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FOR DEBATE: IS MILD COGNITIVE IMPAIRMENT A CLINICALLY USEFUL CONCEPT?

Introduction

In March 2005 *International Psychogeriatrics* published its first "For Debate" section on the topic of "should novel antipsychotics ever be used to treat the behavioral and psychological symptoms of dementia (BPSD)?" (Ames *et al.*, 2005). Following the positive reception of this piece, we have commissioned three further debates, of which this one on mild cognitive impairment (MCI) is the first to be finished. Further For Debate articles on the effectiveness of electroconvulsive therapy in treating the depressed elderly, and the utility of neuroimaging methods in the assessment of dementia are in an advanced stage of preparation and will appear in future issues of the journal. Should any reader have suggestions for other worthwhile debate topics I urge them to contact me at ipaj-ed@unimelb.edu.au as the journal's entire editorial panel is keen to make these debates a regular journal feature.

Most dementias are insidiously progressive illnesses, so it seems obvious that most patients who are to become demented will go through a phase of incipient and worsening cognitive impairment that does not meet criteria for dementia, before finally crossing the diagnostic threshold for that disorder. Because it is desirable to prevent dementia from developing at all, or at least to stave off or minimize the severity of developing dementia, there has been great interest in early identification of individuals who might be at risk of, or who are already developing premonitory dementia symptoms. Ron Petersen and David Knopman have been at the forefront of attempts to push back the boundaries of diagnosable pre-dementia syndromes, and the concept of MCI represents a brave attempt to elucidate a diagnostic entity that can form the target of research on the development (and ultimately the prevention) of Alzheimer's disease (AD). Here they make the case for the clinical utility of the concept. Unfortunately, the further one gets from clear-cut dementia, the greater is the risk that mild syndromes of cognitive impairment will be contaminated by other factors such as depression, medication use, education level and pre-morbid intellectual ability. Pieter Jelle Visser and Henry Brodaty have outlined the major objections to the clinical utility of the MCI concept as currently conceived in their argument which follows. Finally, Serge Gauthier comments on the debate, identifying areas of mutual agreement and outlining possible ways forward. The early detection of those at risk of dementia is critical to reducing the size of the coming dementia epidemic through interventions which are likely to emerge over the

next one or two decades. It is therefore timely and appropriate that *International Psychogeriatrics* should host this debate on such a vital topic, and I thank our contributors for their cogently argued and clearly written contributions, which I expect all readers of the journal to find stimulating, worthwhile reading.

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MCI is a clinically useful concept

Introduction

Mild cognitive impairment (MCI) has become a major issue in the fields of geriatrics, behavioral neurology and geriatric psychiatry. While some have embraced the construct as a step forward in understanding the prodromal stages of dementing disorders, others have assailed the concept as counterproductive and distracting. Perhaps this is appropriate, since any new proposal for the clinical characterization of impaired subjects should undergo strict scrutiny.

What is MCI?

The Mayo Alzheimer's Disease Patient Registry was initiated in 1986 as a longitudinal community-based study of aging and dementia (Petersen *et al.*, 1990). As we evaluated our patients for dementia, we recognized that classifying patients as normal or demented left many patients who were actually in between these two categories, as had others (Fratiglioni *et al.*, 1992). We recognized a group of subjects who appeared to have subtle cognitive deficits, primarily in the memory domain, but were otherwise intact. They were neither normal nor were they impaired enough to warrant the diagnosis of dementia. These subjects were categorized with a separate designator and, when followed longitudinally, appeared to progress to dementia at an accelerated rate over the general population (Petersen *et al.*, 1999). The criteria for the characterization of these subjects included the following: 1) memory complaint preferably corroborated by an informant, 2) memory impairment for age, 3) largely intact general cognitive function, 4) essentially preserved activities of daily living and 5) not demented (Petersen *et al.*, 1999). These initial criteria, while seemingly reasonable, have engendered a great deal of debate. Other groups, in particular, investigators from New York University (NYU) had used the term "mild

cognitive impairment," for many years but they were referring to a specific stage on a rating scale, the Global Deterioration Scale (Flicker *et al.*, 1991). Our criteria were perhaps more specific and explicit than the NYU usage. In addition, our initial criteria emphasized a memory impairment because our work and that of others had strongly suggested that a memory impairment for age was likely the harbinger of what would become clinically probable Alzheimer's disease (AD) (Petersen *et al.*, 1994; Welsh *et al.*, 1991).

In fact, when our subjects were followed longitudinally, they developed AD at a rate of approximately 12% per year, in contrast to the age-matched subjects in our population who were normal, who developed AD at a rate of 1–2% per year (Petersen *et al.*, 2001a). We therefore claimed that MCI, defined in this fashion, was a clinical transitional state between the cognitive changes of aging and the very earliest clinical features of AD.

Historical perspective

This characterization of a degree of cognitive impairment at the extremes of normal was not novel. Several other constructs had been proposed over the years, including benign senescent forgetfulness, late-life forgetfulness, age-associated memory impairment and age-associated cognitive decline (Kral, 1962; Crook *et al.*, 1986; Larue, 1992; Levy, 1994). Most of these entities had been proposed to characterize the extremes of the cognitive changes of normal aging. As such, while some subjects with these entities were likely to progress to dementia and AD, many would not. However, MCI has always been characterized as an abnormal clinical state, prodromal to a form of dementia. As such, this has made it important for public health perspectives and possibly as a potential treatment target.

We pursued the concept of MCI because it offered insights into the earliest stages of dementing illness. Although it became an issue later, pharmacotherapy was never the motivating factor for the development of clinical interest in MCI nor has it been the major stimulus for research (Petersen, 2003a).

Evolving criteria

While the original MCI criteria outlined above pertained largely to a memory deficit, more recently the scope of MCI has been broadened (Petersen, 2003b). It soon became clear that not all forms of MCI progress to AD, and therefore, other presentations of cognitive impairment needed to be considered. At an international conference on MCI in Stockholm in 2003, the construct of MCI was expanded to include other forms of cognitive impairment as shown in

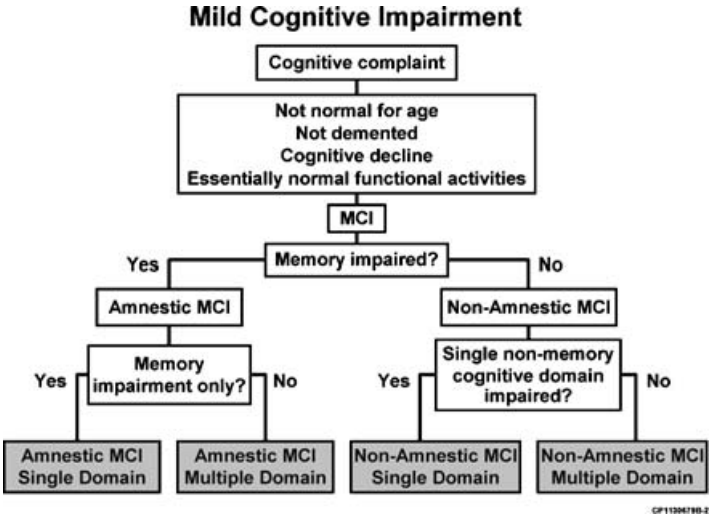

Figure 1. Diagnostic algorithm for determining subtypes of MCI.

Figure 1 (Petersen, 2004a; Winblad *et al.*, 2004). The revised criteria for MCI recognized that a person could have any type of cognitive concern and, if the person's cognitive function was not normal and represented a decline from a previous level, yet the subject did not meet criteria for dementia, then the classification of MCI could be considered. Since a memory component was still acknowledged as of major importance in predicting progression to AD, MCI was divided into two subtypes, amnestic (with memory impairment) and non-amnestic (without memory impairment) (Petersen, 2004a). These two subtypes were further divided into single and multiple domain types depending upon whether other cognitive domains were involved with the subclassification. When these clinical syndromes were combined with putative etiological explanations for their development, predictions regarding the outcomes of these syndromes could be made as is shown in Figure 2. The data corroborating the amnestic subtype are much more plentiful than are those regarding the non-amnestic subtype which is becoming an important area of investigation (Ganguli *et al.*, 2004; Bennett *et al.*, 2002; Lopez *et al.*, 2003a).

Outcome

As mentioned above, the amnestic subtype of MCI progressed to AD at an accelerated rate (Petersen *et al.*, 1999). However, there have been several studies in the literature that claimed that the clinical construct might be unstable, in that 25–40% of the cohort with MCI could revert back to normal after initially being diagnosed with MCI (Larrieu *et al.*, 2002; Ritchie *et al.*, 2001; Visser *et al.*,

2002a). If it were true that a high proportion of patients diagnosed with MCI were later felt to be cognitively normal, it would cast doubt on the utility of the construct. We believe that the empirical basis for this concern arises from methodologically flawed studies. There are several factors that contributed to the methodological problems in published studies of MCI.

Prospective versus retrospective studies

Many of the studies that have shown variable stability of the diagnosis of MCI have arisen from the retrofitting of criteria to previously acquired datasets. For example, Ritchie and colleagues applied neuropsychological criteria in the form of *ad hoc* cut scores for MCI on a previously collected dataset and, in so doing, created an arbitrary set of subjects who were labeled as having MCI using only psychometric criteria (Ritchie *et al.*, 2001). The memory measure used in this study is clearly imprecise. Because the subjects were classified solely on the basis of a brief cognitive assessment, without any clinical assessments, it is not surprising that the diagnostic categorization of subjects proved to be unstable over time.

Similarly, Larrieu and colleagues applied a set of criteria to an existing cohort and used a single measure on one psychometric test as the basis for making the diagnosis of MCI (Larrieu *et al.*, 2002). They subsequently found that 40% of the cohort who had previously been designated as having MCI reverted to normal on the next visit. They implied that the construct of MCI was therefore unstable. We would contend that this does not indict the construct of MCI; rather, it demonstrates the well-known phenomenon that performance on a single psychometric test can vary from one administration to another and consequently, these data demonstrate psychometric fluctuation rather than instability of MCI *as a construct*. In fact, much of the variability in the literature is due either to the retrofitting of criteria to previously acquired data and/or to the lack of consideration of other factors involved, such as the putative etiology of a clinical syndrome.

Etiology

Another factor leading to confusion in the literature stems from the lack of consideration of the presumed etiology of a clinical syndrome. For example, if one were to take only the clinical phenotype of a memory disorder and follow subjects longitudinally, one would expect variable outcomes. Memory disorders, as defined purely psychometrically, could arise from psychiatric disorder, as a consequence of co-morbid systemic conditions, cerebrovascular disease or neurodegenerative disease. If one were to follow a group of individuals who had a memory impairment, without regard to its cause, one would expect that some

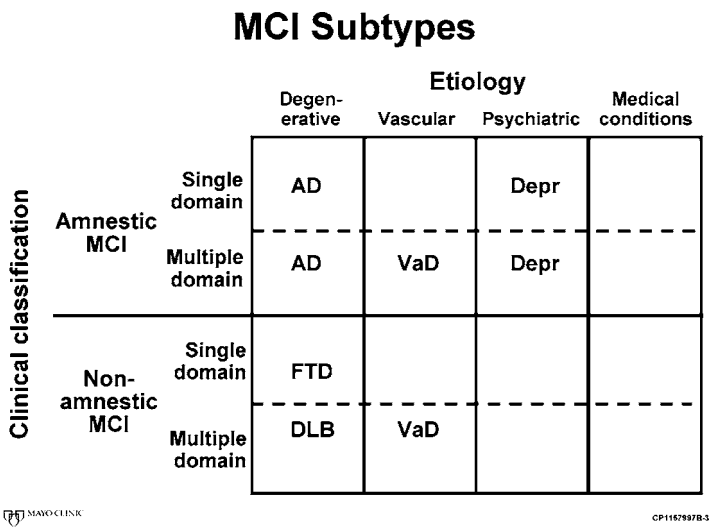

Figure 2. Suspected outcome of MCI subtypes combined with presumed etiology.

of these individuals would get better, some would get worse, and some would remain the same. If all of the individuals were lumped together and followed longitudinally, the outcomes would be expected to be quite variable. Therefore, if one concluded that the clinical phenotype was unstable, they would be correct because that would be the expected outcome.

Many epidemiological studies that are not able to characterize subjects in a complete medical and psychiatric fashion follow this practice and conclude that the construct of MCI is therefore unstable. We would argue that this is an inappropriate approach to the use of the construct. Rather, if investigators would combine a clinical phenotype with a presumed etiology, greater precision would arise in predicting the ultimate outcome, as is demonstrated in Figure 2. For example, if a person with a particular type of memory impairment were to be classified by a more thorough clinical assessment based upon the history from the subject and perhaps an informant, as having a presumed degenerative etiology, the outcome would be much more predictable, likely AD. However, in contrast, if all the etiologies of a particular clinical phenotype were combined, the outcome would be quite variable, as demonstrated in Figure 2. We contend that this degree of sophistication is necessary to accurately assess the stability of the construct of MCI.

Prospective studies

Perhaps the best manner in which to evaluate the clinical utility of the construct of MCI is through longitudinal, prospective clinical studies designed to assess specific MCI criteria. Long-term follow-up over many years is critical. Several

of these prospective studies have begun recently and should yield important information. A population-based prospective study of MCI is under way in Rochester, Minnesota. This study is enroling randomly-selected individuals aged 70–89 years from the community and is categorizing them according to the diagnostic scheme outlined in Figures 1 and 2. Subjects are evaluated by nurses, psychometrists and physicians, and diagnoses are made at a clinical consensus conference involving all individuals who evaluated the subjects. The clinical phenotype and presumed etiology are recorded, and the subjects are re-evaluated every 15 months.

There are several other prospective studies underway, including the Religious Order Study, which has enrolled a cohort of approximately 1,000 nuns and priests (Bennett *et al.*, 2002). The Religious Order study has applied MCI criteria to the subjects who were neither normal nor met criteria for dementia as determined by a combination of psychometric data and clinical assessments. These subjects are then re-evaluated annually and their outcome determined by the clinical consensus. This study has shown that the construct of MCI is a valuable predictor of future dementia because diagnostic criteria have been specified *a priori* and each subsequent evaluation is made independent of previous clinical classification. This type of study yields important data since it is based on both multiple neuropsychological instruments and the judgment of a skilled clinician.

A longitudinal study of aging and cognition is underway in Cache County, Utah, which should also shed light on several of these issues (Zandi *et al.*, 2004). This study is following a cohort of individuals in this population of particularly long-lived individuals. The researchers have developed criteria comparable to MCI and will be able to determine outcomes.

The Cardiovascular Health Study has described the prevalence of MCI in that population including characterizing its subtypes (Lopez *et al.*, 2003a; Lopez *et al.*, 2003b). Lopez and colleagues have applied prospective criteria to this cohort.

In summary, the diverse settings in which MCI has been studied have provided conflicting data for the field. This is in part due to two major methodological differences in the studies, not the least of which includes retrospective versus prospective study designs and the method of implementation of the MCI criteria to the clinical cohort. This implementation has ranged from using a single measure on a single test at one extreme, to the clinical judgment of a consensus group of individuals based on a combination of structured interviews and extensive neuropsychological test data. These differences can have a large impact on the outcomes of the studies.

Semantics

Some of the difficulty with the construct of MCI arises from the variable uses of the term. Many clinicians use it to describe the clinical state characterizing a

transition between cognitive changes of normal aging and dementia. However, others have blurred the issue by referring to the underlying pathophysiologic substrate of MCI (Morris, 2006). That is, by stating that "MCI is AD," they mean to imply that persons with MCI have some of the neuropathological features of AD, while their clinical classification is MCI. However by the definition of dementia, the subjects do not meet criteria for clinically probable AD and therefore confusion arises as to whether this is in fact *clinical* AD or *neuropathological* AD. Therefore, one must be certain as to whether or not the discussion is focusing on clinical features or neuropathological substrates when talking about what MCI is or is not.

Clinical utility

The ultimate question revolves around the utility of MCI as a clinical entity. We believe there is a role for MCI in the armamentarium of the clinician. Most clinicians believe that degenerative processes such as AD must have a transitional state in which some of the symptoms are present but the fully developed clinical syndrome is not present. The most recent amnestic MCI criteria (Petersen, 2004a; Winblad *et al.*, 2004) were developed by an international group of experts. The interest shown by the international community in refining the criteria for MCI speaks to the perceived value of the concept.

Recent clinical trials have been able to implement MCI criteria reliably across multiple clinical sites, as was evident by the Alzheimer's Disease Cooperative Study trial on donepezil and vitamin E for the treatment of MCI (Petersen *et al.*, 2005). The criteria applied in this fashion were also quite specific with 212 of the 214 MCI subjects who progressed to dementia ultimately achieving the diagnosis of possible or probable AD.

Following an evidence-based medicine survey of the literature, the American Academy of Neurology endorsed the construct of MCI as an important clinical entity that clinicians should recognize and follow, since these patients are at an increased risk of progressing to dementia (Petersen *et al.*, 2001a). This practice parameter was reviewed by numerous clinical practice groups in multiple disciplines before it was approved and provides strong evidence for its utility as a clinical entity.

Is MCI different from other clinical entities?

We contend that MCI has more empirical support as a clinical entity than most constructs in the DSM IV (American Psychiatric Association, 1994). A great deal of literature has been generated on MCI, and if one restricts oneself to those studies of a prospective nature, the support for a distinctive, definable clinical

syndrome is evident. There are outcome studies, and some neuropathological data are beginning to emerge (Bennett *et al.*, 2005; Jicha *et al.*, 2006; Petersen *et al.*, 2006; Markesbery *et al.*, 2006).

Kendell's criteria

Some individuals have contended that the construct of MCI does not meet Kendell's criteria (Kendell, 1989). While these criteria are not universally accepted as a construct for clinical practice or research, the interpretation of whether or not MCI fulfils these criteria is debatable. Kendell's criteria are as follows: 1) clarity about identification and description: (criteria for amnestic MCI have been adopted by the National Institute on Aging Alzheimer's Disease Centers program Uniform Data Set and the Alzheimer's Disease Neuroimaging Initiative and an international conference) 2) demonstration of a boundary or point of rarity between related syndromes (MCI can be distinguished from normal aging by means of clinical interview and neuropsychological testing, and from AD by the presence or absence of loss of independence in daily functioning) 3) a distinct course (amnestic MCI progresses to AD at a predictable rate of approximately 10% to 15% per annum in many studies) 4) a distinct treatment response (while no effective treatments have been demonstrated for MCI, this state of affairs is not drastically different from AD, other dementing illnesses, or other psychiatric conditions in the DSM IV) 5) a clear association with fundamental abnormality (the neuropathological substrate of amnestic MCI has been demonstrated in numerous studies to have many features of incipient AD, again in contradistinction to many constructs in the DSM IV) 6) the syndrome has a genetic pattern (amnestic MCI has a similar genetic profile to AD especially with respect to Apolipoprotein E $\in$ 4 carrier status). Consequently, one can make a strong argument that in fact many of Kendell's criteria are met adequately by a construct of MCI. MCI actually conforms to Kendell's criteria far better than many of the accepted clinical entities included in DSM IV.

Conclusion

MCI has become a very popular topic from both the clinical and research perspectives. The literature on MCI has increased geometrically in recent years, a phenomenon that can only be attributed to its perceived utility and explanatory power (Petersen, 2005). Clinicians have found it useful in clinical practice to describe a group of patients who are in a transitional zone between the cognitive changes of normal aging and early AD (or other dementias). Clearly, refinement needs to be done in the broader construct of MCI outside of amnestic MCI. The non-amnestic varieties need to be characterized and followed longitudinally if they are to be clinically useful as prodromal forms of other dementing illnesses.

Nevertheless, since many of these entities have a degenerative substrate, it is quite reasonable that they will likely have a prodromal state which can be characterized with careful longitudinal studies.

The diagnosis of MCI is not to be taken lightly. This diagnosis is not to be placed on anyone who is aging and becomes somewhat forgetful. This is a pathological condition and has certain prognostic features for outcome. Effective treatments have not been demonstrated as yet, but this likely reflects the state of the treatment of dementing illnesses rather than being unique for MCI. If a person in fact meets criteria for MCI, they should be counseled with regard to the potential meaning of this rather than placing a stigma on them. They realize that their clinical symptoms are not normal and consequently characterizing the symptoms for these individuals is useful. This is a clinical diagnosis and should not be relegated to a score on a particular psychometric instrument, battery of instruments, or to a rating scale. In much the same fashion as all other diagnoses in DSM-IV are generated, MCI can be used in a similar fashion. Ultimately, the passage of time will determine whether this construct becomes increasingly useful for clinical practice or gives way to other entities. We believe that this is an important step toward understanding the earliest presentation of many dementing illnesses.

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MCI is not a clinically useful concept

Introduction

Within the spectrum of cognitive disorders Mild Cognitive Impairment (MCI) is a relatively new concept which has become increasingly popular both in clinical practice and in clinical research. Still, the concept of MCI has several shortcomings which limit its utility in clinical practice and research.

What is MCI?

In order to understand the clinical utility of the MCI concept we first need to define what is meant by MCI.

The MCI concept

MCI as a concept refers to cognitive impairment which is in between normal cognitive functioning and dementia.

MCI definitions

The MCI concept has been operationalized in many different ways. We will give a short overview of a number of these definitions in an historical perspective. Probably the amnestic syndrome was one of the first definitions within the MCI concept (Kral and Durost, 1953). It is used for isolated memory performance resulting from somatic or neurological disorders and has become part of the DSM and ICD classification systems (American Psychiatric Association, 1994; World Health Organization, 1992). Between 1976 and 1986, a number of definitions were published to identify subjects whose symptoms were suggestive of dementia but who did not yet meet the criteria for it. Examples are subclinical case organic disorder, a score of 0.5 on the Clinical Dementia Rating scale (CDR), a score of 3 on the Global Deterioration Scale (GDS), and minimal dementia (Berg *et al.*, 1982; Copeland *et al.*, 1976; Reisberg *et al.*, 1982; Roth *et al.*, 1986). These definitions were based on a clinical interview and were part of a global classification system for cognitive impairment ranging from normal cognition to severe dementia. Several terms have been used for these definitions including questionable dementia, mild functional impairment, and MCI (Flicker *et al.*, 1991; Jonker and Hooyer, 1990; Rubin *et al.*, 1989). In 1986 and in 1994, two definitions were proposed for cognitive impairments due to normal aging. These definitions required cognitive complaints and impairment on a memory test (Age-Associated Memory Impairment (Crook *et al.*, 1986)) or on any cognitive test (Aging-Associated Cognitive Decline (AACD) (Levy, 1994)), in the absence of a somatic, neurological, or psychiatric disorder which could explain the impairment. In 1992 and 1994, the ICD and DSM classification systems introduced criteria for cognitive disorder not otherwise specified and mild cognitive disorder which were similar to the AACD criteria, except that the cognitive impairments had to be caused by a specific disorder (American Psychiatric Association, 1994; World Health Organization, 1992). From 1995 onwards, a large variety of MCI definitions has been introduced, including Cognitive Impairment No Dementia, defined as either mild functional impairment or test impairment (Ebly *et al.*, 1995), the Mayo Clinic MCI criteria defined as cognitive complaints and test impairment in the absence of functional impairments (Petersen *et al.*, 1995), MCI defined as just test impairment (Bennett *et al.*, 2002), and MCI defined as cognitive complaints (Visser *et al.*, 2001).

Criteria of MCI definitions

A problem with most MCI definitions listed above is that the criteria used for these definitions are not sufficiently detailed. This may lead to variability in application of the criteria with different samples of MCI subjects as the result. As an example of the problem of application of criteria, we will discuss the criteria of the Mayo Clinic definition (Petersen *et al.*, 1995), which is the most popular definition of MCI.

The Mayo Clinic definition of MCI consists of five criteria. The first criterion requires a cognitive complaint. This has in some studies been defined as complaint by the person *preferably* corroborated by an informant; in other studies it is complaint by the person *or* an informant. The second criterion of MCI requires normal cognition for age or preserved general cognition. It is usual to base this on a Mini-mental State Examination (MMSE) score above a certain threshold, e.g. greater than 24. This does not make allowance for the effects of intelligence, education, language and culture. Also, persons of low intelligence may be more susceptible to MMSE decline than persons with a higher IQ. The third criterion requires objective memory impairment on cognitive tests for age and education, but it is not stated which tests should be used or which cut-off. As a result, test impairment has been defined as impairment according to the clinician's judgement, or using a psychometric cut-off varying in severity from a cut-off between the 55th to 1st percentile relative to healthy controls (Visser *et al.*, 2005). By definition, approximately 7% of the population will be 1.5 standard deviations below the average for the population on any test. If more tests are administered, there is more chance of impairment. In addition, impairment of memory is non-specific. For example impairment of attention, central executive function or comprehension can all manifest as poor memory. The Mayo Clinic group prefer to define test impairment based on clinician judgement, but this is difficult to operationalize, although the counter-argument is that reliance on clinical judgement allows for flexibility and can make allowances for high IQ or low education, and in any case such a system works well for dementia diagnoses (Petersen, 2004b). The fourth criterion that the person needs to be generally functioning normally also lacks precision in the definition. Clearly people with MCI should be able to dress and wash themselves and probably be able to manage housework, catch public transport and pay their bills. But what about subtle impairment, e.g. the ability to weigh up competing investments portfolios and make decisions about finance (Griffith *et al.*, 2003) and how is allowance made for impaired activities of daily living or instrumental activities of daily living for non-cognitive reasons? The fifth criterion states that the subject is not demented but there is a lack of clarity between the boundary of MCI and dementia. Especially, the distinction between amnestic

multiple-domain MCI and early Alzheimer-type dementia is very subtle and ill-demarcated.

Summary

Many definitions have been used to operationalize the MCI concept. These definitions differ from each other in the terms used, assumptions regarding the underlying cause of the cognitive impairment, ways of assessing impairment, and the cognitive domains involved, although there is also overlap between definitions. The criteria of specific MCI definitions are often not well defined. Thus, MCI is an umbrella concept for definitions of cognitive impairment without dementia rather than a well-defined concept with clear criteria. In the remaining part, we will use the term MCI to refer to MCI as a concept and not to a specific MCI definition.

Utility of the MCI concept in clinical practice

We can think of two potential uses of the MCI concept in clinical practice which are not mutually exclusive:

1. MCI as a syndrome: MCI is taken as a description of cognitive dysfunction in non-demented subjects which generally does not improve, and for which the underlying cause should be determined.
2. MCI as a neurodegenerative disorder: MCI is considered as a pre-dementia stage of a neurodegenerative disorder which will progress to dementia at follow-up.

MCI as a syndrome

A syndromal description of cognitive impairment would be useful to help to identify a group of subjects in which the cognitive impairment is due to a specific disorder and in which the cognitive impairment is not likely to improve without any intervention. Such a syndrome would necessitate further diagnostic assessments in order to find the cause, and if the cause remains unclear, it should be an indication to monitor a patient longitudinally. It might also be useful to select subjects who may benefit from "cognition enhancing" drugs. Essentially, criteria for such a syndrome would help to distinguish between "benign" and "malign" forgetfulness. It is useful to take the dementia syndrome as an example. Dementia is a relatively stable condition, as 89% to 99% of the subjects with dementia will remain demented at follow-up (Cunha, 1990; Herlitz *et al.*, 1997; Larson *et al.*, 1986; Reding *et al.*, 1984; Schofield *et al.*, 1995). This is true both in a clinical and population-based settings. Careful examination will identify a specific cause in the majority of these subjects.

No definition of MCI performs similarly in non-demented subjects. First, longitudinal MCI studies have shown that up to 40% of the subjects with MCI will improve at follow-up, particularly in a population-based setting and in younger subjects (Ganguli *et al.*, 2004; Larrieu *et al.*, 2002; Palmer *et al.*, 2002; Ritchie *et al.*, 2001; Visser *et al.*, 2002b; Visser *et al.*, 2000). Second, MCI seems not to be a useful target for cognition-enhancing drugs. In the 1980s and 1990s several drugs have been tested in subjects with AAMI but without success. Recently, a variety of drugs have been tested in subjects with MCI but none of them showed efficacy on the primary end-point (Petersen *et al.*, 2005; Thal *et al.*, 2005). In summary, MCI is not able to characterize subjects who share a prognosis or who may benefit from treatment. Therefore, MCI should not be considered as a syndrome.

MCI as a neurodegenerative disorder

Many studies have shown that the presence of MCI increases the risk for dementia, especially Alzheimer-type dementia (AD). Moreover, the conviction that MCI may represent early AD has spawned trials of drugs that were effective in subjects with AD (Petersen, 2003a). Nevertheless, the notion that MCI represents early AD seems not to be supported by longitudinal, neuropathological, and bio-marker studies:

Longitudinal studies

We have already mentioned that up to 40% of the subjects with MCI reverted to normal at follow-up. This is not consistent with the view that MCI is a neurodegenerative disorder. The conversion rate from MCI to dementia varied considerably in long-term follow-up studies. One study reported a high conversion rate to dementia of 83% after seven years (Petersen *et al.*, 2001a), while other studies found a substantially lower conversion rate: 28% after 10 years (Ganguli *et al.*, 2004), approximately 45% after 10 years (Grober *et al.*, 2000), approximately 40% after seven years (Bennett *et al.*, 2002), and between 25% to 45% after eight years (Morris *et al.*, 2001). This discrepancy in conversion rates can be explained by differences in setting (the conversion rate is higher in clinical studies than in population-based studies (Bruscoli and Lovestone, 2004)), age (older subjects have a higher conversion rate than younger subjects (Visser *et al.*, 2005)), and MCI definition (MCI definitions including memory impairment have an higher conversion rate than MCI definitions without memory impairment (Aggarwal *et al.*, 2005; Rasquin *et al.*, 2005)).

Neuropathological studies

These studies have the advantage of quantifying the key neuropathological lesions, but the disadvantage is that they are necessarily biased towards older subjects and subjects with a neurodegenerative disorder, as these subjects are

more likely to die. One study showed that 96% of subjects with MCI had evidence of a dementing neurodegenerative disorder at neuropathological examination (Morris *et al.*, 2001). However, the subjects included in the neuropathological study were on average 88 years old and 79% of them were clinically demented at time of autopsy. Another study showed that 62% of subjects with MCI (average 85 age years) had probable or possible AD according to the CERAD criteria and that AD neuropathology in subjects with MCI was in between that of healthy control subjects and demented subjects (Bennett *et al.*, 2005). It remains unknown whether these findings also apply to younger subjects with MCI.

Biomarker studies

Many studies have investigated biomarkers of AD in subjects with MCI. Generally, subjects with MCI show biomarker profiles that are intermediate between those of healthy control subjects and subjects with AD. This applies for example to hippocampal atrophy, hippocampal hypometabolism on PET imaging, the frequency of the apolipoprotein E-$\in$4 allele, EEG patterns, and tau protein level in cerebrospinal fluid (Convit *et al.*, 1997; Hampel *et al.*, 2004; Jack *et al.*, 1999; Jelic *et al.*, 2000; Mosconi *et al.*, 2005).

In summary, the longitudinal, neuropathological, and biomarker studies suggest that a diagnosis of MCI is associated with an increased risk for a neurodegenerative disorder but that it should not be equated with it.

Utility of the MCI concept for research

Subjects with MCI might be a useful group to test the diagnostic value of new markers of AD as they have an increased risk for AD. However, one may question whether one needs an MCI concept for this purpose as one may simply select subjects with impairment on a memory tests. MCI is unlikely to be a target for drug studies given its heterogeneity in underlying cause. The fact that recent MCI trials did not show an effect on the major end-points may in part have resulted from this heterogeneity (Visser *et al.*, 2005).

Validity of the syndrome according to Kendell's criteria

Above we have discussed the MCI concept from a utilitarian perspective – whether the concept would be useful for clinical practice or research. There is also a more formal way to evaluate the clinical validity of a cognitive syndrome (Kendell, 1989). The criteria of Kendell for a valid syndrome are: 1) Clarity about identification and description; 2) Demonstration of a boundary or point of rarity between related syndromes; 3) A distinct course; 4) A distinct treatment response; 5) A clear association with fundamental abnormality; 6) The syndrome has a genetic pattern. From the preceding sections, it follows that the MCI

concept does not fit any of the first five criteria. As regards the sixth criterion, although subjects with MCI have an increased frequency of the apolipoprotein E∈4 allele (Petersen *et al.*, 1995), this does not apply to all subjects and therefore this criterion is also not met.

Conclusions

MCI refers to a variety of definitions for non-demented subjects with cognitive impairments. As no single MCI definition defines a clinically useful syndrome or a neurodegenerative disorder, the MCI concept has a limited clinical utility. Moreover, it may rather impede clinical practice and research than help it, due to the huge variability in criteria and terminology and because the underlying cause is heterogeneous. Or as stated by Schneider: "The MCI story is characterized by heterogeneity, uncertainty, ambiguity and poor conceptualization. Cognitive impairment with aging needs continued study and not premature categorization that might unintentionally impede research and understanding" (Schneider, 2005). There are also potential negative psychological effects of an MCI diagnosis – stigma, shame, low self-esteem, depression and anxiety, as well as negative social effects – being treated differently by family and friends, and negative implications as regards insurance, work and driving. Although the MCI concept might be useful to characterize the cognitive impairments of non-demented subjects or to identify subjects at high risk for dementia one can also do so without an MCI concept simply by rating the functional impairment with scales like the CDR or GDS, and testing cognition using cognitive tests. For example, instead of labeling a subject as multiple-domain MCI, it is more informative to say that the subject scores 3 on the GDS and has test impairment in the memory domain and executive function. Such an approach is less ambiguous compared to a definition of MCI and lacks an implicit reference to a disorder or syndrome. Instead of trying to "optimize" MCI criteria, it may be better to develop criteria for specific diseases that may present with MCI, such as pre-dementia AD. In the case of pre-dementia AD, these criteria will have to go beyond measures of cognition, as it is unlikely that pre-dementia AD can be accurately defined on the basis of cognitive measures alone (Visser *et al.*, 2002b).

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Commentary

The current debate about Mild Cognitive Impairment (MCI) is useful in bringing forward for first-line clinicians, as well as clinical researchers, the importance of paying attention to cognitive complaints in aging individuals. Clearly (and thankfully) not all will progress to dementia. Furthermore, many can be helped by primary care practitioners through a basic clinical assessment and treatment of one of the many conditions potentially associated with mild cognitive complaints, such as depression, hypothyroidism, side-effects of anticholinergic drugs, alcohol abuse, nutritional deficiency, sleep apnea. Many times the cognitive complaints will be reversible. In some cases the symptoms will persist or increase over time, and a yearly follow-up and/or a referral to a specialized setting are appropriate, since there is a higher risk of progression to dementia in such individuals, particularly towards Alzheimer's disease (AD).

There is no disagreement between the two sides of this debate on these basic clinical facts. The argument appears more on the use of the label "MCI", with its current connotation in certain parts of the world that it is equivalent to a pre-dementia stage of Alzheimer's disease (AD). The compromise may be to use MCI as a syndrome in clinical practice (mild cognitive complaints without functional impact on daily life), and as an interim diagnosis in a clinical research setting, with qualification based on neuropsychological profile (single/multiple domains, amnestic/non-amnestic) and apparent etiology (pre-dementia, vascular, psychiatric, other medical conditions). It is quite likely that the current diagnostic criteria for AD will be modified to include a pre-dementia stage, where MCI and/or neuropsychiatric symptoms are present without significant functional impairment.

In the current absence of disease-modifying drugs for, are we helping these individuals? Clearly yes, since vascular risk factors can be treated more aggressively, lifestyle changes such as diet, physical and leisure activities can be made, financial matters can be updated and advance directives discussed with family members. Cognitive training is becoming a non-pharmacological option for symptomatic treatment.

The authors of this debate should be congratulated for their dedication in helping a great number of aging individuals while shedding new light on risk factors towards dementia.

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Conflict of interest declarations

David Ames has received financial support to undertake research on the treatment of MCI with a novel drug manufactured by Servier.

Ronald Petersen has served as a consultant for Elan Pharmaceuticals and GE Global Research. He gives talks at universities and medical centers as well as through national organizations through unrestricted educational grants to the institutions from Pfizer, Eisai, Novartis and Johnson and Johnson.

Dr. Knopman has served as an *ad hoc* consultant to GE Healthcare, Myriad Pharmaceuticals and Neurochem Pharmaceuticals in the past two years; and participated in a clinical trial sponsored by Elan Pharmaceuticals.

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