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Review Article

Mild Cognitive Impairment: It's Past, Present, and Future

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As the baby boom generation nears retirement age and average life expectancy continues to rise, Alzheimer's disease (AD) is quickly becoming one of the most relevant disorders of our time. There has been an increasing focus on *early* detection of AD for its various advantages from advanced planning to possible preventive treatment. As such, the main objective of this paper is to explore the transient stage between normal aging and dementia (centered on AD)—how its conceptualization has evolved throughout the past, present, and future. At the core lies the term "mild cognitive impairment" (MCI) as the paper traces its history, current standing, and topics of debate in the field. Its future implications as framed under the impending DSM-5 are discussed.

Keywords: Alzheimer's disease; Mild cognitive impairment

Introduction

A century after its first description by the German psychiatrist Alois Alzheimer, Alzheimer's disease (AD) has since become the most frequent neurodegenerative disorder worldwide. As the baby boom generation approaches retirement age and average life expectancy continues to rise, reports suggest that more than 13.5 million individuals in the United States will manifest AD dementia by the year 2050 (Alzheimer's Association, 2010). The lifetime risk for AD between ages 65 and 100 is now 33% for men and 45% for women (van der Flier & Scheltens, 2005). Problems abound in the public health realm as well. Currently, the annual cost of care for one Alzheimer's patient in the US is projected at 60,000 dollars, and the total costs-of-illness including informal care and caregivers' reimbursement are estimated at 100 billion dollars per year, which translates to roughly 70% of the total US health care costs (Mount & Downton, 2006). Thus, Alzheimer's disease has truly become one of the most pertinent diseases of the twenty-first century. Elucidations of its causes as well as overcoming the associated psychosocial and socioeconomic problems remain necessary and critical tasks for the fields of modern neuroscience and public healthcare (Jellinger, 2006).

Converging evidence from both genetic at-risk cohorts and clinically normal older individuals suggests that the pathological process of AD begins years before the formal diagnosis of clinical dementia. Using established diagnostic criteria and currently available clinical, neuropsychological, imaging, and biological marker examinations, the diagnostic accuracy for AD is approximately 90%. Now it is generally accepted that suspected diagnosis can be made in very early or preclinical stages of the disease, supported by long-term studies that help distinguish it from other dementing processes and to forecast the conversion to manifest dementia (Alexopoulos et al., 2006; Boyle et al., 2006; Storandt et al., 2006).

Thus, an urgent challenge facing clinicians today is reliably detecting dementia in these early stages—in scenarios where often, the distinctions between normal aging and early dementia are quite difficult. Accurate diagnoses at this stage are important in allaying anxieties when dementia is not suspected; whereas in cases of dementia, diagnostic certainty as to the type can have significant ramifications, particularly if the disorder is treatable. In the future, should effective treatment strategies become available for AD, early intervention will prove important in preventing the expression of fulminant symptoms (Welsh-Bohmer & Ogrocki, 1998).

Historically, different names have been used to refer to this subclinical stage, but the most prevalent label in the literature seems to be "mild cognitive impairment" (MCI). This paper will embark upon a comprehensive inquiry into the different lines of research in characterizing this intermediate state. To gain an understanding of early diagnosis, the point of departure will be a general introduction to Alzheimer's disease. It is important to keep in mind that Alzheimer's is a progressive disease related to aging, and thus the bulk of its history deals with efforts to pinpoint its exact causes and their timing while keeping them separate from a baseline decline of normal aging. Out of this search for a clearer diagnosis, researchers have turned toward an increasingly earlier point in the disease progression. Initially, this earlier stage was thought to be part of normal aging-related cognitive deterioration; however researchers have come to conceptualize it as belonging to the disorder end of the decline spectrum.

Eventually, the field settled upon Petersen's "mild cognitive impairment" (MCI) as a suitable label for ubiquitous use. To recognize where MCI stands in present time, the latest revised criteria will be given. Of particular interest here is that this label and its diagnostic as well as practical issues have spurred on an impassioned debate within the field—the two end-to-end opinions obdurately guarded by Petersen and Whitehouse. At this point, I will attempt a personal probing at MCI, pulling together various perspectives. The paper will finally come to a close with a discussion of the DSM-5, the future of mild cognitive impairment.

Alzheimer's disease: Origin and Early History

Although various forms of dementia have been known for a long time, efforts to construct a systemic description of clinical-pathological characteristics of the phenomenon only gained traction toward the end of the nineteenth century, roughly paralleling advances in neuroanatomy, histology, and

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other areas of biology (Berchtold & Cotman, 1998). Alois Alzheimer, a German neuropsychiatrist, was among the first to exploit the newly emerging tools for histologic study of the human brain (Maurer, Volk, & Gerbaldo 1997). At the psychiatric clinic in Frankfurt/Main, he examined a 51-year-old woman named Auguste D. who presented with a five-year history of progressive memory impairment, hallucinations, delusions, paranoid ideas, apraxia, speech, and severe social and behavioral problems. Using the new technological tools, he observed that her brain, in addition to severe atrophy, exhibited neurofibrillary tangles in nerve cells and miliary deposits (corresponding to senile plaques) all over the cerebral cortex.

His brief description of Auguste D. (1907) became the index case for 'Alzheimer's disease (AD),' however the term did not receive broad endorsement until the publication of Kraeplin's textbook (1910) who felt that this presenile form of degenerative dementia with plaques and neurofibrillary tangles should bear Alzheimer's name. A century later, Alzheimer's original report remains a critical milestone in the annals of dementia research. Alzheimer's approach of combining scrupulous clinical observations with systematic neuropathological analysis of brain lesions later became the template for the National Institute on Aging's: a) strategy to develop its external program of research support for AD, and b) emphasis on promoting further interdisciplinary research on the causal relationships between the clinical-pathological phenotypes of dementia (Khachaturian, 2006).

During the first half of the twentieth century, scholarship on dementia focused primarily on the epistemology of the disease and reaching a consensus on the clinical definitions. Progress in understanding the relationship between the behavioral and pathological expressions of dementia was relatively slow, however, mainly due to two impediments: 1) lack of validated standardized clinical assessment tools; and 2) uncertainty in the definition of the clinical phenomenon (Khachaturian, 2006).

Then during the two decades following World War II—a time many would argue marked the start of the modern era of AD research, whether AD changes were simply an accentuation of normal aging gradually began to emerge as a central research question. The challenge of distinguishing brain changes due to pathology from those due to normal aging was confronted in a number of landmark investigations by Blessed, Tomlinson, and Roth (1968) in the mid-1960s. However, the dispute could not be definitively settled without comparisons of clinical, biological, and neuropathological phenotypes of the disease, which became possible in the early 1960s with the introduction of the electron microscope and development of quantitative measures of dementia (Khachaturian, 2006). EM studies allowed Kidd (1963) and Terry (1963) to describe the ultrastructure of neurofibrillary tangles formed by paired helical filaments, and to identify the amyloid core of neuritic plaques (Terry et al., 1964). These early ultrastructural studies enabled a more in-depth characterization and understanding of the molecular neurobiology of the major pathological markers of AD.

Working Toward a Clearer Diagnosis

Twenty years later, basic steps toward a *clinical* diagnosis were taken with the third revision of DSM (3rd ed; DSM-III). DSM-III (American Psychiatric Association, 1980) included the term "AD" as the essential cause of senile age-related dementia, and the operational criteria for the diagnosis of dementias were further enlarged and précised in DSM-IV (American Psychiatric Association, 1994) and in the 10th revision of the Classification of Psychiatric and Behavioral Disorders of the World Health Organization (ICD-10; World Health organization, 1993). In relation, the need for functional measures of severity and objective/quantitative tools to assess mental status became critical to clinical progress in this period. Between 1960 and 1985, several categories of objective clinical measurement tools were developed and validated. These include Mental Status Exams (e.g. Mini-Mental State Examination (MMSE), Short Blessed Test), Global Measures of Dementia Severity (e.g. Clinical Dementia Rating, Clinical Impression of Global Change or CIBIC), and Cognitive Assessment Batteries (Khachaturian, 2006). Such attempts to construct quantitative measures of cognition and instruments for objective evaluation of symptoms were critical to refinements in the characterization of the disease. These advances in assessment of disease severity became the foundation for much of the current "routine clinical workup" and set the standard for clinical staging methods, an essential element of clinical research.

Although many researchers were laboring to develop objective measures for assessing the severity of symptoms, uncertainty about the clinical identity of AD lingered until a landmark editorial which for the first time, framed AD as an important public health and medical issue (Katzman, 1976). This paper was an important step toward recognition of a need for specific diagnostic criteria.

The recent history of efforts to improve the diagnostic resources is marked by publication of *pathological* criteria, the first of which went hand-in-hand with struggles to establish neurobiology of disease program at the National Institute of Aging. The NIA was established in 1974 with congressional authorization to vaguely address the "problems and diseases of the aged," but its implicit directive was to develop and support interdisciplinary research on healthy (normal) aging as well as disorders of aging. The complexities of contrasting normal aging from aging-related diseases required an entirely new infrastructure and research paradigm, which called for organization of the series of Research Planning Workshops. The Neuropathology Panel of this Workshop took the first step toward defining the minimum microscopic criteria necessary for histological diagnosis of AD. The Panel suggested that the term "Alzheimer's disease" be reserved for patients who show a compatible clinical course along with the histopathological and neurochemical changes associated with the disease, thereby bringing together clinical symptomology and biological changes in diagnosis.

Prior to 1984, in the absence of specific diagnostic criteria for AD, the DSM-III criteria for diagnosis of dementia had fulfilled the requirements of clinical research in AD. Finally, this need was addressed with publications of the "Diagnosis of Alzheimer's Disease" (Khachaturian, 1985)—a joint effort of the NIA, the American Association of Retired Persons, the National institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Mental Health; and NINCDS-ADRDA Diagnostic Criteria. Drawing from varied disciplines of neurochemistry, neuropathology, neuroradiology, and psychiatry, these two

papers specified inclusion-exclusion factors and three levels of confidence: probable, possible, and definite.

Although the specificities of these criteria need not be discussed for the purposes of this paper, it is suffice to say that since their publication, substantial progress has been made in the accuracy, sensitivity, and reliability of diagnostic assessment instruments and algorithms. Remarkable advances in understanding the role of genetics (e.g. presence of ApoE 4) and neurobiology of dementia in the following three decades further augmented the accuracy of clinical diagnosis. Consequently, the procedures for clinical assessment steadily advanced towards well-validated algorithms for identification of positive clinical phenotypes (Khachaturian, 2006).

Path to Alzheimer's disease

We have thus far traced the history of the construction and diagnosis of Alzheimer's disease as a lead-in to discussing its early stages. The reader may have noticed that two principal issues have served as a common thread throughout the preceding review, returning repeatedly to the fore of the argument. One is the difficulty of establishing set, universal diagnostic criteria, and another relates to distinguishing normal age-related decline from pathological deterioration. With regard to the first challenge, the etiology of AD is hitherto unknown which makes it inherently impossible to narrow down the diagnostic procedures to a single test or threshold. Despite modern advances, exact knowledge of causation is still far from reach, and at present, the best we can do is generate productive discussions and attempt to reach a consensus upon which a majority of researchers and professionals can agree. The second question of normal versus disordered aging also has spawned considerable debate in the field, and perhaps bears more substantial weight in the preclinical stages of AD, to which we now turn.

Early detection has become one of the most important clinical accomplishments with profound implications across the field of AD: in research, establishing the disease prevalence, initiating treatment when it may have optimal benefits, and understanding the pathobiology of the disease. In this respect, the introduction of the construct of "mild cognitive impairment" (MCI) to the field as a potential precursor or prodrome of the disease served as a significant milepost. However, before expanding upon this particular label, let us step back and examine how the conception of this gray area between cognitively normal aging and dementia has changed throughout.

The Past: History

Cognitive Impairment as a Feature of Normal Aging

Deterioration in cognitive functioning in absence of fully onset dementia has long been considered a normal aspect of aging-related brain changes. Affecting mainly episodic verbal memory, such changes are typically differentiated from neurodegenerative disorders by their far slower progression, relative sparing of visuospatial and language functions, and lesser impact on activities of daily living. However, increased interests in the nature and long-term prognosis of aging-related alterations in cognitive performance have led us to question to what extent they may be considered "normal." The past fifty years have witnessed numerous attempts to define these subclinical changes in cognitive function and to establish their etiology with greater precision.

One of the earliest attempts to characterize subclinical cognitive impairment was Kral's notion of benign senescent forgetfulness (BSF) (1962), referring to patient complaints of a sustained difficulty in recalling detail, commonly seen with accompanying depressive symptoms. While Kral initially considered such complaints to characterize a depressive state ("depressive pseudodementia") suggesting that these individuals did not tend to progress to dementia, long-term follow-up of some of these patients showed that a significant proportion went on to develop vascular dementia. BSF was diagnosed by Kral via an open psychiatric interview; no formal algorithm was proposed. Formal diagnostic criteria for non-dementia cognitive impairment were first proposed by Crook et al. in 1986 for the National Institute of Mental Health (1986). Referring to "age-associated memory impairment" (AAMI), they defined these changes as subjective memory loss in older (age> 50) people, verified by decrement of at least one standard deviation on a formal, objective memory test in comparison with means established for young adults. However, this criterion produced difficulty for the concept because individual memory tests were not specified by the workgroup. Depending on which particular memory test was used, virtually all older individuals may qualify for the diagnosis of AAMI. For example, Smith and colleagues (1991) showed that using a difficult memory test such as the Auditory Verbal Learning Test and using the measure of delayed recall, 90% of otherwise normal elderly subjects would qualify for AAMI. Although the AAMI concept stimulated a great deal of research on memory and aging, the usefulness of this construct as defined was questioned.

In response, Levy (1994) argued that there is little reason to assume that cognitive decline in normal old age should be confined exclusively to memory functions, and in collaboration with the International Psychogeriatric Association and the World Health Organization, proposed a revision of the AAMI construct with the notion of "aging-associated cognitive decline" (AACD). The criteria for AACD not only admit to the possibility of a wider range of cognitive functions being affected (attention, memory, learning, thinking, language, visuospatial function), but also stipulate that the deficit should be defined in reference to norms for older, and not young adults to avoid confounding of decline with age and cohort effects. This refinement takes into account the work of researchers such as Schaie and Willis (1991) who demonstrated that much of the difference in cognitive performance seen between young and elderly cohorts is attributable to generation differences (notably in education and health care) rather than to aging-related brain changes. Studies comparing performance of AAMI and AACD criteria have concluded that indeed, they do not identify the same individuals within general population studies. It was shown that AACD targeted a more severe state of impairment within a larger AAMI group (Richards et al., 1999).

Major international classifications of disease began to recognize subclinical cognitive deterioration linked to normal aging with "age related cognitive decline" (ARCD) in DSM-IV of the American Psychiatric Association (1994). Like

AACD, it pointed to an objective decline in cognitive functioning owing to the physiological process of aging; however, no operational criteria or cognitive testing procedures were specified. It was rather loosely defined as a complaint of difficulties in recalling names, appointments, or in problem-solving, not related to a specific mental problem or a neurological disorder.

Disease Models of Subclinical Cognitive Impairment

As seen, early conceptualizations of subclinical cognitive deficit have in common the theoretical assumption that such changes are distinct from dementia and other pathologies. They considered such alterations as the consequence of inevitable aging-related cerebral changes such as cortical atrophy, which may be considered a normal feature of the aging process. However, as parallel research into the causes of dementia and cerebrovascular disease led to a better understanding of their etiology, it has also been shown that many of the physiological abnormalities in these disorders are also present albeit to a lesser extent in subjects identified as AAMI and AACD. Consequently, elderly persons with subclinical cognitive deficits have become the subject of neurological as well as psychogeriatric research, the question being whether cognitive deficits of this type may be due to underlying brain pathology, which may be potentially treatable. Therefore, alternative concepts have since appeared in the literature linking cognitive disorder to various forms of underlying pathology.

For example, the 10th revision of the International Classification of Diseases (1993) described "mild cognitive disorder" (MCD) which refers to disorders of memory, learning and concentration often accompanied by mental fatigue, which must be demonstrated by formal neuropsychological testing, and attributable to cerebral disease or damage, or systemic physical abuse known to cause dysfunction. The concept of MCD, which was principally developed to describe the cognitive consequences of autoimmune deficiency syndrome but later expanded to include other disorders in which cognitive change is secondary to another disease process, is applicable to all ages, not just the elderly. Attempts to apply MCD criteria to population studies of elderly individuals suggest it to be of limited value in this perspective, casting doubt on its validity as a nosological entity (Christensen et al., 1995) for this age group. DSM-IV (APA, 1994) has proposed a similar entity, mild neurocognitive disorder (MNCD), which encompasses not only memory and learning difficulties but also perceptual-motor, linguistic and central executive functions. While neither MCD nor MNCD provides sufficient working guidelines for application in a research context, they do give formal recognition to subclinical cognitive impairment as a pathological state requiring treatment.

A similar concept of cognitive change resulting from multiple underlying disease processes, but in this case referring to elderly populations, is that of CIND (cognitive impairment no dementia). Developed within the context of the Canadian Study of Health and Aging, the concept is defined by reference to neuropsychological testing and clinical examination (Graham et al., 1997). Individuals with CIND, like MCD and MNCD, are considered to have cognitive impairment attributable to an underlying physical disorder, but may also have a "circumscribed memory impairment," which is essentially a modified form of AAMI. CIND encompasses a wider range of underlying pathologies than MCD and MNCD, including disorders such as delirium, substance abuse and psychiatric illness, which are excluded from the ICD and DSM categories (Ritchie & Artero, 2005).

Mild Cognitive Impairment: Intermediate State between Normal Aging and Dementia

Initial conception

MCD, MNCD, and CIND are all constructs that have been developed with an aim toward research and consider cognitive disorder in the elderly to be: heterogeneous, not necessarily progressive, with treatment being determined by the nature of the underlying primary systemic disease. In contrast, clinical observations of long-term outcomes of cognitive complaints, particularly those patients in memory clinics and neurology departments, led many neurologists to conclude that subclinical cognitive disorder in the elderly is in fact principally, if not exclusively, early-stage dementia. Thus, whereas dementia in the early 1990s was largely considered to be an extension of normal progressive aging-related cognitive deterioration, by the end of the decade, subclinical cognitive deficit began to be perceived as an extension of a pathological process.

In the midst of numerous studies referring vaguely to mild cognitive disorders in relation to dementia, Ronald Petersen of the Mayo Clinic (Petersen et al., 1999) proposed diagnostic criteria for the concept of "mild cognitive impairment" (MCI) in 1997, which has become a household name in the field. Originally defined as memory complaints (preferably corroborated by an informant) and objective memory impairment, against normal general cognitive function and conserved ability to perform activities of daily living, MCI was mainly of an amnestic form and considered by many to be a prodrome of Alzheimer's disease. However, MCI criteria proved difficult to apply for it designated poor cognitive functioning as assessed at one point in time, thus precluding consideration of decline over time. It was also difficult to differentiate from cohort effects, low IQ and education. A later definition (Petersen et al., 1999) improved the initial concept by referring to memory impairment beyond that expected for both age and education level (Ritchie & Artero, 2005).

Building MCI construct

Despite further refinement, subsequent studies using MCI criteria have encountered numerous difficulties. These have been mainly due to the lack of a working definition based on designated cognitive tests and other clinical measures. What has transpired is that population prevalence, clinical features of subjects identified as MCI, and their clinical outcomes vary widely between studies and even within studies where there has been longitudinal follow up (Ritchie & Artero, 2005).

A consensus conference held in Chicago in 1999 confronted many problems facing the MCI concept (Petersen et al., 2001a), notably its two underlying assumptions that it should be confined to isolated memory impairment; and whether it constitutes a prodrome of AD or alternatively

identifies a more clinically heterogeneous group at higher risk of dementia owing to any cause. When the original criteria centering on isolated memory impairment was applied to population studies, they showed that this form constituted only a relatively small group, compared with all individuals with a much broader form of mild deficits in other cognitive domains such as language, attention, visuospatial skills, and executive functioning who needed to be taken into account (Ganguli, Dodge, Shen, & DeKosky, 2004; Larrieu et al., 2002; Ritchie, Artero, & Touchon, 2001). Pulling together results from various research studies, the group concluded that subjects with MCI have a condition that is disparate from normal aging and are likely to progress to AD at an accelerated rate; however they may also progress to another form of dementia or improve.

The group thus proposed subtypes of MCI according to the type of cognitive deficit and clinical outcome, distinguishing MCI Amnestic (MCI with pronounced memory impairment progressing to AD), MCI Multiple Domain (slight impairment across several domains leading to AD, vascular dementia, or stabilizing in the case of normal brain aging changes), and MCI Single Non-Memory Domain (significant impairment in a cognitive domain other than memory leading to AD or another form of dementia). Petersen (2004) has subsequently refined the multiple domain subtypes: 1) amnestic MCI (aMCI); 2) multiple domain amnestic MCI ($mdMCI^+$), characterized by a slight impairment of multiple cognitive domains including memory; 3) multiple domains non-amnestic MCI ($mdMCI^-$), with a slight impairment of multiple cognitive domains but without memory deficits; and 4) single non-memory MCI (snmMCI).

According to the four proposed clinical subtypes of MCI, it is conceivable that they differ in etiology and outcome. In fact, aMCI and $mdMCI^+$ are considered to have a high likelihood of progression to Alzheimer's disease (AD), while snmMCI and $mdMCI^-$ are assumed to convert more frequently to non-AD dementia (Backman, Jones, Berger, Laukka, & Small, 2004; Petersen et al., 2001a; Petersen, 2004). This view was recently confirmed by a German longitudinal study showing that at six-year follow-up, subjects with $mdMCI^-$ were more likely to progress to non-AD dementia, and those with $mdMCI^+$ converted mostly to AD (Busse, Hensel, Guhne, Angermeyer & Riedel-Heller, 2006). Conversely, data from an Austrian community birth cohort study revealed that, after thirty months of follow-up, the aMCI subtype evolved towards both AD and non-AD dementia, while many patients developed AD from non-amnestic MCI as well (Fischer et al., 2007). The contradiction between these two studies gives us a glimpse into the extreme heterogeneity of MCI as a clinical entity in terms of etiology, clinical presentation, and outcome.

The Present: So Where Are We Currently?

Given this extreme heterogeneity, the challenge for the field of MCI has revolved around developing a more uniform diagnostic classification and better defined operational criteria. The existing literature points to a dire lack of consensus on the type and number of cognitive tests as well as cut-off/thresholds used to support or corroborate the diagnosis of MCI, and even at present, there is no formal agreement on a single set of criteria. Part of this disagreement may be due to the fact that MCI is a syndrome defined by clinical, cognitive, and functional criteria, and like dementia, it cannot be diagnosed by a laboratory test—the diagnosis ultimately comes down to a clinical judgment, dependent upon the individual clinician (Albert et al., 2011).

The operationalization of these criteria has generated considerable research, and correspondingly the criteria have evolved through the years. Having discussed MCI in broad terms, I would like to bring the focus back onto MCI and its relation to AD in particular, and ascertain its current place in the literature. Thus, I will cover in detail what constitutes MCI according to the most up-to-date criteria. The workgroup specified below takes a new direction in that it outlines separate criteria for clinical and research use—the latter incorporating newest biomarker findings. The rationale for keeping the two sets of criteria separate will be discussed in the following section of "Debated Issues."

Diagnosis of Mild Cognitive Impairment Due To AD: Latest Revised Criteria

The National Institute on Aging and the Alzheimer's Association recently charged a workgroup with the task of revising the criteria for the early predementia phase of Alzheimer's disease, referred to as "mild cognitive impairment due to AD." Recognizing the importance of incorporating a continuum of impairment—from asymptomatic phase to MCI to dementia onset—into clinical and research practice, the workgroup developed the following two sets of criteria: 1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and 2) research criteria that could be used in clinical research settings, including clinical trials. The second set of criteria integrates the use of biomarkers based on imaging and cerebrospinal fluid measures.

With regards to the first, there are four main criteria: (1) there should be some evidence of a change in cognition in comparison with the person's previous level; (2) lower performance in one or more cognitive domains that is greater than expected for the patient's age and educational background; (3) preservation of independence in functional abilities; and (4) not demented. In order, objective evidence of cognitive decline is necessary for which cognitive testing (e.g. episodic memory tests) is used. A guideline of 1 to 1.5 standard deviations below the mean for their age- and education-matched peers on culturally appropriate normative data is given, although they stress that these are not cutoff scores. Once it has been determined that the clinical and cognitive syndrome of the individual is consistent with that associated with AD but that the individual is not demented, the clinician must then determine the likely primary cause, for example, degenerative, vascular, depressive, traumatic, medical comorbidities, or mixed disease. Typically, this information is derived from further historical information and ancillary testing (e.g., neuroimaging, laboratory studies, and neuropsychological assessment). Genetics (i.e. autosomal genetic mutations for AD and role of APOE genetic variant in increasing risk) is also often considered in making the diagnosis.

In recent years, biological advances have enabled the application of biomarkers to individuals with MCI. Thus, it seems important to incorporate this knowledge into the

diagnostic framework, recognizing however that these recommendations do not have any clinical implications at this time, and that it may be necessary to revise diagnostic recommendations as new information emerges. Two fundamental issues about individuals with MCI may be answered by the use of biomarkers: (1) To build support for the underlying etiology of the clinical syndrome in an individual with MCI, which will have major importance for choosing the correct therapy when effective treatments become available; (2) To determine more accurately the likelihood of cognitive and functional progression to a more severe stage of MCI or to dementia for a MCI patient, and the likelihood that this progression will occur within a defined period.

The current pathological criteria for AD require evidence of beta-amyloid (Aβ) protein deposition in plaques, along with evidence of tau deposition in neurofibrillary tangles. Evidence suggests that together the buildup of these two proteins in the brain is associated with neuronal injury. For clinical research criteria of MCI to be based on the established pathological criteria, they have defined biomarkers in terms of whether they reflect Aβ protein deposition, tau deposition, or signs of neuronal injury. Markers of Aβ deposition include both cerebrospinal fluid (CSF) measures of lower $A\beta_{42}$ levels (Selkoe, 2005; Blennow & Hampel, 2003; Shaw et al., 2009) and positron-emission tomography (PET) evidence of Aβ deposition, using a variety of specific ligands (Fagan et al., 2006). Markers of tau accumulation include CSF measures of increased total tau or phosphorylated-tau (p-tau) (Selkoe, 2005; Blennow & Hampel, 2003; Shaw et al., 2009). Although the two proteins separately are also associated with disorders other than AD, the two biomarkers in combination are extremely informative: together with low CSF $A\beta_{42}$, elevated CSF tau provides a high probability of progression to AD in patients with MCI. Measures of downstream neuronal injury include structural and functional measures, including brain atrophy and hypometabolism or hypoperfusion obtained with magnetic resonance imaging (MRI), PET, and single-photon emission computed tomography (SPECT) imaging (Atiya, Hyman, Albert, & Killiany, 2003; Kantarci & Jack, 2003; Jagust, 2006). However, limitations in current state of knowledge regarding AD biomarkers mandate that considerable work is needed to validate the criteria that use biomarkers and to standardize biomarker analysis for use in community settings (Albert et al., 2011).

Debated Issues

We began our exploration by tracing the origin and history of making Alzheimer's diagnosis. Out of this long-winded search for more clearly defined diagnosis, researchers have increasingly focused on the border zone between normal aging and AD. Although initially this preclinical stage was thought of as part of normal aging decline, by and by investigators began to conceptualize it as belonging to the disordered end of the spectrum. There have been numerous attempts to label this boundary area, and thus far, Petersen's "mild cognitive impairment" seems to have prevailed. The NIA in 2004 noted MCI as a top discovery of the Alzheimer's disease Centers (ADCs) program, and in 2010, more than 1220 publications listed MCI in the title, abstract, or keywords (Elsevier SciVerse Scopus). MCI itself has come a long way in terms of operationalizing criteria, the most recent of which we have just covered in detail. However, it is imperative to note once again that despite many such workgroups and consensus conferences, MCI has remained a diagnosis without a mutually agreed upon criteria among dementia experts and neurologists.

At this point, let us approach mild cognitive impairment from a different angle. MCI has engendered much debate in the field of dementia, which is far from surprising for it inherently deals with a gray area. What are some of the most fiercely debated issues? In the years since the publication of Petersen's seminar article on MCI, many dementia experts remain unconvinced of the need for that label. Strong opinions on either side persist, and those in opposition say that key questions have lingered unanswered for years.

Predicting Alzheimer's disease

One of the central points of debate is the question of how well MCI predicts who will progress to AD. Over the years, Petersen has claimed that 80 to 85% of patients with MCI convert to AD in 6 years. Typically, in his population, they convert at a rate of about 12% per year. According to Petersen, those who do not progress in that time frame are the result of misdiagnosis, overcalling the patient's cognitive problem, or very slow progression (Petersen, 2003). More recently, he asserted that in clinical trials involving patients with amnestic MCI, more than 90% of those with progression to dementia had clinical signs of AD (Petersen, 2011).

However, many people question that 85 percent figure. Some experts like William Thies, Vice President of Medical and Scientific Affairs of the Alzheimer's Association in Chicago, point out that while this figure might hold true in very high-powered academic, neurology referral patient populations, the figure may not generalize to other settings (Schuster, 2004). A number of studies have shown that even when Petersen's criteria are applied strictly, they do not actually identify a group that goes onto develop dementia. For example, one methodologically- strong study in Japan attempted to determine the rate at which subjects with MCI progress to dementia in a cohort of a population-based epidemiological study. Using Petersen's criteria, the investigators determined that of 104 subjects identified as MCI (selected from 1162 community dwellers over 65 years of age), only 10.6% were diagnosed with AD at 5-year follow-up. The annual conversion rate was calculated as 8.5% per 100 person-years. Furthermore, 38.5% of MCI subjects showed a restored MMSE score, returning to normal cognitive status (Ishikawa & Ikeda, 2007). Naturally, naysayers have called for more studies conducted in an epidemiological setting to try to address this question.

In response to the different rates of conversion to Alzheimer's disease seen in different settings, Petersen himself agreed that some epidemiological studies have noted instability of the diagnosis over the years (Schuster, 2004). He commented that part of this is due to the criteria used in the field setting. In an epidemiology study, diagnosis tends to rely more on neuropsychological tests than on clinical judgment; out of practical necessity, the clinician cannot afford to spend hours with the subject. Cognitive tests can be unstable, and without the oversight of a clinician to evaluate the results, the diagnoses made in epidemiological studies are more

algorithmically driven than in clinical research studies which accounts for the unstable rates. Pointing instead to much higher reliability demonstrated in most clinic-based studies, Petersen argues that the instability is more methodologically driven rather than reflecting the inherent instability of the construct of MCI.

However, when primary clinicians make a diagnosis of MCI, the implication is that we know for a certain percentage of the time, these patients will go on to have Alzheimer's disease. But if patients with subclinical impairment as defined actually progress to AD at much lower rates than Petersen describes, then where does the value of this concept lie? In effect, this controversy over rate of conversion essentially becomes part of a bigger question—is MCI a clinically useful entity?

Value of MCI

While an active debate proceeds among dementia experts regarding the clinical value of MCI, two staunchly opposing opinions particularly stand out. For the past decade, they have refused to cede their positions in the field, sometimes resorting to personally-directed charges (Whitehouse, Brodaty, & Petersen, 2006).

MCI is clinically useful

Perhaps the highest mark of recognition regarding the construct of mild cognitive impairment comes from DeKosky who hails it as "a triumph of clinical neurology" (Schuster, 2004, p. 18). He offers kudos to Petersen and others who have succeeded in pushing the detection of potentially predictive signs of dementia so close to the margins of healthy aging. It comes as no surprise then that Petersen, the originator of the term, still strongly advocates the use of MCI diagnosis in clinical settings.

In a relatively recent review, Petersen and colleagues summarized and evaluated the existing research in mild cognitive impairment (Petersen et al., 2009). Detailing a myriad of pertinent issues including MCI's history, criteria, epidemiology, outcomes, predictors, neuropathological analysis and clinical trials, the authors presented ten years' worth of progress that had been made since the first publication in 1999. Citing relevant clinical and neuropathological findings, they clearly demarcate aMCI from AD and build a case for use of the specific term "MCI." Since not all aMCI patients will evolve to AD, they posit that labeling such population as having AD or even prodromal AD is inappropriate, for the patients and families will only "hear" the AD part of the label. Therefore, they believe using an etiologically neutral term (i.e. MCI), coupled with a suspected pathogenesis evidenced by history and ancillary testing, then explaining to the patients the possibility that this term may imply development of AD in the future may be more fitting as a longitudinal approach.

They show that their proposal to use MCI terminology in clinical settings is supported by research. In 2001, the American Academy of Neurology published an evidence-based medicine practice parameter on MCI and recommended that physicians should identify and monitor patients with MCI because these individuals had an increased risk of developing dementia (Petersen et al., 2001b). In addition, a survey undertaken by the same organization to assess the clinical acceptance of the construct indicated that 80% of neurologists use the term "MCI" and find it relevant when describing this type of patient, implying that the construct of MCI is clinically useful and is gaining more widespread acceptance (Roberts, Uhlmann, Petersen, Karlawish, & Green, 2009). Specifically, respondents named several benefits of making a clinical diagnosis of MCI: 1) labeling the problem is helpful (91%); 2) involving the patient in planning for the future (86%); 3) motivating the patient's risk reduction activities (85%); 4) helping the family with financial planning (72%); and 5) prescribing medications useful for treating MCI (65%). Backed by its increasing use by general practitioners and specialists, Petersen argues that MCI is a clinically useful concept and consequently serves a purpose for clinicians.

MCI should not be used clinically

As I reviewed the literature on the opposing side of the controversy, it seemed that Peter J. Whitehouse has perhaps held the most outspoken and obstinate standpoint over the years. His forthright disapproval, perhaps even bordering on hostility is evident in many of his writings, one explicit example of which is: "the term MCI is arbitrary, inconsistently used, and conceptually unclear and of uncertain benefit (and potential harm, namely confusion and stigmatization) for individuals affected by aging-associated cognitive challenges" (Whitehouse, 2007, p. 63).

Two common themes thread Whitehouse's questioning of the MCI label across his many publications. The first is "epistemological" in origin and relates to confusion over the criteria. Whitehouse states that the challenges for the MCI diagnosis are the word "mild" and the phrase "activities of daily living relatively preserved" (Whitehouse, 2004). So unlike in dementia, activities of daily living are regarded as being *relatively* intact in MCI, but he asks, relative to what? Primary physicians' knowledge about their patients' lifestyles varies in degree, and the importance of a patient's subjective complaint is a matter of debate. Psychological testing is said to aid in determining the extent of impairment, but circling back again, what are the criteria that define MCI—test results that are one or two standard deviations below the performance of a reference population? Furthermore, which reference population? (Whitehouse, 2007) In support of his argument, he directs us toward research studies of the course and treatment of MCI that demonstrate considerable variability in the application of such criteria and in clinical outcomes (e.g. Gauthier et al., 2006). Positing that experts could not agree whether MCI was related to normal aging, very early AD, or deserving of a separate label, he ultimately asks: where does one draw the line between MCI and AD?

Aside from questioning the clinical validity of MCI, Whitehouse presents an altogether interesting perspective—one that integrates science, philosophy, and sociology. Thus ethics is another major theme that underlies many of his counter-arguments against MCI. For example, Whitehouse notes the potential impact that the label MCI may have on the significant other of the individual with beginning intellectual decline. When one is labeled as having AD, the partner is often labeled as the caregiver. However, can one be a caregiver of a patient "diagnosed" with MCI or does one just continue the mutual caregiving that hopefully exists already in

a relationship between two people? With a medical diagnosis, the individual who was previously on equal footing with his or her significant other transitions into a class of patients, which fundamentally changes the power relationship to that of a patient and caregiver. The financial and psychological impact that change may bring to their lives is not difficult to imagine (Whitehouse, 2004).

Another example concerns what he identifies as the issue of "truth telling," or communicative ethics of applying the label MCI (Whitehouse & Moody, 2006). When told they have MCI, patients are likely not to know what this new diagnosis really means. Given the two extremes that this diagnosis could entail (i.e. conversion to AD, or uncommon but possible restoration of cognitive function), telling too much or too little of the truth might not seem feasible. He asks, should we then favor an Aristotelian middle way and tell patients "just enough," depending on circumstance? Casting doubt on the subject, Whitehouse states that that style of situation ethics sounds suspiciously like a return to old-fashioned medical paternalism.

A final concern tangentially relates to dispute over diagnostic criteria. Since the inception of MCI, numerous workgroups and consensus conferences have taken place. It is worthy of note that many of these conferences are supported directly or indirectly by industry dollars, a factor that has been shown to influence the interpretation of clinical studies (Korn, 2000). Then how much of those professionals' efforts are geared toward improving the lives of their patients versus creating bigger markets for drugs? Are the interests of researchers in the MCI category the same as that of patients, or is there a divergence of interest? (Whitehouse, 2007) To put it in broader context, is it possible that MCI is a legitimate category for researchers, but not necessarily a term to be routinely invoked in clinical practice? Harkening back to our central question of MCI as a clinically useful entity, Whitehouse makes no mistake of elucidating his position. While MCI may be appropriate to use in research (although problematic), he asserts that the label should *not* be used clinically, and goes as far to mention that some authors are even questioning whether it has limited our thinking in research (Schneider, 2005).

Pulling It Together

Having presented both the facts and opinions as to where MCI stands, let us reevaluate from various perspectives why we demarcate a particular group of cognitive problems and subsume them under this label. As is the case with Alzheimer's, for any disease with progressive symptoms, it is logically possible to construct a syndrome prior to the onset/diagnosis of the full-blown condition. The question is why? For what reasons are we motivated to make such a demarcation? Framing MCI as a demarcation brings attention to the fact that it exists on a continuum and that we are dealing with a boundary problem, which fundamentally becomes an issue of where to draw the line—or whether we should even draw it at all.

In the field of dementia, clinicians have been encouraged to make the diagnosis of AD earlier as previously stated, driven by the belief that assigning an early label will allow advanced planning and initiate early drug treatment. However, the reality is that because cognitive impairment toward the end of life is so common, all individuals should be given the advice from healthcare professionals to plan ahead. Furthermore, as of present, there is no clear evidence that early treatment with currently available medications is necessarily beneficial (Bullock, 2005). This casts some doubt as to whether applying a label is absolutely necessary.

In a related vein, some of the strongest arguments on behalf of the MCI label originate in research. In a research setting, early diagnosis of AD allows investigators to observe and study the process from its beginning stages. In fact, the term MCI was invented to support primary prevention trials, for in order to prevent AD, one must identify those who are not yet afflicted by the condition (Whitehouse & Moody, 2006). Currently, MCI trials may be more common than trials of medications for patients already diagnosed with AD. Their argument is that we should diagnose people with MCI now so that they will be ready when preventive drugs become available. Although most of the completed trials of prevention agents up to date have produced essentially negative results, the verdict is still out: it remains to be seen whether more effective means of intervention will become available.

On the part of the patient, a clinical label may bring comfort—permitting them to formally enter into the medical world, which offers the *hope* of treatment. Patients may find reassuring to know that things happening to their body and/or mind fit into a recognizable pattern and have some predictable sequence and causality, even if only dimly perceived. Applying a label of MCI offers a sense of power and control over some aspect of the individuals' lives. However, this heightened sense of control may be illusory, for the early application of the label which is based on arguably arbitrary quantitative thresholds, may prove inaccurate or at least not predictive of future course. Nonetheless, knowing and putting a name to the condition does serve to reduce patients' self-perception of vulnerability and uncertainty, the significance of which cannot be downplayed.

The spread of the categories of AD and MCI involves repeated negotiation over appropriate terms and the justification for their use. Thus, we need to ask whether the stigma attached to the labels AD and MCI, and the power of the terminology to create social and personal fear balances out the advantages of applying the label. Ultimately, these questions raise far-reaching issues about the meaning of life for patients with cognitive impairment (Whitehouse & Moody, 2006). In a hyper-cognitive society like ours (Post, 2003), do the diagnoses of AD and/or MCI which are often described as the 'loss of the self' diminish our idea of humanity?

The Future: DSM-5 Controversy

It is anticipated that with the release of DSM-5, the controversy over MCI will intensify. This newest revision of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association, 2013), which is scheduled for release in May 2013, has revamped the dementia chapter—previously called "Delirium, Dementia, Amnestic, and Other Cognitive Disorders" under DSM-IV (APA, 1994)—in a major way, which is now titled "Neurocognitive Disorders." DSM-5 has eliminated the term "dementia" and in its place, offered two groups of disorders: major and minor

neurocognitive disorder. Many believed that the word dementia was stigmatizing toward older individuals and not well accepted by younger individuals with HIV dementia (Siberski, 2012). Thus the new term focuses on the decline from a previous level of functioning as opposed to a deficit.

In working toward this category, the Neurocognitive Disorders Workgroup of the DSM-5 Task Force first defined the domains of brain functioning that would be involved in diagnoses of these neurocognitive disorders. Having identified these (complex attention, learning and memory, executive ability, language, visuoconstructional-perceptual ability, and social cognition), they then developed working definitions of the domains and corresponding impairments in everyday functions that the clinician may elicit or observe. The group proposed requiring both subjective reports/observations and objective assessments of cognitive impairment, especially for the less severe entity of "minor neurocognitive disorder." The chief difference between the two groups of disorders being that of severity, they suggest certain thresholds as anchor points for the objective assessments for diagnosis at the syndrome level (major and minor neurocognitive disorder). After the syndromic diagnosis, the clinician selects an etiological subtype, such as Alzheimer's disease (AD). So both minor and major neurocognitive disorders have, for example, an AD subtype. Stated in reverse, AD can be classified as either major or minor depending upon the syndrome thresholds that a given patient meets (Ganguli et al., 2011).

The work group claims that a major innovation for DSM-5 is the proposal to recognize neurocognitive impairment as a focus for diagnosis and treatment, even if it does not rise to the threshold of affecting everyday functioning. It is of particular interest to us that this innovation termed "minor neurocognitive disorder" is a direct parallel to which that we have thus far referred to as "mild cognitive impairment." In fact, the group explicitly draws the parallel in the authors' review of their work (Ganguli et al., 2011). In older adults, the term MCI has been in use for the past decade, describing a state intermediate in severity between normal aging and dementia (mostly Alzheimer's type), and frequently a precursor to dementia (Petersen et al., 2009). The group posits that its objective is for this syndromic disorder to encompass a more diverse group of entities, including mild impairments in younger individuals and impairments that may be transient or static or reversible (Ganguli et al., 2011).

With the instatement of the MCI construct into the DSM, which is widely used for diagnosis by mental health professionals in the United States, the dispute is only likely to become even more ardent. Its now-official status raises potentially alarming concerns. One source of concern draws from issues we have already covered in detail. The presence of nonspecific and arguable symptoms, and blurred distinctions with normal range behaviors would probably lead to many false-positive cases.

Additionally, when a patient is diagnosed with minor neurocognitive disorder due to Alzheimer's disease, the label "minor" could lead the patient to assume that it is indeed "minor" and could inadvertently trivialize or delegitimize the condition. He or she may not fully recognize the seriousness of the diagnosis in terms of disease progression. Subsequently, this lack of recognition could contribute to negative effects, for example, whether the patient complies with treatment; meets with an elder care attorney to construct a will, power of attorney, and advance directive; and seriously addresses issues such as driving and long-term care (Siberski, 2012). The work group itself has expressed concern for this possibility (Ganguli et al., 2011).

Where Does This Leave Us?

We have thus far established that Alzheimer's disease is marked by a long history of semi-successful attempts at defining clear diagnostic criteria, and by virtue of its progressive symptomology, demarcating the point at which degeneration becomes pathological as opposed to normal aging has proven difficult. Out of this exhaustive search, researchers have increasingly zeroed in on a transitional or intermediate state between cognitive changes of normal aging and the earliest features of AD as a possible intervention period to prevent or slow down AD progression. The conceptualization of this time frame has evolved from part of the normal aging process to a disease model, settling upon the term "mild cognitive impairment" (MCI) offered by Petersen. Professionals in the field have vehemently debated upon operationalization of its criteria and clinical value, the two extremes represented by Petersen and Whitehouse. The altercation is only bound to aggrandize with its confirmed inclusion in the DSM-5.

In light of the current research, there are still questions crying out for answer. First, despite the occasional superfluous language that Whitehouse employs, his arguments—certainly representative of an atypical viewpoint in the medical realm—deserve our attention. He asks whether our visions of the potentialities for age-related cognitive changes have been limited by constantly examining them under the frame of deterioration and disease (Whitehouse & Moody, 2006). Our focus, perhaps even obsession on labels such as MCI or AD may be taking away from opportunities to gain wisdom and develop spiritually as we age more than the age-related brain changes themselves. Perhaps this may sound a bit far-fetched, but the underlying question still holds: is the adoption of the clinical term MCI a wise action from the perspective of society as a whole?

That said, the construct of MCI has influenced the field of aging and dementia in several significant spheres. It has brought the spotlight onto the earlier prodromal states of various cognitive disorders, most extensively on AD (Petersen et al., 2009). Research programs ranging from epidemiological studies to investigations of the mechanisms of disease have been significantly influenced by MCI, and the hope is that these explorations will ultimately lead to more effective preventive therapies. There is also a documented need in the field for further development of imaging measures and biomarkers, in other words, more objective and standardized measures, for assessing the asymptomatic or presymptomatic stages of neurodegenerative diseases. Better knowledge of such measures in the MCI stage will augment reliability and sensitivity when predicting the progression to more advanced stages, which persists as one of the most polemic topics in the field. Despite its many characteristics that some merely see as points to improve upon and others view as unsalvageable flaws, MCI has served its due diligence

in stimulating discussions within and in general, progressing the field of dementia—though to what, it remains to be seen.

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