essence of MCI is that the individual's cognitive functioning is worse than expected but not bad enough to be classified as dementia. Dementia is traditionally defined as acquired cognitive impairment sufficient to interfere with social and occupational functioning.⁵ The related concept of cognitive impairment, no dementia (CIND), in its broad original form,⁶ required only absence of dementia and presence of cognitive impairment, and did not require cognition to have declined from a previously higher level. MCI and dementia are both syndromes, the key distinction between them being the severity of the cognitive impairment itself, as reflected in its functional consequences. MCI is more challenging to diagnose than dementia because it must be distinguished not only from dementia, at the upper end of severity, but also from normal cognition, at the lower end of severity.

The most cited definition of MCI is that of the Mayo Criteria,¹ which corresponds to what we now call amnesic MCI. This construct was later expanded by an international working group (Key Symposium Criteria)^{2,3} to include nonmemory domains as well, and to parallel the core MCI

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the author, if any, are provided at the end of the article.

criteria that are embedded in the National Institute on Aging–Alzheimer’s Association (NIA-AA) recommendations for MCI due to Alzheimer disease (AD).⁷ The Key Symposium criterion set is as follows: 1) the person is neither normal nor has dementia; 2) there is evidence of cognitive deterioration shown by either objectively measured decline over time or subjective report of decline by self or informant, in conjunction with objective cognitive deficits; and 3) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired.

CIND,⁶ Mayo,¹ and Key Symposium^{2,3} criteria all defined MCI at the syndrome level, with etiology to be specified at the next stage of diagnosis. Yet, over the years, a substantial proportion of the MCI literature explicitly or implicitly focused on older adults whose mild impairment represents impending dementia due to AD. Thus in many circles the term MCI became synonymous with early AD; some authors referred to MCI as a risk state or risk factor for AD, while others argued that it was merely early AD. The NIA-AA workgroup in 2011 resolved this etiologic ambiguity by providing guidelines for the diagnosis of MCI due to AD⁷; in 2012, the Movement Disorders Society published guidelines for the diagnosis of MCI due to Parkinson disease (PD).⁸

The *DSM-5*⁴ introduced the term neurocognitive disorder (NCD). The terms dementia and MCI were avoided because their use is closely associated with geriatric disorders, while NCD encompasses acquired cognitive impairment of all causes at all ages. It comprises 2 syndromes, major NCD and mild NCD, distinguished by the severity of the cognitive impairment. The clinician diagnoses one or the other syndrome before proceeding to diagnose its etiologic subtype, for which criteria are also provided within the *DSM-5*. In major NCD, the cognitive impairment is sufficient to compromise independent everyday functioning; in mild NCD, the individual remains functionally independent, although everyday activities may be more effortful and require compensatory strategies. Major NCD subsumes the entity usually called dementia, and allows the continued use of the term dementia where it is customary to do so, as in geriatrics. Note that major NCD also extends

to cases where severe impairment in a single domain renders the individual functionally dependent. Mild NCD corresponds to the state usually called MCI, and can involve impairment in one or more cognitive domains. At the syndrome level for both mild and major NCD, memory is not necessarily one of the impaired domains. At the level of the etiologic subtypes, the diagnostic criteria specify impairment in specific domains that are characteristic of the given disorder, e.g., memory impairment in NCD due to AD, language and executive function impairment in NCD due to frontotemporal lobar degeneration.

The *DSM-5* mild NCD syndrome criteria were developed with due consideration of the Key Symposium criteria,^{2,3} to which they are conceptually similar. They are intended primarily for use by clinicians who have sufficient expertise to take a history, conduct an examination, and exert clinical judgment. It is left to researchers to further operationalize the criteria for specific study purposes. However, the structure of the *DSM-5* diagnostic approach may enhance the way MCI criteria are broadly framed. The *DSM-5* criteria for all mental disorders include 1) core diagnostic criteria, 2) subtypes of the disorder, and 3) specifiers for the disorder. Criteria are distinct from 1) associated or supportive features, 2) risk and prognostic factors, 3) diagnostic markers, and 4) functional consequences of the disorder.

DIAGNOSTIC CRITERIA Each criterion should be unambiguous; taken together, the core criteria should be both necessary and sufficient for that mental disorder to be diagnosed. Although not stated in the *DSM-5*, the core criteria could be further divided into features that must be present (inclusion criteria) and must be absent (exclusion criteria).

Incorporating the contents of the Key Symposium criteria for MCI^{2,3} and NIA-AA⁷ recommendations for MCI into this structure, the inclusion criteria for MCI could be stated as either (1) and (2), or (3):

1. Subjective impression of decline in cognitive functioning, including impressions by the patient, by a family member or other informant, or the clinician. This criterion remains context-dependent and difficult to operationalize. In a clinical setting where the patient or family is seeking services for the cognitive impairment, a subjective concern is assumed to be present. Where care is being sought

for an unrelated condition and cognitive concerns are detected incidentally or only on questioning, their clinical significance may vary. In some research settings, such concerns may be required for participation. In others, patients' or relatives' concerns may be elicited by standardized questions. In all settings, expectations of normal aging-related cognitive losses will color the expression of concerns.

2. Measurable objective cognitive deficit in one or more domains of cognition, based on formal neuropsychological assessment or bedside cognitive screening. In the *DSM-5*, cognitive domains are delineated and described but no specific tests are named; specific thresholds are not included in the criteria, but are suggested within the accompanying text. Test performance should fall between the expected ranges for normal cognition and for dementia. Typically, normal-range performance is 1 SD on either side of the mean, and dementia-range performance is 2 SDs below the mean. Thus, MCI range performance would fall between 1 and 2 SDs below the mean for the individual's peer group, on any test with appropriate norms. Expert clinical judgment or complex algorithms would be required to classify individuals with atypical presentations, e.g., one domain impaired in the dementia range and another in the MCI range.

In the *DSM-5*, the inclusion criteria for mild NCD are framed as "evidence of modest decline in one or more cognitive domains" based on both subjective concerns and objective measurement. Individuals who meet one but not the other criterion cannot be diagnosed with mild NCD, which can be challenging when the individual lacks self-awareness and there is no reliable informant. Here, the clinician's independent observations of change in the patient's cognition take on prime importance. Objective performance below the expected level (based on appropriate norms) is taken to indicate that decline has occurred. *DSM-5* mild NCD includes no stand-alone option of serially measured objective cognitive decline, as in the third inclusion criterion in the Key Symposium^{2,3} definition below.

3. Evidence of decline over time on objective cognitive tasks, greater than expected for age, without falling into the dementia range. Implementing this criterion requires serial cognitive assessments, not always available. Even when serial assessments have been conducted, further challenges could include variable test-retest reliability, practice effects, and lack of norms for rate of decline.

The exclusion criteria in the Key Symposium definition might be framed as follows:

1. Absence of significant impairment/loss of independence in everyday functioning. For *DSM-5* mild NCD, an inclusion criterion is that everyday functioning may have become more effortful and require the use of compensatory strategies, but the individual is not dependent on others for these functions⁴ (see Functional consequences, below). This criterion requires sufficient self-awareness on the part of the individual or family member or other reliable informant. Available rating scales can be useful but it remains important for the diagnostician to compare the individual's current everyday functioning with his or her own previous level.
2. Absence of substantial impairment in general mental status, usually measured by some threshold on a global screening measure; this criterion was included in the Mayo criteria¹ but not in the Key Symposium criteria.^{2,3}
3. In the *DSM-5*, the presence of another mental condition (e.g., depression, delirium, intoxication, psychosis) that could account for the observed impairment. Alternatively, rather than exclude these individuals, the practitioner could classify them as having MCI, and then designate the other mental disorder as the etiologic subtype. The latter approach was suggested in a critique of the *DSM-5*⁹ and was also the original approach to defining CIND.⁶

Dementia with a clearly defined threshold could be considered an additional exclusion criterion, as in the Key Symposium definition.^{2,3} However, the above criteria already indicate that the cognitive deficits must be mild, and that independence in everyday functioning must be essentially preserved. Thus, the additional criterion of absence of dementia could be redundant.

Subtypes. Subtypes of a mental disorder, if provided, must be mutually exclusive and jointly exhaustive, i.e., all individuals with that disorder should be classifiable under one or other subtypes.

For MCI diagnosis, the most salient subtypes are etiologic, e.g., MCI due to AD, cerebrovascular disease, traumatic brain injury, or HIV infection.⁴ When the individual already is diagnosed with MCI, the additional subtype criteria would be the specific characteristics of the causal entity being considered. These characteristics could reflect expert consensus criteria for that entity, when available. For example, for MCI due to AD, these features could mirror the guidelines of the NIA-AA workgroup for probable and possible AD (prominent memory deficits; insidious onset and gradual progression; typical findings on neuroimaging; where applicable, the presence of autosomal dominant genes; and relevant biomarker profiles if and when they have been validated and approved for clinical use).⁷ Criteria for MCI subtypes due to

(for example) PD and traumatic brain injury would similarly reflect the corresponding expert consensus criteria⁸ or position.¹⁰ Adopting this approach, the *DSM-5* is able to provide diagnostic criteria in parallel format for multiple etiologic subtypes, facilitating differential diagnosis. Certain research settings may require a greater degree of specificity (at the expense of sensitivity) than in the clinical setting; e.g., the Research Criteria for AD¹¹ explicitly require a minimum symptom duration of 6 months, and an episodic memory deficit that does not improve or normalize with cueing or recognition testing.

At the level of the etiologic subtype, and particularly for research diagnosis, exclusion criteria for one subtype might include strong evidence of other etiologic subtypes that are sufficient to explain the presence of MCI. Importantly, exclusion of any cause is relevant only at the etiologic subtype level and not at the level of the broad syndrome of MCI. Further, comorbidity is the norm rather than the exception, particularly in older adults. For example, MCI in a given older individual often represents both degenerative and vascular brain disease.¹² For clinical purposes, it should be possible to diagnose both as present. For research purposes, depending on objectives, a given study might choose to include or exclude cases with mixed etiology. Research criteria may not always be applicable in the clinical setting; certain data required for research diagnosis may not be available to the clinician, who does not have the luxury of “excluding” patients whose characteristics do not neatly match research criteria. Clinical criteria should be able to accommodate additional background or ancillary information unique to a given patient.

For descriptive purposes, MCI is also frequently subtyped according to its cognitive profile, e.g., the number of affected domains (e.g., single domain vs multidomain), or the cognitive domains that are affected (e.g., amnesic vs nonamnesic), or even more specifically a “hippocampal memory profile.”^{13,14} For diagnostic purposes, if a typical neuropsychological profile has been established for a given etiologic subtype, it could be included as a diagnostic criterion rather than a cognitive subtype. Much of this work has been done relative to AD, to identify MCI characteristics that increase the likelihood of progression to AD dementia. Subtypes with established prognostic significance would have utility in both clinical and research settings.

Specifiers. Specifiers for a mental disorder refer to additional features that may or may not be present, that may not be mutually exclusive, and whose presence has some form of clinical or prognostic significance.

It can be difficult to denote further severity levels within MCI, which is already characterized as “mild.” In the *DSM-5*, at the syndrome level, severity specifiers

(mild, moderate, and severe) are provided for major NCD (dementia) but not for mild NCD (MCI). For a given etiologic subtype of MCI, such as AD, severity or stage can be specified, e.g., early or late MCI,¹⁵ pre-MCI and MCI,¹⁶ with appropriate anchors in cognitive test performance, everyday functional ability, or both. Various combinations of biomarkers may some day allow stages of a given underlying pathologic process to be used as diagnostic specifiers to enhance utility.

In the *DSM-5*, the presence of concomitant behavioral features (such as depression or psychosis) is listed as a specifier at both levels of NCD.⁴ They are not present in every case, and are not specific to any neurocognitive disorders, thus neither necessary nor sufficient for diagnosis of the neurocognitive disorder itself. However, they are often the focus of treatment and research, and have prognostic value.¹⁷ The utility of behavioral specifiers for MCI criteria outside the psychiatric setting is worth exploring.

In earlier editions of the *DSM*, early vs late onset was specified in the diagnosis of dementia due to AD.¹⁸ This distinction was removed in the *DSM-5* because the age 60 threshold between early and late onset was arbitrary, and because age at onset does not seem to define a specific pathologic entity. Thus, formal specifiers can be updated as knowledge accrues. However, clinicians may still find it useful to distinguish between earlier and later onset cases, e.g., with respect to the social consequence of AD at different life stages, and researchers may find it useful to select study participants or stratify certain analyses by age at onset.

Associated features supporting diagnosis. Associated features supporting diagnosis are frequently present and consistent with the disorder, but neither necessary nor sufficient for the mental disorder to be diagnosed. This is a heterogeneous group of features; some may be additional symptoms, others may be risk or prognostic factors, and some may have utility as specifiers. That is, some but not all associated features can be specifiers. In psychiatric practice, the presence of behavioral symptoms has sufficient clinical utility to be listed in the *DSM-5* as specifier of the diagnosis of both major and minor NCD, but this may vary across settings. A positive family history of dementia (except in autosomal dominant familial cases) is also often present in MCI but does not enhance diagnostic utility at our present state of knowledge. Thus, family history is an associated feature that is a risk factor, consistent with diagnosis, of potential clinical relevance in working with a given patient or family, but not useful as a diagnostic specifier.

Diagnostic measures and markers. Diagnostic measures and markers reflect the underlying pathology of the disease that causes the mental disorder, and should

reflect adequate sensitivity and specificity for the disorder.

This is consistent with the NIH definition of biomarkers.¹⁹ Diagnostic markers are tools, some of which may rise to the level of diagnostic criteria. In MCI, markers will likely reflect the underlying biology of etiologic subtypes and possibly of disease stages, varying accordingly in sensitivity and specificity. For MCI due to AD, specific neuropsychological tests are characterized by some authorities as diagnostic measures or markers.²⁰ Relevant autosomal dominant genes would be diagnostic in some early-onset familial cases; other biomarkers could include medial temporal atrophy, CSF levels of β -amyloid and tau proteins, temporoparietal glucose metabolism, and amyloid imaging on PET scans, all of which are currently designated as for research only.²¹ Although sometimes referred to as a biomarker for MCI,²² *APOE* $\epsilon 4$ genotype would not be a diagnostic marker (see Risk factors, below). Positive serology is a diagnostic marker for MCI due to HIV infection; positive genetic testing for CAG repeats on chromosome 4 is a diagnostic marker for MCI due to Huntington disease.⁴

Risk factors. Risk factors are independent of the disorder and underlying disease pathology, and promote or contribute to the development of the disorder.

The clearest examples of independent risk factors are greater age, positive family history, and the *APOE* $\epsilon 4$ gene, for AD. The risk of AD increases with advancing age, thus the likelihood of MCI being caused by AD is relatively high in the ninth and tenth decades of life. Likewise, the *APOE* $\epsilon 4$ gene increases the risk of developing AD up to around age 80; individuals can have this gene but not develop the disease, and can develop the disease without having the gene; and it seems likely that carrying the gene hastens the onset of disease.²³ Neither age nor family history nor *APOE* $\epsilon 4$ is necessary or sufficient for the diagnosis of AD, and therefore none of these can be considered diagnostic criteria.

FUNCTIONAL CONSEQUENCES A diagnostic criterion for MCI is preserved functional independence despite impaired cognition. By definition, impairment in everyday functioning would move the individual across the threshold into dementia. It could be argued that the functional impairment is a consequence of the cognitive impairment. The International Classification of Function²⁴ states that the consequences of a disorder cannot be treated as diagnostic criteria for that disorder; however, functional impairment can be used to assess the severity of the disorder once it has been independently diagnosed. In practice, most clinicians view the presence (or at least

the degree) of functional impairment as the boundary between MCI and dementia. Perhaps as the MCI criteria continue to evolve, a way will be found around this potential circularity. Clinically, we must first determine whether everyday function is impaired, then whether the impairment represents a decline for that individual, and how much of the functional impairment is due to the cognitive impairment. Whether or not a given level of cognitive impairment results in functional impairment depends in large part on the cognitive demands or challenges of a given individual's everyday activities.

DISCUSSION Over the past decade, the literature on MCI has revealed wide ranges of prevalence, incidence, and outcome, reflecting the variety of operational definitions and criterion sets in use. Demand is growing for a unified set of MCI diagnostic criteria. Expert clinical judgments will increase in reliability as the diagnostic criteria become less ambiguous. As the field moves ahead and expert groups convene to update the criteria for overall MCI and its various etiologic subtypes, the *DSM-5* framework deserves consideration as a model. It could help disentangle cause from consequence, maximize internal consistency, and minimize redundancy and ambiguity. In turn, these advances should make the diagnostic criteria easier for both clinicians and researchers to implement, thus enhancing reliability of diagnosis. We can maintain conceptual rigor by clearly distinguishing among core diagnostic features (inclusion as well as exclusion criteria), subtypes, specifiers, associated features, and risk factors. We can demand a distinction between criteria for the broad or generic MCI syndrome and criteria for its etiologic subtypes, with suitable anchor points. Each level of classification, subtyping, and specification should delineate increasingly homogeneous subgroups with enhanced likelihoods of having common underpinnings and prognosis. Identifying the additional features that are not diagnostic criteria (i.e., neither necessary nor sufficient for diagnosis), but may influence prognosis, can further improve the predictive value of the overall diagnosis. This framework would facilitate the creation of clinical profiles by selecting a mixture of these features, validated by some external criterion (such as progression to dementia, or response to a particular intervention). At the very least, these are testable hypotheses, going forward.

ACKNOWLEDGMENT

The author thanks Dr. Deborah Blacker for comments on an earlier version of the manuscript.

STUDY FUNDING

Supported by grant K24 AG022035 from the National Institute on Aging, NIH, US DHHS.

DISCLOSURE

Dr. Ganguli is funded in part by grants AG023651 and K24 AG022035 from NIA. The author has no commercial/industrial or philanthropic support. The author was a member of the Workgroup on Neurocognitive Disorders for *DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition)* of the American Psychiatric Association. The APA has not reviewed this manuscript and is not required to do so. Go to Neurology.org for full disclosures.

Received May 27, 2013. Accepted in final form September 4, 2013.

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