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Mild cognitive impairment: historical development and summary of research

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This review article broadly traces the historical development, diagnostic criteria, clinical and neuropathological characteristics, and treatment strategies related to mild cognitive impairment (MCI). The concept of MCI is considered in the context of other terms that have been developed to characterize the elderly with varying degrees of cognitive impairment. Criteria based on clinical global scale ratings, cognitive test performance, and performance on other domains of functioning are discussed. Approaches employing clinical, neuropsychological, neuroimaging, biological, and molecular genetic methodology used in the validation of MCI are considered, including results from cross-sectional, longitudinal, and postmortem investigations. Results of recent drug treatment studies of MCI and related methodological issues are also addressed.

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The conceptual development of MCI

Families, caregivers, and physicians of persons with Alzheimer's disease (AD) generally find it difficult to pinpoint, even in retrospect, the precise onset of a patient's cognitive impairment. The development of dementia due to a degenerative neurological illness typically proceeds insidiously over several years from a state of cognitive normalcy to progressively severe stages of global intellectual dysfunction. While consensus criteria for diagnosing dementia and AD have been published and widely adopted (*Diagnostic and Statistical Manual of Mental Disorders [DSM]*,[1] National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA][2]), guidelines for distinguishing between normal age-related cognitive decline (ARCD) and the transitional levels of intellectual performance that precede the onset of dementia have been slow to emerge. In fact, clinical investigators have grappled with the problem of defining the boundaries of normal cognitive aging for over 40 years. In 1962, Kral[3] coined the term "benign senescent forgetfulness" (BSF) to describe a population of nursing-

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Selected abbreviations and acronyms

AAMI	*age-associated memory impairment*
AD	*Alzheimer's disease*
ARCD	*age-related cognitive decline*
CDR	*Clinical Dementia Rating*
CIND	*cognitive impairment–no dementia*
DAT	*dementia of the Alzheimer's type*
fMRI	*functional magnetic resonance imaging*
GDS	*Global Deterioration Scale*
MCI	*mild cognitive impairment*
MRS	*magnetic resonance spectroscopy*
PET	*positron emission tomography*
SPECT	*single photon emission computed tomography*

home residents with mild memory deficits that were anticipated to remain stable over time. Subsequently, this concept has undergone many refinements resulting in a proliferation of proposed entities including age-associated memory impairment (AAMI),[4] age-consistent memory impairment (ACMI),[5] late-life forgetfulness (LLF),[5] and ARCD.[1] These constructs were intended to identify subjects whose cognitive performance had deteriorated below values established for young adults, but were not expected to undergo significant further decline and were not believed to harbor neuropathological changes. Nevertheless, a paucity of carefully collected follow-up data makes it impossible to validate this hypothesis and it remains unclear whether meeting diagnostic criteria for any of these syndromes really implies cognitive stability. In contrast to these proposed definitions of "normal" brain aging, Levy's "aging-associated cognitive decline" (AACD)[6] included subjects who performed below normative levels for their own age-group making a pathological basis more likely.

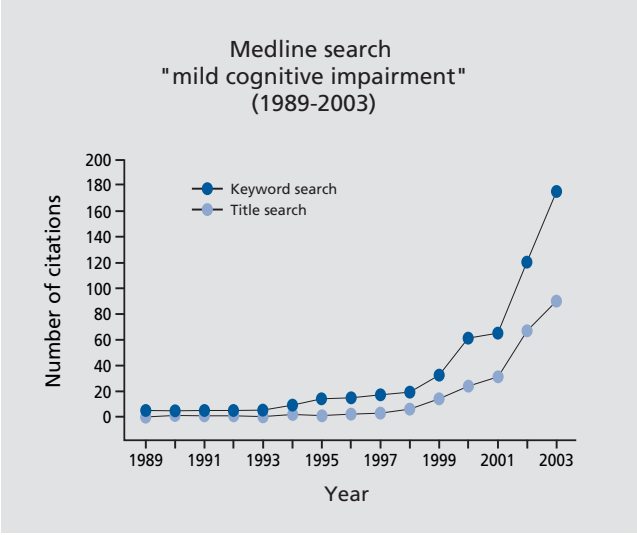

Figure 1. Results of Medline searches for the number of citations detected for the term "mild cognitive impairment" between 1989 and 2003. Separate searches were conducted for the term as a keyword and as a title.

In the 1980s, global clinical staging scales for the study of AD were developed to more rigorously classify the broad spectrum of intellectual performance found in geriatric populations. Two of the most commonly used scales, the Global Deterioration Scale (GDS)[7] and the Clinical Dementia Rating (CDR),[8] both recognized the need to categorize subjects without dementia who nevertheless exhibited some evidence for cognitive dysfunction. Subjects classified as GDS stage 3 or CDR stage 0.5 were considered cases of "questionable," "borderline," or "preclinical" AD, whose cognitive status was intermediary between normal/AAMI/ARCD levels and mild dementia. Other global dementia scales have defined similar transitional stages, for example, "minimal dementia" from the Cambridge Mental Disorders of the Elderly Examination (CAMDEX)[9] and "limited cognitive disturbance" from the Comprehensive Assessment and Referral Evaluation (CARE).[10] Other constructs, such as isolated memory loss,[11] mild cognitive disorder,[12] mild neurocognitive disorder,[1] and cognitive impairment–no dementia (CIND),[13-15] were intended to capture similar levels of overall intellectual performance.

It was in this historical context that the expression "mild cognitive impairment" gradually entered the lexicon of the aging and dementia literature. In 1988, Reisberg et al[16] used it as a descriptive term coinciding with the GDS stage 3. Three years later, the term appeared in the title of an article by Flicker et al describing GDS stage 3 subjects at risk for dementia.[17] In 1995, Petersen et al[18] used mild cognitive impairment (abbreviated as MCI) as an independent diagnostic category not linked to a previously defined rating scale. In this case, the diagnosis was applied to nondemented research subjects who retained normal global cognitive function without impairment on tasks of daily living, but had subjective memory complaints and scored below age-adjusted norms on memory tests. Subsequent years have witnessed further elaboration, refinement, and redefinition of the concept with interest growing markedly[19] as exemplified by the exponential increase in published articles utilizing the term *(Figure 1)*.

To a large extent, this explosion of interest reflects a shift of emphasis in dementia research away from established disease and toward early diagnosis with the recognition that effective therapy may be impossible once advanced neurodegenerative pathology and tissue loss ensues. Clearly, there are several conceptual advantages to the establishment of MCI as a diagnostic category for patients at risk for dementia. From the standpoint of clinical trials, access to samples of nondemented patients likely to undergo accelerated cognitive decline would greatly facilitate the testing of drugs aimed at arresting disease progression. Likewise, longitudinal studies designed to validate early biological or neuroimaging markers of AD pathology also require access to at-risk populations. Finally, the increase in public awareness of AD is driving more patients with mild memory complaints to physicians, who therefore need better diagnostic tools for estimating prognosis. This need will become increasingly acute as the population ages and as new treatments become available.

Criteria for diagnosis of MCI

While the notion of MCI as a transitional stage between cognitive normalcy and dementia is easy enough to grasp, it is presently unclear whether an operational definition can be made sufficiently precise to define a unique and useful diagnostic entity. Part of the difficulty lies in the concept itself. Should MCI be construed as a syndrome with multiple etiological explanations or should the concept be constrained to denote only patients with prodromal AD?[20,21] Advocates of the former interpretation have proposed a multitude of MCI subtypes corresponding to the likely underlying neuropathological or psychiatric diagnosis. For example, some proponents of this view suggest vascular[22] and frontotemporal[23] subtypes of MCI. Such a strategy, however, may open the door to an unwieldy proliferation of subtypes that could weaken the concept by excessively widening its scope (eg, hypothyroid MCI, brain tumor MCI, etc). It is therefore unclear whether MCI should be considered the early stage of a specific disease, a syndrome, or a syndrome constrained by the exclusion of certain other diagnoses *(Figure 2)*.[24] The recognition that alternative neuropsychological presentations such as aphasia, ideomotor dyspraxia, or prominent behavioral and affective abnormalities may be relevant with respect to other neurodegenerative dementias has prompted additional MCI subtypes based on the principal form of cognitive deficit present. For example, Petersen[22] has proposed a "multiple-domain MCI" for patients exhibiting dysfunction across a range of neuropsychologic modalities, "single nonmemory cognitive domain MCI" for patients whose cognitive symptoms reflect circumscribed impairment in a nonmemory domain, and "amnestic MCI" where memory loss is the predominate reason for impairment. Amnestic MCI has been proposed as the subtype most likely to portend a diagnosis of AD. Because memory symptoms are salient in most patients with early AD, this suggestion has certain face validity. Nevertheless, neuropsychological studies reveal that patients diagnosed with MCI have deficits in several cognitive domains[25-29] casting suspicion on whether pure amnestic MCI, strictly speaking, actually exists. A recent European Alzheimer's Disease Consortium/ Alzheimer's Disease Cooperative Study (EADC/ADCS) consensus statement[30,31] has expanded the initial concept of amnestic MCI to allow for the presence of other nonmemory deficits *(Figure 3)*. In addition to eliminating cases that meet criteria for dementia, it has been suggested that MCI ought not include patients with impairments in activities of daily living (ADL).[22] The stipulation that ADL impairment should be exclusionary, however, ignores the commonly observed subtle difficulties with complex tasks requiring organization and planning that MCI patients frequently experience.[31] Thus, the EADC/ADCS revised criteria allow for mild decline in complex ADL.[30,31] Requiring

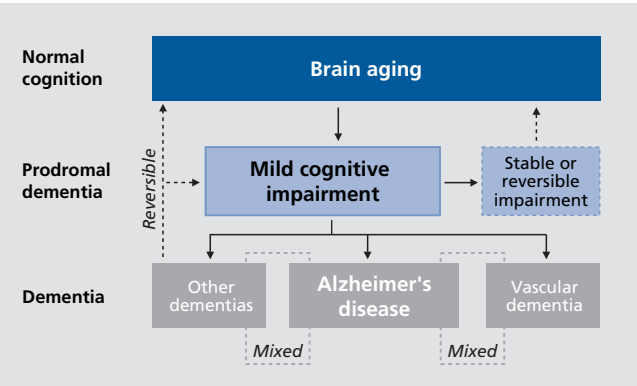

Figure 2. A conceptual model of mild cognitive impairment (MCI) as prodromal dementia. A minority of persons diagnosed with MCI may remain stable or even improve over time. Although individuals with MCI may decline to vascular or other forms of dementia, the majority of declining MCI patients evaluated in research clinics receive a diagnosis of AD (either in pure form or mixed with other dementia subtypes).
Adapted from reference 24: Golomb J, Kluger A, Garrard P, Ferris S. *Clinician's Manual on Mild Cognitive Impairment*. London, UK: Science Press; 2001. Copyright © 2001, Science Press.

the presence of subjective memory complaints may also be too restrictive. Many patients with borderline dementia deny symptoms of memory loss and impaired awareness of cognitive deficits has been recently described in MCI.[32] In practice, reports of impairment from family members or other informants often substitute for subjective complaints by the patient.

Regardless of how these conceptual and taxonomic problems are resolved, the successful implementation of MCI as a diagnostic category would seem to depend on the development of a precise set of definitional rules. Nevertheless, despite nearly 10 years of clinical research, a single universally recognized standard has yet to emerge. In general, the difficulty in formulating an operational definition for MCI reflects tension between precisely enumerated rules using cut-scores on staging instruments or psychometric tests and broader criteria that are more conceptual in nature. The former strategy results in a diagnosis that can be established more reliably, but may be too narrow in scope and too complex for routine clinical purposes. The latter strategy, however, may allow too much flexibility of interpretation and result in criteria that are harder to implement consistently. Inevitably, a compromise solution will need to be reached, but some investigators may argue that existing constructs based on semi-structured clinical interviews such as GDS stage 3 or CDR stage 0.5 should form the main basis for diagnosis. Despite the lack of universally accepted diagnostic criteria, an increasing number of groups have been reporting research on MCI populations defined using the classification schemes described above or variations of these methods. The diagnosis is typically made when the clinical context, imaging data, and laboratory results exclude structural, toxic/metabolic, ischemic, or primary psychiatric factors in favor of neurodegenerative processes as the most likely causative mechanism. Regardless of the specific criteria employed, clinicians with experience diagnosing dementia are probably more in agreement than not when characterizing such patients as nondemented, but cognitively impaired. It is therefore likely that samples of MCI patients, particularly when defined in dementia research centers, share enough attributes to give the diagnosis overall "face validity."

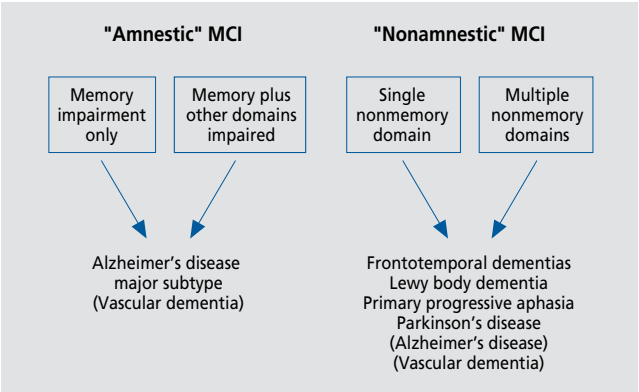

Figure 3. European Alzheimer's Disease Consortium (EADC)/Alzheimer's Disease Cooperative Study (ADCS) consensus on mild cognitive impairment (MCI) subtypes.[30] In this scheme, amnestic MCI consists of cases either with memory impairment alone, or accompanied with deficits in other cognitive areas. Similarly, nonamnestic MCI includes individuals with a deficit in a single nonmemory domain and cases with impairment in multiple nonmemory domains.

Prevalence of MCI

For a comprehensive treatment of epidemiological characteristics of MCI see the article by Ritchie in this issue.[33] The prevalence of MCI in older adults has been difficult to determine. This is due, in part, to the lack of consensus on diagnostic criteria for MCI that can be applied in epidemiological studies, the discrepancies in the age ranges examined, and the demographic characteristics of the samples employed. Due to the protracted time course of MCI and because the population of persons with dementia undergoes an accelerated rate of attrition due to death, the prevalence of persons with MCI at risk for AD is expected to outnumber cases actually diagnosed with AD. A review of population-based investigations of MCI prevalence has observed widely varying rates across studies.[34] An estimate of the prevalence rate of MCI can be derived from data reported on elderly from the Canadian Study of Health and Ageing.[15] On the basis of pooled samples of community and institutional Canadian elderly aged 65 years and older, the estimated prevalence of CIND was 16.8%. This compared with a prevalence of 8.0% for all types of dementia combined. Since CIND is comprised of a number of categories, including circumscribed memory impairment, depression, drug use, mental retardation, etc, it is likely that it is more inclusive than current definitions of MCI. The category of circumscribed memory impairment (the most frequent category of CIND) is probably less inclusive than current definitions of MCI, and has a prevalence of 5.2%. Therefore, the prevalence rate of MCI can be estimated to be between 5.2% and 16.8%. Yesavage et al[35] have employed a Markov model to estimate the most likely prevalence of MCI at spe-

cific ages. MCI prevalence increased as a function of age: 1% at age 60; 6% at age 65; 12% at age 70; 20% at age 75; 30% at age 80; and 42% at age 85.

Validation of MCI

Establishing the validity of a clinically defined condition such as MCI depends on it having properties that are distinct from those used to establish the diagnosis. Several strategies have been used to validate the concept of MCI including the following:

- Longitudinal studies demonstrating that MCI groups are at increased risk for dementia.
- Cross-sectional studies demonstrating that MCI patients exhibit psychometric, neuroimaging, and biomarker characteristics that are intermediary between normal subjects and those with dementia.
- Neuropathological studies demonstrating that MCI patients evidence either unique brain changes that would justify a new diagnostic category, or brain changes consistent with an early stage of a dementing disorder.

Longitudinal outcome in MCI

Several studies have examined rates of conversion to dementia among clinical samples diagnosed with MCI. Despite the use of different diagnostic criteria, these studies all demonstrate conversion rates that are higher than the incidence of dementia in the general population, thus lending overall validity to the notion that MCI patients are at increased risk for significant cognitive decline. Bruscoli and Lovestone[36] identified 19 longitudinal studies published between 1991 and 2001 that reported conversion rates from MCI to dementia.[11,17,21,31,37-51] Although large differences in conversion were observed across these studies (2% to 31%), the calculated mean annual conversion rate was 10.24% (95% confidence interval [CI] 6.9%-11.9%). This figure was slightly more than five times the mean incidence of dementia for similarly aged individuals (estimated to be 1.82%; 95% CI 1.38%-2.38%), based on results from previously published reports.[52,53]

The highly disparate conversion rates across studies most likely reflect several confounding factors including (i) differences in definitional criteria for MCI; (ii) cross-rater and cross-center reliability differences in the implementation of criteria for both MCI and dementia; (iii) differences in study populations (eg, community versus research clinic); (iv) differences in follow-up interval; and (v) variable use of cholinesterase inhibitors and other potentially protective drugs. In the series reviewed by Bruscoli and Lovestone,[36] the single largest factor accounting for variability in decline was the source of the MCI subjects: research clinic subjects had higher conversion rates than community-living volunteers. The impact of subtle differences in definitional criteria on conversion rate is highlighted by a report by Morris et al,[21] who subdivided CDR=0.5 patients into three groups based on the CDR subscale scores. These groups, defined as (i) uncertain dementia of the Alzheimer type (DAT), (ii) incipient DAT, and (iii) DAT, represented increasing degrees of clinical confidence that prodromal AD was present. Results of survival analyses indicated that the 5-year rates of progression to dementia (defined as a CDR≥1 at follow-up) were 19.9% for the uncertain DAT group, 35.7% for the incipient DAT group, and 60.5% for the DAT group. This compares with a 5-year rate of progression of 6.8% for controls classified as having a CDR=0 at baseline.

Cross-sectional neuropsychological differences in MCI

For a thorough review neuropsychological methods used in MCI see the article by Hahn-Barma et al in this issue.[54] A number of studies have compared neuropsychological test performance in subjects diagnosed as cognitively normal, MCI, and AD. In general, MCI patients have been found to perform more poorly than normal subjects on a variety of tests that also separate mildly demented patients from normal individuals. Results from several of these studies are summarized in *Table I*.[16,17,21,25,40,55-59]

While mean neuropsychologic test score differences are found to separate groups of normal, MCI, and mild dementia subjects, significant overlap has been noted.[25,55] These results highlight the inherent heterogeneity of MCI as a diagnostic entity comprised of both patients with early neurodegenerative disease and more benign forms of ARCD. Interest has therefore focused on the use of neuropsychological test instruments to predict longitudinal outcome in MCI.

Psychometric prediction of dementia in MCI

The following review is meant to be representative rather than exhaustive, concentrating on studies that have reported on the predictive accuracies of cognitive/psychometric instruments. A number of studies have assessed

longitudinal decline in MCI groups. Rubin et al[60] followed 16 individuals with MCI (CDR=0.5) over 7 years and found that 69% had declined to dementia by the end of the third year; no other cases converted beyond that time. No formal neuropsychological test data were reported, but the memory subscale of the CDR at baseline predicted 100% of the nondecliners and 64% of the decliners. Similarly, Daly et al[43] studied 123 MCI elderly over a 3-year interval and found that 18.7% declined to AD. The sum of six subscales from the CDR (along with information from a clinical interview) correctly identified 90% of the nondecliners and 83% of the decliners.

Flicker et al[17] followed 32 normal (GDS=1-2) and 32 MCI cases (GDS=3) over a 2-year follow-up interval and found that 72% of the mildly impaired group progressed to a dementia diagnosis. Classification analyses of the four cognitive tests that showed poorer scores at baseline among the decliners yielded high levels of specificity and sensitivity. These four tests assessed verbal recall, visuospatial recall, and two aspects of language function. The verbal recall test (learning a shopping list) was the best single predictor, correctly classifying 95% of the nondecliners and 90% of the decliners. Kluger et al[48] studied 213 nondemented elderly (GDS=1-3) over an average follow-up interval of 3.8 years. Of the 87 MCI (GDS=3) cases followed, 68% declined to dementia. Cut-scores from a paragraph delayed recall test assessing recent memory correctly identified 92% of the decliners and 79% of the nondecliners, yielding an overall predictive accuracy of 87%. A diagnostically more restrictive subset of this MCI sample (N=71) was also examined, of whom 66% declined to a diagnosis of probable AD. This same paragraph cut-

Study	Setting/MCI definition	No. of subjects		Psychometric domains showing decline in elderly patients with MCI (versus normal controls)
		Normal	MCI	
Reisberg et al,[16] 1988	Clinical research center MCI (GDS=3)	60	44	Recent memory, language/semantic memory, attention, and psychomotor function
Storandt and Hill,[55] 1989	Clinical research center Questionably demented (CDR=0.5)	83	41	Recent memory, language, and speeded psychometric function
Mitrushina et al,[56] 1989	Clinical research center Outliers of well-functioning elderly	19	19	Recent memory and language
Morris et al,[57] 1991	Clinical research center Questionably demented (CDR=0.5)	4	10	Recent memory, language, speeded psychometric function, and comprehension
Flicker et al,[17] 1991	Clinical research center MCI (GDS=3)	32	32	Recent and remote memory, language, concept formation, and psychomotor function
Kluger et al,[25] 1997	Clinical research center MCI (GDS=3)	41	25	Recent memory, language, and fine and complex motor/ psychomotor function
Petersen et al,[40] 1999	Clinical research center MCI (abnormal memory)	234	76	Recent memory and language/semantic memory
Morris et al,[21] 2001	Clinical research center Three CDR=0.5 subgroups: DAT, incipient DAT, and uncertain DAT	177	227	Recent (episodic), semantic memory, executive/psychomotor and visuospatial function, and attention
Grundman et al,[58] 2004	Multiple memory disorder centers MCI: CDR=0.5 and objective memory impairment	107	769	Recent memory, language, and psychomotor function

Table I. Studies examining cross-sectional psychometric differences between normal and mild cognitive impairment (MCI) elderly people. GDS, Global Deterioration Scale; CDR, Clinical Dementia Rating; DAT, dementia of the Alzheimer's type.
Updated from reference 59: Kluger A, Golomb J, Ferris SH. Mild cognitive impairment. In: Nawab Qizilbash, ed. *Evidence-Based Dementia Practice*. Oxford, UK: Blackwell Science; 2002:341-354. Copyright © 2002, Blackwell Science.

score correctly identified 96% of the decliners and 83% of the nondecliners, providing an overall accuracy of 92%. Similar findings have been reported by Tierney et al[41] for a cognitively diverse sample of research clinic–based, nondemented elderly individuals (GDS=2-3), by Devanand et al[38] for individuals with scores of CDR=0 to 0.5, as well as by Masur et al[28] for nondemented, healthy community-residing elderly, who are likely to be comprised of both normal and MCI individuals.

An overview of relatively large-sample longitudinal studies (N>70) that have reported predictive accuracies of either individual or small sets of baseline neuropsychological test scores for predicting subsequent decline to dementia is provided in *Table II*.[28,38,41,44,48,59,61,62] These studies are organized according to the composition of the nondemented samples at baseline: (i) primarily normal/AAMI/ARCD elderly; (ii) various combinations of normal and MCI cases; or (iii) only MCI cases. One general pattern that emerges from this organizational scheme is "the greater the proportion of MCI cases in the nondemented sample, the greater the subsequent rates of decline." The reported predictive accuracies include specificity versus sensitivity and/or negative predictive value versus positive predictive value. The specificity of a test signifies the percentage of all truly nondeclining cases accurately classified by the predictor variable, while the sensitivity indicates the percentage of all truly declining cases accurately classified by the predictor variable. The negative predictive value denotes the percentage of all cases classified by the predictor variable as nondeclining cases that actually do not decline, while the positive predictive value indicates the percentage of all cases classified by the predictor variable as declining cases that actually do decline. The overall accuracy identifies the total percentage of subjects (true nondecliners plus true decliners) accurately classified by the predictor variable. The results of these studies assessing putative cognitive predictors of dementia indicate that a small set of psychometric measures can relatively accurately detect pathological decline in nondemented (especially MCI) elderly people. The best single predictors were measures of recent verbal/visuospatial learning and memory, especially from tests of delayed recall. Other predictors that have been frequently identified include assessments of

Study/nondemented sample	N	Decline at follow-up (%)	Specificity (%)	Sensitivity (%)	Predictive value (%)	
					Negative	Positive
• *Samples containing normal elderly at baseline*						
Fuld et al,[61] 1990 Community-based study	474	11.8	84.0	57.0	89.0	39.0
Dal Forno et al,[62] 1995 Community-based study	196	12.2	–	–	91.0	62.0
• *Samples containing various combinations of normal and MCI elderly at baseline*						
Masur et al,[28] 1994 Community-based study	317	20.2	94.0	50.0	88.1	68.1
Tierney et al,[41] 1996 Memory-impaired sample	123*	23.6	94.0	76.0	–	–
Devanand et al,[38] 1997 Memory-clinic–based study	75	41.3	76.9	81.0	83.3	73.9
Kluger et al,[48] 1999	213	34.7	92.8	72.9	86.6	84.4
Research-clinic–based study	179*	31.3	95.1	87.5	94.4	89.1
Grober et al,[44] 2000 Community-based study	264	12.1	80.0	85.0	-	-
• *Samples containing MCI elderly at baseline*						
Kluger et al,[48] 1999	87	67.6	78.6	91.5	81.5	90.0
Research-clinic–based study	71*	66.2	83.3	95.7	90.9	91.8

Table II. Summary of relatively large-sample studies (N>70) examining the accuracy of neuropsychological measures in predicting decline to dementia. MCI, mild cognitive impairment. *Decline to Alzheimer's disease.
Reproduced from reference 59: Kluger A, Golomb J, Ferris SH. Mild cognitive impairment. In: Nawab Qizilbash, ed. *Evidence-Based Dementia Practice.* Oxford, UK: Blackwell Science; 2002:341-354. Copyright © 2002, Blackwell Science.

language function and psychomotor integration.

It is apparent that not all elderly who are classified as MCI eventually decline to dementia, at least over follow-up intervals of several years. If the definition of MCI at baseline is based on global staging scales (CDR=0.5 or GDS=3), a trade-off can be observed between the added strictness in the definition imposed by additional psychometric criteria and the proportion of decliners observed at follow-up. But this added sensitivity comes at a cost: some decliners will not be identified. Illustrating this point are data described in *Table III*, representing a recalculation of results from a previous longitudinal report.[48] If MCI is defined as all elderly with a baseline GDS=3 (a relatively lax criterion), 68% (59 of 87 cases) of this group will decline at follow-up, roughly 4 years later. If additional criteria are imposed on top of the global scale scores (ie, progressively poorer performance on a test of delayed paragraph recall), the percentage of this group that will eventually decline increases substantially. For example, if the definition of MCI is based on GDS=3 as well as a recall score of ≤4 at baseline, 98% (45 of 46 cases) of this group will decline, but nearly one-quarter of the future decliners (14 of the 59 decliners) will be missed using this relatively strict definition. It is very likely that similar patterns of trade-offs will occur with any sensitive psychometric, biological, or imaging marker when combined with a global scale score definition of MCI. For example, as has been seen, the stratification of the CDR stage 0.5 by the additional clinical criteria suggested by Morris[21] results in divergent expectations with respect to rapidity of decline to dementia.

Knowledge of these trade-offs has been helpful in selecting enriched MCI samples for drug-treatment trials. Often, only those MCI cases (identified initially by global rating scale classifications) with heightened risk of future decline based on poor memory scores are included in the treatment studies. The strictness of the criterion can be adjusted, depending on the degree of risk associated with the particular investigational compound.

Pathological basis of MCI

Most MCI patients identified in research clinics who decline to dementia can be retrospectively diagnosed with probable early stage AD. Such patients may therefore already harbor neuritic plaques and neurofibrillary tangles (NFTs), the classically recognized histolopathological hallmarks of AD. In a large study of 109 community-dwelling older adults without dementia,[63] 33% were found at autopsy to have neocortical neuritic plaques and NFTs suggesting a pathological diagnosis of AD. Methodological considerations preclude knowing how many of these cases actually had MCI, but the findings prompt speculation that gradations of AD-related pathology could explain the milder degrees of intellectual dysfunction prevalent in nondemented populations. The nature of the brain changes that distinguish pathological from normal aging and constitute the basis for MCI are now becoming less obscure.

On the basis of a large autopsy series of 2661 cases, Braak and Braak[64] identified six age-associated stages of neurofibrillary change where early NFT formation is restricted to the entorhinal and transentorhinal regions of the medial temporal lobe and occurs in the absence of amyloid plaques. In autopsy studies of normal subjects without any cognitive impairment (CDR=0), investigators have found NFTs to be ubiquitous, but generally confined to the entorhinal cortex and hippocampus[65] with densities, particularly for the CA1 region, that increase exponentially with advancing age.[66] While most of these cognitively normal cases had either no amyloid deposition or only diffuse nonfibrillar plaques, between 18% and 45% may also exhibit neuritic plaques that are predominately concentrated in the limbic regions of the medial temporal lobe.[65-67] It is therefore apparent that some cognitively normal subjects harbor "preclinical" brain changes consistent with a pathological diagnosis of early AD; presumably, such individuals will eventually

	MCI definition	Decline to dementia (%) (N_1/N_2)	Declining cases missed (%) (N/59)
Lax	GDS=3 and any recall score	68 (59/87)	0 (0/59)
↕	GDS=3 and recall ≤ 10	73 (58/79)	2 (1/59)
	GDS=3 and recall ≤8	81 (56/69)	5 (3/59)
	GDS=3 and recall ≤6	90 (54/60)	8 (5/59)
	GDS=3 and recall ≤4	98 (45/46)	24 (14/59)
Strict	GDS=3 and recall ≤2	100 (34/34)	42 (25/59)

Table III. Trade-off between strictness of mild cognitive impairment (MCI) criterion (based on New York University [NYU] delayed paragraph recall) and decliners missed. GDS, Global Deterioration Score. Recalculated from data in Kluger et al.[48]

develop MCI and dementia upon longitudinal observation. Virtually all CDR=0.5 (MCI) subjects studied by Price and Morris were found to have neuritic plaques distributed more diffusely, involving neocortical as well as limbic regions.[21,66] These data indicate that MCI, defined as CDR=0.5, may represent early AD more often than previously believed. Such observations, however, must be reconciled with the widely disparate rates of longitudinal decline exhibited by MCI subjects. As discussed previously, the etiological heterogeneity of MCI is most likely influenced by clinical diagnostic criteria as well as the characteristics of the population sampled.

Current research therefore supports the view that a slow progressive increase in medial temporal (entorhinal, perirhinal, and hippocampal) neurofibrillary pathology is the histopathological signature of normal brain aging and generally occurs with minimal or no cognitive consequences. These changes may, however, underlie the more subtle and benign memory deficits observed in normal aging and could represent the pathologic basis for AAMI/ARCD. The emergence of neuritic plaques within the medial temporal lobe and neocortex, however, may be the pathological substrate of MCI and signal the onset of AD *(Figure 4)*. Why some persons with medial temporal AD pathology are unimpaired (CDR=0), while others exhibit MCI is at present uncertain, although the explanation may, in part, reflect the emergence of neuronal loss within the entorhinal cortex,[68,69] a more widespread neocortical localization of plaques and tangles,[66] and, perhaps, changes in synaptic morphology and density.[70] Although they are less pronounced, neurofibrillary changes also affect the nucleus basalis of Meynert in aging and become more pronounced with MCI.[71] While cholinergic deficiency could therefore also account for the symptoms of MCI, this has been called into question due to the lack of associated reductions in cortical choline acetyltransferase activity.[72]

Neuroimaging findings in MCI

Structural imaging

Given the clinical and pathological results described above, it is understandable that neuroimaging research in MCI has focused on the medial temporal lobe, with particular emphasis on such structures as the hippocampus and entorhinal cortex. The accumulation of AD pathology affecting this anatomy is reflected in volume loss[73] and, although hippocampal atrophy is not specific to AD,[74-77] magnetic resonance imaging (MRI) studies conducted on postmortem brains have shown hippocampal volume reductions that correlate with the Braak stage of neurofibrillary degeneration.[78,79] In vivo studies confirm that hippocampal atrophy is a frequent characteristic of MCI[80-83] and can predict the occurrence of subsequent dementia.[46,84,85] Hippocampal atrophy has also been demonstrated in nondemented subjects destined to develop AD due to the amyloid precursor protein (APP) 717Val-Gly mutation.[86] Up to one-third of highly functioning cognitively normal older adults exhibit milder degrees of hippocampal atrophy that correlate with diminished delayed recall performance.[87,88] Hippocampal volume loss in these cases may not always reflect the presence of AD pathology,[74] but might correspond to benign age-associated neurofibrillary changes. More recent MRI studies have found atrophy of the entorhinal cortex in MCI patients[89-91] with greater volume reductions in cases that decline to dementia.[92] Nevertheless, it is unknown whether entorhinal atrophy precedes hippocampal atrophy during the pathogenesis of AD or whether MRI measurements of the entorhinal cortex correlate better than volume measurements of the hippocampus with a diagnosis of MCI.[93] It is likewise unclear if either measure is a better predictor of risk for subsequent decline.[88,91]

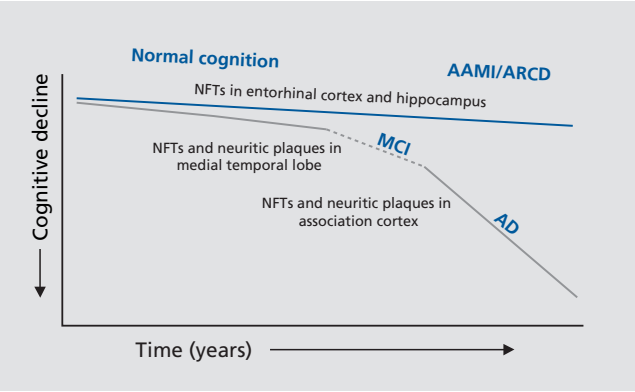

Figure 4. Schematic representation of the distinction between normal (upper curve) and pathologic (lower curve) brain aging. This view, supported by recent clinical pathological studies, suggests that minimal cognitive decline is associated with an age-dependent accumulation of medial temporal lobe neurofibrillary change. The emergence of mild cognitive impairment (MCI) is preceded by the appearance of neuritic plaques as well as neurofibrillary degeneration, both of which become more concentrated and widely distributed with the progression of cognitive symptoms. AAMI, age-associated memory impairment; ARCD, age-related cognitive decline; AD, Alzheimer's disease; NFT, neurofibrillary tangle.

Structural MRI studies have begun to examine medial temporal lobe volumes as predictors of MCI. An earlier study of highly functioning cognitively normal subjects found baseline measurements of hippocampal size to predict subsequent changes in memory performance and the development of MCI.[94] More contemporary studies have analyzed scans at two or more time points to calculate volumetric rates of change.[95-98] These studies confirm that higher rates of atrophy affecting medial temporal lobe structures can predict longitudinal cognitive decline and the emergence of MCI. Such results also highlight the potential for using structural MRI as outcome measures in pharmacological trials targeting MCI subjects. At present, however, it is uncertain whether neuropsychological decline can be more robustly detected over a shorter time interval than structural radiographical change.

Functional imaging

Functional imaging research in MCI has included studies using positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS).

Positron emission tomography

PET studies using the radiotracer 2-deoxy-2[^{18}F]fluoro-D-glucose (^{18}FDG) have been employed for over 20 years to study regional rates of glucose utilization in the brain. AD patients tend to exhibit characteristic metabolic reductions in the temporal and parietal association cortices[99-101]; a distribution that coincides with the neuropathological distribution of AD pathology. FDG studies in patients with MCI have demonstrated similar topographic patterns, as well as metabolic reductions in the posterior cingulate gyrus.[102-106] Subjects at high genetic risk for AD (due to apolipoprotein E4 [ApoE-4] homozygocity) also exhibit glucose utilization reductions in regions similar to those that become involved in AD.[107] Evidence is conflicting concerning the presence of metabolic reductions within the medial temporal anatomy affected in early AD. Some groups have not found differences,[108] while others have reported decreased glucose utilization rates affecting the hippocampus and other limbic structures including the mammilary bodies, amygdala, and medial thalamus.[109,110] One study found metabolic reductions within the entorhinal cortex to be associated with longitudinal decline to MCI and AD.[111] These studies, however, draw their conclusions from small samples and purport to measure structures that challenge the spatial resolving power of the equipment. Despite statistical adjustments for atrophy, it seems possible that tissue loss may be confounding these results, particularly given the findings from numerous structural imaging studies reviewed previously. Cerebral perfusion imaging using SPECT may also be useful in predicting subsequent dementia among patients with MCI.[112,113]

Functional magnetic resonance imaging

Brain activity following a stimulus can be localized with fMRI, a technique that is sensitive to the small changes in blood oxygenation associated with increased regional metabolic demand. Using visual memory tests to activate the medial temporal lobe, MCI subjects were found to exhibit a smaller fMRI response than cognitively normal subjects, though differences between MCI and AD were not detected.[114] Another fMRI study found poor activation within the hippocampus in all MCI subjects, while some had normal entorhinal cortex responses suggesting anatomical heterogeneity with respect to memory processing.[115] A recent MCI study[116] found that visual memory test performance correlated with medial temporal lobe activation but, surprisingly, activation was more extensive in patients who developed dementia compared with those who remained stable. Like PET and structural MRI studies, nondemented patients at high genetic risk for dementia may exhibit decreased patterns of brain activation compared with controls.[117]

Magnetic resonance spectroscopy

Using proton MRS (^{1}H-MRS), several groups have found brain metabolite concentrations for *N*-acetylaspartate (NAA) and myoinositol (MI) to distinguish AD patients from controls although conflicting results have been reported for choline.[118] Decreased NAA concentration relative to creatine (NAA/Cr) is considered to be an MRS marker of diminished neuronal density and viability. Elevations in MI/Cr ratios are less specific, but may be associated with glial activation and other neurochemical processes; it is unclear how this may relate to AD pathogenesis. Compared with normal controls, some investigators have found increased MI/Cr in the posterior cingulate gyrus and white matter of MCI patients.[119,120]

Nondemented Down's syndrome patients at high risk for AD also have elevated MI/Cr ratios.[121] A recent study observed that decreased medial temporal lobe NAA/H_2O ratios distinguished MCI patients from normal controls, while increased parietotemporal MI/H_2O distinguished MCI cases from AD.[122] Further research will determine whether MRS can identify a specific metabolite signature that differentiates early AD pathology. Some evidence, however, suggests that while NAA/Cr may be a nonspecific marker for age-related neuronal dysfunction and cognitive decline, MI elevations may be a better index of neuropathology.[123]

Imaging AD pathology

Recently developed amyloid imaging tracers for PET have resulted in pilot studies with promising initial findings.[124,125] The positron-emitting [^{11}C]benzothiazole derivative known as Pittsburgh compound-B (PIB) has been shown to effectively discriminate a group of 16 mild AD patients from cognitively normal controls in a recently published PET study.[124] The absence of PIB retention within white matter or cerebellar regions (the latter an area of nonfibrillar β-amyloid [Aβ] accumulation) suggests that this agent may specifically image the neuritic plaque deposits that characterize early AD. Although MCI cases were not included, 7 patients were very mildly impaired, as evidenced by Mini-Mental State Examination (MMSE) scores ≥ 27. The patterns of PIB uptake for 3 of these mildly impaired cases were indistinguishable from control values casting some early doubt on the sensitivity of this technique for identifying MCI cases with AD pathology. Further research will undoubtedly clarify the potential of PIB and other amyloid imaging techniques for making an early diagnosis of AD and monitoring progression of pathology over time.

Biological markers of AD pathology in MCI

Over the past decade, several groups have compared cerebral spinal fluid (CSF) from AD patients with fluid from cognitively normal controls in an effort to identify biological markers indicative of AD pathology. Although a large number of candidate markers have been examined, recent interest has focused on observations that CSF concentrations of tau, a microtubule-associated protein comprising NFTs, is elevated in AD,[126,127] while levels of the 42 residue form of the Aβ peptide ($A\beta_{1-42}$) are decreased.[128] As reviewed in this issue by Hampel and Blennow,[129] multiple studies over recent years have confirmed that these biomarkers can effectively discriminate control subjects from demented patients with a clinical diagnosis of AD. Averaging across 43 studies while fixing diagnostic specificity at 90%, these authors[130] found mean sensitivities of over 80% for CSF measurements of total tau and $A\beta_{1-42}$. Overall discrimination may be somewhat improved by detecting the abnormally phosphorylated forms of tau (phospho-tau) that occur in neurons undergoing neurofibrillary degeneration in AD.[131,132] Nearly all groups who have studied CSF tau and $A\beta_{1-42}$ in MCI populations have found mean concentrations to be intermediary between AD and control values, but closer to the AD levels in patients who decline to dementia.[133-138] These results highlight the biological heterogeneity of MCI and suggest that phospho-tau measurements, in particular, could be useful in identifying cases of prodromal AD. As a potential index of AD pathological burden, tau and $A\beta_{1-42}$ concentrations could be useful outcome measures in treatment studies. Some preliminary evidence, however, suggests that repeated measurements may not always correlate with disease progression.[136] It also remains to be determined whether these CSF markers are better predictors of cognitive decline than the structural and functional imaging techniques reviewed previously. Clearly, longitudinal studies in MCI using combinations of brain imaging, psychometric testing, and CSF sampling need to be performed before these questions can be addressed.

Genetic markers of AD pathology in MCI

It is now well recognized that persons carrying the ε4 isoform of ApoE are at increased risk for developing late-onset AD.[139] While overexpression of the ε4 allele might be expected in MCI compared with normal controls, its frequency would not be likely to reach the levels seen in AD, since MCI cases comprise not only preclinical AD, but also other more benign conditions predisposing to cognitive impairment. In one large study, the prevalence of nondemented persons with at least one copy of the ε4 allele was 22%, while in AD the frequency was 64%.[140] Values intermediary between these estimates were found in several studies of nondemented memory impaired individuals who appear to satisfy criteria for the diagnosis of MCI.[14,18,141,142] Two large population-based studies found that ε4 status was a significant risk factor for MCI.[143,144]

Most studies have found ε4 to exert a cognitive impact on nondemented older adults. In community samples of nondemented elderly, although one cross-sectional study did not find a significant relationship between ε4 status and cognition,[145] other longitudinal studies found ε4 to be a predictor of accelerated cognitive decline.[146-148] According to one report,[149] nondemented subjects who carried an ε4 allele were more likely to have subjective memory complaints than those without ε4. In studies of cognitively normal persons with high MMSE scores, the impact of age on memory performance (and memory change over time) was more pronounced in ε4 homozygotes relative to those without ε4.[150-152] These latter reports indicate that ε4 may subtly influence cognitive performance even before the onset of MCI; it is unknown whether this influence can precede the emergence of AD pathology. Although epidemiological and longitudinal clinical data support ε4 as a risk factor for dementia and cognitive decline, its utility as a predictor of clinical outcome in MCI populations needs to be compared with imaging, biomarker, and neuropsychological variables.

Treatment of MCI

The treatment of MCI is reviewed in detail by Gauthier later in this issue.[153] Currently, there are no pharmacological treatments for MCI with proven efficacy or regulatory approval. However, clinically there appears to be growing use in MCI of the marketed AD treatments, donepezil, rivastigmine, galantamine, and memantine. A number of clinical trials in MCI patients have been conducted, thus far with mixed results. For example, a 6-month, placebo-controlled trial of donepezil failed to show significant efficacy on the primary end points, but did show efficacy on some secondary cognitive measures.[154]

Since a high proportion of "amnestic" MCI patients (presumably representing cases of prodromal AD) progress to an AD diagnosis within several years, 2- to 4-year "survival" clinical trial designs have been conducted with MCI patients in which "conversion" to AD is the primary outcome. Such studies are used to determine if a treatment can slow the progression of symptoms. For example, a 3-year trial of vitamin E, donepezil, or placebo failed to show an effect on conversion of vitamin E, but did demonstrate a benefit of donepezil at 6, 12, and 18 months.[155] Since there was no benefit at 2 to 3 years, these results for donepezil are consistent with a symptomatic effect that lasts for up to 18 months. A similar 2-year trial of galantamine in MCI failed to show a benefit on the primary end points, but there was some benefit on a secondary cognitive measure.[156] Results of a 3- to 4-year conversion trial of rivastigmine have not as yet been reported, but a similar 4-year trial of the anti-inflammatory drug rofecoxib failed to show any clinical efficacy.[157] Despite the mixed and generally disappointing results of these initial MCI clinical trials, an important general finding is that when the patients progressed to dementia over the course of the trial, the specific diagnosis was almost always AD. This result provides some validation for the operational criteria used to select cases with "amnestic/AD type" MCI.

Conclusion

The concept of MCI in the elderly has evolved over the past 40 years to the point where study of MCI is at the cutting edge of research on the early pathology, early diagnosis, and early treatment of AD. The broad syndrome of MCI, defined clinically as a state of mild impairment that is intermediate between the decline associated with brain aging and the clear deficits that occur in dementia, is clearly heterogeneous with respect to outcome and underlying etiology. However, it is apparent that the major MCI subgroup consists of individuals destined to progress to a diagnosis of AD. As reviewed above, this conclusion is supported by growing number of cross-sectional and longitudinal studies, as well as by studies examining postmortem neuropathology and in vivo neuroimaging and biomarker correlates of AD. Furthermore, since it is feasible clinically to operationalize the identification "amnestic" MCI cases who are likely to have very early AD, such individuals have become an important research group for inclusion in clinical trials designed to examine agents that may slow the progression of AD.

Although clearly valuable as a research tool, it may be debated whether physicians in clinical practice should consider a diagnosis of MCI for individual patients. Because MCI is a heterogeneous entity comprising a variety of neuropathological and psychiatric disorders, and because dementia is not an inevitable outcome, the term may carry too little prognostic and diagnostic weight to legitimize its widespread use on a case-by-case basis. Furthermore, the lack of universally agreed upon criteria and the public's unfamiliarity with the concept

could result in increasing uncertainty, anxiety, and misunderstanding. Rather than invoking MCI, patients might be better served if their physicians simply conveyed an opinion regarding the most likely underlying pathological mechanism. For example, a patient with progressive memory loss and poor neuropsychological test performance might be told that early AD pathology is likely, while a patient with minimal objective memory impairment could be informed that such an explanation is less plausible. If medical, neurological, or brain imaging evidence supports other etiologically relevant conditions, this too could be imparted to patients as alternative or contributing factors. It might therefore be asked whether any additional information is gained by adding MCI to the diagnosis. On the other hand, patients and families might be comforted by the MCI label, provided that it is properly explained as a "risk" condition, rather than as a definitive diagnosis of "early AD." Regardless of the unresolved issues and possibly premature nature of MCI as a psychiatric or neurological "diagnosis" in a patient care setting, the MCI concept has had, and will continue to have, great relevance and importance to research on the causes, early diagnosis, and early treatment of AD. ❑

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Deterioro cognitivo leve: desarrollo histórico y resumen de investigaciones

Este artículo de revisión investiga de manera general el desarrollo histórico, los criterios diagnósticos, las características clínicas y neuropatológicas, y las estrategias terapéuticas que se relacionan con el deterioro cognitivo leve (DCL). El concepto de DCL se incluye dentro del contexto de otros términos que han sido desarrollados para caracterizar la vejez con grados variables de deterioro cognitivo. Se discuten los criterios basados en evaluaciones de escalas clínicas globales, rendimiento en pruebas cognitivas y rendimiento en otros dominios del funcionamiento. También se revisan aproximaciones que utilizan metodología clínica, neuropsicológica, de neuroimágenes, biológicas y de genética molecular empleadas en la validación del DCL, incluyendo resultados de investigaciones transversales, longitudinales y postmortem. Además se consignan resultados recientes de estudios farmacológicos en el DCL y temas metodológicos afines.

Déficit cognitif léger : développement historique et résumé de la recherche

Cet article retrace à grands traits le développement historique, les critères diagnostiques, les caractéristiques cliniques et neuropathologiques ainsi que les stratégies du traitement du déficit cognitif léger (mild cognitive impairment, MCI). Le concept de MCI est étudié conjointement avec d'autres termes créés pour qualifier les personnes âgées présentant des degrés variables de déficit cognitif. Les critères basés sur des échelles de comportement clinique global, les résultats de tests cognitifs et des bilans relatifs à d'autres domaines fonctionnels sont également passés en revue. Nous abordons les méthodes cliniques, neuropsychologiques, de neuro-imagerie, biologiques et de génétique moléculaire utilisées pour confirmer le MCI, y compris les résultats issus d'études transversales, longitudinales et post-mortem. Nous présentons également les résultats d'études sur de nouveaux médicaments pour traiter le MCI et les questions méthodologiques qui s'y rattachent.

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