LOUIS PASTEUR UNIVERSITY - STRASBOURG I

Ecole Doctorale des Sciences de la Vie et de la Santé

And BASEL UNIVERSITY

Discipline : Medical sciences

Field : Neuropsychology

DOCTORAL DISSERTATION

Prepared by Emilie RITTER

Submitted for the degree of Doctor of Philosophy in the University Louis Pasteur of Strasbourg and the University of Basel

Topographical recognition memory and autobiographical memory in amnestic mild cognitive impairment: a longitudinal study

Presented in the university Louis Pasteur of Strasbourg on Monday 7th May 2007

Examining Committee:

Pr Lilianne Manning (Supervisor) in collaboration with Dr Olivier Despres
Pr Andreas U. Monsch (Co-supervisor)
Dr Christian Kelche (Louis Pasteur University Reporter)
Pr Klaus Opwis (External Reporter)
Pr Adrien Ivanoiu (External Reporter)

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“All those moments will be lost in time
Like tears in rain”

“*Tous les souvenirs se perdront dans l’oubli*
Comme les larmes dans la pluie“

Blade runner
A movie from Ridley Scott,1982

To all the participants who generously accepted to be assessed for this study

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Abstract

Mild cognitive impairment (MCI) is defined as one or more cognitive deficit(s) of not sufficient severity to constitute a dementia but of greater severity than that of healthy individuals of the same age and education level (Petersen et al., 2001). When the cognitive deficit concerns memory, it is called amnestic MCI (aMCI). It has been shown that individuals with aMCI are at a high risk of developing dementia of Alzheimer type (Petersen et al., 1999). Moreover, the finding of medication for slowing cognitive decline of Alzheimer's disease (AD) and waiting for new more efficient ones (Roberson & Mucke, 2006) renders research on aMCI, and thereby preclinical markers, of crucial interest. However, the aMCI syndrome may have causes other than neurodegenerative diseases, such as depression, and no standardized method exists to distinguish incipient demented aMCI patients from those who will not develop dementia. The main purpose of this study is to detect specific markers of preclinical dementia to discriminate aMCI patients who will develop dementia from those who will not. To this end, we performed a two-year longitudinal study aiming to examine cognitive evolution of aMCI patients in order to discriminate declining from non-declining aMCI patients. At the end of the study, we compared declining aMCI's cognitive performances at baseline with those of the non-declining to detect markers of preclinical dementia. Based on their neural substrates, we theorized that deficits in topographical recognition memory and autobiographical memory (AbM) could be neuropsychological markers of incipient dementia. The aMCI patients who declined cognitively were considered as *evolving aMCI*. Results showed that aMCI was an heterogeneous syndrome leading to evolving aMCI in a limited proportion whereas additional depression strongly increased the risk of becoming evolving aMCI. With regard to topographical recognition memory, aMCI patients were impaired and this memory was not sensitive to depression. Nevertheless, longitudinal results indicated that deficits in topographical recognition memory were not specific to the evolving aMCI condition. In the case of AbM, no specific deficit was found. These preliminary results may be useful for very large scale studies targeting neuropsychological markers of AD. Only a very accurate diagnosis of evolving aMCI will allow efficient early medical treatment.

Résumé détaillé en français

Depuis quelques années, le concept *amnestic Mild Cognitive Impairment* (aMCI) définit un état transitoire entre le vieillissement normal et la démence de type Alzheimer (DAT). Les patients aMCI présentent des troubles isolés de la mémoire qui ne sont pas suffisamment sévères pour constituer une démence (Gauthier et al., 2006 ; Petersen et al., 2001). Cependant, une proportion importante de ces patients estimée entre 11 et 33% évolue vers une DAT en deux ans (Ritchie, 2004), alors que la prévalence dans la population générale n'est que de 2% (Petersen et al., 1999). En 2006, Gauthier et al. ont adopté l'idée que le MCI pouvait être dû à d'autres causes que la neurodégénérescence, telles que la dépression. Néanmoins, malgré la découverte de certains traitements de la maladie d'Alzheimer (MA) stabilisant temporairement la détérioration cognitive (Kurz et al., 2004 ; Potkin, 2002, pour revue), il n'existe pas, à notre connaissance, de protocole diagnostique standardisé permettant de distinguer un état de aMCI évoluant vers la démence (aMCI évolutif), d'un état de aMCI qui ne développera pas la démence (aMCI non-évolutif). L'objectif principal de cette thèse était de rechercher des marqueurs neuropsychologiques de la DAT dans sa phase préclinique afin de distinguer les patients aMCI évolutifs des non-évolutifs.

Dans ce but, nous avons procédé à un suivi longitudinal de patients aMCI, pendant deux ans, afin d'étudier leur évolution cognitive et de discriminer les deux groupes de aMCI. A la fin de l'étude, nous avonc comparé les performances cognitives des patients aMCI évolutifs avec celles des non-évolutifs lors de l'évaluation neuropsychologique initiale, pour détecter des marqueurs de la DAT en phase pré-clinique. De plus, en se basant sur les principales régions cérébrales sous-tendant la mémoire de reconnaissance topographique et la mémoire autobiographique, vulnérables précocement aux lésions de la MA, nous avons supposé que des déficits dans ces deux formes de mémoires pourraient être des candidats pour des marqueurs neuropsychologiques de la MA.

Les résultats révèlent non seulement une hétérogénéité du syndrome de aMCI, en accord avec des études précédentes (e.g., Ritchie et al., 2001 ; Zanetti et al., 2006), mais aussi un risque aggravé de déclin cognitif chez les patients aMCI en présence de dépression, ce qui confirme l'étude de Modrego et Ferrandez (2004).

Tandis que la dépression est généralement associée à un dysfonctionnement frontal (e.g., Kalayam & Alexopoulos, 1999), les données de la littérature montrent que lors de tâches sollicitant la mémoire de reconnaissance topographique, l'activité neuronale des lobes temporaux médians (LTM) et plus spécifiquement l'hippocampe et le gyrus

parahippocampique chez le sujet sain, est particulièrement accrue dans l'hémisphère droit chez les sujets sains (Cipolotti & Maguire, 2003; Ekstrom et al., 2003 ; Maguire et al., 2001). Or ces structures présentent un dysfonctionnement chez les patients aMCI évolutifs (Dickerson et al., 2004). Le fait que les LTM sont précocement atteints lors d'une MA, qu'ils sont impliqués dans la mémoire de reconnaissance topographique et qu'ils ne sont apparemment pas altérés lors d'une dépression, nous a conduit à émettre l'hypothèse que les patients aMCI évolutifs présenteraient des déficits dans la mémoire de reconnaissance topographique non liés à la dépression. Les résultats montrent que les patients aMCI présentent un déficit de la mémoire de reconnaissance topographique et que la dépression n'a pas d'influence sur ce déficit (Ritter et al., 2006). Par contre, l'étude longitudinale indique que les déficits de mémoire de reconnaissance topographique chez les patients aMCI ne permettent pas de distinguer ceux qui déclineront cognitivement de ceux qui resteront stables.

La mémoire autobiographique est un système de mémoire permettant l'encodage, le stockage et le rappel des évènements personnels vécus sur l'ensemble de la vie. Cette étude a trois objectifs. (i) Selon la théorie des traces multiples (Nadel & Moscovitch, 1997), les souvenirs autobiographiques récents sont moins représentés par les traces mnésiques liant les informations enregistrées du néocortex au LTM, que les souvenirs les plus anciens. Les souvenirs autobiographiques récents seraient ainsi plus vulnérables aux lésions cérébrales. En considérant le fait que les LTM sont les régions affectées le plus précocement lors de la MA, nous avons supposé que les patients aMCI évolutifs présenteraient un déficit plus important dans le rappel des souvenirs autobiographiques récents que dans le rappel des souvenirs les plus anciens. (ii) La récupération de souvenirs autobiographiques positifs (i.e., agréable, joyeux) est associée à un pic d'activation au niveau de la région entorhinale, tandis que celle des souvenirs autobiographiques négatifs est associée avec une activation du gyrus temporal moyen droit (i.e., désagréable, triste) (Piefke et al., 2003). Etant donné que les premières lésions de la MA ont été localisées dans le cortex entorhinal (Braak et al., 1999), nous avons fait l'hypothèse que les aMCI évolutifs présenteraient un déficit dans le nombre de souvenirs autobiographiques positifs rappelés. (iii) Il a été observé que les souvenirs autobiographiques récents présentent une intensité émotionnelle plus élevée que les souvenirs plus anciens (Piefke et al., 2003). De plus, la récupération de ces souvenirs récents est associée à des activations bilatérales dans le cortex rétrosplénial s'étendant jusqu'au cortex postérieur cingulaire (Piefke et al., 2003). Un hypométabolisme de cette même région a été trouvé chez des patients aMCI qui ont développé par la suite une démence de type Alzheimer (Chételat et al., 2003a; Kogure et al., 2000; Nestor et al., 2003). Bien que le cortex rétrosplénial et le cortex posterieur cingulaire soient aussi impliqués dans des fonctions de la mémoire

autobiographique autres qu'émotionnelles, sur la base de ces observations, nous avons supposé que nos patients aMCI évolutifs rappelleraient des souvenirs autobiographiques récents d'intensité émotionnelle moins élevée que les sujets contrôles ou les patients aMCI non-évolutifs. Les résultats montrent que le nombre de souvenirs récents autobiographiques rappelés, la valence et l'intensité émotionnelle de ces souvenirs ne diffèrent pas significativement entre les patients aMCI évolutifs, les patients aMCI non-évolutifs et les sujets contrôles.

Ces résultats préliminaires pourraient servir de piste de recherche pour des études longitudinales à grande échelle afin de trouver des marqueurs neuropsychologiques de la MA. Seul un diagnostic clinique très précis de aMCI évolutif permettra d'ouvrir la voie à des interventions thérapeutiques précoces.

Références : seuls sont cités ci-dessous les articles non référencés dans la bibliographie

-Kurz, A., Farlow, M., Quarg, P., Spiegel, R. (2004). Disease stage in Alzheimer disease and treatment effects of rivastigmine. *Alzheimer Dis Assoc Disord*, 18(3):123-8.

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Abbreviations

AACD: aging-associated cognitive decline

AAMI: age-associated memory impairment

AbM: autobiographical memory

AbMs: autobiographical memories

AD: Alzheimer's disease

aMCI: amnestic mild cognitive impairment

amnMCI: patients with amnestic mild cognitive impairment without depression

amnMCI+DEP: depressive patients with amnestic mild cognitive impairment

CANTAB: Cambridge Neuropsychological Test Automated Battery

CDR: clinical dementia rating

CIND: cognitive impairment-no dementia

DAT: dementia of Alzheimer type

DEP: depressive patients without cognitive impairment

DMS: delayed matching-to-sample task

DR-T: word list delayed-recall task

DSM: Diagnostic and Statistical Manual of Mental Disorders

DWI: diffusion-weighted MRI

EC: entorhinal cortex

fMRI: functional magnetic resonance imaging

FTD: frontotemporal dementia

fv-FTD: frontal variant of the frontotemporal dementia

GDS: Goldberg's Depression Scale

GNT: Graded Naming Test

HCP: hippocampal area

IADL: Instrumental Activities of Daily Living

IR-T: word list immediate-recall task

m-aMCI: multiple domain aMCI

MCI: mild cognitive impairment

MMSE: Mini Mental Status Examination

m-non-aMCI : multiple domain non-aMCI

MRI: magnetic resonance imaging

MTL: medial temporal lobe

MTT: multiple trace theory

NC: normal control subjects

NFT : neurofibrillary tangles

PAL: paired-associates learning

PCC : posterior cingulate cortex

PET : positron emission tomography

PHG: parahippocampal gyrus

PTSD: post traumatic stress disorder

QD: questionable dementia

rCBF: regional cerebral blood flow

s-aMCI: single domain aMCI

SD : standard deviation

SemD: semantic dementia

s-non-aMCI: single domain non-aMCI

SPECT: single photon emission computed tomography

TRMT : Topographical Recognition Memory Test

VBM: voxel-based morphometry

VD: vascular dementia

General introduction

Mild cognitive impairment (MCI) is defined as one or more cognitive deficit(s) of not sufficient severity to constitute a dementia but of greater severity than that of healthy individuals of the same age and education level (Petersen et al., 2001). When the cognitive deficit concerns memory, it is called amnestic MCI (aMCI). It has been shown that individuals with aMCI are at a high risk of developing dementia of Alzheimer type (DAT; Petersen et al., 1999). Moreover, the finding of medication for slowing cognitive decline of Alzheimer's disease (AD) and waiting for new more efficient ones (Roberson & Mucke, 2006) renders research on aMCI, and thereby preclinical markers, of crucial interest. However, the aMCI syndrome may have causes other than neurodegenerative diseases, such as psychiatric diseases, and no standardized method exists to distinguish incipient demented aMCI patients from those who will not develop dementia. The main purpose of this study is to detect specific markers of preclinical dementia to discriminate aMCI patients who will develop dementia from those who will not. To this end, we performed a two-year longitudinal study aiming to examine cognitive evolution of aMCI patients in order to discriminate declining from non-declining aMCI patients. At the end of the study, we compared declining aMCI's cognitive performances at baseline with those of the non-declining to detect markers of preclinical dementia. Based on their neural substrates, we theorized that deficits in topographical recognition memory and autobiographical memory could be neuropsychological markers of incipient dementia.

This thesis comprises 7 chapters. The first three chapters deal with theoretical foundations of the present work. Since aMCI is related to DAT, for better understanding, chapter 1 begins the theoretical backgrounds with the definitions of dementia and AD, before addressing the main subject of this thesis, aMCI and preclinical markers of AD. Chapters 2 and 3 provide an overview of autobiographical memory and topographical recognition memory respectively, addressing cognitive psychology, neural substrates and behavioral data in AD and/or MCI cases. Chapters 4, 5, 6 and 7 develop the experimental work of the thesis. Chapters 4 and 5 report on the results of the baseline and longitudinal studies respectively, of our aMCI patients, and chapters 6 and 7 focus on topographical recognition memory and autobiographical memory respectively, in aMCI patients.

Theoretical background

1 Mild cognitive impairment

As already mentioned in the general introduction of the current thesis, aMCI is characterized by a cognitive state of high risk of developing dementia and more particularly, DAT. Therefore, for better understanding, I shall begin this first chapter with definitions of dementia and AD, before addressing the main subject of this thesis, aMCI and preclinical markers of DAT.

1.1 Dementia and Alzheimer's disease

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994), dementia is defined by a very prominent memory impairment (in acquiring new information or in recalling new information stored). In addition to memory impairment there is one (or more) of the following cognitive disturbances: aphasia, apraxia, agnosia and/or dysexecutive disturbance. The cognitive disturbances cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

AD is a neurological disorder with initial memory impairment progressing relentlessly to dementia although in some atypical forms of AD, clinical presentation at onset is associated with visual symptomatology (Hof et al., 1997). AD was first described in 1906 by Alois Alzheimer, a German neurpathologist and psychiatrist. Alzheimer characterized the hallmarks of the disease describing a 51 year-old woman single case with memory disturbances, and two abnormal molecular structures in the brain: neurofibrillary tangles (NFT) and neuritic plaques, these latter being mostly constituted by extracellular aggregations of the amyloid β protein. AD was named later on in 1912 by Kraepelin (Möller & Graeber, 1998).

Clinical criteria used for a provisional diagnosis consist of the *National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association* (NINCDS/ADRDA; McKhann et al., 1984) criteria for possible or probable AD. However, diagnostic accuracy for probable AD is relatively low even at expert research centres where sensitivity is around 80% and specificity 70% (Knopman et al., 2001). A definite diagnosis of AD can only be made by neuropathology (McKhann et al., 1984), which is regarded as the gold standard. *DSM-IV* (American Psychiatric Association, 1994), including the DAT criteria, is another diagnostic instrument. Probable AD can be categorized as mild (early), moderate (middle), or severe (late) dementia (see fig. 1). In both of the above criteria, the critical definition for AD is a gradual onset and continuing decline as opposed to,

for instance, a sudden onset in vascular dementia. From the initial symptoms, disease progression can last up to 25 years, although typically the duration ranges from eight to 10 years. Without medical treatment or supervision, death often results from malnutrition or pneumonia. Some studies support the view that there is probably a transitional phase of cognitive impairment before a person reaches full criteria for dementia (fig. 1; Petersen, 2000). This transitional phase has been labelled by various names, such as mild cognitive impairment (MCI; e.g., Bozoki et al., 2001; Petersen et al., 1999). The duration of transition between normal aging and mild dementia remains to be determined.

Thus, AD would be not only characterized by dementia stages, but also by a preclinical dementia stage with mild cognitive impairment that does not interfere with social or occupational functioning.

1.2 Mild cognitive impairment

1.2.1 History

The concept of a memory impairment developing with aging was probably addressed first by Kral (Kral, 1962) with the term “benign senescent forgetfulness”. This term referred to memory changes that were relatively stable and not indicative of a progressive disorder. In 1986, the National Institute of Mental Health coined the term “age-associated memory impairment” (AAMI) including a subjective memory impairment, normal general cognition, no dementia, and an objective memory impairment one standard deviation (SD) below that of young adults (Crook et al., 1986). The limit of this concept was that no individual memory tests were specified, resulting in the possibility that all older individuals may qualify for the diagnosis of AAMI. With the International Psychogeriatric Association, Levy (1994) suggested a revision of the AAMI construct with the notion of “aging-associated cognitive decline” (AACD). Persons with AACD may have deficits in memory, attention, language, or visuospatial skills of at least one SD below age and education norms. Deficits are not sufficiently severe to impair functional activities. Another term, proposed by DSM-IV (American Psychiatric Association, 1994), “aging-related cognitive decline”, refers to the normal aging process without neurological or psychiatric disorders. Nevertheless, this concept did not address the issue of normal aging and incipient disease. The International Classification of Disease 10 (1992) proposed the concept of a mild cognitive disorder referring to an impairment of memory or concentration not due to dementia or other nervous system disorders but, rather, to systemic illness. Finally, the Canadian Study of Health and Aging developed the concept of “cognitive impairment-no dementia” (CIND; Graham et al.,

1997). This model includes all individuals falling in between healthy and demented states. It encompasses many disorders, from circumscribed memory impairment to chronic alcohol and drug use, psychiatric illness, mental retardation and vascular pathologies. Thus, CIND represents cognitive impairment that may or may not progress to dementia.

In the preceding paragraph, it has been shown that some terms are related to normal aging and others to pathology. With regard to AD, the concept of a transitional phase between normal aging and dementia would have been introduced by Flicker et al. (1991; in Dubois & Albert, 2004) and has been called variously incipient dementia, prodromal AD, isolated memory impairment and MCI (e.g., Bozoki et al., 2001; Petersen et al., 1999). According to Petersen and Morris (2003), mild cognitive disorder of ICD-10 (1992) is tangentially related to the notion of MCI whereas CIND encompasses MCI. The term MCI was first used in association with stage 3 of the Global Deterioration Scale for ageing and dementia (Flicker et al., 1991; Reisberg et al., 1982). This scale identifies seven clinical stages, four of which range from normality to mild dementia. People at Global Deterioration Scale stage 3 have subtle deficits in cognition and may have some impairment in executive functioning that affects complex occupational and social activities. Another system assessing the boundaries of ageing and dementia is the Clinical Dementia Rating (CDR; Hughes et al., 1982) including a stage of questionable dementia, i.e., some patients may have MCI whereas others mild dementia.

1.2.2 Clinical features of MCI

Petersen et al. (1999) argued that the Global Deterioration Scale and CDR severity rating scales are not diagnostic instruments, and that severity scores may confuse MCI with mild dementia. They focused on the amnesic aspect of MCI, that became the “amnestic” subtype of MCI in 2001 (aMCI). Petersen and the Mayo Clinic research group (2001) used the aMCI inclusion criteria: 1) memory complaint, preferably corroborated by an informant; 2) objective memory impairment inferior to 1.5 SD matched for age and education; 3) largely normal general cognitive function; 4) essentially intact activities of daily living; 5) not demented. Petersen and Morris (2003) pointed out that these criteria were *clinical*. That meant they were employed during a consensus meeting involving behavioural neurologists, neuropsychologists, geriatricians and nurses who had assessed the patients in a fashion similar to that used to make the diagnosis of dementia or AD.

Petersen and Morris (2003) indicated that subjective memory complaints are not reliable criteria by which to diagnose aMCI. Although they can reflect an affective state (e.g., Mol et al., 2006; Ritchie et al., 1996), they can also predict a subsequent cognitive decline

(e.g., Geda et al., 2006; Geerlings et al., 1999). Busse et al. (2003) indicated that subjective memory impairment did not seem to be very useful for the prediction of dementia if objective data on cognitive performance were available. Objective memory impairment is usually assessed by learning over trials or delayed recall on a multiple-trial free-recall task such as the Auditory Verbal Learning Test (Rey, 1964) or, possibly, the Wechsler Memory Scale-Revised or III, Logical Memory II, or Visual Reproduction II (Wechsler, 1987). In general, when delayed recall measures are assessed in a group, the MCI patients tend to fall 1.5 SD below age- and education-matched subjects from the Mayo normative data sample (Petersen et al., 1999). Likewise, the criterion of normal general cognitive function (e.g., attention, language, visuospatial function, problem solving…) involves a clinical judgment. Although not impaired, in group studies some of these domains are statistically reduced relative to control subjects of approximately 0.5 SD or less (Petersen & Morris, 2003). The activities of daily living are derived from a history taken from the subject and the informant and are documented using the Record of Independent Living and CDR (Morris, 1993; Smith et al., 2000; Weintraub, 1986). Finally, once the memory changes, general cognition and daily living have been assessed by the clinician, he/she makes it sure that the patient does not meet standard criteria of dementia (DSM-III-R, DSM-IV, or NINCDS-ADRDA).

Whereas Petersen et al. (1999) focused on the amnesic aspect of MCI, we have seen that the MCI term of CDR and Global Deterioration Scale includes other mild cognitive deficits than memory. Consequently, Petersen et al.'s (1999) MCI term became the "amnestic" subtype of MCI in 2001 (aMCI). Winblad et al. (2004) proposed that MCI "(i) refer[s] to cognitive deficits measurable in some form or another, and (ii) represent[s] a clinical syndrome that can be utilized to classify persons who do not fulfill a diagnosis of dementia, but who have a high risk of progressing to a dementia disorder". They recommended a MCI classification process (see fig. 2) in which the first step is a cognitive complaint by patients and/or informants. After the clinician has determined that the person is neither normal nor demented, but presents with a decline in cognitive functioning that does not cause impairment in functional activities, he/she determines the subtype of MCI by means of neuropsychological tests. The different subtypes distinguish between the presence or not of the impaired memory and the number of cognitive deficits. If the MCI patient presents only with impaired memory, then he/she is single domain amnestic MCI; if the patient has other cognitive impairments in addition to the memory disorder, then he/she is multiple domain aMCI. If the MCI patient presents with cognitive disorders not related to memory, then he/she is single domain non-amnestic MCI when there is one single cognitive impairment other than memory (e.g.; language and visuospatial), or multiple domain non-aMCI when there are

several cognitive impairments other than memory. Gauthier et al. (2006) pointed out that standard neuropsychological tests had established that poor performance on delayed recall indicated a high risk of progression to AD (Artero et al., 2003; Bäckman et al. 2005).

Finally, some disorders other than dementia, such as psychiatric disorders (e.g. depression) or medical disorders (e.g. trauma, sleep disorders or nutritional deficiencies) may contribute to cognitive impairments similar to those of incipient dementia (Aloia et al., 2004; Barnes et al., 2006; Geda et al., 2006; Lindeboom & Weinstein, 2004). Thus, when persons with MCI are followed over time, some progress to DAT or other dementia types, but some remain cognitively stable or even recover (Winblad et al., 2004). Following these observations, the criteria of MCI have been enriched by the addition of neuropsychiatric troubles and medical disorders as possible causes of MCI (Table 1; Gauthier et al., 2006; Petersen & Morris, 2005; Winblad et al., 2004). This new model emphasizes the limit of the syndrome of the MCI: the same subtypes of MCI may have different etiologies. For example, aMCI with single or multiple domain features may be caused by either prodromal AD or depression and in some cases by both at the same time, whereas the multiple domain non-aMCI subtype may be caused by prodromal dementia with lewy bodies or prodromal vascular dementia. The fact that MCI may be due to different possible causes led to intense research on markers of preclinical dementia to discriminate MCI patients who will develop dementia from those who will not.

1.2.3 Demographics and longitudinal data

The present section will address the prevalence and the conversion rate to dementia of different subtypes of MCI: single domain aMCI, multiple domain aMCI and single domain non-aMCI. Table 2 synthesizes the studies presented below.

Larrieu et al. (2002) examined community-dwelling individuals of the PAQUID (personnes âgées QUID) cohort, a prospective study, aged 65 years and older, in southwestern France. Among 1654 subjects, 58 were single domain aMCI (3.5%). This prevalence was similar to those of the community-dwelling studies of Busse et al. (2003) and Ritchie et al. (2001) who found 3% of single domain aMCI people among 1045 subjects aged 75 and over, and 3.2% among 833 individuals older than 60 years, respectively. The prevalence of the single domain aMCI is much higher in clinical cohorts with memory complaints who contact Memory Clinic. Thus, Rasquin et al. (2005) reported a prevalence of single domain aMCI of 14.4% among 118 patients older than 55 years. However, the difference of prevalence could come from the fact that these individuals were younger than those of the two preceding

studies and that the sample size was smaller. Variability of studies in terms of age ranges, sample size and origin of the sample renders difficult prevalence estimation of aMCI.

Concerning the conversion rate of dementia of the single domain aMCI, Larrieu et al. (2002) found that 8.3% per year of aMCI people progressed to AD as opposed to 1.7% per year of normal older people, over a five year period. The authors estimated the stability of the single domain aMCI across time and reported that among the 58 single domain aMCI at baseline, 24 (41.4%) were classified as normal and only 4 (6.9%) still had aMCI at 2-year follow-up. They also pointed out that this high rate of remission of aMCI could be due to the fact that diagnosis was only based on psychometric tests, unlike Petersen et al.'s study (1999), in which neurological, biological and neuroimaging examinations were performed in addition to neuropsychological assessment. Moreover, memory tests to screen single domain aMCI patients were not the same as Petersen et al. (1999); they used only the Benton's Visual Retention Test (Benton, 1965), a visual recognition memory test whereas Petersen et al. (1999) used the Auditory Verbal Learning Test (Rey, 1964) and the Wechsler Memory Scale-Revised (Wechsler, 1987). The Mayo research clinic group enrolled over 1900 subjects aged 65 years and above from Rochester, Minnesota, and followed them longitudinally on an annual basis for over 15 years (Petersen et al., 1990; 1999). They observed that single domain aMCI patients progressed to AD at a rate of 10% to 12% per year against 1% to 2% per year in normal control subjects (Petersen et al., 1999). After approximately six years, 80% of the aMCI cohort had declined into dementia (Petersen et al., 2001; see fig. 3). The two latter studies show that the assessment procedure is a highly variable factor in the rate of conversion of the single domain aMCI. In Ritchie et al.'s (2001) study, among 27 subjects classified as single domain aMCI by means of a memory test of 'learning and recalling first names', only two (7.4%) retained this diagnosis in wave 2 after one year. Twenty-one new cases of a single domain MCI appeared in wave 2, of whom only four (17.4%) were still considered to have single domain aMCI one year later. Receiver operating characteristics revealed an inability of the single domain aMCI to predict dementia status. From these results, the authors claimed that single domain aMCI was not temporally stable. Again, this inability to predict dementia could be due to the memory test used to diagnose single domain aMCI, among other variable factors.

Studies about multiple domain MCI vary in terms of definition, especially in terms of the cognitive functions assessed. In the following studies, the multiple domain aMCI definition refers to impairment on two or more cognitive domains including memory. Zanetti et al. (2006) showed that the prevalence of multiple domain aMCI was 8.5% in 400 community-dwelling people older than 65 and that 26% converted into subcortical vascular

dementia after a 3-year follow-up, the remaining multiple domain aMCI had stable cognitive impairment during this period. The single domain aMCI patients represented 7.8% of the sample and 35% developed into AD, whereas 65% remained stable. Meyer et al. (2002) recruited multiple domain aMCI from the community (mean age = 67.9; SD = ± 9.00) and found that 73 of 291 (25.1%) had met the criteria. Over a longitudinal follow-up (of about 4 years), 47.9% of the multiple domain aMCI developed AD, 20.5% vascular dementia (VD), and 31.5% exhibited persistent MCI or showed improvement at the time of data analysis. Moreover, the study failed to find differences between VD and AD in their predementia spectra of cognitive impairments. Bennett et al. (2002) followed 708 older participants of the Catholic clergy for up to 7 years, and found 26.6% of multiple domain aMCI (mean age = 78.6; SD = ± 6.8). During the follow-up, 34% of the multiple domain aMCI developed AD, a rate 3.1 times higher than those without cognitive impairment. Rasquin et al.'s study (2005) was one of the few studies to investigate the single domain non-aMCI for the development of AD or VD, in addition to aMCI and multiple domain aMCI. One hundred and eighteen participants older than 55 years were recruited from clinical cohorts in Maastricht and followed for 2 years. The multiple domain subtype of MCI (including memory impairment or not) was most prevalent (63.5%) and the aMCI least (14.4%). The single domain non-aMCI subtype represented 22.0% of the sample. The authors also recruited a cohort of 80 first-time stroke patients and found 73.8% of multiple domain MCI (including memory impairment or not), 26.2% of single domain non-aMCI but 0% of single domain aMCI. Results of the follow-up study revealed that multiple domain MCI had the highest sensitivity (percentage of patients detected positive among patients with disease) for both AD (80.8%) and VD (100%). Single domain aMCI had the highest specificity (percentage of patients detected negative among patients without disease) for AD (85.9%) and VD (100%). By contrast, the single domain non-aMCI subtype had a very low sensitivity for both AD and VD (3.8% vs 0%; respectively) and similar specificity (72.8% vs 73.8%; respectively), in line with the fact that this latter subtype of MCI is thought to be a prodrome of frontotemporal dementia (Gauthier et al., 2006). Yaffe et al. (2006) studied 327 patients with MCI (250 with single domain aMCI, 34 with single domain non-aMCI subtype, and 43 with multiple domain MCI including memory or not) who were followed longitudinally for 3 years. In the aMCI single and multiple domains, 76% progressed into AD and 50% to VD whereas all of the patients of the single domain non-aMCI subtype developed frontotemporal dementia.

In summary, these studies revealed that the prevalence and the conversion rate to dementia of the different subtypes of MCI are related to factors of variability such as sample size, age, origin of sample and screening tests, especially memory tests screening the single

domain aMCI subtype. These data highlight the importance to take into account all of these factors to carry out MCI studies. In spite of this variability, the multiple domain aMCI subtype seems to be the most sensitive to AD and VD. Results concerning the single domain aMCI subtype are more diverging; it would be specific either to both AD and VD or only to AD. As for the single domain non-aMCI subtype it would be sensitive and specific to frontotemporal dementia.

In the current thesis, I will focus on the single domain aMCI, from now on referred to as aMCI.

1.2.4 Pathogenesis

There is a paucity of studies about the neuropathological substrate of aMCI. Indeed, very few cases of patients who died while their clinical diagnosis was aMCI, are reported. Petersen et al. (2006) autopsied the brains of 15 aMCI patients and found that whereas the regional involvement by NFT was associated with clinical impairment across the spectrum of healthy to aMCI to AD, the amyloid burden of aMCI patients was more similar to that of the healthy individuals. Thus, they concluded that neuropathological features of aMCI seemed to be intermediate between those of ageing and those of very early AD. With regard to vascular lesions, it was reported that MCI patients (any subtype of MCI) had intermediate levels of cerebral infarctions between people without cognitive impairment and demented patients (Bennett et al., 2005).

These pathological observations show that the aMCI syndrome is an intermediate level between healthy ageing and dementia.

1.2.5 Neuroanatomy of brain structures damaged early on in AD

Based on neuropathology and neuroimaging studies, the medial temporal lobe (MTL), the retrosplenial and posterior cingulate cortices are known to be altered very early on in AD (e.g., Braak & braak, 1991; Chételat et al., 2003a; Dickerson et al., 2004; Kogure et al., 2000; de Toledo-Morrell et al., 2004). Thus, their alterations may constitute preclinical markers of dementia. Therefore, in order to better understanding the following section “Markers of preclinical AD”, the neuroanatomy of these three neural structures will be described in the current section.

The MTL is not a homogeneous region but consists of different structures that can be distinguished on the basis of histological patterns and their connectivity with other regions

(Amaral & Insausti, 1990). According to Amaral's terminology (Lavenex & Amaral, 2000; Amaral, 1999), these structures are the hippocampus proper, dentate gyrus, subicular complex (subiculum, presubiculum and parasubiculum), and entorhinal, perirhinal, and parahippocampal cortices (fig. 4). The entorhinal cortex (EC) corresponds to the anterior parahippocampal gyrus (PHG), while the parahippocampal cortex makes up the posterior PHG. Most memory studies use the term hippocampus to refer to the hippocampal formation. In Amaral's terminology, this latter includes the dentate gyrus, the hippocampus (*cornu ammonius* fields, CA1-CA3), the subicular complex and the EC. The perirhinal and parahippocampal cortices are reciprocally connected to the hippocampus, via the EC. More precisely, the perirhinal and parahippocampal cortices convey inputs from unimodal and polymodal association cortices to the hippocampus via the EC, which in turn projects efferent connexions back to the neocortex (Lavenex & Amaral, 2000).

The cingulate gyrus is part of the limbic system. It lies, on the medial wall of the cerebral hemisphere, immediately above the corpus callosum and extends beyond and below the splenium of the corpus callosum (Morris et al., 2000). It is subdivided into two major structures, the retrosplenial cortex and the cingulate cortex, the posterior cingulate cortex (PCC) arching around the retrosplenial cortex (fig. 5). Both retrosplenial and posterior cortices have reciprocal connections not only to each other, but also to the mid-dorsolateral prefrontal cortex (Goldman-Rakic et al., 1984; Kobayashi & Amaral, 2000; Morris et al., 2000), parahippocampal cortex (Suzuki & Amaral, 1994), presubiculum and EC, as well as thalamic nuclei (Amaral & Cowan, 1980).

1.2.6 Markers of preclinical DAT

As already seen earlier, the fact that aMCI may be due to different possible causes raises the question of how to discriminate aMCI patients who will develop dementia from those who will not. This question led to intense research on preclininal markers of dementia. Early diagnosis of AD is currently based on clinical and neuropsychological assessment (neurological, cognitive and behavioural assessments). Imaging data allowed increased accuracy of the diagnosis in assessing atrophy or dysfunction of a cerebral structure. On this basis, I shall review the recent studies concerning markers of incipient dementia using structural magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) techniques, and neuropsychology.

1.2.6.1 Markers of preclinical DAT and structural MRI

Based on the sequence of NFT deposition in the transentorhinal, entorhinal cortices and then hippocampal formation in the development of early AD pathology (Braak & Braak, 1991 and 1996; Braak et al., 1999), it has been suggested that atrophy of these structures might predict progression to DAT in aMCI patients. Some studies used the region-of-interest analysis on the hippocampus and the EC to examine this hypothesis. Killiany et al. (2002) found that the volume of the EC distinguished the patients who were to develop dementia with considerable accuracy (84%), whereas the hippocampal measure did not. DeToledo-Morrell et al. (2004) reported that although entorhinal and hippocampal volumes were found to be independent predictors of the likelihood of conversion to DAT, it was the right hemisphere entorhinal volume that best predicted conversion with a concordance rate of 93.5%. Other studies have produced less clear-cut results, which might reflect difficulties in delineating the EC on MRI (e.g., Du et al., 2001; Scheltens et al., 2002). However studies using a standardized visual rating scale, which permits easier assessment of MTL atrophy, did not obtain better predictive accuracy than those using volumetric methods (on the order of 80 to 90%) (e.g.; Korf et al., 2004; Visser et al., 2002). By contrast, a recent study, performing measurement of hippocampal apparent diffusion coefficient with diffusion-weighted MRI (DWI) improved the prediction of development of DAT (Kantarci et al., 2005). DWI quantifies the alterations in water diffusiveness resulting from microscopic structural changes, which may be apparent earlier than the macroscopic change in AD. Nevertheless, this study limited neural exploration to the hippocampus and did not observe microstructure of the EC in the aMCI patients.

Voxel-based morphometry (VBM) is an automated method of measuring brain atrophy. It objectively maps gray matter loss after anatomical standardization analogous to that used in functional neuroimaging. The advantage of VBM over analyses based on region of interest is an unbiased result from exploration of the whole brain. This approach has been reported to show higher accuracy of discriminating AD and controls than preceding methods. Hirata et al. (2005) showed that significant decline in gray matter in the bilateral EC distinguished evolving aMCI patients from age-matched controls with an accuracy of 87.8%. Besides the EC, another VBM study found that MCI patients who developed DAT had greater atrophy in the bilateral superior temporal gyri, and right inferior frontal gyrus compared with those who did not progress (Bell-McGinty et al., 2005). Nevertheless, MCI patients of this study included both MCI of the amnestic subtype and MCI of the non-amestic subtypes, which may have extended vulnerable neural structures to early AD.

Results obtained by the different techniques used to explore cerebral structures support the idea that hippocampal and entorhinal atrophies in aMCI patients are predictive of cognitive decline, most particularly a loss of gray matter in the EC.

1.2.6.2 Markers of preclinical DAT and fMRI

In spite of the different functional neuroimaging techniques used in the studies (PET, SPECT, rCBF, fMRI; see pages 13 and 14 for abbreviations), the heterogeneity of the aMCI groups (single- or multi-domain aMCI, different age groups, different stages along the aging-MCI-AD continuum) and the different cognitive tasks undertaken by the participants, several brain structures have been found vulnerable to very early AD: temporoparietal cortex, PCC and PHG.

In a PET study, Chételat et al. (2003a) showed that 100% of the aMCI with hypometabolism in the right temporoparietal cortex converted to DAT. Chételat et al. (2005) reinforced these results further by reporting that metabolic defects in this area were predictive of subsequent cognitive decline in aMCI patients.

Chételat et al.'s (2003a) PET study also showed that 94% of aMCI with hypometabolism in the right posterior cingulate gyrus converted to DAT. In particular, Kogure et al. (2000) reported that aMCI patients who progressed to DAT had, as a first sign, a reduction of regional cerebral blood flow (rCBF) in the retrosplenial cortex. Ries et al. (2006) compared the functional integrity of the PCC between aMCI patients and healthy older adults. They used two fMRI tasks known to elicit activation in this structure: a visual episodic recognition task and a self-appraisal task. In the latter, a set of trait adjectives was presented to the participants who had to decide whether each word described him/her. The authors hypothesized that PCC activation would uniformly attenuate across tasks because of the structural vulnerability of this region to AD pathology. Results showed that in the healthy older adults, the PCC was the sole region commonly active during both tasks. On the episodic retrieval task, comparisons between healthy subjects and aMCI patients revealed significantly attenuated PCC activation in the aMCI group. By contrast, no significant difference between the groups was found in PCC activation during the self-appraisal task. The authors suggested that this result could come from the differences in the nature of memory retrieval required in both tasks. Indeed, unlike the episodic recognition task, the self-appraisal task is related to highly rehearsed information about the self without spatio-temporal context; it belongs to personal semantic memory. These results reflected functional degradation of the PCC in aMCI patients during episodic retrieval whereas its role was more preserved in the self-

appraisal task. This study, in addition to revealing impaired PCC in aMCI, highlighted the importance of the nature of the memory to detect brain structure dysfunction.

Chételat et al. (2003b) attempted to explain the dysfunction between the PCC and MTL observed in aMCI patients. They examined the relationships between brain alterations, as measured by both structural MRI and functional PET, and episodic memory performances in aMCI patients. The latter underwent a verbal memory task where either encoding or retrieval was preferentially probed. Results revealed both encoding and retrieval deficits in aMCI. The encoding impairment correlated with hippocampal area (HCP; including amygdala, anterior hippocampus and Brodmann area 34) atrophy and hypometabolism, while retrieval deficits were related to both HCP atrophy and posterior cingulate hypometabolism. A metabolic reduction observed by PET reflects both neuronal lesions and synaptic dysfunction. As the HCP is altered early on AD lesions (Braak et al., 1999; Braak & Braak, 1991) and the PCC is highly interconnected with the HCP structures, the authors suggested a mechanism whereby retrieval impairment in aMCI is subtended by posterior cingulate functional disruption as a result of decreased connectivity with the atrophied HCP. This suggestion supported the view that PCC dysfunction would result from remote effects of the MTL.

Other studies suggested that compensatory alterations in the connecting cortical areas of the MTL might occur as a result of neural reorganisation following early AD damage. Dickerson et al. (2004) found that the right PHG was functionally modified in evolving aMCI before the first clinical signs of dementia. In a 2.5 year-long longitudinal follow-up study, they showed that aMCI patients who had progressed to DAT presented a larger extent of fMRI activation in the right PHG during encoding of complex pictures at baseline whereas they performed as well as the stable aMCI in the picture recognition task (the sample included both single and multiple domain aMCI). The extent of MTL activation correlated with postscan memory test performance. The authors suggested that the larger activation of the PHG reflected a compensatory response to the evolution of AD. Indeed, pathology in the medial temporal regions may reduce the density of the neurons that rapidly fire in response to a stimulus. This decrease of density may induce recruitment of adjacent areas that would be reflected by a larger extent of fMRI response and allow evolving aMCI to obtain the same recognition score as the stable aMCI. Hämäläinen et al. (2006) reinforced Dickerson et al.'s (2004) proposition, also finding compensatory neuronal response in aMCI patients. The authors explored changes in fMRI activation in relation to underlying structural atrophy comparing elderly controls, aMCI and AD patients. The fMRI paradigm consisted of associative encoding of novel picture-word pairs. Structural analysis of the brain was

performed using VBM and hippocampal volume. Behavioral data indicated that encoding performance was similar between controls and aMCI, but that AD patients performed more poorly than controls. The VBM revealed that aMCI patients compared to controls had significant gray matter atrophy in the left anterior hippocampus but no significant differences were found between aMCI and AD. Moreover, the hippocampal volume indicated that controls and aMCI patients were similar whereas AD patients had global hippocampal atrophy. The aMCI patients exhibited significantly greater fMRI responses in the fusiform gyrus, the posterior PHG and the hippocampus when compared to controls. By contrast, the AD patients did not reveal greater activations in any brain areas when compared to either aMCI patients or controls. Like Dickerson et al. (2004), the authors suggested that this increased activation in the aMCI patients might reflect compensatory mechanisms, i.e. activation of differential neuronal networks in order to compensate for the evolving dysfunction of the MTL while trying to achieve the level of controls in the behavioural performance. Importantly, the authors found a negative correlation between hippocampal volume and fMRI activation in the posterior PHG, indicating that patients with smaller hippocampal volumes elicited stronger parahippocampal activation. No such correlation was found either in the controls or the AD patients. Considering these results and that the VBM indicated that the hippocampal atrophy in aMCI was located in the anterior part of the hippocampus, the authors suggested that the increased posterior MTL activation might be an attempt to compensate for the atrophy in the anterior MTL structures.

These last studies showed hypometabolism of the PCC and hyperactivation of the PHG associated with hippocampal atrophy. Dickerson et al. (2005) addressed the question of the chronology between increased/decreased activation and atrophy of the MTL in the evolution of AD. They compared three groups of older persons: i) cognitively intact individuals, ii) aMCI patients, and iii) mild AD patients. All participants performed a face-name associative task during fMRI scanning, and were tested for recognition of stimuli in postscan. The aMCI patients did not differ from the older controls in their performance on the post-scan recognition memory task whereas AD patients performed more poorly. The fMRI analysis showed that, on the one hand, aMCI patients had a greater extent of hippocampal activation than controls, and, on the other hand, that AD patients had a lesser extent of hippocampal activation than controls and aMCI patients. Concerning the EC, aMCI patients did not differ from controls in extent of activation, but patients with AD showed a lesser extent of activation than both the preceding groups. Hippocampal or entorhinal volumes did not differ in aMCI patients and controls, but AD patients had smaller volumes for both brain structures. These results thus suggested that functional alterations within MTL regions during

the evolution of AD pathology may precede the development of significant atrophy. They also supported the hypothesis that there is a phase of increased MTL activation very early on in the course of AD followed by a phase of decreased activation.

In summary, MRI data report that atrophy of the MTL in AD would alter connected brain structures (e.g., PCC and the temporoparietal cortex) in a chronological progression firstly by increased activation (probably reflecting a compensatory mechanism), then by decreased cerebral activity and finally by atrophization. In contrast to the evolution of NFT in AD, fMRI data seem to report that the hippocampus would be altered before the EC. Further studies are needed to explain these differing observations.

1.2.6.3 Markers of preclinical AD and neuropsychology

To date no neuroimaging techniques allow detection of AD but if this technique is coupled with clinical assessment, then diagnosis is far more accurate (Thomas-Anterion & Laurent, 2006). The first cognitive symptoms of AD would be episodic memory impairment (Collie & Maruff, 2000; for a review). Both encoding and retrieval have been observed to be impaired in aMCI (Chételat et al., 2003b) although some authors found that encoding was more altered than retrieval in aMCI (Wang & Zhou, 2002). This pattern matches the known distribution of neuropathology (Braak & Braak, 1991; 1999) and imaging studies (see preceding section), which first involves the MTL.

The main criteria to choosing a test are sensitivity, e.g. ability to detect very early AD, and specificity, e.g. their ability to differentiate AD patients from healthy subjects or patients with other diseases. Based on the localization of the first NFT lesions in the EC, supported by dysfunction of this cerebral region observed by imaging techniques, research will focus on tests sensitive and specific to damage of this cerebral region. Deficit in recognition memory has been reported to be associated with lesions of adjacent structures of the hippocampus but not the hippocampus proper nor its diencephalic target (Aggleton & Shaw, 1996; Aggleton & Brown, 1999). Consistent with this, Barbeau et al. (2004) designed a visual delayed matching-to-sample task (DMS48) to assess visual recognition memory in aMCI patients. They obtained scores between those of control subjects and patients with mild AD on the DMS48. Seventy eight percent of them had impaired scores (1.5 SD below the mean). Examining the same aMCI sample as Barbeau et al. (2004) in a SPECT study, Guedj et al. (2006) found two different subgroups of aMCI. Those who succeeded in the DMS48 exhibited relative hypoperfusion of the left prefrontal cortex, which included orbitoventral and dorsolateral areas. In contrast, those who failed on the DMS48 showed bilateral relative hypoperfusion of the temporal lobes including bilateral entorhinal, perirhinal, hippocampal, and temporobasal

cortices, extending to the temporo-occipital junctions. These results suggest that the DMS48 may be useful to detect aMCI patients at a high risk of AD. Ivanoiu et al. (2005) tested recognition memory by means of the “Doors” Test (Baddeley et al., 1994) in aMCI patients. Follow-up assessment after 12 to 18 months allowed them to differentiate aMCI patients who had developed DAT (evolving aMCI) from those who had not (stable aMCI). Baseline cognitive comparisons revealed that the part A of the “Doors” Test could discriminate between both aMCI groups (mean of evolving aMCI: 6.6/12, SD: 2.9; mean of stable aMCI: 9.9/12, SD: 3.0; $p< 0.05$), unlike a verbal cued recall task which was nevertheless sensitive to aMCI. Another visual free delayed-recall test (the “Shapes” Test; Baddeley et al., 1994) was also significantly lower at baseline in the evolving aMCI patients than in the stable ones, and was more sensitive than the visual recognition memory test (mean of evolving aMCI: 4.4/12, SD: 3.1; mean of stable aMCI: 8.9/12, SD: 2.7; $p< 0.05$). On this basis, Ivanoiu et al. (2005) proposed that when performance on visual memory tests (recognition and free-delayed recall tasks) is impaired, as well as on verbal memory tests, the risk of evolution to DAT is high.

Two complementary studies examined questionable dementia (QD) individuals with subjective complaints of memory loss but without objective memory impairment, as well as aMCI patients. Two years after the initial assessment, some QD patients had developed DAT (qualified as “converters”). A test of spatial learning, the paired-associates learning (PAL) test (Sahakian et al., 1988) from the Cambridge Neuropsychological Test Automated Battery (CANTAB), was revealed to be sensitive and specific to QD converters (Blackwell et al., 2004; Lee et al., 2003; Swainson et al., 2001). Another advantage of the PAL was its insensitivity to depression and frontotemporal dementia. Furthermore, with the addition of a difficult object-naming test -the Graded Naming Test (GNT; McKenna & Warrington, 1980) of the same battery- outcome was predicted with a very high level of accuracy (100% for the 40 patients of this sample). These results suggested that semantic memory/language would be impaired early on in the course of AD. This impairment in MCI patients implies dysfunction beyond the hippocampus and the EC, extending into more lateral neocortical regions. Dudas et al. (2005), who found that aMCI patients had deficits in both episodic and semantic memory, are in agreement with this idea although they did not distinguish converter aMCI from non-converters. Consistently, Chételat et al. (2005) reported that delayed episodic memory and category and semantic autobiographical fluencies were predictive of subsequent cognitive decline in aMCI patients (lower initial scores were associated with greater decline). By contrast, episodic autobiographical fluency was not predictive of further cognitive decline. The authors suggested that in aMCI patients, those with lower delayed recall or semantic memory performances would deteriorate more rapidly than those with higher performances.

In summary, aMCI patients with deficit in episodic memory and more particularly in recognition and visuospatial memory associated with semantic memory impairments would be at a high risk of developing dementia.

In spite of the important variability of aMCI in terms of prevalence and conversion rate to dementia, some preclinical markers appear to be reliable for the prognosis of aMCI: (i) EC and hippocampal atrophy for structural MRI markers; (ii) hypometabolism in the temporoparietal cortex and the PCC, and greater extent hippocampal and PHG activation for functional markers and (iii) deficits in non-verbal recognition, visuospatial and semantic memory tests for neuropsychological markers.

2 Autobiographical memory (AbM)

In the preceding sections, we have reported that the MTL and the retrosplenial/PCC areas are among the first brain structures to be impaired by AD. Therefore, tests sensitive and specific to damage of these cerebral regions would be of great interest for research on neuropsychological markers of AD. On this basis, in the experimental work of the present study, we examined AbM and emotion related to this memory in aMCI patients, both sustained by the MTL and the retrosplenial/PCC areas. Thus, an overview of AbM and the associated emotion functioning is provided in the present chapter, outlining their definition and neural substrates, as well as behavioral data in the context of AD.

2.1 AbM in Endel Tulving's model of episodic memory

2.1.1 Multiple memory system

In traditional thought, there was only one "kind" of memory, although in the 19th century some philosophers and experimentalist psychologists suggested that memory was a composite faculty (Maine de Biran, 1804, in Maine de Biran, 1929; James, 1890). In the 1960s, observations of *dissociations* in amnesic patients — the ability of patients to exhibit instances of fully preserved learning and memory in the face of otherwise profound memory deficits— argue for multiple memory systems. In 1972, Tulving elaborated his multiple memory system distinguishing episodic and semantic memory in terms of content. The former referred to personally experienced events, while the latter referred to general facts. Memory systems have been defined as organized structures of more elementary operating components, the latter consisting of a neural substrate and its behavioral or cognitive correlates (Tulving, 1972, p. 386). Tulving's model has been further developed and refined supported more recently by functional neuroimaging investigations (Tulving, 2002 for a review).

Schacter and Tulving (1994) argued for distinctions among five major memory systems: procedural memory refers to the memory of skills which at an earlier time had been acquired slowly and with effort, but after acquisition are retrieved nonconsciously and largely automatically (e.g., learning to ride a bike, acquiring reading skills); the perceptual representation system (PRS) can be viewed as a collection of domain-specific modules that operates on perceptual information about the form and structure of words and objects; working memory maintains and manipulates items in memory for a relatively short period of time (mental calculation); semantic memory refers to knowledge of language, concepts, and facts that are shared by individuals within a culture and not tied to a particular spatio-temporal

context (e.g., knowledge that Paris is the capital of France); episodic memory is considered as a distinct neurocognitive (brain/mind) system that enables humans to consciously re-experience, spatially and temporally, specific events in their own lives (e.g., when I went to the cinema one month ago). It includes information about both the content of the experience and the spatial and temporal context in which it occurred.

It is important to note that the term 'episodic memory' is used in two different ways in the literature (Kopelman and Kapur, 2001; Wheeler et al., 1997). Thus, recalling an experimental stimulus (e.g., words or pictures) and the context in which it was presented ("an event") can have the same status as recalling events in one's own life. However, unlike the former, the latter information is self-related and therefore corresponds to autobiographical episodic memory. More recently, based on neuroimaging studies, Gilboa et al. (2004) suggested AbM as a separate system. Accordingly, in the current dissertation, I shall distinguish the term *AbM* from *episodic memory*, except in Tulving's theory where I shall keep the latter term.

2.1.2 Self, autonoetic awareness and subjective sensed time

In the current view, memory systems are not only described in terms of the nature of the stored information but they also rely on different forms of consciousness (see Tulving, 1985, 2001, 2002; Wheeler et al., 1997; Wheeler, 2000 for detailed reviews). In this section, I will only cite episodic, semantic and procedural memory systems as in Tulving's paper "memory and consciousness" published in 1985.

Autonoetic (self-knowing) awareness, involved in episodic memory, is a feeling of one's experiences in the continuum of subjective time that extends both backward into the past and forward into the future (Tulving, 2001). The form of autonoetic awareness that extends into the past refers to the term "remembering" or conscious recollection. Thus, episodic memory requires a traveller ("self"), subjective sensed time and autonoetic consciousness, which confer its unicity in comparison with other memory systems. Based on neuropsychological and developmental studies, Wheeler et al. (1997) proposed that autonoetic capacity was underpinned by the frontal lobe. In the same way, semantic memory is characterized by *noetic* (knowing) awareness and procedural memory by *anoetic* consciousness. Noetic awareness is one's ability to be aware of information about the world without a sense of self and mental time travel, whereas in *anoetic* consciousness, the information is retrieved in the absence of consciousness and consequently of mental time travel (Tulving, 1985).

2.1.3 AbM and personal semantic memory

Based on the first definition of episodic memory (Tulving, 1972, 1983), AbM has been regarded as episodic in nature. Besides past personal events, one's autobiography implies personal knowledge not tied to a particular spatio-temporal context. In 1988, Tulving et al. reported the case of the patient KC who could not evoke any autobiographical memories (AbMs) but could recall general knowledge of his past. On the basis of this observation, the authors proposed distinguishing AbM between an episodic component and a semantic component. The semantic component has been termed as "personal semantic memory" by Tulving et al. (1988) and as "personal semantics" by Kopelman et al. (1989).

2.2 Cerebral substrates of AbM

Recent neuroimaging data of AbM reveal an interactive network of predominantly left-lateralized and medial brain regions (Svoboda et al., 2006 for a review). This network mainly involves the MTL, considered as the "epicenter" of the AbM network by Gilboa et al. (2005), and the retrosplenial/posterior cingulate cortices (Maguire, 2001a; Svoboda et al., 2006; both for reviews).

2.2.1 The role of the MTL in memory

There are two main theories concerning the role of the MTL in human memory. According to the *standard model of consolidation* (Squire & Alvarez, 1995), episodic and semantic memory consolidation processes begin when information, registered initially in the neocortex, is integrated by the MTL and related structures in the diencephalon (anterior thalamus and mammillary bodies) to form a memory trace that consists of an ensemble of bound hippocampal complex-neocortical neurons (Moscovitch, 1995, 2000; Moscovitch et al., 2005). The MTL are considered to be temporary memory structures, needed to store and retrieve memories only until consolidation is complete. Permanent memories are consolidated either in the adjacent regions of the MTL or in the lateral temporal neocortex (e.g., Bayley et al., 2003; Manns et al., 2003). The time it takes for consolidation corresponds to the temporal extent of retrograde amnesia (RA) following lesions of the MTL and diencephalon. RA means that memories acquired most recently are most severely affected whereas more remote memories are retained normally, having been fully consolidated before the injury. Studies are divergent concerning the duration of consolidation: from just a few years for Graham and Hodges (1997) to 10 years for Reed and Squire (1998), to over 10 years for Rempel-Clower et al. (1996). Such a model can explain on the one hand, impairment of recent memories in amnesic syndromes and early AD where the MTL is affected at the very beginning of the

disease, and, on the other hand, impairment of remote memory in semantic dementia, where the neocortex is damaged whereas the MTL is relatively spared at the early stages. The standard model did not draw a distinction between episodic and semantic memory systems. Thus, damage to the MTL is thought to cause temporally graded RA for both episodic and semantic memory, i.e., patients show an equal impairment in the retrieval of recently acquired semantic as well as episodic memories, while all remote memories are recalled normally. However, clinical studies revealed contradictory issues in relation to this theory: the types of memories that are affected and the duration and extent of RA. Indeed, evidence of global episodic amnesia (regardless of the time period) resulting from MTL damage (Nadel & Moscovitch, 1997; Fujii et al., 2000; Cipolotti et al., 2001) and RA severity varying between both types of memory systems, episodic or semantic (Kapur, 1999, for a review), cannot be explained by the standard model of consolidation.

To account for these data, Nadel and Moscovitch (1997) formulated the *multiple trace theory* (MTT), which was recently updated (Moscovitch et al., 2005; see also Moscovitch et al., 2006). Like the standard model, the MTL (and possibly the diencephalon) encodes information that is consciously attended to and binds the neocortical (and other) neurons that represent that experience into a memory trace. In this theory, the MTL is not a temporary memory structure, but is considered as a pointer, or index, to the neurons of posterior association cortices where the details of one's life experiences are stored. Instead of a prolonged consolidation process as in the standard model, each time a memory is retrieved, a new hippocampally mediated trace is created. Consequently, old memories are represented by more or stronger MTL-neocortical traces than new ones, and they are therefore less susceptible to brain damage (Moscovitch et al., 2005). As long as a memory retains its vividness and detail it is dependent on the MTL, no matter what their age. The temporal extent and severity of RA for episodic memory, therefore, is related to the extent and location of MTL damage (Moscovitch et al., 2006). In the MTT, the consolidation of semantic memory is the same as in the standard model: semantic memory benefits from MTL contribution for a limited period after which it can be supported solely by the neocortex. Some episodic memories lose their episodic character with time, retaining only the gist of the event and becoming more semantic or generic (repeated, temporally extended events). Once transformed, they are no longer mediated by the MTL but by adjacent neocortex (Addis et al., 2004; Moscovitch et al., 2006 for a review; Piolino et al., 2003). Consequently, in this dissertation, I will adopt the term of episodic AbMs for AbMs with episodic character and generic AbMs for those which lost their episodic character.

2.2.2 Retrosplenial and posterior cingulate cortices in memory

The only case about AbM with (tumoral) damage to the retrosplenial cortex is described by Gainotti et al. (1998). The patient AP presented with retrograde amnesia for past personal event limited to the last 10 years, together with non verbal anterograde memory deficits. By contrast, the personal semantic memory seemed to be preserved. In fMRI studies, Gilboa et al. (2004) and Piefke et al. (2003) found that the retrosplenial cortex was more active for recent memories than for remote ones. Moscovitch et al. (2005) claimed that these findings was consistent with the hypothesis that this structure is needed to activate, integrate, and construct generic visual representations in the posterior neocortex (Conway & Pleydell-Pearce, 2000), which may be more plentiful for recent than for remote memories. More precisely, the posterior areas are thought to store the multimodal representations (sounds, visual images, smells and other sensory components) associated with one's life experiences. Neuropsychological findings point out the role of visual imagery (as used here, "visual imagery" means pictorial or object imagery, not linguistic imagery such as the shape of letters or words) in recollection of autobiographical events (Rubin, 1995; Greenberg et al., 2005). For instance, patients who exhibited particular visual imagery deficit, specifically an impairment of long-term visual memory, following damage to the occipital lobes were impaired in retrieval of vivid personal memories (e.g., Greenberg et al., 2005; Rubin & Greenberg, 1998). The function of the retrosplenial cortex contrasts with that of the PCC, which is apparently directly associated with retrieval of vivid personal memories (Moscovitch et al. 2005).

2.3 AbM and emotion

The study of emotion in cognition has only been developed for a few years as it has been viewed as too subjective and contradictory to reason (Damasio, 1994 and 2000). However, some cognitive neuroscientists postulated that emotion interacts with all aspects of cognition (Dolan, 2002; Phelps, 2006), especially with memory. Indeed, in addition to the AbM characteristics described by Tulving, emotion is another component very often involved in AbM.

2.3.1 Definition of emotion

Emotion is not a unitary concept but consists of at least four major components (Clore & Ortony, 2000; Kolb & Taylor, 2000) involving (i) a physiological component characterized by the activation of the autonomic and central nervous systems. In particular, it is described in terms of visceral and musculoskeletal changes, and a range of neurochemical and

neuroanatomical processes; (ii) a behavioural component referring to different behavioural acts such as escape, attack or defence; (iii) a subjectively-experienced component which is the subjective feeling usually referred to as "affect", in other words, how an emotion is felt by a subject; (iv) a cognitive component which refers to the conscious assignment of value or emotional meaning to an external or internal event (e.g., perception, thought, attitude; see Denkova et al., 2006).

In neuropsychological studies, verbal assessment of emotion typically involves asking subjects to rate valence or intensity of emotion. Valence refers to attribution of a subjective positive or negative value to an event, while intensity refers to how strongly an emotion is subjectively experienced.

2.3.2 Influence of emotion on AbM

From a cognitive standpoint, emotion and memory interact at various stages of information processing, from the encoding and consolidation of memory traces to their retrieval.

Emotion influences AbM. Some studies demonstrated that subjects recall emotional items better than neutral ones (see Hamann, 2001; LaBar & Cabeza, 2006 for reviews). The general improvement of memory for emotional material is called "the emotional enhancement effect". Studies on healthy people have demonstrated that emotional experiences tend to be well-remembered. In particular, emotional memories are more vivid than neutral ones, i.e., they may be remembered better and with more sensory-perceptive details (e.g., Comblain et al., 2005; Schaefer & Philippot, 2005; Talarico et al., 2004). Retrieval of vivid AbMs seems to be affected by intensity of emotion rather than its valence (Talarico et al., 2004). Interestingly, Piefke et al. (2003) observed that recent AbMs of healthy young adults had a higher emotional intensity than childhood memories.

Emotional disorders cause deficits in AbM. For instance, depressive patients show difficulties when they are asked to recall episodic AbMs, whereas they tend to recall spontaneously more generic AbMs than healthy subjects (Williams & Dritschel, 1992). Moreover, they retrieve fewer positive memories than control subjects (Lemogne et al., 2005). In post traumatic stress disorder (PTSD) vivid and distorted memories of the traumatic experience come to mind involuntarily (Brewin et al., 1996; Conway et al., 2004). However, patients with PTSD show poor recall in retrieving voluntarily episodic AbMs (e.g., Harvey et al., 1998; McNally, 1997; Raes et al., 2005).

2.3.3 Cerebral substrates of emotion in AbM

It has been reported that patients with right-sided MTL damage recall fewer negative and high-intensity emotional memories than patients with left-sided MTL, while the latter show performances similar to the control subjects (Buchanan et al., 2006). This study is in agreement with Piefke et al.'s fMRI study (2003), where negative AbMs were associated with activation in the right middle temporal gyrus. By contrast, the authors reported that the retrieval of positive AbMs was associated with an activation peak in the bilateral entorhinal region. These findings provide evidence that the right temporal lobe plays a crucial role in emotional AbMs, especially in negative ones. Amygdala is another cerebral structure which would also be associated with positive and negative AbMs. Indeed, some functional imaging studies have demonstrated increased amygdala activity in response to highly arousing positive and negative stimuli (Hamann & Mao, 2002; Hamann et al., 2002). But these results remain much debated in the majority of investigations (Denkova et al., 2006; Maguire & Frith, 2003). Finally, Piefke et al. (2003) suggested that the retrosplenial cortex was involved in recent higher emotional intensity.

To summarize, emotion is a complex cognitive process. It has an influence on AbM, the most emotional AbMs tending to be the best remembered. Several cerebral structures have been reported as being involved in the emotion of AbM: the MTL, the amygdala and the retrosplenial cortex.

2.4 AbM impairment in mild AD

Some of the brain structures underlying AbM were detected through functional neuroimaging as being the first to be damaged in MCI: the PCC (Chetelat et al., 2003a; Nestor et al., 2003), more particularly the retrosplenial cortex (Nestor et al., 2003; Kogure et al., 2000), and the MTL (e.g.; Dickerson et al., 2005 and 2004; deToledo Morell et al., 2004). To our knowledge, only one study has examined AbM in aMCI (Chételat et al., 2005): a semantic AbM fluency task had predictive power on cognitive decline in aMCI patients but not the episodic AbM fluency task. However, no indication was given concerning AbM performances between stable and evolving aMCI at baseline. Other studies on AbM were undertaken in mild AD patients (Eustache et al., 2004; Gilboa et al., 2005; Ivanoiu et al., 2006; Piolino et al., 2003) and established comparisons between demented patients and healthy subjects. In the following paragraph, I will describe one of these studies to account for AbM deficits related to mild AD processes. Moreover, both consolidation theories will be examined through mild AD cases.

2.4.1 Lifespan distribution of AbMs in mild AD

Piolino et al. (2003) examined the presence of temporally graded AbM loss in three pathologies: AD (13 patients), semantic dementia (SemD; 10 patients) and frontal variant of the frontotemporal dementia (fv-FTD; 15 patients). As already seen, the MTL is affected at the very beginning of the disease in AD. SemD involves semantic disorders arising from an atrophy of the polar and inferolateral regions of the temporal lobe, with relative sparing of the MTL in the early stages. Fv-FTD is characterized by behavioral changes and executive deficits related to predominant frontal lobe atrophy. For each group, the illness was at the early stage of dementia (MMSE ≥ 20/30), diagnosed within the last two years at the most. The AbM task assessed the ability to recall detailed specific events from five time periods covering the entire lifespan: (i) 0-17 years old; (ii) 18-30 years old; (iii) > 30 years old except for the last 5 years; (iv) last five years except for the last 12 months; (v) last 12 months. The authors used two different total scores: AM taking into account both episodic and generic AbMs, EM for episodic AbMs. Results revealed that patients' total performances for both scores were poorer than the control subjects', with SemD patients being less impaired than AD and fv-FTD patients. For the AM scores, performance on time periods differed from one group to another (fig. 6 A): AD patients showed a temporal gradient, with more memories for the two most remote periods; SD patients demonstrated the reverse trend, with the most recent period being better preserved; fv-FTD patients did not present any time gradient. The EM scores were worse for all patients compared with the controls, except for the last 12 months for the SemD patients (fig. 6 B). AD patients and fv-FTD patients presented with an ungraded autobiographical amnesia in contrast to SemD patients showing a reversed temporal gradient. AD patients' memory profile between AM and EM scores highlighted their difficulty in retrieving episodic AbMs compared with more generic AbMs. The authors suggested these results supported the view that preserved remote memories in AD have a predominantly semantic character (Cermak, 1984; Butters & Cermak, 1986; Warrington & Mc Carthy, 1988). This idea was reinforced by SemD patients' episodic memory profile where remote memories deteriorated and recent ones were preserved. As seen above, these patients have damaged anterior temporal lobes. Since this cerebral structure has a role in semantic memory, this may again imply that remote AbM acquires a semantic nature whereas recent memories remain episodic (Cermak, 1984). The relative preservation of the 18-30 years old time period in SemD patients' strictly episodic memories was unclear. It could be explained as a reminiscence bump the same as that witnessed in the control group. However, this preservation was observed in only 4 of the 10 SemD patients. This observation leads the authors to call to mind the heterogeneity of this group. The Fv-FTD patients' difficulty to

retrieve episodic AbMs regardless of the time period and poorly detailed generic AbMs revealed a deficit of access to episodic AbMs related to frontal lobe atrophy. Indeed, frontal lobes have been reported engaged in the active process of retrieval, i.e., initiation of recall (e.g., Jetter et al., 1986), strategic process (Kopelman et al., 1999; Kopelman & Stanhope, 1998; Levine et al., 2004) and temporal indexing recollection (Baddeley & Wilson, 1986; Stuss et al., 1994) from long term memory.

The heterogeneity of gradient in each demented group shows that AbM is widely distributed across brain and that MTL, lateral temporal neocortex and frontal lobes play a crucial role in performance of AbM tasks.

2.4.2 Consolidation theories and AbM in mild AD patients

In Piolino et al.'s (2003) study, AD patients' profile could be explained by the MTT: the profile of the performances for the AM score (which concerned semanticized memories more than episodic ones) is in keeping with a limited role of the MTL, whereas the profile of the performances for the EM score (episodic AbMs) may be compatible with a permanent role of the MTL. SemD patients' profile could be explained by both the standard and the MTT consolidation models: the former suggesting a deficit of stored information situated in the temporal neocortex and the latter suggesting a deficit of access as the temporal neocortex is needed to gain access to AbMs. Although the results of this study are in line with both consolidation theories, other studies support the MTT more. For instance, Gilboa et al. (2005) used multivariate analysis with partial least squares (PLS) through which they could identify brain region volumes that co-varied together in relation to memory measures. This statistical method ensured that the extent of mild AD patients' deficit in episodic AbMs was strongly related to the amount of tissue loss from anterior temporal neocortex and MTL structures but not from the frontal lobes. The fact that memory scores for different lifetime periods covering the whole life were all associated to the same degree with volumes of the MTL was in favour of the MTT.

To sum up, mild AD patients have an ungraded amnesia in episodic AbMs and remote lifetime periods are mainly made up of generic AbMs. The severity of the deficit in episodic AbMs is related to the amount of tissue loss in bilateral MTL. Moreover, episodic AbM retrieval involves the MTL independently of the age of memory that is in favour of the MTT over the standard consolidation model.

3 Spatial memory

We have seen earlier that aMCI is a syndrome with different etiologies such as dementia, psychiatric and/or medical disorders. Research on neuropsychological markers distinguishing cognitive impairments due to incipient dementia from another non-evolving cause is therefore of crucial interest to prescribe patients the appropriate medication at the earliest possible stage. The general aim of the experimental work presented in here is to detect specific preclinical markers of dementia. Whereas depression is generally associated with prefrontal cortex dysfunction (e.g., Kalayam & Alexopoulos, 1999), a cerebral structure which is not vulnerable to early AD, the PHG is reported to be a structure damaged early on in evolving aMCI (see above). This latter structure has been found to be activated, among other conditions, during building recognition memory tasks (Ekstrom et al., 2003) which refer to topographical recognition memory. As already mentioned, deficit in non-verbal recognition memory would allow to discriminate aMCI patients who would develop dementia from those who would not (see above). Moreover, topographical recognition memory is a subcomponent of spatial memory, known to be impaired early on in AD and leading to spatial disorientation for both familiar and unfamiliar places (Mapstone et al., 2003). On this basis, for the purpose of the present study, we have examined whether deficits in topographical recognition memory in aMCI patients could be a neuropsychological marker of AD in its preclinical dementia stage. Therefore, it is important to understand spatial memory functioning before describing the experiment performed in the context of this work. In this chapter, definition and neural substrates of spatial memory will be addressed, together with deficits associated with aging, aMCI and AD.

3.1 Definition of spatial memory

Spatial memory involves the ability to encode, store and retrieve information about spatial locations, configurations or routes (Kessels et al., 2001). This cognitive function enables us to remember the location of objects, to find our way around our environment and to recognize familiar places. This last ability is called *topographical memory*. Moscovitch et al. (2005) proposed to distinguish between spatial memories that consist of detailed perceptual-spatial representations of experienced environments, related to episodic AbM, and those that consist of schematic representations of the topography, corresponding to schematic topographical memory and related to semantic memory. We can also note that some spatial memory tasks are related to episodic memory without autobiographical component (e.g. topographical recognition memory tasks).

Studies on healthy subjects and brain-damaged patients showed that spatial memory is not a unitary cognitive function, but requires many different abilities (Maguire et al., 1999; Postma et al., 2004). For instance, topographical disorientation has been reported associated with perceptual disturbances related to a deficit for landmark and building recognition even in familiar surroundings (Landis et al., 1986; Patterson & Zangwill, 1944). By contrast, other cases showed preserved abilities to recognize buildings and landmarks whereas the memory for their place in space and spatial relationships was dysfunctional (e.g., Bottini et al., 1990; Maguire et al., 1996a). In this line, Kessels et al. (2001) argue that there is a distinction between spatial memory (i) for routes or paths during exploration of new environments (i.e. navigation), requiring sequential processing of spatial information, and (ii) knowledge about spatial layouts, such as that involved in memory for object location. In turn, object-location memory can be divided further into (i) exact metric (or 'coordinate') processing and (ii) memory for relative relations between objects and their features (Kosslyn, 1987; Lansdale, 1998; Postma et al., 2000).

Spatial information may be processed by egocentric or allocentric spatial representations of the environment. The egocentric system provides a record of an object's location relative to some part of the body (retina, head, trunk, etc; Cycowicz, 2000 for a review; King et al., 2004). For instance, route learning is based initially on coordinates in an egocentric frame of reference, coupling landmarks to direction with reference to the self (e.g., 'turn to my left at the store'; Byrne, 1982, in Moscovitch et al., 2005). Thus, the main feature of this learning is inflexibility in that changes in landmarks or detours lead to disorientation. The allocentric system is based on mental maps which are spatial representations where object's location is relative to other objects, features, or landmarks in the environment. As a result, maps are flexible representations that do not depend on any single landmark or route to navigate from one place to another (Moscovitch et al., 2005).

3.2 Cerebral substrates of spatial memory

Spatial memory deficits have been observed in hippocampally-lesioned rodents, primates (Redish & Touretzky, 1997) and humans (Nunn et al., 1998; Smith, 1987). More precisely, it has been suggested that the right hippocampus is especially important in spatial memory in humans (Kessels et al., 2001; Smith & Milner, 1981 and 1989). In addition, dissociation was highlighted between egocentric and allocentric spatial memories (e.g. Aguirre & D'Esposito, 1999; Kessels et al., 2001). O'Keefe and Nadel's cognitive map theory (1978) presupposes that the right hippocampus stores spatial information in the form of an allocentric (or exocentric) cognitive map of the environment (Moscovitch et al., 2006; for a

review). Supporting this theory, further studies showed that the MTL and superior and medial temporal gyri were activated during allocentric tasks (Aguirre & D'Esposito, 1999; Maguire et al., 1999; Rosenbaum et al., 2004). Moreover, Holdstock et al. (2000) reported that a patient with a focal bilateral hippocampal lesion was impaired in allocentric spatial memory tasks, whereas egocentric performance was spared. By contrast, parietal and frontal cortices would support egocentric processing (Aguirre & D'Esposito, 1999; Rosenbaum et al., 2004). As in the standard model of consolidation and the MTT, the cognitive map theory agrees that information registered initially in the neocortex is integrated by the MTL and related structures in the diencephalons to form a memory trace. However, unlike the standard theory and the MTT, the cognitive map theory does not posit with regard to the consolidation process; that is, it does not distinguish between maps acquired recently and those acquired a long time ago.

In addition to the cognitive map theory, clinical and neuroimaging studies revealed involvement of different neural bases for different spatial memory processes.

Spiers et al. (2001) tested the ability of patients with unilateral anterior temporal lobectomy to navigate accurately in ten locations in a virtual town, to recognize scenes from the town compared with lures, and to construct an accurate map of the town. The right temporal lobectomy patients were impaired on all three spatial tasks compared to controls, taking longer routes, recognizing fewer scenes and making poorer maps. The left temporal lobectomy patients performed at a level intermediate to the controls and right temporal lobectomy patients on the three tasks. Individuals with right parahippocampal lesions are disoriented in new locations but not in familiar ones and have difficulty learning locations based on new allocentric spatial configurations. Partly illustrating this point, Luzzi et al. (2000) reported the case of a PHG-damaged patient who showed deficits in locating landmarks, while he could recognize and recall environmental landmarks. Completing the assumed role of the parahippocampal region, Epstein et al. (2001) examined patients who suffered from damage to the posterior parahippocampal complex after vascular incidents. They were tested for encoding and recognition on topographical scenes (i.e.Lego® and real scenes photographs) and objects (i.e.Lego® and real objects photographs). Lego blocks retain only the geometric organisation of a stimulus. Patients were more impaired when the stimuli were scene-like spatial layouts than when they were objects for both Lego blocks and real scenes/objects. In contrast, performance was normal on a famous landmark recognition task and on the production of accurate maps of premorbidly learned places. Taking these results together, the authors concluded that the posterior parahippocampal complex (i) is selectively involved in the ability to encode novel information about the geometry of surrounding space

into memory, but not the geometry of novel objects, and (ii) might play a more critical role in the encoding of new spatial information than recognition or recall. Neuroimaging investigations reported additional data concerning the role of the hippocampus and parahippocampus in healthy subjects. There is some evidence that parahippocampal cortical areas are required for two-dimensional (2D) representations of scenes, with the hippocampus also being required when memory for locations in three-dimensional (3D) space is needed (Burgess et al., 2002; for a review). Consistently, the right PHG would be selectively involved in 2D spatial memory tasks, such as topographical recognition memory tasks, unlike the hippocampus (Cippolotti & Maguire, 2003; Ekstrom et al., 2003; Maguire et al., 2001). Another role was nevertheless found for the parahippocampus: wayfinding in very simple environments on the basis of perception or learned stimulus-response associations, without requiring knowledge of relative locations within the environment (O'Craven et al., 1999). By contrast, neuroimaging studies where a town layout was learned from watching film footage of travel through it (Maguire et al., 1996b), generating and describing routes through a real city (Maguire et al., 1997) or recalling a route learned in the real world before scanning (Ghaem et al., 1997), have shown activation extending into the hippocampus proper. A PET study, where subjects had to navigate and find their way around a 'virtual reality' town reported activation of the right parahippocampus and hippocampus when the navigation between two locations was successful (Maguire et al., 1998). Moreover, Maguire et al. (2000) showed that the size of the hippocampus in London taxi-drivers correlated with years of experience of driving a taxi and with performance on tests of their knowledge of London streets.

Suzuki et al. (1998) reported the case of a 70-year-old woman with pure topographical disorientation following haemorrhage in the right medial parietal lobe. She could not navigate in the real world and judge viewpoints of buildings despite a good ability to draw maps, describe routes and identify objects and buildings. The authors suggested that her spatial disorientation was probably due to an impaired viewpoint judgment caused by a lesion in the right medial parietal lobe. The retrosplenial and/or PCC, on the other hand, are believed to code information about headings in allocentric space (Maguire, 2001b; Takahashi et al., 1997).

The studies commented on above showed that lesions to the hippocampus, parahippocampal, parietal and posterior cingulate or retrosplenial cortices contribute to different types of spatial memory deficits thereby suggesting their role in spatial information processing. Thus, the right hippocampus is involved in allocentric object location memory

and in wayfinding through complex environments. The parahippocampal gyrus is more generally involved in tasks requiring the processing of spatial scenes and navigation in very simple environments on the basis of perception. This cerebral structure is also crucial for the identification of salient landmarks, such as buildings. The posterior parietal lobe is necessary for representing spatial information in terms of egocentric coordinates. The retrosplenial and /or PCC, on the other hand, are believed to code information about headings in allocentric space. These neural structures have reciprocal, anatomical connections with each other and with the hippocampus, forming a spatial network (fig. 7).

3.3 Age impacts on spatial memory

Normal aging is associated with a decline in spatial learning, among other cognitive processes including episodic memory, attention and working memory (Kausler, 1994). Several studies reported a decreased allocentric spatial navigation in healthy elderly subjects (Erikson & Barnes, 2003; Lacreuse et al., 1999; Moffat et al., 2006). Lemay & Proteau (2003) observed that elderly people were less efficient than young ones in long-term memorization of spatial relations between different objects. By contrast, the encoding of egocentric information was relatively undisturbed. Moffat et al. (2006) showed that compared to young subjects, subjects over 60 years of age presented with dysfunction in neuronal networks underlying allocentric spatial navigation: fMRI data revealed right posterior hippocampus, bilateral PHG, retrosplenial cortex and parietal lobe regions hypoactivations. Moreover, the intensity of activation correlated positively with the performance in the spatial navigation task.

3.4 Spatial memory in aMCI and AD

Impairments of spatial memory are one of the first symptoms experienced by patients with damage to the MTL due to AD (e.g., Kolb & Wishaw, 1996) as much for new environments as for familiar places (Mapstone et al., 2003). In dementia, both allocentric and egocentric strategies are impaired (Cherrier et al., 2001) whereas in normal aging, only the allocentric processing is (Moffat et al., 2006). As regard to the the aMCI stage, several studies have reported impairment of the allocentric strategy in aMCI patients (Burgess et al., 2006; Grön et al., 2006). These results are in line with the fact that the MTL is altered early by AD lesions and that it is involved in allocentric spatial memory. Grön et al. (2006) investigated the effect of galantamine, an acetylcholinesterase inhibitor used as a current treatment of AD, on spatial navigation in aMCI patients using unknown complex virtual mazes in fMRI. aMCI patients' pooled neural activation was examined during the navigation task in a pre-session

before administering galantamine and in a post-session one week after the administration. Navigation-related increased neural activations due to cholinergic enhancement were observed in the right middle occipital and middle temporal gyri, right fusiform gyrus, right PCC, right hippocampus and left anterior parts of the PHG. Based on the literature, the authors suggested that improved posterior lateral and medial temporal recruitment on processing was linked to allocentric aspects of navigation, in that these regions process the topography and landmarks of the virtual surroundings. Indeed, efficient topographic memory in the maze task of the study was necessary to avoid perseverative navigational errors. The PCC activation was coherent with previous studies which reported activation in navigational tasks (Fujii et al., 2004; Grön et al., 2000). The increased activity of the hippocampus and posterior areas observed in this study following galantamine treatment was attributed to the fact that this inhibitor has been shown to increase the number of nicotinic receptors in the hippocampus and neocortex and to improve synaptic plasticity within a few days (Ikonen et al., 1999). In addition to allocentric impairment in aMCI, two recent studies (Arata, 2006; Weiner, 2006) showed that aMCI patients were impaired in both egocentric and allocentric strategies and that their performance fell between that of AD patients and healthy controls.

Rosenbaum et al. (2005, cited in Moscovitch et al. 2005) examined spatial memory in a taxi-driver with AD. The patient had extensive bilateral MTL degeneration, most particularly in the parahippocampal region, but with relatively preserved temporal neocortex. His performance was compared to that of a former taxi-driver whose encephalitis left him with left temporal neocortical damage but less extensive hippocampal atrophy, and to those of eight age-matched controls. They were assessed in a 5 km^2 section of downtown Toronto which contained many of the city's landmarks. All the participants were familiar with the area, though they had visited it rarely if ever in the last decade. The AD patient had deficits in recognition of major landmarks from their picture though he had no difficulty in describing their function or spatial location. Subsequent tests showed that he had equal difficulty in visual recognition of world landmarks, such as the Eiffel Tower, but not of famous faces. Moscovitch et al. (2005) suggested that these results pointed to a landmark agnosia associated with degeneration of the PHG which was preserved in the other participants. It was also reported that spatial navigation based on allocentric information was spared in the AD patient, although volumetric analysis confirmed that atrophy claimed over 50% of the hippocampus and inferior temporal cortex. This last result contrasted with another study where both allocentric and egocentric strategies were impaired in AD patients (Cherrier et al., 2001). Two main suggestions are possible. Firstly, Rosenbaum et al.'s AD patient may have benefited from the spatial training required by his profession, leading to the formation of brain reserve

capacity. Brain reserve capacity is determined by the number of neurons and their synaptic and dendritic arborisation together with lifestyle-related cognitive strategies. A low reserve capacity has been linked with early presentation of some pathological changes of AD (Mayeux, 2003). Thus, the former taxi-driver patient could compensate spatial deficits due to AD thanks to his brain reserve capacity. Secondly, spatial navigation in the city of Toronto was based on schematic representations of the topography, corresponding to old semantic memories. According to both consolidation theories (the standard theory and the MTT), old semantic memories are no longer dependant on the MTL but the adjacent temporal neocortex, which is preserved in Rosenbaum et al.' s AD patient.

Essentially, normal ageing is associated with a decline in the allocentric representation but not with the egocentric one. However DAT is associated with deficits in both representations whilst aMCI has deficits in both representations but at an intermediate level between normal ageing and dementia. Nevertheless, it is important to consider the premorbid level of a patient in spatial memory tasks which can allow a compensation of some AD deficits, such as in former taxi-driver AD patients.

To summarize this chapter, spatial memory is a complex cognitive function with many subcomponents. Distinct neuronal networks are involved in the spatial memory tasks (mainly the hippocampus and the parahippocampal, parietal, retrosplenial and frontal cortices). The spatial information processing is based on two representations - egocentric and allocentric. Normal ageing is linked to decreased allocentric strategy, DAT is related to deficits in both egocentric and allocentric strategies and lastly aMCI is connected with deficits in both strategies but to a degree that is between that of normal ageing and dementia.

Experimental work

Synopsis and hypotheses

As outlined in Chapter 1, patients with the aMCI syndrome are at a high risk of developing DAT. However, in spite of there being medication to slow the cognitive decline of AD, no standardized method exists to distinguish incipient demented aMCI patients from those who will not develop dementia. Clinical cognitive neuropsychology could strongly improve the accuracy of such a diagnosis. Nevertheless, the most sensitive tests for AD may also be vulnerable to other disorders. For instance, delayed free recall tasks, very sensitive to early memory impairment in AD, are also vulnerable to depression. The main purpose of this study is to search for specific markers of AD in its preclinical dementia stage. To this end, the thesis' experimental work comprises 3 studies:

Study 1

One hundred and thirty seven participants were recruited in the community-dwelling population to diagnose aMCI people according to Petersen et al.'s criteria (2001) and to follow them for two years. This longitudinal study aimed to examine cognitive evolution of aMCI patients in order to discriminate aMCI patients who would cognitively decline from those who would remain stable or recover. At the end of the study, we compared declining aMCI's cognitive performances at baseline with those of the non-declining to detect markers of preclinical dementia.

Based on their neural substrates, we theorized that deficits in topographical recognition memory and autobiographical memory could be neuropsychological markers of incipient dementia, as presented in studies 2 and 3.

Study 2

Whereas depression is generally associated with prefrontal cortex dysfunction (e.g., Kalayam & Alexopoulos, 1999), the PHG is reported to be a structure impaired early on in evolving MCI (Dickerson et al., 2004; DeToledo Morell et al., 2004). The latter structure has been found to be activated, among other conditions, during building recognition memory tasks (Ekstrom et al., 2003) which refer to topographical recognition memory. This memory is a subcomponent of spatial memory, known to be impaired early on in AD and leading to spatial disorientation for both familiar and unfamiliar places (Mapstone et al., 2003). On the basis of these observations, we examined whether topographical recognition memory was impaired in aMCI patients and whether depression altered this memory (Ritter et al., 2006).

Study 3

To our knowledge, no study has examined AbM performance and emotion of AbM between declining and non-declining aMCI. However, AbM per se and its emotional component involve neural structures damaged early on in AD, such as the retrosplenial cortex (Nestor et al., 2003; Kogure et al., 2000) and the MTL (e.g. Dickerson et al., 2005 and 2004; deToledo Morell et al., 2004). Therefore, the investigation of these cognitive processes could improve the differential diagnosis between declining and non-declining aMCI. In this study, we compared AbM performance and emotion (valence and emotional intensity of AbM) in declining and non-declining aMCI patients.

4 Preliminary study

4.1 Subjects

A pool of 137 French-speaking subjects aged between 55 and 70 years old, with at least 9 years of education were recruited from retired associations and from the lecture-attending retired population at Strasbourg's university in Alsace in 2004. Inclusion criteria to participate in the present study were a Mini Mental Status Examination (MMSE; Folstein et al., 1975) score equal or superior to 26/30 (for norms see Crum et al., 1993) and absence of known neurological and/or psychiatric conditions apart from depressive symptoms screened by Goldberg's depression scale (GDS; Goldberg et al., 1988). Additionally, participants who had had heart attacks, fainting fits, hypoxia, prolonged headaches, severe general illnesses or patients being on antidepressant medication were also excluded from the study. Finally, the participants were asked if they had diabetes, hypercholesterolemia and hypertension, but these criteria were not exclusive.

4.2 Tests

The neuropsychological examination was conducted in a single session lasting 90-120 minutes. The entire battery of tests was given to all 137 subjects. aMCI was diagnosed (for criteria see the following section) by assessing the following domains: (i) global cognitive functioning using the MMSE and a complementary scale (Dubois and Pillon, unpublished, Salpêtrière Hospital, Paris; see Appendix page 82); (ii) verbal (Similarities subtest from the French version of Wechsler Adult Intelligence Scale-Revised, 1989) and nonverbal reasoning (Advanced Progressive Matrices; Raven, 1965) and (iii) a premorbid verbal IQ estimation (Beauregard, 1971); (iv) a task sensitive to frontal lobe dysfunction (a phonological fluency task; Benton, 1968) and (v) a verbal anterograde memory test. The last test included 12-unrelated word list immediate- and delayed-recall tasks (IR-T and DR-T; respectively). During the learning task, three presentations of the list were given; after each one the participants were asked to recall as many words as possible. The total score of the immediate recall task was the mean of the two higher scores. Delayed free recall was tested 30 minutes after the third trial. Finally, we added a four-item version of the Instrumental Activities of Daily Living Scale (IADL; Lawton and Brody, 1969), which included the most sensitive items (telephone use, use of transport, responsibility for medication intake, and budget management; Barberger-Gateau et al., 1993).

4.3 Diagnosis of aMCI and depression

The participants were diagnosed as presenting aMCI according to Petersen et al.'s criteria (2001): (i) Subjective memory complaint ("Do you sometimes have memory problems?"); (ii) memory performances inferior to -1.5 SD of age- and education-adjusted norms based on the results of the verbal delayed-recall task (the cut-off was 3/12 correct responses for nine years of education and 4/12 for more than nine years); (iii) normal general cognitive functioning evaluated by the MMSE and the Salpêtrière complementary scale; (iv) normal activities of daily living assessed by the four-item version of the IADL; (v) absence of dementia: the aMCI patients obtained a score of the MMSE of 26/30 or higher and they had no deficits in cognitive domains other than verbal anterograde memory. GDS which comprises of four screening questions and five probe questions was used to detect cases of depression. The probe questions were used only if there was at least one positive screening response. For a score higher than 2 out of 9, the sensitivity to major depressive disorder (DSM-III; APA, 1980) was 85% and the specificity was 96%. Therefore, we considered individuals to be depressed if their score was higher than 2. According to aMCI criteria, 24 aMCI patients and 27 individuals without cognitive impairment were selected. After depression screening for both groups, we identified nine aMCI-depressive patients (amnMCI+DEP ; two men), fifteen aMCI-non-depressive patients (amnMCI; seven men), ten non-aMCI-depressive patients (DEP; one man) and seventeen non-aMCI-non-depressive or normal control subjects (NC; six men). The remaining non-selected participants did not belong to any of the previous interest groups. The NC and the DEP obtained normal scores in all the tests. Age, education levels and the MMSE scores were not significantly different between the groups, and DEP and amnMCI+DEP patients' depressive scores were similar (see Table 3).

5 Longitudinal study

5.1 Method

5.1.1 Tests

The neuropsychological follow-up examinations were conducted in a single 180-minute session. A break was usually given about half way through each session to minimize fatigue. Some tests were added to the first assessment in order to improve the validity of our study. A 25-item version of the Face Recognition Memory Test (Warrington, 1984) and the Rey-Osterrieth complex figure test (Osterrieth, 1944; Rey 1941), where a 30-minute free

delayed recall was added to the 3-minute free delayed recall, allowed us to study different memory tasks. In addition to the phonological fluency task (Benton, 1968), executive functions were assessed by the Stroop colour-word test (Stroop, 1935) since it was shown that early AD was associated with inhibition deficits (Amieva et al., 2002) and that depression was not related to this deficit (Swainson et al., 2001). The Verbal and Performance IQ were assessed by a shortened version of the WAIS-R (Warrington et al., 1986) consisting of four verbal subtests (i.e. Arithmetic, Similarities, Digit Span and Vocabulary) and three performance subtests (i.e. Picture completion, Bloc design and Picture arrangement).

5.1.2 Longitudinal diagnosis

Longitudinal diagnoses were assigned according to the results of the assessments at one and two years subsequent to the initial diagnosis (NC, DEP, amnMCI and amnMCI+DEP), i.e., in 2005 and 2006, and characterized cognitive evolution of each individual. Based upon Gauthier et al.'s criteria (2006; see introduction section MCI), longitudinal diagnoses consists of: (i) "evolving aMCI" for amnMCI and amnMCI+DEP patients whose memory impairments evolved or for whom other cognitive impairments appeared over the longitudinal follow-up; DEP and NC individuals could be also classified as "evolving aMCI" if their results decreased further on at least one memory test and eventually if they presented with impairment in other cognitive domains; (ii) "non-evolving aMCI" for amnMCI and amnMCI+DEP patients who remained cognitively stable over the longitudinal follow-up; DEP and NC individuals could also be classified as "non-evolving aMCI" if they developed further memory impairment on at least one memory test and eventually other cognitive impairments detected in 2005 that remained stable from 2005 to 2006; (iii) "non-aMCI" for the participants who presented with cognitive impairments except in memory; for instance, for NC who developed cognitive impairments other than memory or for patients diagnosed aMCI in 2004, who recovered from memory impairment in 2005 but developed other cognitive deficits; (iv) "controls" for NC and DEP individuals who did not further develop cognitive impairment over the follow-up or for amnMCI and amnMCI+DEP patients who were at the cut-off point of the norm for the word list 30-minute delayed-recall task at initial assessment (4/12), who improved in this memory task and did not further develop cognitive impairments over the follow-up.

The longitudinal diagnosis was based on the observation that AD is characterized by gradual relentless cognitive deterioration (Cummings, 2000; Khachaturian, 1985) and that cognitive impairments in addition to memory disturbance increased the risk of developing dementia (Rasquin et al., 2005). Moreover, since MMSE is variably sensitive to detection of

very subtle cognitive impairment (Ivanoiu et al., 2005; Meyer et al., 2002), we mainly considered performance evolution on specific cognitive tests. Thus, some patients diagnosed as evolving aMCI could have no decreased performance on the MMSE whereas they did have decreased performance on specific neuropsychological tests over the longitudinal follow-up. It is nevertheless important to note that any of our evolving patients could have already belong to the dementia diagnosis since cognitive deficits were not sufficient to cause significant impairment in social or occupational functioning (DSM-IV; APA, 1994) .

5.2 Results

5.2.1 Diagnostic outcome at 24 months after baseline

Eleven out of 51 subjects and patients were no longer available or traceable when re-test was needed after baseline (2 amnMCI+DEP, 1 amnMCI, 4 DEP and 4 NC). The 11 participants did not differ significantly from the remaining sample for age ($U = 168.5$; $p = 0.24$), baseline general cognitive level (MMSE) ($U = 176.0$; $p = 0.31$), premorbid IQ ($U = 157.5$; $p = 0.15$) and GDS ($U = 167.5$; $p = 0.27$), but not for education level where the people who dropped out tended to be less educated ($U = 139.5$; $p = 0.07$).

The longitudinal diagnosis was attributed to the 40 remaining participants (Table 4; 7 amnMCI+DEP, 14 amnMCI, 6 DEP and 13 NC). Eight of the twenty one patients (38.1%) with aMCI in 2004 progressed to evolving aMCI over the two years (28.6% for amnMCI and 57.1% for amnMCI+DEP). Four patients (28.6%) with amnMCI and two with amnMCI+DEP (28.6%) in 2004 were cognitively stable at follow-up and therefore met the non-evolving aMCI diagnostic criteria after two years. Four of the amnMCI (28.6%) and one of the amnMCI+DEP patients (14.3%) in 2004 showed objective improvement in memory over the follow-up and were consequently considered as controls. Two of the amnMCI (14.3%) were non-aMCI. Among the amnMCI+DEP in 2004, one patient (evolving aMCI) was still depressed in 2006. Among the amnMCI in 2004, two patients (one evolving aMCI and one non-aMCI) were depressive in 2006.

Three DEP (50%) became non-aMCI and three other (50%) remained cognitively normal within two years although two were still depressive in 2006 (one control and one non-aMCI).

Two NC (15.4%) progressed to evolving aMCI, one (7.7%) to non-evolving aMCI and three (23.1%) were non-aMCI. Seven NC (53.9%) who remained cognitively normal within two years, were consequently considered as controls in the longitudinal diagnosis. Two of the NC from 2004 (one control and one non-aMCI) became depressive in 2006.

A binomial test was performed to verify whether one of the four groups had a specific risk to decline cognitively. To this end, the 15.4% of NC who progressed to evolving aMCI were considered as the reference point for rate of conversion and a binomial test was applied to the DEP, amnMCI and amnMCI+DEP groups. The results indicated $P(S_{6=0})=0.36$ for the DEP who developed evolving aMCI (0 DEP converted into evolving aMCI), $P(S_{14=4})=0.11$ for the 4 amnMCI out of 14 who became evolving aMCI, and $P(S_{7=4})=0.01$ for the 4 amnMCI+DEP out of 7 who declined cognitively. Thus, only the amnMCI+DEP had a conversion rate to evolving aMCI which differed significantly from the NC.

Among the 40 subjects and patients remaining for the longitudinal examination, the six non-aMCI patients (3 NC, 1 DEP and 2 amnMCI at baseline) were deleted from the statistical analysis due to the cognitive heterogeneity of the group (they all had different cognitive impairments, e.g., deficits in attention, visuo-spatial function or language). These 8 participants did not differ significantly from the remainder of the sample with regard to age ($U = 93.0$; $p = .24$), education level ($U = 79.5$; $p = .10$), and baseline general cognitive level (MMSE) ($U = 91.0$; $p = .21$), but not with regard to the depressive level where the people who dropped out were more depressive than the remaining group ($U = 67.0$; $p < .05$).

Performance comparisons at baseline were performed between evolving and non-evolving aMCI and controls to detect markers of cognitive decline.

5.2.2 Demographic characteristics at baseline: evolving aMCI compared with non-evolving aMCI and controls

There were no significant differences between the controls, non-evolving and evolving aMCI in terms of GDS, age, education level and estimated premorbid IQ (Table 5). With regard to the MMSE, ANOVA revealed a trend of effect ($F(2, 29)=2.57$, $p= .09$) and post-hoc tests indicated that non-evolving aMCI patients tended to score lower than the controls ($p= .09$), but there were no significant differences between evolving and non-evolving aMCI patients, nor between evolving aMCI patients and controls (Table 5). Diabetes, hypercholesterolemia and hypertension were equally represented in the three groups ($Chi^2 = 1.44$, $p= .49$; $Chi^2 = 1.33$, $p= .51$; $Chi^2 = .53$, $p= .77$; respectively).

5.2.3 Cognitive test performance characteristics at baseline: evolving aMCI compared with non-evolving aMCI and controls

ANOVA revealed an effect of longitudinal diagnosis for the word list immediate-recall task ($F(2,29)=4.82$, $p< .02$), the word list delayed-recall task ($F(2,29)=10,7$, $p< .01$), the

Attention task of Dubois and Pillon's complementary scale of the MMSE ($F(2,29)=7.06$, $p< .01$), the copying time of the Rey-Osterrieth figure ($F(2,29)=4,21$, $p< .05$), the Rey-Osterrieth figure 3-minute free delayed recall ($F(2,29)=5,49$, $p< .01$) and the block design subtest of the WAIS-R ($F(2,29)=12,8$, $p< .01$) (see Table 6).

Post-hoc tests indicated that for the word list immediate- and delayed-recall tasks, evolving and non-evolving aMCI performed significantly more poorly than the controls ($p< .01$ for both evolving and non-evolving aMCI). No significant difference was found between evolving and non-evolving aMCI ($p= .69$ for the immediate recall; $p= .96$ for the delayed recall).

With regard to the Attention task, evolving aMCI performed significantly more poorly than the controls ($p< .01$) and the non-evolving aMCI tended to perform more poorly than controls ($p= .07$). No significant differences were found between both evolving and non-evolving aMCI ($p= .16$).

With reference to the time taken to copy the Rey-Osterrieth figure, evolving aMCI's performance was significantly slower than that of controls and non-evolving aMCI ($p< .05$ for both controls and non-evolving aMCI), but controls and non-evolving aMCI had similar copying times ($p= .68$).

In the case of the Block Design subtest, controls' scores were significantly better than those of evolving and non-evolving aMCI ($p< .01$ and $p< .02$; respectively), and evolving aMCI tended to have lower performance than non-evolving aMCI ($p= .06$).

With regard to the Rey-Osterrieth figure 3-minute free delayed recall, evolving aMCI performed significantly more poorly than the controls ($p< .02$) but no significant difference was found between evolving and non-evolving aMCI.

In order to examine evolving aMCI patients' cognitive disturbance associated with the Rey-Osterrieth figure 3-minute free delayed recall and the copying time, correlations were carried out in the evolving aMCI between the significant tests. Two significant correlations were found: Block Design vs copying time of the Rey-Osterrieth figure ($r= -.64$; $p< .05$) and Block Design vs the Rey-Osterrieth figure 3-minute free delayed recall ($r= .67$; $p< .05$).

Given the small sample size, it was not possible to make subgroups of depressive patients. However, to verify whether depression influenced the tests which had significant or trend effects between groups, we carried out correlations with depression severity, in the aMCI groups (the sum of evolving and non-evolving aMCI patients). The Attention subtest tended to correlate with GDS ($r= - .43$, $p= .08$) but not the other tests.

5.2.4 The usefulness of baseline neuropsychological measures in predicting diagnostic outcome at 24 months

The copying time of the Rey-Osterrieth figure was the only parameter which differentiated evolving aMCI patients from both non-evolving aMCI and controls at baseline. A cut-off score of 1 SD above the mean of the controls for the time of correctly copying the Rey-Osterrieth figure, classified 6,7% of the controls, 28,6% of the non-evolving aMCI, and 50% of the evolving aMCI patients.

5.2.5 Longitudinal cognitive change at 12 and 24 months from the initial assessment across evolving aMCI, non-evolving aMCI and controls

The longitudinal evolution of cognitive domains was assessed by repeated measures of ANOVAs, with one between-subjects variable, “longitudinal diagnosis” (evolving aMCI, non-evolving aMCI and control groups), and one within-subjects variable, “time of neuropsychological assessment” (i.e., 2004, 2005 and 2006).

Only tests with significant or trend effect are mentioned below.

a) Effect of time of neuropsychological assessment

Repeated measures of ANOVA revealed effects of time on the verbal immediate-recall task ($F(2,58)=10.3$, $p< .01$), the verbal delayed-recall task ($F(2, 58)=13.9$, $p< .01$), the copying time of the Rey-Osterrieth figure ($F(1,29)=5.24$, $p< .05$), and the Rey-Osterrieth figure 30’-delayed-recall ($F(2, 29)=7.67$, $p< .01$). Post-hoc tests indicated that performances of the whole sample improved from 2005 to 2006 for the verbal immediate-recall task ($p< .01$) and the copying time of the Rey-Osterrieth figure ($p< .02$). Performances of the whole sample on remaining tests evolved differently: the verbal delayed-recall task scores increased from 2004 to 2005 ($p< .01$) but not from 2005 to 2006 ($p= 0.10$); by contrast, no evolution was found on the Rey-Osterrieth figure 30’-delayed-recall over the longitudinal follow-up.

b) Effect of longitudinal diagnosis

Longitudinal diagnosis had some effects on the scores of the following tasks: the verbal immediate-recall task ($F(2,29)=11.3$, $p< .01$), the verbal delayed-recall task ($F(2, 29)=18.1$, $p< .01$), the Attention task $F(2, 29)=8.23$, $p< .01$), the Rey-Osterrieth figure copy ($F(2, 29)= 5.70$, $p< .01$), the copying time of the Rey-Osterrieth figure ($F(2, 29)=6.63$, $p< .01$), the Rey-Osterrieth figure 3’-delayed-recall ($F(2, 29)=12.8$, $p< .01$), the Rey-Osterrieth figure 30’-delayed-recall ($F(2, 29)=7.67$, $p< .01$), the Picture Completion subtest of the WAIS-R ($F(2, 29)=4.08$, $p< .05$) and the block design subtest ($F(2, 29)=7,78$, $p< .01$). Post-hoc tests indicated that non-evolving aMCI had slightly lower scores of MMSE than controls ($p< .02$) and that evolving aMCI tended to be lower ($p= .08$) than controls. Analyses also

revealed that controls' scores on the verbal immediate- and delayed-recall tasks and the block design subtest were better than those of evolving and non-evolving aMCI ($p < .01$ between controls and both evolving and non-evolving aMCI for the two first tests; $p < .01$ and $p < .05$, respectively for the block design subtest); by contrast, there was no significant difference between evolving and non-evolving aMCI. With reference to the Attention task, the Completion subtest of the WAIS-R and the copying time of the Rey-Osterrieth figure, evolving aMCI had poorer performances than controls and non-evolving aMCI ($p < .01$ for the Attention task, comparison with both controls and non-evolving aMCI; $p < .05$ for the Completion subtest, comparison with both controls and non-evolving aMCI; $p < .01$ and $p < .02$ for the copying time of the Rey-Osterrieth figure compared with controls and non-evolving aMCI, respectively).

c) Effect of interaction

Finally, "time of neuropsychological assessment" × "longitudinal diagnosis" interactions or trend of interactions were found for the following tests: the Rey-Osterrieth figure copy ($F(2, 29)=2.78$, $p= .08$), the Rey-Osterrieth figure 30'-delayed-recall ($F(2, 29)=8.28$, $p < .01$), the block design subtest ($F(2, 29)=2.64$, $p= .09$). Post-hoc tests revealed the following cognitive evolutions between 2005 and 2006: for the Rey-Osterrieth figure copy and the Rey-Osterrieth figure 30'-delayed-recall (see fig. 8), the results for the evolving aMCI decreased ($p < .01$; for both latter tests), but didn't for the controls or the non-evolving aMCI; for the Block Design subtest, controls tended to improve ($p= .08$) but the evolving and the non-evolving aMCI did not.

5.3 Discussion

5.3.1 Diagnostic outcome of the aMCI and non-aMCI patients

This study reports the longitudinal cognitive results of a community-dwelling group recruited two years ago. At that time, participants were diagnosed as aMCI-depressive patients (amnMCI+DEP), aMCI-non-depressive patients (amnMCI), non-aMCI-depressive patients (DEP) and normal control subjects (NC) who had neither cognitive impairment in the cognitive functions assessed in the present study nor depressive symptoms. The current study showed that when aMCI is associated with depression, the risk to develop evolving aMCI (57.1%) is higher than in aMCI (28.6%) or depression (0%) only. These results are in line with a previous study reporting that in aMCI patients the presence of depression increased the risk of developing dementia and accelerated its evolution (Modrego et al., 2004). Comparatively, fewer amnMCI patients were classified as evolving aMCI over the timeframe.

Comparison with other studies is difficult given the small size of our sample, the paucity of population-based longitudinal studies and the different age ranges of participants used in these studies. For instance, Busse et al. (2003) followed community-dwelling aMCI patients and found that 33% converted to DAT after 2.6 years, which is consistent with our study. Nevertheless, the age of the patients was 75 and above. More importantly, our data are in accordance with Modrego et al. (2004) who pointed out that patients with aMCI and depression were at over twice the risk of developing DAT as those without depression. In the present study, the remaining amnMCI patients were considered as non-evolving aMCI (28.6%), or as having recovered from memory impairment (becoming either controls (28.6%) or non-aMCI patients (14.3%)). This observation is consistent with previous studies demonstrating that aMCI criteria applied to general population was not a homogenous syndrome and that it was not a temporally stable entity for many patients (Busse et al., 2003; Ganguli et al., 2004; Larrieu et al., 2002; Ritchie et al., 2001). It is not yet possible to make suggestions concerning DEP patients at the present stage of our investigation given the small number of patients. Most of the NC subjects remained without cognitive impairment although two (18.6%) developed evolving aMCI. This result is higher than the estimated AD incidence of normal control subjects, 1% to 2% per year (Larrieu et al., 2002; Petersen et al., 1990 and 1999). However, Larrieu et al.'s study (2002) followed 1654 participants for 5 years in the general population and Petersen et al. (1999) studied over 1900 participants for over 15 years. Such a considerable sample size difference makes comparison impossible with the present study and suggests that our rate of evolution is overestimated due to the small size of our sample.

5.3.2 Neuropsychological characteristics at baseline

Neuropsychological baseline comparisons (assessment of 2004) on the present study revealed that the copying time of the Rey-Osterrieth figure was significantly longer in evolving aMCI patients than in the controls and the non-evolving aMCI, and that this effect did not seem to be sensitive to depression. By contrast, no significant difference was found between evolving and non-evolving aMCI patients on the MMSE at baseline. This result was in accordance with Ivanoiu et al. (2005) who followed evolving aMCI patients up to the beginning of dementia. Moreover, our study confirmed that MMSE is not sensitive to subtle cognitive changes (Meyer et al., 2002). Other tests such as the verbal immediate-recall task (IR-T), the verbal delayed-recall task (DR-T), the Attention task, and the Rey-Osterrieth figure 3'-delayed-recall task were sensitive to aMCI but were not specific to evolving aMCI.

Difficulties in IR-T and DR-T have been reported in aMCI but did not allow distinction between evolving and non-evolving aMCI (Ivanoiu et al., 2005). Although free recall tasks are known to be very sensitive to dementia, they may be aspecific due to the influence of other factors such as advanced age, psychiatric diseases and general illnesses. In our study, evolving and non-evolving aMCI did not differ in terms of age, they had no psychiatric disease except depression and their scores on GDS were similar. By contrast, with regard to general illnesses, the proportion of hypertension was higher in the evolving aMCI than in the non-evolving aMCI and controls, but not the diabetes, nor the hypercholesterolemia. Previous studies showed that hypertension, hypercholesterolemia, atherosclerosis, coronary heart disease, smoking, obesity and diabetes increased the risk of developing AD (Kivipelto et al., 2001; Mayeux, 2003; Sparks et al., 2002). Nevertheless, it is not known whether these factors drive to plaque and tangle formation or whether they induce cerebrovascular pathology, which adds to clinically silent disease pathology thereby exceeding the threshold for dementia (Blennow et al., 2006). These observations did not allow us to determine the cause of the memory impairment in the non-evolving aMCI patients. Further studies using neuroimaging and biological data would be required to observe differences between evolving and non-evolving aMCI patients. Concerning attentional processing, some studies reported that attention deficit in aMCI patients would increase the risk of developing DAT (Meyer et al., 2002; Perry & Hodges, 1999). However, it was shown that attention was impaired in older depressed patients (e.g., Lockwood et al., 2002) increasing aspecificity of attention deficit to differentiate incipient demented patients from the non-demented (Swaison et al., 2001). The sensitivity of attention to depression was confirmed in the present study with the trend of correlation between depression severity and the Attention task scores in the total evolving and non-evolving aMCI group. Therefore, as it was suggested in Blackwell et al.'s study (2004), attention deficit in aMCI patients could not be considered as a specific marker of AD.

Sensitivity of the Rey-Osterrieth figure 3'-delayed-recall task to aMCI has already been reported in MCI patients evaluated by CDR 0.5, but it was not known whether they were evolving or not toward DAT (Kasai et al., 2006). In contrast, another study using a test to evaluate immediate recall of four simple figures succeeded in differentiating evolving from non-evolving aMCI patients (Ivanoiu et al., 2005). This result which is in not in accordance with our data may result from the sample of older aMCI who were diagnosed as having AD after 12 to 18 months and were therefore in a more advanced stage than the evolving aMCI of the current sample. Interestingly, our results indicated that both aMCI groups were impaired on the earlier recall of the Rey-Osterrieth figure (the 3'-delayed-recall) whereas they were not on the later one (the 30'-delayed-recall) compared with controls. In fact, controls decreased a

little between the 3- and the 30-minute recalls but the aMCI did not - probably because they were very low on the earlier recall. This result suggests that aMCI deficit would concern encoding but that this latter would still be sufficiently preserved to allow retention of information. In addition to the encoding deficit, the correlations in the evolving aMCI between the Block Design vs the copying time of the Rey-Osterrieth figure, and the Block Design vs the Rey-Osterrieth figure 3-minute free delayed recall suggested that the deficit in the copying time of the Rey-Osterrieth figure and the Rey-Osterrieth figure 3-minute free delayed recall were due to visuoconstructive difficulties. In contrast, no association between the Block Design and the Rey-Osterrieth figure 3-minute free delayed recall tasks was found in the non-evolving aMCI group. This result suggests that non-evolving aMCI patients have only a memory deficit not related to a visuoconstructive impairment. Thus, evolving aMCI patients would present with visuoconstructive deficits too mild to be detected by the Rey-Osterrieth figure copy but sufficient enough to be associated with a slower copy time and non-verbal memory deficits. Another hypothesis would be that our evolving aMCI patients would be cognitively slowed down (correlation between the Block Design vs the copying time of the Rey-Osterrieth figure). In turn, this cognitive slowdown would be caused of memory deficit (correlation between the Block Design vs the Rey-Osterrieth figure 3-minute free delayed recall). However, several studies which reported early visuospatial deficits in mild AD patients (e.g., Harciarek & Jodzio, 2005; Perry & Hodges, 2000) sustain the former proposition and suggest that our evolving aMCI patients with visuoconstructive deficits could be at a very high risk of developing dementia.

5.3.3 Longitudinal cognitive evolution

Cognitive evolution was disparate according to the tests and the groups. Thus, evolving aMCI patients' scores decreased over the time on the Rey-Osterrieth figure copy and the Rey-Osterrieth figure 30'-delayed-recall but the non-evolving aMCI and the controls' scores didn't. Moreover, only the controls tended to improve on the Block Design subtest. These results indicate that evolving aMCI patients' cognitive evolution was specifically impaired on 2-dimension visuoconstructive and visual memory tasks. By contrast, a 3-dimension visuospatial task (the Block Design subtest) did not allow distinction between evolving and non-evolving aMCI patients' cognitive evolution. The copying time of the Rey-Osterrieth figure diminished over the time for the three groups, an effect which may be due to a priming effect. With regard to memory, the decreased Rey-Osterrieth figure 30'-delayed-recall over the time, the baseline deficit in the 3'-delayed recall for both aMCI groups and their stability on this task over the time, suggested (as already mentioned above) that aMCI

had an encoding deficit not sufficient enough to impair retention at baseline, but evolving over time (after one year) as witnessed by the decreased retention in the evolving aMCI group. Consistently, a longitudinal study following individuals several years before the beginning of dementia showed that the Benton Visual Retention Task score, a visuospatial memory task, declined over the time (Amieva et al., 2005). In the present study, other scores such as those of the IR-T and DR-T improved over the time independently of the groups although aMCI groups' performance remained lower than that of the controls. Verbal free recall is known to be strongly related to the left temporal region (Kopelman et al., 1998) rendering this result surprising if based on the gradual hippocampal degradation in AD. However, a single-case study that followed an aMCI patient for 11 years before the onset of DAT showed that practice effect was present in verbal recall even though performance was weak at the initial assessment (Godbolt et al., 2005). Following the practice effect, further gradual decline was seen as the patient became symptomatic, almost six years before DAT diagnosis. Dickerson et al. (2004 and 2005) observed a larger activation of the PHG and hippocampus in evolving aMCI patients whereas they had no deficit in the fMRI memory task. According to the authors, some compensatory alterations in the connecting cortical areas of the MTL might occur as a result of neural reorganization following early AD damage. In this line, we suggest that our evolving aMCI patients may have benefited of a compensatory neural reorganization that allowed the observation of a practice effect on the IR-T and DR-T.

5.4 Conclusion

In summary, the present study showed that aMCI was a heterogeneous syndrome leading to evolving aMCI in a limited proportion whereas additional depression strongly increased the risk of becoming evolving aMCI. At baseline, longer copying time of the Rey-Osterrieth figure was sensitive and specific to evolving aMCI compared with non-evolving aMCI and controls. Over time, evolving aMCI patients' performance decreased on the Rey-Osterrieth figure copy and the Rey-Osterrieth figure 30'-delayed-recall. Both these observations at baseline and over the timeframe suggested that evolving aMCI presented with subtle visuoconstructive deficits in addition to their memory impairment. However, an extended time longitudinal study with further neuropsychological tests, neuroimaging and biological data would be required to observe cognitive evolution of the non-evolving aMCI, and specific differentiation from the evolving aMCI.

6 Topographical recognition memory in aMCI: a two-year longitudinal study (Ritter et al., 2006)

6.1 Introduction

Although aMCI presents a high risk of developing DAT (Petersen et al., 2001), this category includes both patients who will develop DAT (termed as "evolving" aMCI) and others who won't (termed as "stable" aMCI). Prediction of deterioration to dementia in cases of aMCI may be confused with other disorders due to lack of specificity on selective memory tests. In particular delayed free recall, considered to be the most sensitive task to detect patients in the early phase of dementia (Welsh et al., 1991), is also vulnerable to depression (Portella et al., 2003) among other disorders. This suggests that some cases may be erroneously labelled as incipient dementia. Moreover, this problem is further confounded by the fact that late-life depression and incipient dementia are not mutually exclusive; there is an over-representation of depressive symptoms in early dementia (Baquero et al., 2004). Tests sensitive to AD but not to depression would thus be potentially most useful to studies researching on neuropsychological markers of preclinical DAT.

Whereas depression is generally associated with prefrontal cortex dysfunction (e.g., Kalayam & Alexopoulos, 1999), the parahippocampal gyrus (PHG) is reported to be a structure damaged early on in evolving MCI (Dickerson et al., 2004; DeToledo Morell et al., 2004). This latter structure has been found to be activated, among other conditions, during building recognition memory tasks (Ekstrom et al., 2003) which refer to topographical recognition memory. This memory is a subcomponent of spatial memory, known to be impaired early on in AD and leading to spatial disorientation for both familiar and unfamiliar places (Mapstone et al., 2003). In line with this observation, topographical recognition memory was found to be impaired in an evolving aMCI patient (Godbolt et al., 2005) who was tested by means of the Topographical Recognition Memory Test (TRMT; Warrington, 1996).

The fact that the PHG seems to be vulnerable in an early stage in the process leading to DAT, together with its role in topographical recognition memory and bearing in mind that the PHG does not appear to be associated with depression, led us to hypothesize that aMCI patients evolving toward DAT would show impaired performance on the TRMT, and that this performance would be insensitive to depression. Therefore, we examined topographical recognition memory in aMCI patients, with or without depression, and in single-depression patients.

6.2 Methods

The preceding chapter informed us that different groups of patients aMCI or not and depressive or not (amnMCI, amnMCI+DEP, DEP and NC) were recruited from the community-dwelling in 2004 at baseline (preliminary study). These groups of patients/subjects were followed for two years and were further classified as different cognitive states: evolving aMCI, non-evolving aMCI and controls.

In the current study, the Topographical Recognition Memory Test (TRMT; Warrington, 1996) was used for research purposes. During the learning phase of the test subjects were requested to look at each of the 30 colour photographs of places for three seconds. Recognition memory was tested immediately afterwards using a three-choice format (each stimulus item being paired with two very similar distracter items). The test takes about seven minutes.

6.3 Data analyses.

6.3.1 Preliminary study

For each test, inter-group differences were analysed by a series of ANOVAs, with one inter-subject variable, the "group" factor (i.e., amnMCI, amnMCI+DEP, DEP and NC). If significant main effects were shown ($p < .05$), pairwise group differences were analysed by Student-Newman-Keuls post-hoc tests.

6.3.2 Longitudinal study

Comparisons at baseline were performed between the longitudinal diagnosis groups by a series of ANOVAs, with one inter-subject variable, the "group" factor (i.e., evolving aMCI, non-evolving aMCI and controls groups). If significant main effects were shown ($p < .05$), pairwise group differences were analysed by Student-Newman-Keuls post-hoc tests. The longitudinal evolution of the TRMT was evaluated by repeated measures of ANOVAs, with one between-subjects variable, “longitudinal diagnosis” (i.e., evolving aMCI, non-evolving aMCI and controls groups) and one within-subjects variable, “time of neuropsychological assessment” (i.e., 2004, 2005 and 2006).

6.4 Results

6.4.1 Preliminary study

6.4.1.1 Analyses of variance

Table 7 shows the mean scores of the TRMT for each group. The "aMCI" factor had a significant effect on the TRMT ($F(1, 47)=10.2$, $p< .01$) but not the “depression” factor ($F(1, 47)=1.12$, $p= .29$). A posteriori analysis (Student-Newman-Keuls test) revealed that both the amnMCI and amnMCI+DEP patients exhibited significantly inferior performances than the NC ($p< .03$ for both groups). Furthermore, the NC’s TRMT scores were not significantly different from the DEP ($p = .23$). Likewise, the aMCI groups (amnMCI and amnMCI+DEP) obtained TRMT scores, which did not yield significant differences ($p = .78$). Although there was an overlap between aMCI patients and cognitively intact DEP patients, ANOVA showed that depression had no effect on the TRMT. The overlap was due to three DEP patients, who presented with an isolated deficit of topographical recognition memory not associated with depression (see below for specificity of the TRMT).

6.4.1.2 Sensitivity and specificity

On the one hand, cut-off score of 1.5 SD below the mean of the NC subjects for scores on the TRMT correctly classified 85.2% of the non-aMCI individuals (94.1% of the NC subjects and 70% of the DEP) and 37.5% of the aMCI patients (33.3% of the amnMCI and 44.4% of the amnMCI+DEP). On the other hand, a cut-off score of 1.5 SD below the mean of NC subjects for scores on the IR-T correctly classified 92.6% of the non-aMCI individuals (94.1% of the NC subjects and 90.0% of the DEP) but only 29.2% of the aMCI patients (33.3% of the amnMCI and 22.2% of the amnMCI+DEP). Table 7 showed that no other test besides the IR-T and the TRMT distinguished aMCI from non-aMCI individuals. Moreover, the TRMT had a higher sensitivity to aMCI and IR-T a higher specificity.

6.4.2 Longitudinal study

6.4.2.1 Comparison of baseline topographical recognition memory performance

No significant difference between the three groups diagnosed two years after the initial assessment were found on the TRMT at baseline ($F(2,29)=1.81$, $p= .18$).

Repeated measures of ANOVA revealed effects of time of neuropsychological assessment ($F(2,58)=11.0$, $p< .01$), of longitudinal diagnosis ($F(2,29)=3.54$, $p< .05$), but no

time × longitudinal diagnosis interaction ($F(4,58)= 0.74$, $p= .57$) for the TRMT. Post-hoc tests indicated that the performance on the TRMT improved from 2004 to 2005 ($p< .01$) and from 2005 to 2006 ($p< .01$) for the three groups. Moreover, controls' performances tended to be better than those of evolving and non-evolving aMCI ($p= .08$ for the evolving aMCI and $p= .07$ for the non-evolving aMCI), but there was no significant difference between evolving and non-evolving aMCI patients ($p= .62$).

6.5 Discussion

In the preliminary cross-sectional study, we were able to document that the aMCI group performed significantly more poorly on the TRMT than the non-aMCI group and that depression was not related to this deficit. Its independence of depression agrees with the general observation that recognition memory is not altered by depression (for review, see Austin et al., 2001). In the present work, 37.5% of the aMCI patients were impaired on the TRMT. Barbeau et al.'s study (2004) reported that 78% of the aMCI failed on the DSM 48, a visual recognition memory test. Whereas our aMCI patients were selected on Petersen et al.'s criteria (2001) from retired associations and from a lecture-attending retired population, Barbeau et al.'s were drawn from a memory clinic where biological and medical neuroimagery data had been performed. This guaranteed their sample homogeneity and, probably, the increased percentage of failure on the DSM 48.

Longitudinal study showed that this test lost its sensitivity when comparisons were performed at baseline between longitudinal diagnosis groups (controls, evolving and non-evolving aMCI patients). Improvement in performance was also observed for the three groups over the time but the improvement of evolving and non-evolving aMCI patients tended to be less than controls over the time. Although these results could be due to the small sample size, some explanations can be found. A single-case study showed that an aMCI patient did not have deficit in the TRMT five years before AD diagnosis and that he became impaired at least nine months before diagnosis (Godbolt et al., 2005). Thus, the TRMT would be impaired shortly before the beginning of dementia. Another study reported that the "Doors" Test (Baddeley et al., 1994), a visual recognition memory test, allowed differentiation of evolving aMCI from stable aMCI (Ivanoiu et al., 2005). However evolving aMCI patients in this study were older (age mean: 71.8, SD: 4.7) than the evolving aMCI patients in the present study (mean age: 62.9, SD: 4.33). Results of both studies suggest that our evolving aMCI would not be in a sufficiently advanced evolution toward dementia to clearly detect deficits in topographical recognition memory.

A second hypothesis concerning the non-sensitivity of the TRMT to evolving aMCI would come from the fact that spatial memory is not a unitary cognitive function, but requires many different competences within which specific deficits could be quantified. More precisely, spatial memory tests can be solved by using the allocentric or egocentric strategies. The allocentric system can provide a record of an object's location relative to other objects, features or landmarks in the environment. The egocentric system provides a record of an object's location relative to some part of the body (retina, head, trunk, etc; Cycowicz, 2000 for a review; King et al., 2004). Tests of object-location memory in which the participant's viewpoint is changed between presentation and tests (shifted-view tests) would be solved by the allocentric system but not the egocentric. By contrast, tests of object-location memory in which the viewpoint remains the same (same-view tests) could be solved by both egocentric and allocentric memory. Parietal and frontal cortices are solicited during egocentric tasks (Aguirre & D'Esposito, 1999; Rosenbaum et al., 2004) whereas MTL and superior and medial temporal gyri are activated during allocentric tasks (Aguirre & D'Esposito, 1999; Holdstock et al., 2000; Maguire et al., 1999; Rosenbaum et al., 2004). From a neuroanatomical point of view, one can suppose that evolving aMCI would be more impaired on a memory task specific to allocentric strategy than controls of the same age, but not on an egocentric task. Surprisingly, recent preliminary studies of our team (Arata, 2006; Weiner, 2006) observed that aMCI is connected with deficits in both strategies but to a degree that is between that of normal ageing associated with decreased allocentric strategy (Moffat et al., 2006), and dementia associated with deficits in both egocentric and allocentric strategies (Cherrier et al., 2001). These results are consistent with hypometabolism reported in the right temporoparietal cortex of evolving aMCI patients (Chételat et al., 2003a and 2005). In line with this observation, a previous study using a computerized spatial memory task where participants had to recall the original place of patterns on the screen (a same-view task), showed that this task was sensitive to cognitive decline of questionable AD patients (Swainson et al., 2001). Given that this task would solicit either allocentric or egocentric strategy, one can suggest that declining questionable AD patients were impaired on both strategies. In the TRMT there is neither exact same-view distracters (in which objects were intentionally moved without changing the viewpoint) nor exact shifted-view distracters (in which the participant's viewpoint is changed between presentation and tests). Following this idea, the TRMT would not assess specific components of spatial memory, not allowing detection of specific deficit. Further studies of topographical recognition memory with shifted-view and object-moved photograph recognition tasks are needed to determine whether evolving aMCI patients can be detected by specific deficit in topographical recognition memory.

6.6 Conclusion

TRMT was sensitive to the aMCI condition but not to depression in the preliminary cross-sectional study. Nevertheless, the longitudinal study revealed that it was not sensitive to the evolving aMCI. We suggested that either our evolving aMCI were not in a sufficiently advanced evolution toward AD or that they were impaired on a component of the spatial memory not specifically targeted by the TRMT. Further studies of more precise topographical recognition memory tests are needed to investigate topographical recognition memory components in evolving aMCI.

7 Autobiographical memory and evolving aMCI

7.1 Introduction

AbM is considered as a memory system that enables re-experience of detailed spatially and temporally specific events from one's whole life (Schacter and Tulving, 1994; Tulving, 2002). Some studies observed that mild AD patients' AbM temporal distribution adhered to Ribot's law (Ribot, 1881), i.e. remote periods were relatively preserved compared with recent periods (Eustache et al. 2004; Piolino et al., 2003). Further analyses of these studies revealed that (i) remote periods contained much more generic AbMs (repetitive events without any particular spatio-temporal context) than recent ones, whereas (ii) episodic AbMs were recalled with an ungraded autobiographical amnesia. Both observations are in favour of the MTT (Eustache et al. 2004; Piolino et al., 2003). Indeed, firstly, according to this theory, some generic AbMs would be old episodic memories which would have lost with time their episodic character and become more semantic. Once transformed, they would be no longer mediated by the MTL but by adjacent neocortex (Addis et al., 2004; Moscovitch et al., 2006 for a review; Piolino et al., 2003), less damaged than the MTL in mild AD patients. Secondly, ungraded amnesia of episodic AbMs would reflect involvement of the MTL independently of their remoteness. A recent study supported this result showing that the extent of mild AD patients' deficit in episodic AbMs was strongly related to the amount of tissue loss from the MTL and that this association was not related to the remoteness of the AbM (Gilboa et al., 2005). From a neuropathological point of view, at the stage of aMCI (stages III and IV of Braak & Braak, 1991 and 1996; Braak et al., 1999), NFT lesions are restricted to the MTL. With evolution of the disease and start of dementia, the density of NFT not only increases in the MTL but also extends to the adjacent neocortex. Moreover, based on the MTT, recent episodic AbMs are less represented by MTL-neocortical traces than the old ones, the former therefore being more susceptible to brain lesions (Moscovitch et al., 2005). Considering these issues, we hypothesized that given the lower density of NFT lesions in evolving aMCI patients' MTL compared with mild AD patients, episodic AbMs of the former would be impaired only on the most recent lifetime periods, instead of being ungraded, and more particularly on the details of episodic AbMs. By contrast, evolving aMCI patients would not have deficit in generic AbMs (the adjacent neocortex being preserved); the distribution of these categories of AbMs should be graded in evolving aMCI the same as in the controls with more remote generic AbMs than recent ones.

A second section of the present study concerned valence of AbM. An fMRI study reported that the retrieval of positive (happy) AbMs in healthy young adults was associated with an activation peak in the entorhinal region (Piefke et al., 2003). By contrast, negative (sad) AbMs were associated with activation in the right middle temporal gyrus. Both these activations were independent of the remoteness of the memory. Involvement of the EC in positive AbMs supported a previous study (Padovan et al., 2002) showing that positive information was more vulnerable to AD where the EC is severely damaged, among other brain structures (Braak & Braak, 1991 and 1996; Braak et al., 1999). Considering that the first lesions of AD would be located in this cerebral region, we hypothesized that evolving aMCI patients would be impaired on the number of happy AbMs but not on the sad ones, regardless of the remoteness of the memory. However, it is important to note that in Piefke et al.'s study (2003), no distinction was made between episodic and generic AbMs. Given that episodic and generic AbMs would not be sustained by the same brain structures (Addis et al., 2004), one can wonder whether emotion accompanying each category of AbMs is sustained or not by the same cerebral structures. For instance, if EC activation principally sustained emotion related to positive episodic AbMs, then evolving aMCI patients may be impaired on positive episodic AbMs but not on positive generic ones. For this issue, we will compare positive/negative episodic and generic AbMs between groups across different lifetime periods.

In the third and last section, we considered AbM emotional intensity. Several studies reported that the retrosplenial cortex was involved in emotional processing (Maddock, 1999; for a review). More particularly, Piefke et al. (2003) observed that recent AbMs of healthy young adults had a higher emotional intensity than childhood memories. The authors also showed that retrieval of recent AbMs was associated with bilateral activations in the retrosplenial cortex extending into the PCC. Based on their results, the authors suggested that this activation could reflect an involvement of the retrosplenial cortex and the PCC in emotion processing. A comparable region has been found in patients with hypometabolism who progressed from aMCI to DAT (Chételat et al., 2003a; Kogure et al., 2000; Nestor et al., 2003). Although acknowledging the existence of the other non-emotional functions of the retrosplenial cortex and PCC related to AbM (Conway & Pleydell-Pearce, 2000; Ries et al., 2006), on the basis of Piefke et al.'s suggestion (2003) and the retrosplenial cortex and PCC hypometabolism in early AD, we hypothesized that evolving aMCI patients would have less emotional intensity on recent episodic and/or generic AbMs.

7.2 Methods.

In a preceding section, we were informed that different groups of patients aMCI or not and depressive or not (amnMCI, amnMCI+DEP, DEP and NC) were recruited from the community-dwelling in 2004 at baseline (preliminary study). These groups of patients/subjects were followed for two years and were further classified as different cognitive states: evolving aMCI, non-evolving aMCI and controls.

In the present study, a modified version of the Crovitz Test (Graham & Hodges, 1997) was used for research purposes. Participants were asked to produce detailed AbMs in response to ten specific cue words, for instance “book”, “baby”, or “door” across four different lifetime periods: 0-19 years old, 20-39 years old, 40-55 years old and the last 12 months. An example of a question was: “Could you tell me a memory related to a book when you were between 20 and 39 years old?”. The division into the three first lifetime periods was done to obtain homogenous episodes between subjects/patients with respect to the past. The period between the age of 56 years and the last 12 months was not assessed given the different ages of the sample (between 57 and 72). The last 12 months period was used to examine recent AbMs across evolving aMCI patients, controls and non-evolving aMCI patients. There was no time limit to avoid deficits due to slowed cognitive processes. When participants did not retrieve episodic but generic AbM, they were given a single verbal prompt: “Can you think of a particular scene of the event you are telling me related to this word?”, to ensure that they had no episodic AbM; if they gave an episodic AbM, then it was included in the statistical evaluation, otherwise the generic AbM was. Each memory was scored on a five-point scale according to Graham and Hodges (1997). The scale took into account the specificity of the content of AbM (episodic or generic AbM): 0 for an absence of answer or no relation to the question; 1 for a semantic definition such as “Books are used to read”; 2 or 3 for generic AbMs not detailed or detailed, respectively; 4 or 5 for episodic AbMs associated with a specific temporal and spatial context not detailed or detailed, respectively. The numbers of episodic and generic detailed/not detailed AbMs were determined and the total number of episodic or generic AbMs was the sum of AbMs across all the lifetime periods. After recalling an AbM, participants were asked to tell whether they felt the memory was happy, sad or neutral (no emotion) at the time of the interview. Moreover, they had to rate the intensity of the happy or sad emotion for each AbM on a scale between 1 (very mildly happy or sad) and 5 (very strongly happy or sad). Neutral AbMs were rated 0. Mean of intensity was calculated for each lifetime period for each participant.

7.3 Statistical analyses

Distribution of AbMs across the different lifetime periods was evaluated by repeated-measures ANOVAs on the numbers of detailed/not detailed episodic AbMs, episodic/generic AbMs, valenced AbMs and the AbM mean intensity with one between-subjects variable, "longitudinal diagnosis" (evolving aMCI, non-evolving aMCI and control groups), and one within-subjects variable, "lifetime periods" (0-19 years old, 20-39 years old, 40-55 years old and the last 12 months). Depressive patients (five from the controls and two from the evolving aMCI groups) were deleted from the statistical analysis to avoid effect of depression on AbM which is known to be associated with more negative AbM (Lemogne et al., 2005).

7.4 Results.

7.4.1 Demographic characteristics at baseline: evolving aMCI compared with non-evolving aMCI and controls

Analyses were performed on 10 subjects of the control group, 8 evolving aMCI and 7 non-evolving aMCI patients. There were no significant differences between the groups in terms of GDS, age, MMSE, education level or estimated premorbid IQ (Table 8). By contrast, the number of men compared with women was different across the groups (Chi^2 = .09; p= .05). The controls and evolving aMCI groups included a majority of women, whereas the non-evolving aMCI group included more men. Studies examining gender effect on AbM in healthy subjects showed that, behaviourally, there were no significant gender differences in memory performance or emotional intensity of memories (Buchanan et al., 2006; Piefke et al., 2003). Thus, the different ratios between the three groups should not have an impact on AbM results.

7.4.2 Episodic and generic AbMs in evolving aMCI patients

7.4.2.1 Temporal distribution of episodic AbMs across groups

No longitudinal diagnosis effect (F(2, 22)= .02, p= .98) nor lifetime period effect (F(3, 66)= .10, p= .96) nor lifetime periods × longitudinal diagnosis interactions (F(6, 66)=2,09, p= .07) were found for the number of episodic AbMs (see Table 9). Thus, evolving aMCI patients' episodic AbM distribution was similar to that of the two remaining groups.

With regard to our hypothesis that evolving aMCI would be impaired on detailed recent episodic AbMs, statistical analyses revealed no longitudinal diagnosis effect (F(2, 22)= .09, p= .91) nor lifetime periods effect (F(3, 66)= .13, p= .94) nor lifetime periods ×

longitudinal diagnosis interactions (F(6, 66)= 1,44, p= .21) for the number of detailed AbMs. These results indicated that evolving aMCI had no particular deficit in detailed episodic AbMs. Moreover, more detailed episodic AbMs than non-detailed AbMs were recalled overall, independent of the group (F(1,22)=157.9, p< .01; based on the total number of detailed and not detailed episodic AbMs across the different lifetime periods.

7.4.2.2 Temporal distribution of generic AbMs across groups

A lifetime period effect was found in the number of generic AbMs (F(3, 66)=3,32, p< .05), but no effect of longitudinal diagnosis nor interaction between the two factors emerged (F(2, 22)= .10, p= .90; F(6, 66)= .83, p= .55; respectively). Post-hoc tests indicated that the 0-19 and 20-39 lifetime periods had or tended to have more generic AbMs than that of the last 12 months (p< .02 and p= .08; respectively) and that no significant difference was found between the remaining lifetime periods (see fig. 9 and Table 9). These results showed that there was a gradient of generic AbMs with more memories in the more remote lifetime periods (0-19 years old and 20-39 years old) than in the most recent one (the last 12 months) for the three groups.

Moreover, regardless of the group, more episodic AbMs than generic were recalled (F(1, 22)=128,7, p< .01; based on the total numbers of episodic and generic AbMs across the different lifetime periods).

7.4.3 Valence of AbM

7.4.3.1 Temporal distribution of positive episodic AbMs across groups

No effects of longitudinal diagnosis (F(2, 22)= .09, p= .91), lifetime period (F(3, 66)=1,67, p= .18), nor lifetime periods × longitudinal diagnosis interactions (F(6, 66)=1,38, p= .24) were revealed for the number of positive episodic AbMs (see Table 9). Thus, evolving aMCI patients had no deficit in positive episodic AbMs compared with controls and non-evolving aMCI patients.

Moreover, much more positive episodic AbMs were recalled than negative and neutral episodic AbMs (F(2, 44)=103,4, p< .01; based on the total number of positive, negative and neutral episodic AbMs across the different lifetime periods). By contrast, the total number of the negative and neutral episodic AbMs did not significantly differ (p= 0.55).

7.4.3.2 Temporal distribution of positive generic AbMs

A lifetime period effect was found in the number of generic positive AbMs (F(3, 66)=4,23, p< 0,01), but no longitudinal diagnosis effect (F(2, 22)= 0,02, p= 0,98) nor lifetime

periods × longitudinal diagnosis interactions (F(6, 66)=1,12, p= 0,36) appeared. Post-hoc tests showed that the 0-19 and 20-39 lifetime periods had more generic positive AbMs than that of the last 12 months (p< 0.01 and p< 0.05; respectively; see table 9). These results showed a gradient of positive generic AbMs with more memories in the earlier lifetime periods (0-19 years old and 20-39 years old) than the most recent one (the last 12 months) for the three groups. Moreover, the evolving aMCI had no deficit in positive generic AbMs.

7.4.3.3 Temporal distribution of negative episodic AbMs between groups

Repeated ANOVAs yielded a trend on longitudinal diagnosis effect for the number of negative episodic AbMs (F(2, 22)=2,91, p= .08), but no lifetime period effect (F(3, 66)= 2,11, p= .11) nor lifetime periods × longitudinal diagnosis interactions (F(6, 66)=1,78, p= .12). Post-hoc tests showed that evolving aMCI patients had more negative episodic AbMs than controls (p= .05) independent of the remoteness of the AbMs (see Table 9). There was no significant difference between evolving and non-evolving aMCI (p= .10) although the latter had a similar number of negative episodic AbMs compared with controls (p= .90). Our aim being to discriminate evolving from non-evolving aMCI, we performed comparisons of negative episodic AbMs excluding controls. Repeated ANOVAs revealed a trend of longitudinal diagnosis effects for the number of negative episodic AbMs (F(1, 13)= 3,63, p= .08). Post-hoc tests showed that evolving aMCI patients tended to have more negative episodic AbMs than non-evolving aMCI (p= .07).

The reduced number of negative generic AbMs made it impossible to carry out analysis.

Although the depressive patients had been removed, a depression effect might be possible since the sensitivity of GDS was not 100% (see chapter 4). Therefore, to ensure that the higher number of negative episodic AbMs given by evolving aMCI was not an effect of depressive symptoms, we carried out correlations between the GDS score and the total number of negative episodic AbMs in evolving aMCI patients. No correlation was found (r= -.36, p= .37).

7.4.3.4 Temporal distribution of neutral episodic AbMs between groups

A trend of lifetime period effect was found in the number of neutral AbMs (F(3,66)=2.28, p= .09), but no longitudinal diagnosis effect (F(2,22)= .28, p= .76) nor lifetime periods × longitudinal diagnosis interactions (F(6,66)= .19, p= .98) appeared. Post-hoc tests

showed that the 0-19 years old lifetime period tended to have more neutral episodic AbMs than the 20-39 and 40-55 years old periods (p= .07 and p= .08; respectively; see Table 9).

The reduced number of generic AbMs made it impossible to carry out analysis.

7.4.4 Intensity of AbMs

A lifetime period effect was found in the AbM intensity ($F(3,66)=4.25$, $p< .01$), but no longitudinal diagnosis effect ($F(2,22)= .74$, $p= .49$) nor lifetime periods × longitudinal diagnosis interactions ($F(6,66)=1.06$, $p= .40$) appeared. Post-hoc tests indicated that the 0-19 years old period had significantly less intense AbMs than the other periods ($p< .02$ for all the comparisons; see fig. 10 and Table 9). In view of the fact that participants were free of the AbM valence they recalled (in Piefke et al. (2003) the AbM valence was imposed), some patients may have not recalled positive or negative AbM in a given lifetime period. For this reason, it was not possible to know whether this lifetime period effect concerned more positive or negative AbMs.

7.5 Discussion.

In the first section, we hypothesized that evolving aMCI patients would have a deficit in the most recent lifetime periods but not in the earliest for detailed episodic AbMs, whereas we did not expect a deficit in generic AbMs. Results did not show any impairment on either episodic or generic AbMs. Moreover, the distribution of generic AbMs was graded with less recent AbMs relatively compared with remote ones for the three groups. Thus, even though the MTL is supposed to be damaged in the aMCI stage (Braak and Braak 1991 and 1996; Braak et al., 1999), no deficits were detected in this memory. From these results, we had several suggestions. Firstly, the small sample size could have prevented us from observing some deficit. Secondly, the Crovitz Test may have little sensitivity to AbM deficit at a very early stage of AD where patients may still compensate. Further studies are required to extend research on AbM in the aMCI syndrome. For instance, in the present study, when participants did not retrieve episodic but generic AbM, they were prompted to give an episodic AbM; it would be interesting to take into account only the first AbM, be it episodic or generic, in the statistical analysis. In this case, if a higher number of generic AbMs was observed in evolving aMCI, it might be due to a difficulty of access to AbM. In addition, measuring the retrieval time of access of AbM should be carried out since if longer in evolving aMCI, it could also reflect a difficulty of access.

In the second section, we were interested in the AbM valence in evolving aMCI patients. We hypothezised that evolving aMCI patients would recall less positive AbMs

(either episodic or generic or both) than controls and non-evolving aMCI patients, independent of the remoteness of the AbM. Although we did not observe such a result, statistical analyses revealed that evolving aMCI patients tended to recall more negative episodic AbMs than controls independently of the remoteness of the AbM. With regard to the comparison between evolving and non-evolving aMCI patients, a trend was also found but given the small sample size, no conclusion could be drawn. Further studies are required to investigate more precizely valenced AbMs in evolving aMCI patients. Additional parameters could be included in the Crovitz Test such as imposing rules on the type of AbM recalled - negative, positive and neutral AbMs- rather than allowing patients freedom to retrieve any valenced AbM. Although no correlation was found between the GDS score and the total number of negative episodic AbMs in evolving aMCI patients, another hypothesis could be that some depressive symptoms might be sensitive to the Crovitz Test but not to GDS.

In the last section, we assumed that evolving aMCI would have less emotional intensity on the recent AbMs than non-evolving aMCI patients and controls. Results indicated that there was no difference across the three groups. Thus, from Piefke et al.'s suggestion (2003) that retrosplenial cortex would be involved in emotional processing, we suggest that this neural structure is not critical in this processing. Some functional imaging studies have demonstrated increased amygdala activity in response to highly arousing positive and negative stimuli (Hamann and Mao, 2002; Hamann et al., 2002). Although in our study it was not possible to separate positive from negative AbMs as explained above (see Results), the fact that the amygdala of aMCI patients is not yet damaged may explain the absence of group effect on emotional intensity. Finally, we found that the most remote AbMs (those of the 0-19 years old lifetime period) were significantly less intense than the other more recent lifetime periods independently of the longitudinal diagnostic. This result supports the fact that evolving aMCI are not significantly different from the other groups in terms of emotional intensity. Moreover, it is consistent with Piefke et al.'s study (2003), where recent AbMs were more emotionally intense than remote ones in young healthy subjects regardless of valence.

7.6 Conclusion

In spite of the small size of our sample, the present study provides evidence that AbM is not impaired in evolving aMCI patients in terms of number of episodic AbMs, valence and emotional intensity. It was proposed to include additional parameters to the current version of the Crovitz Test.

General conclusion and perspectives

The main purpose of the present thesis was to search for specific preclinical markers of DAT. The two-year longitudinal study of the current work followed aMCI patients in order to examine their cognitive evolution and to distinguish evolving from non-evolving aMCI patients. Results showed that aMCI was an heterogeneous syndrome leading to evolving aMCI in a limited proportion whereas additional depression strongly increased the risk of becoming evolving aMCI. Moreover, at baseline, longer copying time of the Rey-Osterrieth figure was sensitive and specific to evolving aMCI compared with non-evolving aMCI and controls. Over time, evolving aMCI patients' performance decreased on the Rey-Osterrieth figure copy and the Rey-Osterrieth figure 30'-delayed-recall. Both these observations at baseline and over the timeframe suggested that evolving aMCI presented with subtle visuoconstructive deficits in addition to their memory impairment. Another hypothesis was that they were cognitively slowed down. The heterogeneity observed in the aMCI sample highlights the importance of leading longitudinal studies with very large samples, coupling neuropsychological tests, neuroimaging and biological data to improve the evolving aMCI diagnosis. In particular, based on our results and litterature, research should focus on : (i) EC atrophy for structural MRI markers; (ii) hypometabolism in the temporoparietal cortex and the PCC, and greater extent hippocampal and PHG activation for functional markers and (iii) deficits in non-verbal recognition, semantic memory and visuoconstructive tests for neuropsychological markers. With regard to the influence of depression in the present dissertation, Gauthier et al. (2006) pointed out that aMCI could have different origins such as degenerative, vascular, psychiatric and medical disorders. Thus, future neuropsychological studies on aMCI could improve differential diagnosis including behavioral data from patients suffering from known degenerative, vascular, psychiatric and medical disorders.

Our second study examined topographical recognition memory in aMCI patients. Topographical recognition memory is known to be mainly underlain by the PHG, a neural structure impaired early on in AD and not affected by depression. On this basis, we hypothesized that deficit in topographical recognition memory might be a specific neuropsychological marker of AD. Results showed that this memory was impaired in aMCI patients but was not sensitive to depression. Nevertheless, longitudinal results indicated that deficits in topographical recognition memory were not sensitive to the evolving aMCI condition. This insensitivity was probably due to the absence of specific spatial memory components targeted by the TRMT. An ongoing fMRI study will allow (a) assessment of

allocentric and egocentric components of topographical recognition memory in evolving aMCI patients, and (b) verification of whether this cognitive task reveals neural dysfunction as has already been observed in aMCI patients in preceding fMRI studies.

The last study investigated AbM performance and emotion of AbM across non-evolving and evolving aMCI and controls. Indeed, AbM per se and its emotional component involve neural structures damaged early on in AD, such as the retrosplenial cortex and the MTL. Comparisons revealed no significant differences across the three groups. A new modified version of the Crovitz test could include additional parameters such as measuring the retrieval time of access of AbM, and imposing rules on the type of AbM recalled - negative, positive and neutral episodic/generic AbMs- rather than allowing patients freedom to retrieve any type of AbM.

Perspectives are twofold: on the one hand, the single domain aMCI entity seems to be too rigid to be used as a clinical entity. The multiple domain aMCI entity is more adapted to the current observations but requires the inclusion of specific cognitive deficits. Indeed, Ivanoiu et al. (2005) and Blackwell et al. (2004) reported that deficits in non-verbal recognition memory, visuospatial memory and semantic memory were predictive of evolution to dementia in aMCI patients. Moreover, the visuoconstructive deficits observed in our evolving aMCI patients and presence or not of depression should be considered as additional criteria to multiple domain aMCI. On the other hand, the current results obtained with the Crovitz Test and the TRMT should be taken into account for further studies on neuropsychological markers of AD. These latter should target (i) valence for AbM, and (ii) allocentric and egocentric systems for spatial memory.

On a more practical point of view, this dissertation is in line with the necessity to develop Memory Clinics in France for prevention of dementia consisting in systematic longitudinal follow-up of healthy older subjects and patients, and to facilitate access of MCI patients for research.

Appendix

Scores of the global cognitive functioning: MMSE and the complementary scale (Dubois and Pillon, unpublished, Salpêtrière Hospital, Paris)

Total scores are in parentheses: attention (/15) was scored by summing Attention subtest of the MMSE (/5) and forward (/6) and backward (/4) digit spans of the Salpêtrière scale; spatial and temporal orientation (/10) was assessed with the MMSE; language (/18) was composed of Naming, Repetition, 3-stage command, Reading and Writing of the MMSE and Naming of the Salpêtrière scale (ten drawings of objects (eg. Racket) or animals (eg. Camel)) (/10); praxies in the Salpêtrière scale required the subject to copy gestures without meaning (/4); visuo-constructive activities were evaluated by copying a circle and a diamond (/1), two intersecting pentagons (MMSE, /1), and by reproducing block designs (Salpêtrière scale, /3).

Figures

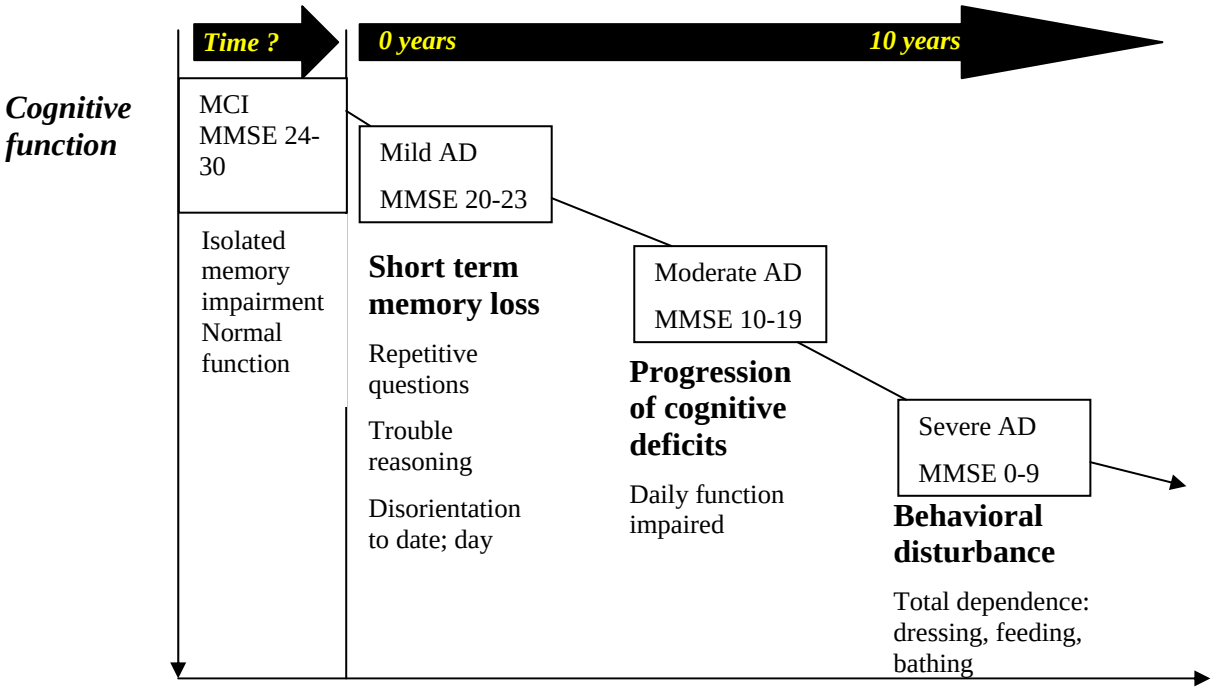

Fig. 1. Clinical course of AD. From Petrella et al. (2003, p. 319).

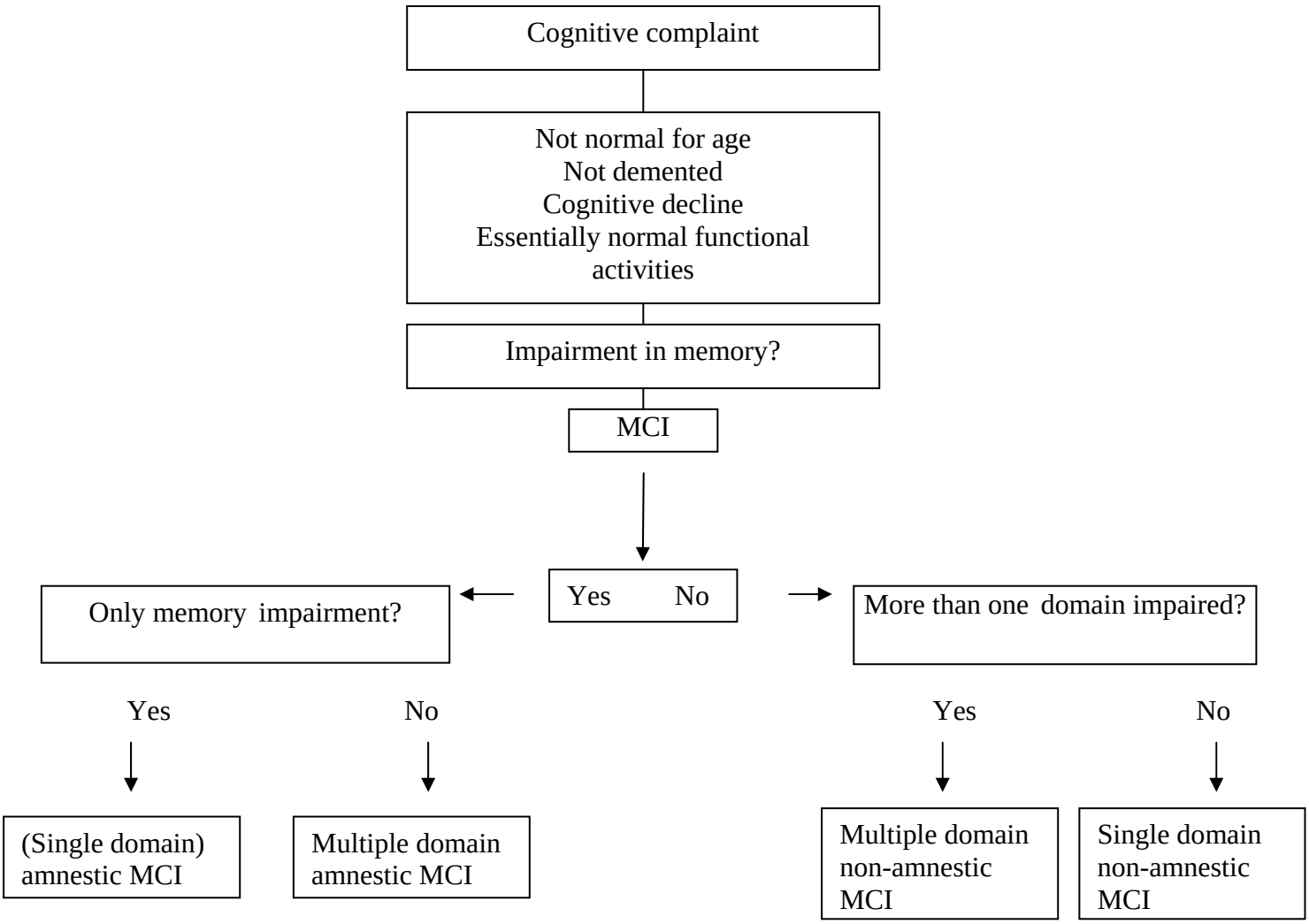

Fig. 2. Schema to diagnose the different subtypes of MC (From Winblad et al., 2004; page 243).

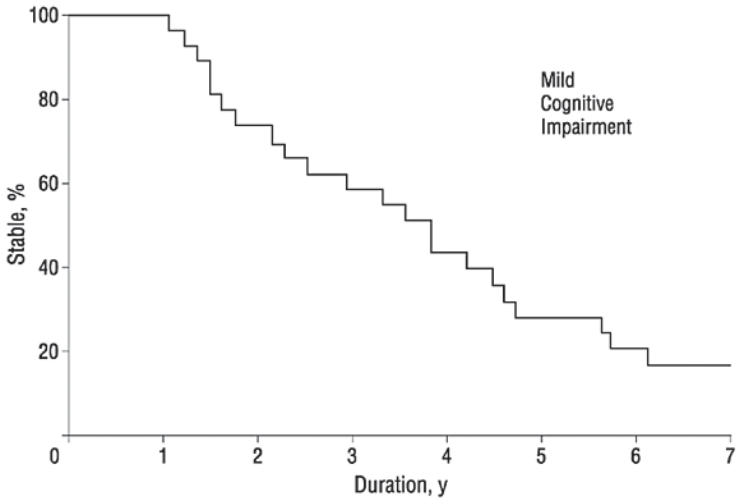

Fig. 3. Survival curve of aMCI patients for 6 years. **y**: years. From Petersen et al. (2001; page 1986).

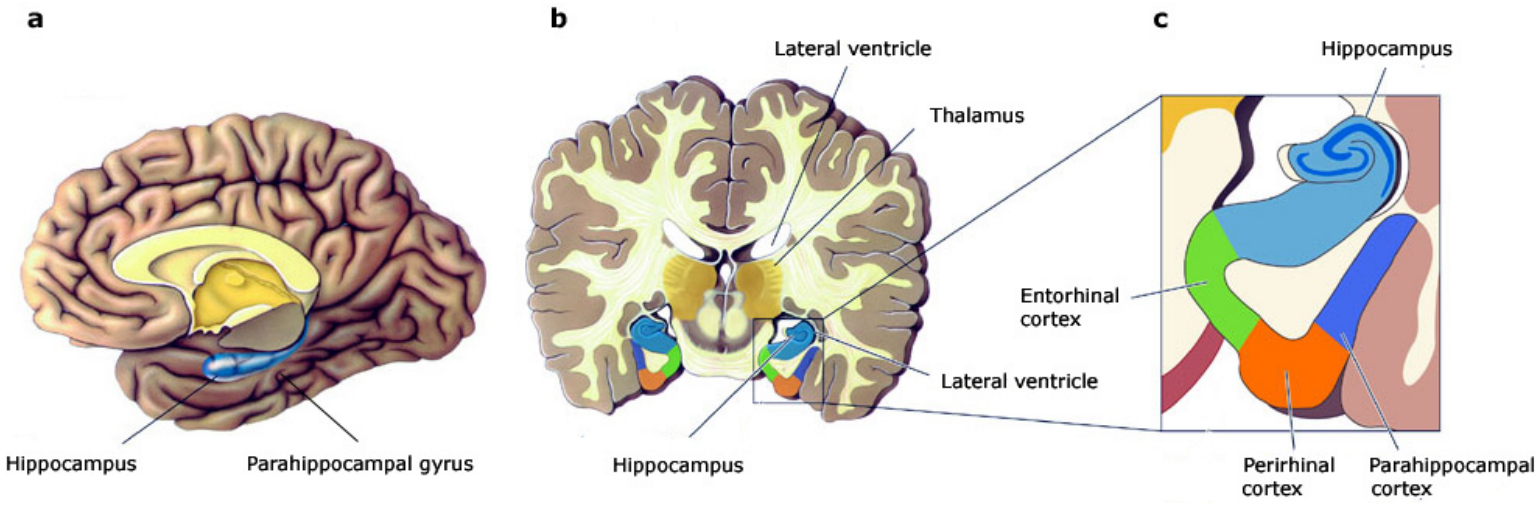

Fig. 4. The medial temporal lobe in (a) medial view, (b) coronal view and (c) detailed view (taken and adapted from Bear, Connors, and Paradiso. *Neuroscience: Exploring the Brain*).

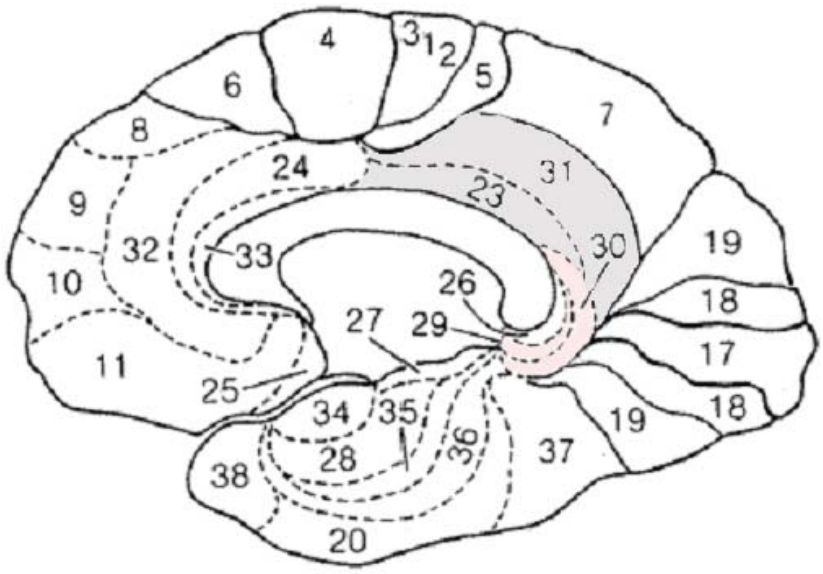

Fig. 5. Sagittal view of the right hemisphere showing Brodmann areas, in particular, the posterior cingulate region comprising the posterior cingulate cortex (BA 23, 31) and the retrosplenial cortex (BA 29, 30).

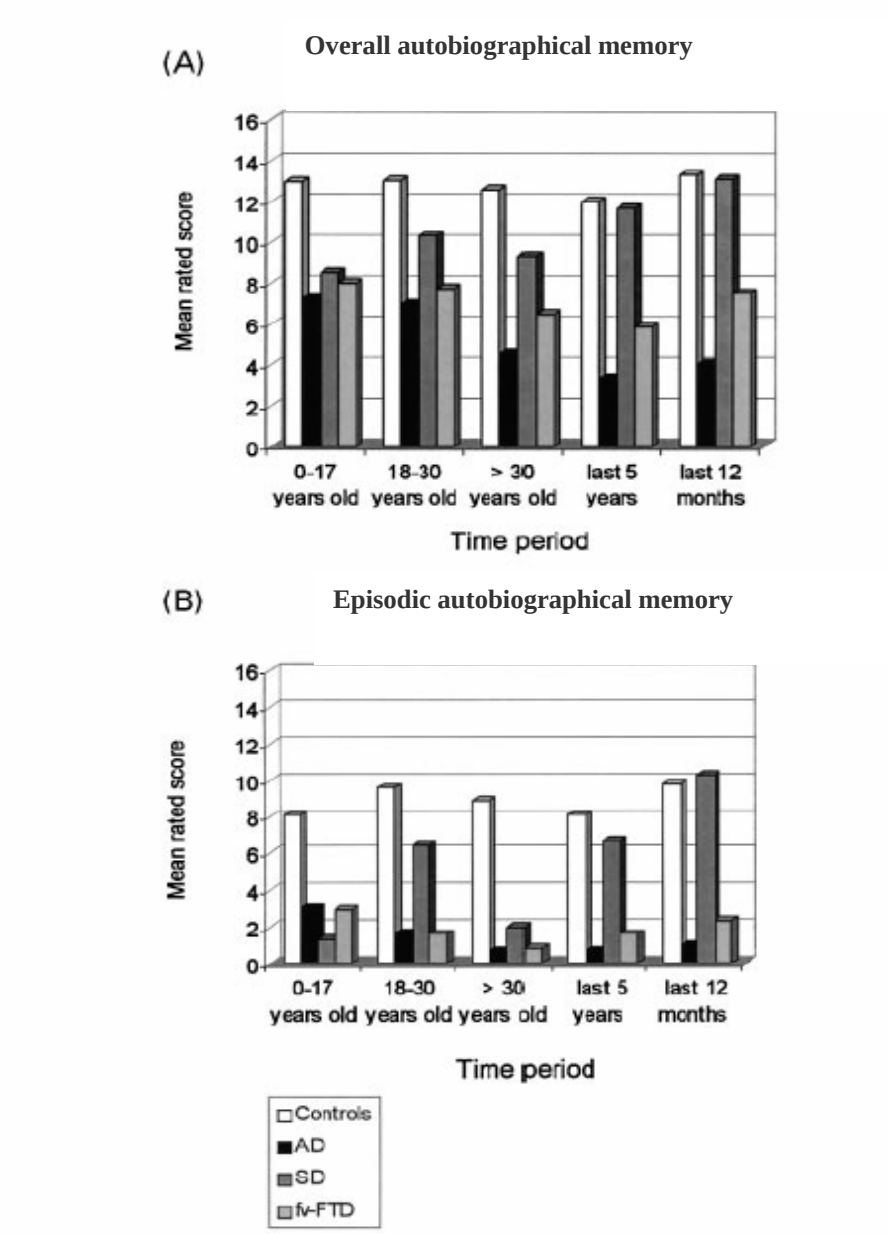

Fig. 6. Patient's results on the AbM task compared with those of the control subjects for each time period: (A) overall AbM score (AM) and (B) episodic memory score (EM). AD: Alzheimer disease; fv-FTD: frontal variant of frontotemporal dementia; SemD: semantic dementia. Controls (N=18); AD (N=13); SemD (N=10); and fv-FTD (N=15). From Piolino et al. (2003).

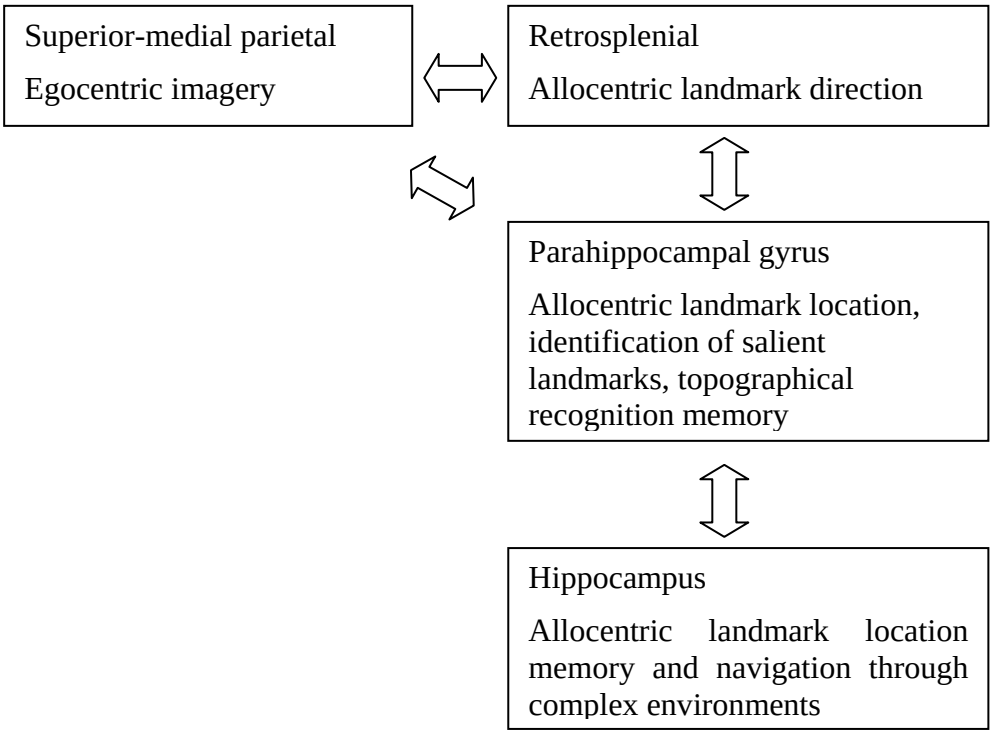

Fig. 7. Illustration of a hippocampal-neocortical framework of spatial memory. The arrows connecting regions represent reciprocal anatomical connections. Adapted from Moscovitch et al. (2006).

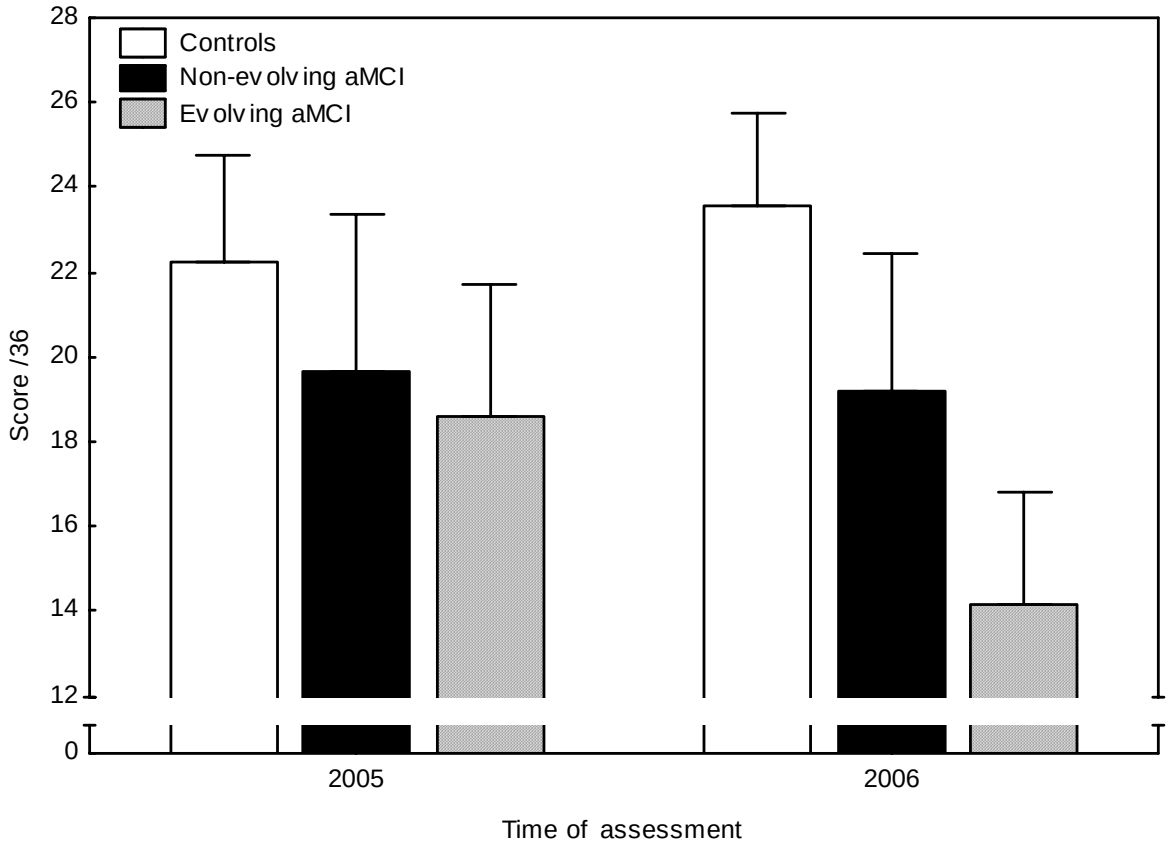

Fig. 8. Evolution of the performance on the Rey-Osterrieth figure 30'-delayed-recall over the follow-up

* p< .01

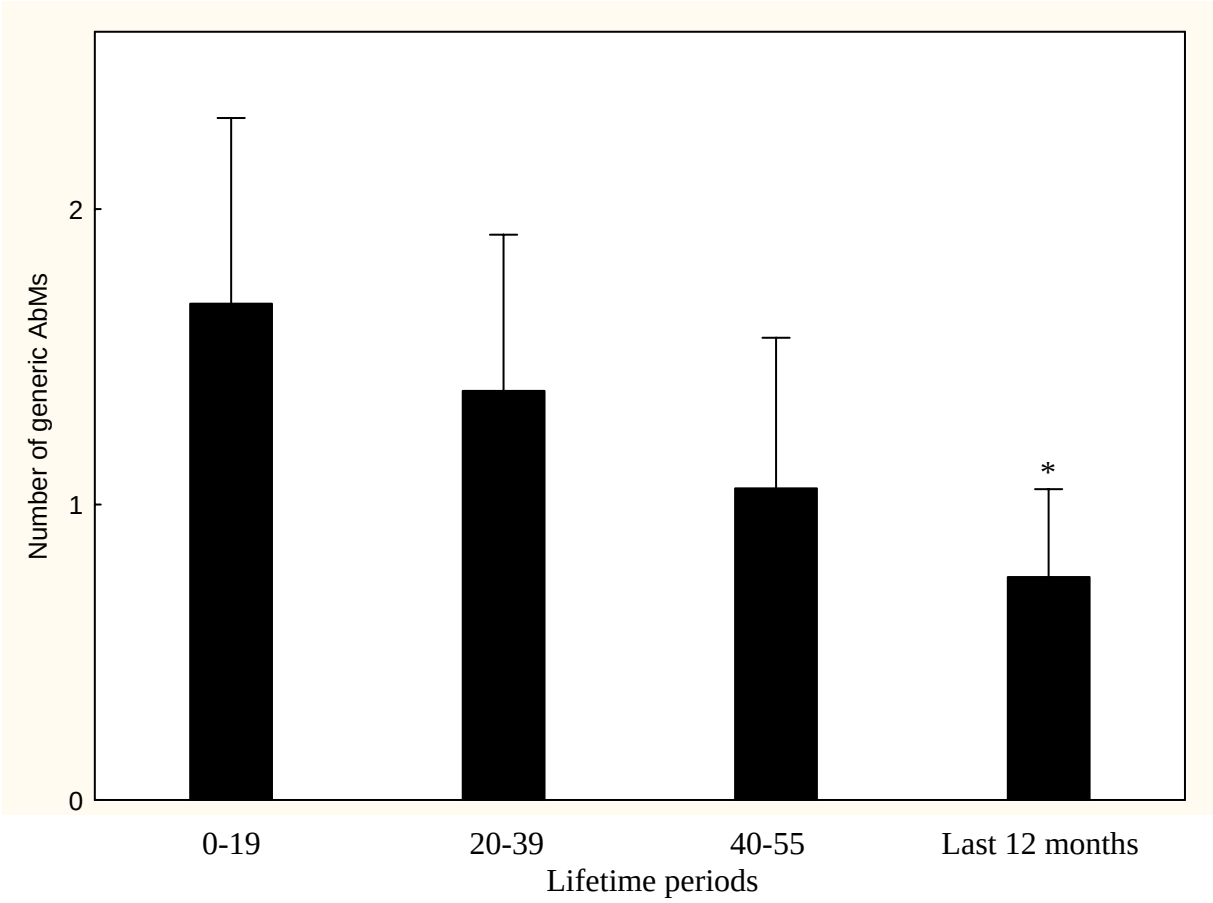

Fig. 9. Temporal distribution of the number of generic AbMs for the three mixed groups.

* p< .02, compared with the 0-19 lifetime period.

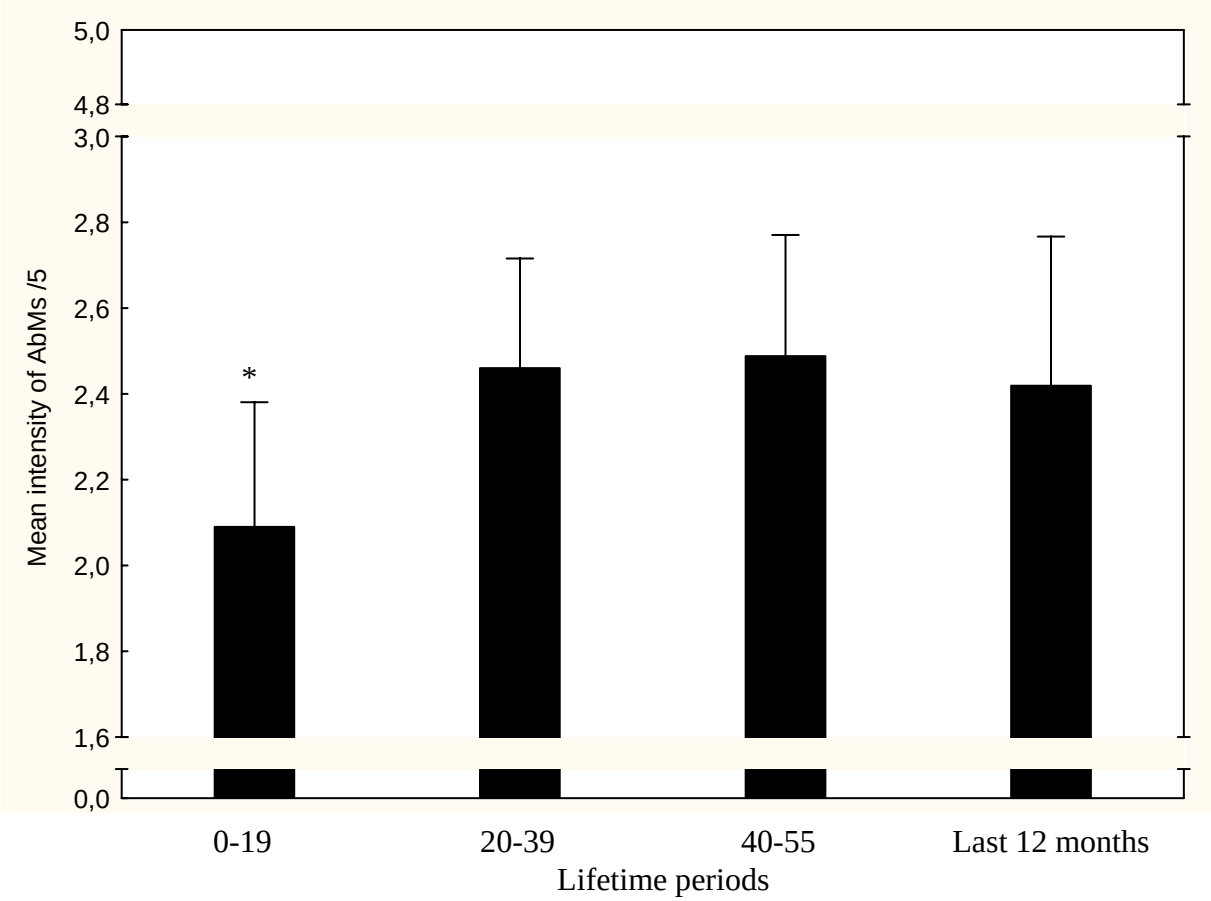

Fig. 10. Intensity of AbMs for each lifetime periods in the three mixed groups.

* p< .02 compared with the 20-39, 40-55 and last 12 months lifetime periods.

Tables

Table 1. Outline of the syndrome of mild cognitive impairment.

Cause						
Clinical classification			Degenerative	Vascular	Psychiatric	Medical disorder
	Amnestic mild cognitive impairment	Single domain	AD		Depression	
		Multiple domain	AD	VD	Depression	
	Non-amnestic mild cognitive impairment	Single domain	FTD			
		Multiple domain	DLB	VD		

Note. **AD**: Alzheimer disease; **DLB**: dementia with Lewy bodies; **FTD**: frontotemporal dementia; **VD**: vascular dementia. From Gauthier et al. (2006; page 1265)

Table 2. Longitudinal studies investigating different types of MCI.

Study	Conversion rate of dementia	Prevalence	Number of participants	Age (range or mean, ± SD)	Duration of the study	Population
s-aMCI						
Busse et al. (2003)	In 2.6 years : AD, VD and dementia not further specified : 33%	3%	1045	> 75	2.6 years	Community
Larrieu et al. (2002)	AD: 8.3% per year	2.8%	1658	> 65	5 years	Community
Petersen et al. (1990; 1999)	In six years: AD: 80% 10-12% per year	-	> 1900	> 65	< 15 years	Community
Rasquin et al. (2005)	In 2 years : AD : 23.5%	14.4%	118	> 55	2 years	Memory clinic
Rasquin et al. (2005)	In 2 years : AD: 0%	0%	80	> 55	2 years	Stroke patients
Ritchie et al. (2001)	In 3 years Senile dementia: 11.1%	3.2%	833	> 60	3 years	Community
Zanetti et al. (2006)	In three years: AD: 35%	7.8%	400	> 65	3 years	Community
s-non-aMCI						
Rasquin et al. (2005)	In 2 years : AD : 3.8%	22%	118	> 55	2 years	Memory clinic
Rasquin et al. (2005)	In 2 years : AD : 0%	26.2%	80	> 55	2 years	Stroke patients
Yaffe et al. (2006)	In three years : FTD: 100%	-	34	72.9 (±9.3)	3 years	MCI
m-aMCI						
Bennett et al. (2002)	In seven years: AD: 34%	26.6%	708	78.6 (±6.8)	7 years	Catholic clergy
Meyer et al. (2002)	In four years: AD: 47.9% VD: 20.5% Stable or recovered: 31.5%	25.1%	291	67.9 (±9)	4 years	Community
Zanetti et al. (2006)	In three years: SCVD: 26% Stable: 14%	8.5%	400	> 65	3 years	Community
m-aMCI and m-non-aMCI mixed						
Rasquin et al. (2005)	In 2 years : AD : 28%	63.5%	118	> 55	2 years	Memory clinic
Rasquin et al. (2005)	In 2 years : AD : 8.8%	73.8%	80	> 55	2 years	Stroke patients
s-aMCI, m-aMCI and m-non-aMCI mixed						
Yaffe et al. (2006)	In three years : AD: 76% VD: 50%	-	327	72.9 (±9.3)	3 years	MCI

Note. AD: Alzheimer's disease; **FTD**: frontotemporal dementia; **m-aMCI**: multiple domain aMCI; **m-non-aMCI** : multiple domain non-aMCI ; **s-aMCI**: single domain aMCI; **s-non-aMCI**: single domain non-aMCI ; **SCVD** : subcortical vascular dementia; **SD**: standard deviation; **VD**: vascular dementia.

Table 3. Demographic data of the different groups.

Group	Non-aMCI		aMCI		Analysis of Variance (ANOVA) Followed by Newman-Keuls Tests (if p< .05)
	Group 1 **NC (N=17)**	**Group 2** **DEP (N=10)**	**Group 3** **amnMCI (N=15)**	**Group 4** **amnMCI+DEP (N=9)**	
Age **Range: 55-70**	61.9 (4.63)	61.5 (4.90)	63.1 (3.66)	60.6 (2.88)	**p = .19**
Years of education	12.2 (3.34)	13.0 (3.27)	13.7 (3.15)	14.4 (3.75)	**p = .43**
MMSE /30	28.9 (1.17)	28.9 (1.10)	28.7 (1.18)	28.1 (1.45)	**p = .38**
GDS /9	0.25 (0.58)	3.70 (0.95)	0.67 (0.90)	3.89 (1.05)	**p < .01** (Group 2=Group 4)>(Group 1=Group 3

Note. amnMCI, patients with amnestic mild cognitive impairment without depression; **amnMCI+DEP**, depressive patients with amnestic mild cognitive impairment; **DEP**, depressive patients without cognitive impairment; **GDS**, Goldberg's depression scale; **MMSE**, Mini Mental Status Examination; **NC**, Control subjects. Values are expressed as means with standard deviations in parentheses.

Table 4. Cognitive evolution over the two-year longitudinal follow-up (between 2004 and 2006).

Diagnosis at baseline in 2004 Longitudinal diagnosis in 2006	**Number of NC**	**Number of DEP**	**Number of amnMCI**	**Number of amnMCI+DEP**
Number of evolving aMCI	2 (15.4%)	0	4 (28.6%)	4 (57.1%)
Number of non-evolving aMCI	1 (7.7%)	0	4 (28.6%)	2 (28.6%)
Number of non-aMCI	3 (23.1%)	3 (50%)	2 (14.3%)	0
Number of controls	7 (53.9%)	3 (50%)	4 (28.6%)	1 (14.3%)

Note. amnMCI, patients with amnestic mild cognitive impairment without depression in 2004; **amnMCI+DEP**, depressive patients with amnestic mild cognitive impairment in 2004; **DEP**, depressive patients without cognitive impairment in 2004; **NC**, Control subjects in 2004. Values are expressed as means with standard deviations in parentheses.

Table 5. Demographic, cognitive and depression score data of the control and evolving aMCI groups at baseline.

	Controls **N=15**	**Evolving aMCI** **N=10**	**Non-evolving aMCI** **N=7**	**Analysis of Variance (ANOVA)** Followed by Newman-Keuls Tests (if $p < .05$)
Ratio M/F	**4/11**	**2/8**	**5/2**	**-**
Age **Range: 55-70**	61,7 (± 4.51)	62.9 (± 4.33)	62.6 (± 3.91)	**p = .79**
Years of education	14.1 (± 3.73)	13.5 (± 3.06)	14.7 (± 2.75)	**p = .77**
MMSE	29.3 (± 0.88)	28.7 (± 0.95)	28.3 (± 1.25)	**p = .09**
Premorbid IQ	122.4 (± 6.49)	120.6 (± 10.8)	126.1 (± 2.48)	**p= .35**
GDS /9	1.47 (± 1.96)	2.10 (± 1.97)	1.57 (± 1.62)	**p = .71**

Note. GDS, Goldberg's depression scale; **IQ**, intellectual quotient; **MMSE**, Mini Mental Status Examination ; **ratio M/F**, ratio males/females. Values are expressed as means with standard deviations in parentheses.

Table 6. Mean scores and standard deviations on the neuropsychological tests per group at baseline

	Controls N=15	**Evolving aMCI** N=10	**Non-evolving aMCI** N=7	**Analysis of Variance (ANOVA)** Followed by Newman-Keuls Tests (if $p < 0.05$)
Verbal immediate-recall task /12	8.80 (± 1.53)	7.40 (± 1.08)	7.14 (± 1.41)	**p < .05 Controls> Evolving aMCI = non-evolving aMCI**
Verbal delayed-recall task /12	6.00 (± 2.00)	3.10 (± 1.45)	3.14 (± 1.57)	**p < .01 Controls> Evolving aMCI = non-evolving aMCI**
Attention /15	13.8 (± 1.01)	12.4 (± 0.84)	13.0 (± 0.82)	**p < .01 Controls> Evolving aMCI = non-evolving aMCI**
Phonological fluency task "P" for one minute	15.7 (± 5.63)	12.5 (± 3.72)	16.1 (± 4.02)	**p = .20**
Phonological fluency task "M" for one minute	13.1 (± 4.49)	12.2 (± 4.19)	13.6 (± 3.78)	**p = .79**
Raven /12	8.73 (± 1.84)	8.60 (± 1.90)	9.57 (± 2.00)	**p = .54**
Similarities /20	14.2 (± 3.53)	13.2 (± 2.25)	13.3 (± 1.98)	**p = .65**
Premorbid IQ	122.5 (± 6.49)	120.6 (± 10.8)	126.1 (± 2.48)	**p = .35**
Stroop	-0.76 (± 6.24)	-3.31 (± 5.57)	-2.46 (± 3.53)	**p = .52**
Rey-Osterrieth figure copy /36	34.4 (± 0.91)	33.8 (± 1.14)	34.7 (± 1.98)	**p = .32**
Copying time of the Rey-Osterrieth figure (seconds)	140.5 (± 41.5)	203.9 (± 68.2)	147.4 (± 62.6)	**p < .05 Controls = Non-evolving aMCI < evolving aMCI**
Rey-Osterrieth figure 30'-delayed recall /36	22.3 (± 3.85)	18.6 (± 5.85)	19.6 (± 4.95)	**p = .16**
Face Recognition Memory Test /25	23.6 (± 1.12)	22.2 (± 1.81)	22.1 (± 2.79)	**p = .10**
Vocabulary /20	12.9 (± 2.05)	12.1 (± 3.35)	11.9 (± 1.46)	**p = .55**
Arithmetic /20	12.5 (± 2.03)	12.0 (± 2.58)	13.1 (± 1.35)	**p = .55**
Picture arrangement /20	12.5 (± 2.03)	12.0 (± 2.58)	13.1 (± 1.35)	**p = .24**
Picture completion /20	12.4 (± 3.40)	10.4 (± 2.22)	11.6 (± 1.99)	**p = .25**
Block design /20	12.9 (± 2.47)	10.9 (± 2.59)	11.7 (± 2.87)	**p = .09**

Note. IQ, intellectual quotient. Values are expressed as means with standard deviations in parentheses.

Table 7. Mean scores and standard deviations on the neuropsychological tests per group of the preliminary study (2004).

Group	Non-aMCI		aMCI		Analysis of Variance (ANOVA) Followed by Newman-Keuls Tests (if $p < 0.05$)
	NC (N=17)	**DEP (N=10)**	**amnMCI (N=15)**	**amnMCI+DEP (N=9)**	
TRMT /30	26.7 (± 2.69)	25.1 (± 3.11)	23.1 (± 2.59)	22.8 (± 4.76)	**p < .01** NC = DEP > amnMCI = (amnMCI+DEP)
Verbal immediate-recall task /12	8.64 (± 1.22)	8.30 (± 1.44)	7.10 (± 1.67)	7.33 (± 1.30)	**p < .02**
Verbal delayed-recall task /12	6.88 (± 1.69)	6.70 (± 2.21)	3.07 (± 1.49)	2.78 (± 1.09)	**p = .01** NC = DEP > amnMCI = (amnMCI+DEP)
Attention /15	12.9 (± 1.09)	13.0 (± 2.16)	13.1 (± 1.10)	13.0 (± 0.87)	**p = .97**
Phonological fluency task "P" for one minute	15.4 (± 5.45)	15.9 (± 4.43)	12.7 (± 4.06)	13.8 (± 3.83)	**p = .29**
Raven /12	8.18 (± 1.98)	7.90 (± 1.85)	9.00 (± 1.81)	7.44 (± 2.65)	**p = .30**
Similarities /20	12.9 (± 2.63)	14.8 (± 3.23)	13.3 (± 2.89)	13.4 (± 2.74)	**p = .47**
Premorbid verbal IQ	120.1 (± 7.89)	123.1 (± 5.88)	120.6 (± 10.0)	122.6 (± 5.94)	**p = .74**

Note. amnMCI, patients with amnestic mild cognitive impairment without depression; **amnMCI+DEP**, depressive patients with amnestic mild cognitive impairment; **DEP**, depressive patients without cognitive impairment; **NC**, normal control subjects; **TRMT**, Topographical Recognition Memory Test. Values are expressed as means with standard deviations in parentheses.

Table 8. Demographic, cognitive and depression score data of the control and evolving and non-evolving aMCI groups.

	Controls **N=10**	**Evolving aMCI** **N=8**	**Non-evolving aMCI** **N=7**	**Analysis of Variance (ANOVA)** Followed by Newman-Keuls Tests (if $p < 0.05$)
Ratio M/F	4/8	1/7	5/2	**-**
Age **Range: 57-72**	64.8 (± 4.77)	63.9 (± 3.94)	64.6 (± 3.91)	**p = .89**
Years of education	14.7 (± 4.17)	12.6 (± 2.56)	14.7 (± 2.75)	**p = .36**
MMSE (2006)	29.4 (± 0.92)	29.4 (± 0.74)	29.4 (± 0.79)	**p = .99**
Premorbid IQ	122.6 (± 7.26)	119.5 (± 12.0)	126.1 (± 2.48)	**p= .32**
GDS /9 (2006)	0.46 (± 0.82)	0.25 (± 0.71)	0.29 (± 0.76)	**p = .83**

Note. GDS, Goldberg's depression scale; **IQ**, intellectual quotient; **MMSE**, Mini Mental Status Examination ; **ratio M/F**, ratio males/females. Values are expressed as means with standard deviations in parentheses.

Table 9. AbM data in the controls (group 1), and the evolving and non-evolving aMCI patients (groups 2 and 3; respectively)

Lifetime periods	**0-19 years old**			**20-39 years old**			**40-55 years old**			**Last 12 months**			**ANOVA Longitudinal diagnosis**
Groups	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	***ANOVA Lifetime periods***
Mean nb of episodic AbMs	7.20 (1.69)	7.36 (1.69)	6.86 (1.86)	6.60 (2.80)	7.75 (1.49)	7.29 (2.29)	6.80 (2.25)	6.88 (2.23)	7.57 (2.76)	7.90 (2.76)	6.88 (1.96)	6.29 (3.50)	**p = .98** ***p = .96***
Mean nb of generic AbMs *	1.70 (1.16)	1.63 (1.77)	1.71 (1.60)	1.60 (1.51)	1.13 (0.64)	1.43 (1.40)	1.20 (1.23)	1.25 (0.89)	0.71 (1.50)	0.30 (0.48)	1.25 (0.89)	0.71 (0.76)	**p = .90** ***p< .05***
Mean nb of positive episodic AbMs	4.50 (1.58)	4.00 (0.93)	4.71 (1.70)	4.60 (2.12)	5.25 (2.05)	5.14 (1.68)	5.10 (2.03)	4.50 (2.51)	5.29 (2.14)	6.20 (2.35)	5.38 (1.60)	4.43 (3.15)	**p = .91** ***p = .18***
Mean nb of positive generic AbMs *	0.90 (1.29)	1.38 (1.51)	1.43 (1.72)	1.20 (1.14)	0.50 (0.53)	1.14 (1.46)	0.90 (0.99)	0.75 (0.71)	0.29 (0.49)	0.20 (0.42)	0.38 (0.52)	0.43 (0.79)	**p = .98** ***p< .01***
Mean nb of negative episodic AbMs	1.10 (0.74)	2.00 (1.51)	0.29 (0.49)	0.80 (0.79)	1.50 (1.31)	1.14 (1.35)	0.80 (0.79)	1.75 (1.17)	1.00 (0.82)	0.60 (1.07)	0.63 (0.52)	0.71 (0.76)	**p = .08** ***p= .11***
Mean nb of negative generic AbMs °	0.20 (0.42)	0.13 (0.35)	0	0	0	0.14 (0.38)	0.10 (0.32)	0.38 (0.52)	0	0	0.63 (0.52)	0.14 (0.38)	-
Mean nb of neutral episodic AbMs	1.60 (1.35)	1.38 (1.60)	1.86 (1.57)	1.20 (0.79)	1.00 (1.41)	1.00 (0.82)	0.90 (0.57)	0.63 (1.19)	1.29 (1.25)	1.10 (1.60)	0.88 (1.64)	1.14 (1.07)	**p = .76** ***p= .09***
Mean nb of neutral generic AbMs °	0.60 (0.70)	0.13 (0.35)	0.29 (0.76)	0.40 (0.52)	0.63 (0.52)	0.14 (0.38)	0.20 (0.42)	0.13 (0.35)	0.43 (1.13)	0.10 (0.32)	0.25 (0.46)	0.14 (0.38)	-
Mean intensity *	2.11 (0.92)	2.46 (0.51)	1.69 (0.43)	2.44 (0.73)	2.48 (0.53)	2.46 (0.48)	2.60 (0.85)	2.66 (0.68)	2.21 (0.20)	2.46 (0.99)	2.52 (0.77)	2.29 (0.60)	**p = .49** ***p< .01***

Note. Values are expressed as means with standard deviations in parentheses.

* Significant effect of the "lifetime periods" factor.

° No statistical analyses undertaken due to the too small number of AbMs.

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