Neuropsychological methods in mild cognitive impairment

The concept of mild cognitive impairment (MCI) was introduced to fill the gap between cognitive changes associated with normal aging and those associated with dementia. Such cognitive changes indicate a deviation from normal aging, but are insufficient to evoke dementia and do not indicate loss of autonomy. MCI is thus a transitional state before dementia. MCI covers a range of disorders and raises the question of population heterogeneity; three MCI subcategories have been defined to reduce this heterogeneity. Recognizing MCI is only a first step; for a given patient, it is more important to try to identify the disease responsible, which is now possible using neuropsychology and neuroimaging. Here, we introduce the concept of "prodromal stage" for various degenerative diseases, and propose replacement of the amnestic MCI subcategory with "prodromal Alzheimer's disease," for which we present the neuropsychological characteristics.

Mild cognitive impairment (MCI) is a concept that was introduced by Flicker et al[1] and the Mayo Clinic group[2,3] to fill the gap between cognitive changes associated with normal aging and those associated with dementia. The concept of MCI draws attention to cognitive disturbances that occur before the clinical diagnosis of dementia. The cognitive changes, measured by neuropsychological test scores, indicate deviation from normal aging and do not involve loss of autonomy. Nevertheless, these MCI criteria are not fully specified or generally agreed upon. As a consequence, studies of MCI conducted by different research groups have divergent results (eg, the number of patients with MCI who develop frank dementia of the Alzheimer's type in follow-up studies).[3-5]

Heterogeneity of the MCI population

In 2001, an international group of experts suggested the subdivision of MCI into three subcategories[6]:

- *Amnestic MCI*, characterized by memory complaint, preservation of activities of daily living, and objective and isolated memory impairment (compared with age and education norms).
- *Multiple cognitive domain MCI*, characterized by multiple areas of cognitive impairment (without associated memory deficit) not sufficiently severe to constitute dementia.
- *Single cognitive domain (other than memory) MCI*, characterized by a deficit of a specific domain as aphasia or executive dysfunction reflecting prodromal primary progressive aphasia or frontotemporal dementia.

In order to limit the heterogeneity of the population concerned by MCI, it will soon be possible to identify the underlying pathological disorders before the affected patients meet the criteria of dementia *(Table I)*, using specific neuropsychological assessments and, in some cases, neuroimaging. This is the case, for example, for the following:

- *Frontotemporal degeneration* can be identified well before the stage of clinical dementia in the presence of apathy and/or behavioral disinhibition coupled with a progressive disturbance in executive functions.
- *Primary progressive aphasia* can be identified early on the basis of anomia with speech apraxia and phonetic disintegration associated with limited atrophy of left perisylvian region.

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- *Diffuse Lewy body* disease is characterized by early-onset hallucinations, cognitive fluctuations, and extrapyramidal signs, often appearing before the development of clinical dementia.
- *The cerebrovascular origin of cognitive disorders* can be easily recognized at the early stages with appropriate combination of clinical history, neurological examination, and neuroimaging.
- *Alzheimer's disease* (AD) can also be identified at a prodromal stage.

Amnestic MCI or "prodromal AD"

We would like to discuss the subcategory of amnestic MCI and introduce the concept of "prodromal AD" *(Table II)*.[6-9] AD patients constitute the most important subgroup of patients with MCI, and can be identified before appearance of fully developed clinical dementia. Indeed, long before the onset of clinical dementia, AD is already at work on the brain, following a rather predictable route. Neuropathological changes are present in mesial temporal regions (hippocampal formations, parahippocampal gyrus, and entorhinal cortex), which are critical regions for long-term episodic memory. AD can be recognized as an "amnestic syndrome of the hippocampal type" long before the appearance of other cognitive disturbances.
The presence of AD in its earliest, predementia stages, may be detectable by use of specific memory tests aimed at distinguishing the characteristic pattern of memory disorders associated with the disease. In order to distinguish the amnestic syndrome of prodromal AD from other memory disorders encountered in the aged population (encoding deficits due to depression, impaired retrieval of information, etc), it is necessary to find evidence for the specific storage deficit that characterizes AD. For that purpose, it is particularly important to use a memory test that isolates the storage stage.
The procedure of the Free and Cued Selective Reminding test[10,11] allows an accurate analysis of deficit by distinguishing the encoding, retrieval, and storage processes *(Figure 1)*. In this task, the 16 items to be learned are presented to the patient on four different cards, one card with four items at a time. None of the items is a prototype of its category. The patient is asked to point to and read aloud each item (eg, grapes) in response to its category cue (eg, fruit). When all four items of a card are correctly named, the card is removed and immediate verbal cued recall is assessed, in the order of identification, by providing each category cue (eg, what was the fruit?). Whenever a patient is unable to recall an item in response to its cue, the procedure of pointing and naming is performed again. Once immediate cued recall for a group of four items on one card is completed, the next card is presented. The learning phase of the 16 items is followed by an intercurrent task

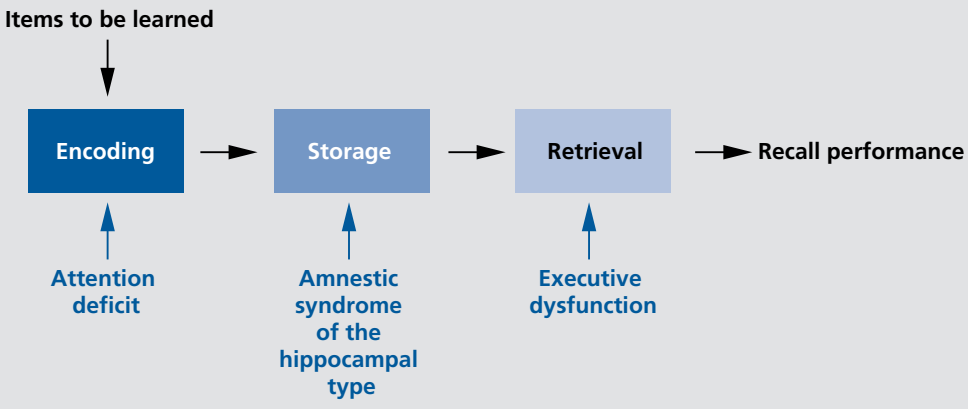

Figure 1. Specific episodic memory processes.

to obtain recall from secondary memory. Three successive recall trials are performed with free recall, and with cued recall for those items that are not retrieved with free recall.

This procedure involves a reinforced and controlled encoding stage, which helps monitor for the attention deficit or impaired retrieval usually met in normal aging, and isolates a genuine memory deficit due to a selective deficit of storage.

A deficit of retrieval is characterized by a low free recall with a normalization of performance with cueing or recognition. This pattern is observed in many disorders, such as depression or executive dysfunction or even in normal aging. Impaired storage is characterized by a very low performance in free recall, which is only marginally improved with cueing. This pattern is observed in patients with lesions of the hippocampus and related structures, such as AD. Therefore, before deciding that a patient has a true amnestic syndrome (ie, putative AD), it must be established that information has been registered and cannot be retrieved, even with the use of facilitation techniques (no effectiveness of cueing or recognition).

Amnestic syndrome of the hippocampal type

This syndrome is defined by an impaired free recall associated with a limited effect of cueing on recall (reflecting storage impairment), together with many intrusions and false positives on recognition. This profile has been called amnestic syndrome of the hippocampal type,[11] and is highly suggestive of AD (provided effective encoding of information had been checked previously). In contrast, it is not encountered in patients with depression, where encoding deficits are predominant, or in patients with frontotemporal degeneration, vascular dementia, or even normal aging, where impaired free recall is greatly improved or normalized with cueing or recognition.[12,13] Interestingly, the hippocampal-type memory profile has also been observed in the early stages of AD, in patients without dementia (Mini-Mental State Examination score >25), and in a prospective study of elderly people who became demented within 5 years.[11,14] This most likely means that episodic memory is a constant, early, and reliable neuropsychological marker of the disease in relation to early involvement of mesial temporal structures.[15]

Diagnosis	Clinical criteria (progressive onset of disorder)	Neuroimaging: location of atrophy
Primary progressive aphasia (PPA)	- Anomia - Speech apraxia - Phonetic disintegration	Left perisylvian
Frontotemporal degeneration (FTD)	- Behavioral disorders: apathy or disinhibition - Executive dysfunction	Frontal
Diffuse Lewy body disease (DLB)	- Early hallucinations - Cognitive fluctuations - Extrapyramidal signs	Mesial temporal Parieto-occipital

Table I. Differential prodromal dementia.

Diagnosis	Clinical criteria (progressive onset of disorder)	Neuroimaging: location of atrophy
"Prodromal AD" or "MCI of the Alzheimer type"	- Memory complaints by the patient and by the family - Normal activities of daily living or mildly impaired complex activities - Amnestic syndrome of the "hippocampal type" defined by: • Deficit of free recall, despite controlled encoding • Ineffective effect of cueing or impaired recognition • Numerous intrusions	Hippocampal

Table II. Diagnostic criteria for "prodromal AD."
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It appears to be possible to identify patients with prodromal AD, even today, using specific neuropsychological tools that demonstrate an amnestic syndrome of the hippocampal type.[8] Once this hippocampal amnesia has been found, neuropsychological testing should seek normal performance in other cognitive domains, such as language, praxia, gnosia, and executive functions. Subtle deficits of executive functions such as working memory and verbal fluency impairment can be observed at this stage.

We believe that the diagnosis of the predementia stage of AD will soon benefit from the combination of neuropsychology and structural and functional neuroimaging, focused on the hippocampal formations and related structures.[16,17] We propose clinical diagnostic criteria with high specificity for MCI of the Alzheimer type or prodromal AD. This may help clinicians to identify the largest subgroup of patients with MCI.

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