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Extent and Neural Basis of Semantic Memory Impairment in Mild Cognitive Impairment

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Abstract. An increasing number of studies indicate that semantic memory is impaired in mild cognitive impairment (MCI). However, the extent and the neural basis of this impairment remain unknown. The aim of the present study was: 1) to evaluate whether all or only a subset of semantic domains are impaired in MCI patients; and 2) to assess the neural substrate of the semantic impairment in MCI patients using voxel-based analysis of MR grey matter density and SPECT perfusion. 29 predominantly amnestic MCI patients and 29 matched control subjects participated in this study. All subjects underwent a full neuropsychological assessment, along with a battery of five tests evaluating different domains of semantic memory. A semantic memory composite Z-score was established on the basis of this battery and was correlated with MRI grey matter density and SPECT perfusion measures. MCI patients were found to have significantly impaired performance across all semantic tasks, in addition to their anterograde memory deficit. Moreover, no temporal gradient was found for famous faces or famous public events and knowledge for the most remote decades was also impaired. Neuroimaging analyses revealed correlations between semantic knowledge and perirhinal/entorhinal areas as well as the anterior hippocampus. Therefore, the deficits in the realm of semantic memory in patients with MCI is more widespread than previously thought and related to dysfunction of brain areas beyond the limbic-diencephalic system involved in episodic memory. The severity of the semantic impairment may indicate a decline of semantic memory that began many years before the patients first consulted.

Keywords: Long-term memory, mild cognitive impairment, neuroimaging, semantic memory

INTRODUCTION

At the dementia stage of Alzheimer's disease (AD), the memory dysfunction is characterized by a severe impairment in episodic memory [1, 2]. There is also

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evidence that semantic memory is impaired at this stage of the disease, as demonstrated by impaired performance on tasks that require naming and recognizing famous people, as well as on category fluency and confrontation naming tasks [3–5]. In addition, impaired semantic memory has been well documented in early stages of AD, i.e., patients with "minimal" AD (e.g., [6–8]).

Mild cognitive impairment (MCI) refers to a syndrome that is defined by mild and progressive cognitive decline, prevailing in the memory domain, and preserved independence in daily life. Patients with MCI are at high risk for AD. While impaired recall of recently learned information is a defining criterion of MCI [9], patients with MCI also show impaired semantic memory, as observed most often on category fluency tasks, as well as on tasks assessing naming of famous faces and probing semantic knowledge about famous people [5–16].

While most studies focused on category fluency and tasks assessing naming or knowledge about famous people, it remains unknown whether other types of semantic knowledge are also impaired. Some studies report impaired ability to name objects [10–13] and famous monuments [11] in patients with MCI. Knowledge about historical facts has also been found to be diminished [14]. Other studies report preliminary data indicating that MCI patient are also impaired on short batteries that assess knowledge about famous public events [12, 15, 16] and cultural knowledge [17]. Acquisition of new words that entered the dictionary recently is likewise poor in these patients [18]. Thus, there is converging evidence that the semantic impairment in MCI is found across different semantic domains. These findings suggest that the memory difficulties in MCI may be more widespread and more severe than initially thought. The memory impairment in MCI patients may thus extend beyond classic anterograde amnesia, also affecting semantic knowledge that was acquired over a lifetime (retrograde memory).

Impaired memory in AD is generally attributed to hippocampal damage because of the critical role of this structure in memory and because it is affected by neurofibrillary tangles in the course of the disease [19, 20]. More recently, there has been evidence that impaired episodic memory in patients with AD is related to dysfunction that extends beyond the hippocampus and involves a limbic-diencephalic network [21, 22]. Similar findings have been reported in patients with MCI [23]. However, the neural substrate of the semantic memory impairment observed in MCI patients remains to be determined [11, 24]. Cortical regions implicated in semantic cognition typically include the temporal poles, the inferior and lateral temporal lobes, regions of the parietal lobes as well as the left inferior prefrontal cortex [25, 26]. Semantic memory deficits in MCI patients are therefore likely to be related to a neural dysfunction that extends beyond the limbic-diencephalic network supporting episodic memory, and particularly outside the hippocampus. If this assumption is true, it would suggests that the neural dysfunction at the MCI stage may be more widespread than generally considered.

The aims of the present study were thus twofold: 1) To evaluate whether semantic deficits in predominantly amnestic MCI patients affect several semantic domains including general factual cultural knowledge; knowledge about historical facts; knowledge about geographical facts; knowledge about famous public events; famous face naming, and knowledge about famous persons; and 2) To assess the neural substrate of the semantic impairment in these patients using voxel-based analysis of grey matter density on MRI and of brain perfusion on 99mTc-ECD SPECT.

METHODS

Patients and control subjects

29 patients meeting criteria for MCI [9] from the Marseille Memory study, a study aimed at identifying neuropsychological and neuroimaging predictors of conversion to AD, were included (protocol AP-HM PHRC 2001/54). Inclusion criteria were: normal activities of daily living (assessed during a clinical interview and requiring an IADL score of 0, [27]); Mini-Mental Status Exam (MMSE) $\geq$25 [28], a memory complaint (as assessed during a clinical interview and using a rating scale), an objective memory impairment upon formal neuropsychological evaluation, largely normal general cognitive function, essentially intact activities of daily living and no dementia. The memory impairment was defined in terms of impaired performance on either delayed free recall of a word list (the French adaptation of the FCSRT, [29]) or on the delayed Logical Memory subtest of the WMS-III [30]), using a cut-off score of 1.5 SD below the mean of matched control subjects [9]. Prior to the inclusion into the study, all patients underwent a comprehensive neuropsychological assessment that included the following tests: the Modified Wisconsin Card Sorting Test, the Stroop test, matrix reasoning of the WAIS-III, the Frontal Assessment Battery, Trail Making Test A and B, Benton's facial recognition test,

Benton's Judgment of line orientation, and the Hamilton depression scale. Detailed results of these tests are not reported in this study since control subjects did not complete these tasks (published norms were used instead). Patients with a clear deficit in one or more cognitive domains other than memory on this neuropsychological assessment were excluded. Thus, overall, our patients can be described as being predominantly amnestic MCI. Other exclusion criteria were a history of systemic and neurological disease and a modified Hachinski ischemic score ≥ 2 [31]. Routine, pre-inclusion, brain CT scan and/or MRI, as well as biological and psychiatric screening were performed in order to exclude non-degenerative causes of memory impairment. Patients who acquired the French language during adulthood were excluded. This study was approved by the local institutional ethics committee and all patients and control subjects signed informed consent.

Patients were matched with control subjects on each of the following features: 1) age; 2) years of education; and 3) socio-professional status achieved during life. Socio-professional status was evaluated using the standard classification of the main French statistical institute (catégories socio-professionnelles, Institut National de la Statistique et des Études économiques). 29 control subjects, strictly matched for age, education, and socio-professional status were included into this study. Demographic characteristics of both groups are presented in Table 1.

Patients with MCI were followed longitudinally every 18 months in order to assess conversion to AD. 12 of the 29 patients fulfilled criteria for probable AD [32] after either 18 or 36 months follow-up.

Semantic memory tests

The battery used in order to assess semantic memory in this study consisted of five different tests.

Famous face naming task

The subjects were presented with photographs of 40 faces of famous people, one by one, presented in shades of gray, and were asked to name them. The response was considered to be correct if the subject provided at least the surname, which led to a naming score (max = 40). If unable to find the name of the person, the subjects were asked to provide as much semantic information as they could about each famous face. A famous person was considered to be correctly identified if at least two correct semantic details were provided [33]. An identification score was derived by adding correctly named faces and correctly identified faces (max = 40), with the underlying assumption that correct naming required identification. Subtracting the naming score from the identification score allowed computing an index of proper name anomia. Famous people belonged to a wide variety of public domains (actors, singers, comics, politicians). For each famous person, the decade during which they were most famous was estimated using dictionaries and submitted to consensus among authors (number of famous people per decade: 30 s and 40 s: 7; 50 s: 5; 60 s: 8; 70 s: 7; 80 s: 7; 90 s and 2000 s: 6). Analyses were then carried out per decade to determine if a gradient emerged in both groups of subjects.

Information subtest of the WAIS-III [34]

This standard subtest allows assessing knowledge about general cultural facts that are typically acquired over a lifetime. It consists of 28 questions on various cultural topics. Both raw scores and scaled scores were analyzed in this study.

Didactic acquisition questionnaire (DAQ)

The DAQ was designed in our laboratory in order to assess basic knowledge about historical and geographical facts learned in primary and secondary school (therefore during childhood, several decades before

Table 1
Demographic characteristics of the patients with MCI and control subjects

	Patients with MCI	Control subjects	*p*
N	29	29	
Age (mean; SD; min-max)	68.97 (6.61) 58–80	68.79 (6.40) 57–80	0.98
Years of education (mean; SD; min-max)	13.17 (4.09) 7–22	12.41 (3.12) 6–17	0.50
Men/women	17/12	14/15	
Socio-professional achievement			
- businessmen	2	3	
- whitecollars and other higher intellectual professions	10	10	
- intermediary professions	6	6	
- employee, clerk	9	9	
- bluecollar	1	0	
- housewife	1	1	

assessment). One questionnaire was about French history and a second one about French geography. Each consisted of 20 questions. The type of knowledge that was evaluated was elementary (as indicated by control subjects' close to ceiling performance). Raw scores (max = 20) for each questionnaire were analyzed in this study.

Short-EVE

This test assesses knowledge about public events [16, 35]. It originally consists of 30 different public events, among which we selected 10 (2 for each from the past 5 decades). For each event, the structure of the questionnaire was the following: free recall (2 points), multiple choice questions requiring the selection of the correct answer among three choices (1 point). At this point, all subjects were informed of the correct answer of the multiple choice question in order to facilitate retrieval. Two closed questions ensued, which focused on specific details about the event (2 points). The last question concerned the decade during which the event occurred (1 point). Subjects were allowed to use a sheet of paper on which a time axis had been represented. The total maximum score was 60 (10 events × 6 points). We also analyzed scores for each type of question (free recall, multiple choice question, closed questions and decades), as well as for each decade in order to identify a possible temporal gradient.

Semantic memory composite Z-score

In order to obtain an overall estimate of the integrity of semantic memory in each subject, the performance of each control subject and patient on the main measure of each test was transformed into a Z-score using the control group's mean and standard deviation. These Z-scores for each test were then averaged in order to obtain the semantic memory composite Z-score for each subject. This semantic memory composite Z-score was then used as the variable that was correlated with MR density and SPECT perfusion on a voxel by voxel basis.

Behavioral statistical analyses

Comparisons between two groups (control subjects versus MCI and non-converters versus converters) were carried out using non-parametric sums of ranks Mann-Whitney *U* tests since homoscedasticity (using Bartlett's test) or normality (using Kolmogorov-Smirnov's test) were frequently violated. The Mann-Whitney U test does not rely on normality assumptions and has the advantage of being insensitive to outliers. We used chi-square statistics to compare performance of MCI patients and controls on each of the question of the Information subtest. The level of significance was set at $p < 0.05$. Size of effects was computed for all significant differences using Cohen's d. Standard deviations were weighted by sample size when n was not equal between groups [36]. Values of d are discussed according to recommendations: around 0.5 is considered a medium effect and >0.8 a large effect [37].

Furthermore, we provide for the main measure of each test a graphical representation of the dispersion of the performance of each group using box-plots. Boxes represent the 25th and 75th percentiles, the lines in the boxes the medians. Notches display the variability of the median between samples. Box plots whose notches do not overlap have different medians at the 5% significance level based on a normal distribution assumption. Comparisons are reasonably robust for other distributions, however, and statistical comparisons reported in the text were carried out independently of this graphical representation. Upper and lower lines of whiskers represent minimum and maximum performance. Circles are outliers in each group, i.e., subjects whose performance fall outside minimum or maximum values of ±1.5 the difference between the 25th and 75th percentile.

Anatomical MRI imaging and analyses

Brain imaging was performed using a 1.5 T Magneton Vision Plus imager (Siemens, Erlangen, Germany) with morphological 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequences (TE/TR = 407 ms/9.7 ms, flip angle 12, 128 contiguous slices, matrix = 256^2, isotropic voxel 1.25 mm × 1.25 mm × 1.25 mm).

Perfusion SPECT imaging

Regional cerebral blood flow (rCBF) was studied at baseline using single-photon emission computed tomography (SPECT). Patients received an injection of 740 MBq of technetium-99 m-ethyl cysteinate dimer (99 mTc-ECD), and were kept at rest for 1 h, in a quiet surrounding with their eyes closed. SPECT image acquisitions were performed using a double-head rotating gamma camera (ECAM, Siemens) equipped with a fan beam collimator. Data were collected in 64 projections of 40 s spread through 360 degrees. Tomographic 3D reconstructions were performed using a filtered back projection algorithm.

Neuroimaging statistical analysis

A voxel-by-voxel analysis was performed using SPM5 (Welcome Department of Cognitive Neurology, University College, London) to study correlations with performance on semantic memory tasks in the group of patients with MCI.

Images were initially converted from the DICOM to the Analyze format using MRIcro (http://www.mricro.com), and transferred to SPM5. MR and SPECT data were then standardized on the Montreal Neurological Institute (MNI) atlas by using a 12-parameter affine transformation, followed by nonlinear transformations and trilinear interpolation. Dimensions of the resulting resampled voxels were 1.5 mm × 1.5 mm × 1.5 mm for MR images, and 2 × 2 × 2 mm for SPECT images. MR gray matter segmentation was performed on the normalized T1-weighed images. The images were then smoothed with a Gaussian filter in order to blur individual variations in gyral anatomy, and to increase signal-to-noise ratio, according to spatial resolution (FWHM = 8 mm for MR images, and 12 mm for SPECT images). The resulting SPECT images were divided by cerebellar rCBF to control for individual variations in global SPECT measures.

Age and education level were considered as a nuisance variables in the different analyses performed, and the SPM maps thresholded at $p = 0.001$ (uncorrected for multiple comparisons), with at least 20 voxels. MNI coordinates were finally transformed into Talairach's coordinates with a nonlinear transformation, and anatomical localization of most significant voxels identified using Talairach Daemon (http://www.talairach.org).

RESULTS

Neuropsychological data of control subjects and patients with MCI are reported in Table 2. Performance of patients with MCI on the delayed free recall of the French adaptation of the FCSRT [29] was severely impaired. As expected, the performance of the MCI group on the MMSE (mean = 27.21, SD = 1.15, [28]) was below that of control subjects. There was no difference between MCI patients and control subjects on the WAIS-III digit span subtest [34], indicating that working memory was intact. The patient's performance on matrix reasoning of the WAIS-III was within normal limits using normative data from the French population, as well as their performance on a standard confrontation naming test [38], overall indicating that the main cognitive deficit in these patients was in the realm of memory.

Table 2
Neuropsychological performance of control subjects and patients with MCI on standard tests (mean, SD in brackets). Control subjects did not undergo the WAIS-III Matrix reasoning subtest (thus scaled scores with a mean of 10 and SD of 3 are reported in the table) and the confrontation naming subtest (80 pictures to be named, max performance = 80)

	Control subjects	MCI patients	*p*
MMSE	28.83 (1.10)	27.21 (1.15)	$P < 0.001$
Lexical fluency "P" in 2 min	26.38 (6.40)	18.90 (5.79)	$P < 0.001$
FCSR test-delayed free recall	12.90 (1.93)	4.41 (2.90)	$P < 0.001$
WAIS-III digit span	10.93 (3.43)	9.72 (3.02)	$P = 0.21$
WAIS-III Matrix reasoning	–	9.93 (2.14)	–
Confrontation naming (DO80)	–	79.38 (1.24)	–

Famous faces naming task

The famous face naming score of MCI patients was significantly below that of control subjects matched for age and educational level (m = 23.59, SD = 7.61 versus m = 34.34, SD = 4.24, $p < 0.001$, Cohen's d = 1.82; Fig. 1A). MCI patients also scored below controls on identification (providing semantic information about famous people) (m = 32.83, SD = 5.60 versus m = 37.65, SD = 2.91, $p < 0.001$, Cohen's d = 1.13; Fig. 1B). In addition, MCI patients showed proper name anomia (number of correctly identified famous persons that could not be named: m = 3.31, SD = 2.54 in control subjects versus m = 9.24, SD = 3.86 in MCI patients, $p < 0.001$, Cohen's d = 1.85). Differences between groups differed significantly for all decades of famousness, when considering both naming and identification. Cohen's d for each period for naming revealed that there was no trend for any gradient (Fig. 1C).

Information subtest of the WAIS-III

MCI patients performed significantly more poorly than control subjects (raw scores: m = 13.86, SD = 5.91 versus m = 22.48, SD = 4.29, $p < 0.001$, Cohen's d = 1.65, Fig. 2A). Results between groups using scaled scores were very similar.

Because the questions on this subtest are supposed to be increasingly difficult, and because we were interested in assessing whether MCI patients would also be impaired on "easy" questions, we assessed whether

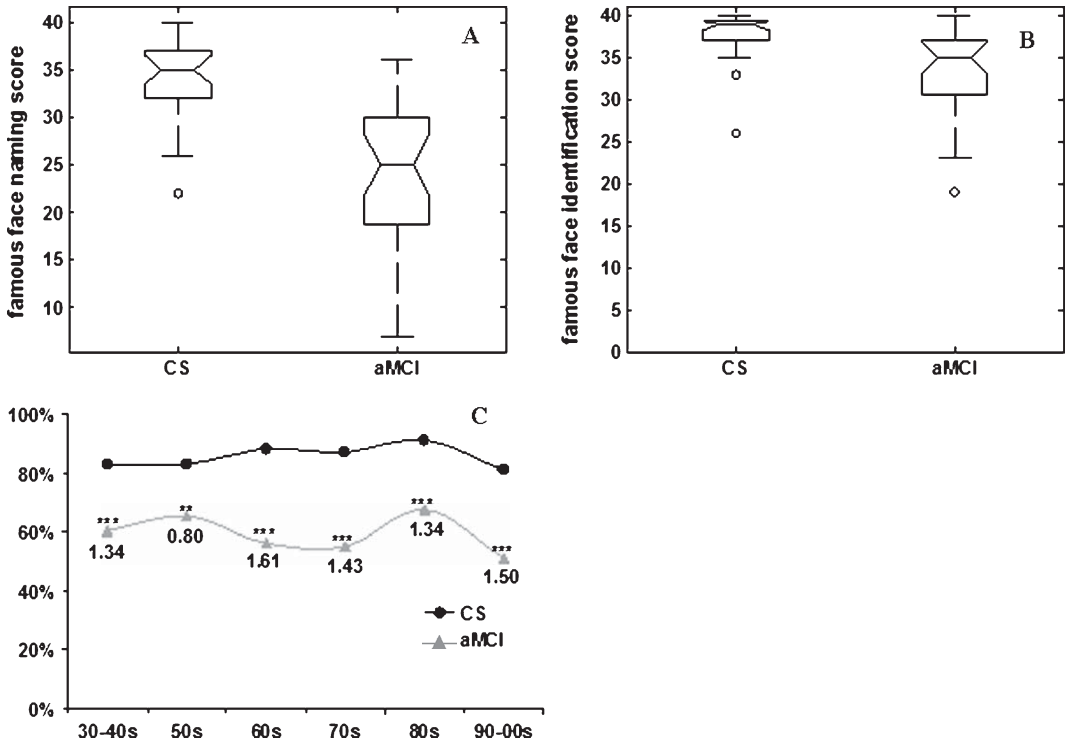

Fig. 1. A) Box plot of the distribution of the famous faces naming scores in MCI patients and control subjects. B) Famous faces identification score. C) Naming scores according to the period of famousness. Numbers for each period are Cohen's d. ***$p < 0.001$, **$p < 0.01$.

there was a significant difference between controls and MCI subjects for each question. The results indicate that MCI patients were impaired on most of the questions (See plot, Fig. 2B). We defined "easy" questions as being correctly answered by more than 90% of control subjects, which seems a reasonable assumption given that it means that only two controls out of 29 were unable to answer the question. Five questions met this criterion (Q8, Q12, Q13, Q14, Q16). The mean number of control subjects succeeding on these questions was 94% (SD = 2%). By contrast, the mean number of MCI patients succeeding on these same questions was only 50% (SD = 7%), indicating difficulties of MCI patients even on these "easy" questions.

History and geography didactic acquisition questionnaire (DAQ)

Patients with MCI performed significantly worse than control subjects on the history DAQ (m = 11.96, SD = 4.75 versus m = 16.54, SD = 3.65, $p < 0.01$, Cohen's d = 1.08, Fig. 3A) as well as on the geography DAQ (m = 15.96, SD = 3.04 versus 19.02, SD = 1.73, $p < 0.001$, Cohen's d = 1.24, Fig. 3B).

French public events battery (short-EVE)

We first compared the performance between groups on the short-Eve by averaging scores for all subtests. Patients with MCI performed well below control subjects (m = 26.68, SD = 10.14 versus m = 43.71, SD = 9.17, $p < 0.001$, Cohen's d = 1.76, Fig. 4A). It is noteworthy that the patients performed significantly below control subjects on all individual measures (Table 3), including when they were asked to choose a correct answer among three in a multiple choice format (Fig. 4B).

The patients' performance significantly differed from that of controls regardless of the decade considered, even for the oldest events (Fig. 4C). Analyses of Cohen's d indicated that the impairment was similar across all decades except for the most recent period, which was most impaired.

Semantic memory composite Z-score

Figure 5 plots the semantic memory composite Z-score at baseline for each subject within each group.

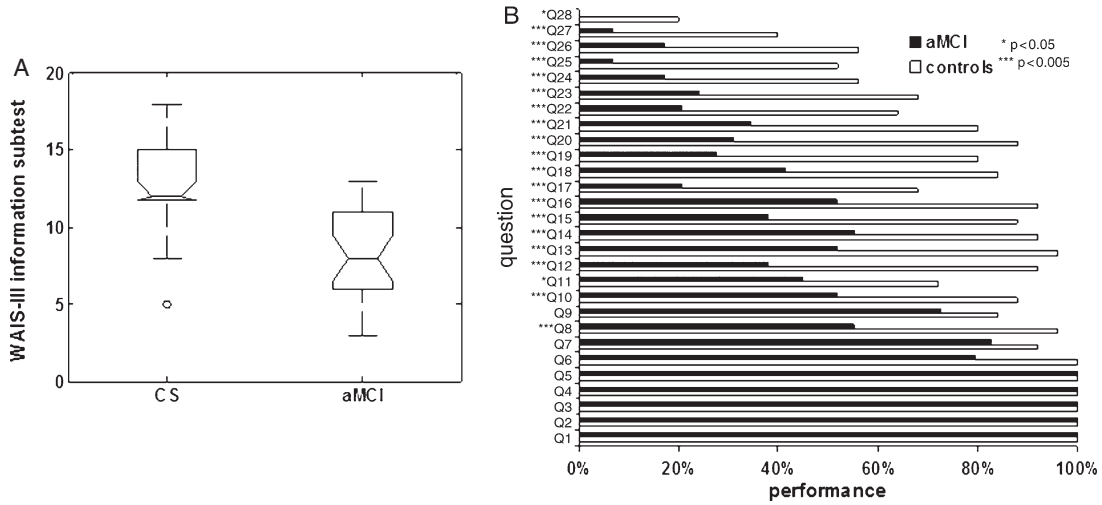

Fig. 2. A) Box plots of the distribution of the raw scores on the Information subtest for each group. B) Performance of patients with MCI and controls for each question of the Information subtest.

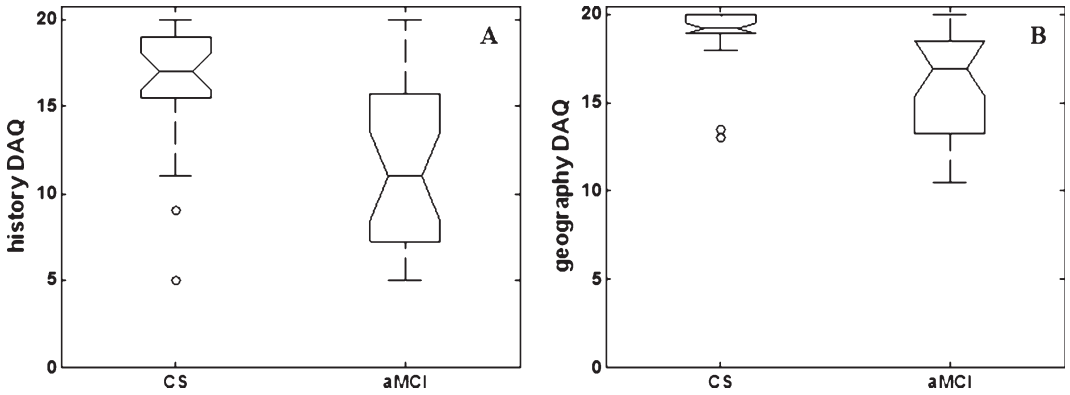

Fig. 3. Box plots of the distribution of the performance on the history DAQ (A) and geography DAQ (B) for each group.

Table 3
Performance of subjects and MCI patients on the different sections of the short-EVE

	Control subjects (mean, SD)		MCI patients (mean, SD)		p	Cohen's d
Free recall	14.93	4.09	8.39	4.84	<0.001	1.46
Multiple choice questions	9.79	0.50	8.64	1.70	0.002	1.04
Closed questions	12.68	3.87	5.93	3.45	<0.001	1.84
Decade of the event	6.32	2.02	3.71	1.54	<0.001	1.47

Correlation with recall

In order to assess whether performance on the semantic tasks correlated with recall, we computed a correlation between the composite semantic Z-score and either lexical fluency or delayed free recall on the FCSRT. No correlation was found (with lexical fluency, $R^2 = 0.07$, with delayed free recall, $R^2 = 0.03$).

Correlation with grey matter intensities

The composite Z-score correlated across the group of patients both with anterior subhippocampal structures bilaterally (entorhinal and perirhinal cortex), the anterior hippocampus bilaterally as well as the left anterior cingulate and the superior temporal gyrus bilaterally (Fig. 6 and Table 4).

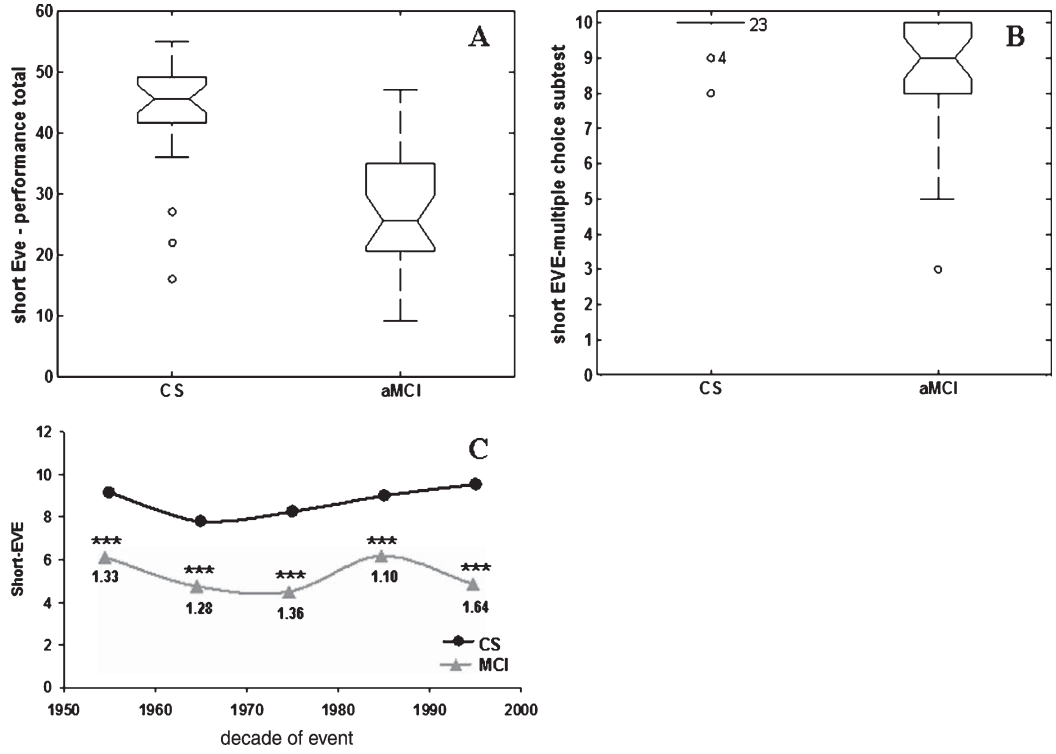

Fig. 4. Performance on the short-EVE questionnaire assessing knowledge about famous public events. A) Total performance on the short EVE of the group of control subjects vs the group of patients with MCI. B) Performance of both groups on the multiple choice questions. C) Performance of both groups across decades. Numbers represent Cohen's d values. ***$p < 0.001$.

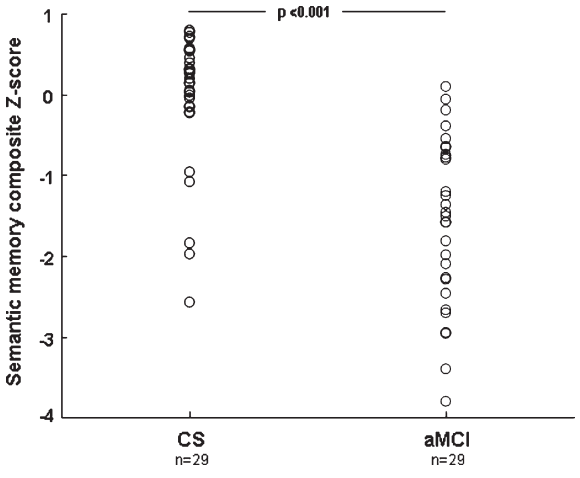

Fig. 5. Dispersion of the semantic memory composite Z-scores in each group. Each circle represents one subject. Note that 5 control subjects appear to have poor semantic memory.

Correlation with SPECT perfusion

The semantic memory composite Z-score correlated with SPECT perfusion in left medial temporal lobe structures comprising both a cluster in the hippocampus (Fig. 7A, Table 5) and a cluster in entorhinal/perirhinal cortices (BA20/BA36, Fig. 7B).

Follow-up

MCI patients were followed longitudinally at 18 months and 36 months so that conversion to probable AD could be assessed. Out of the 29 patients, 12 converted to probable AD after either 18 or 36 month. Hence, two subgroups of patients were compared, one group comprising patients who did not convert during this follow-up ("non-converters") and the other comprising those who converted ("converters"). Converters were slightly older than non-converters (m = 70.00, SD = 5.70 versus 68.24, SD = 7.27, $p = 0.04$) but did not differ in terms of years of education (m = 12.42, SD = 4.27 versus m = 13.71, SD = 4.00, $p = 0.51$). They did not differ either in terms of their general neuropsychological assessment, except for the lexical fluency task (Table 6). In particular, comparison of either delayed free recall or efficiency of delayed cueing on the Free and Cued Selective Reminding Test indicated that the two subgroups did not differ on this memory test.

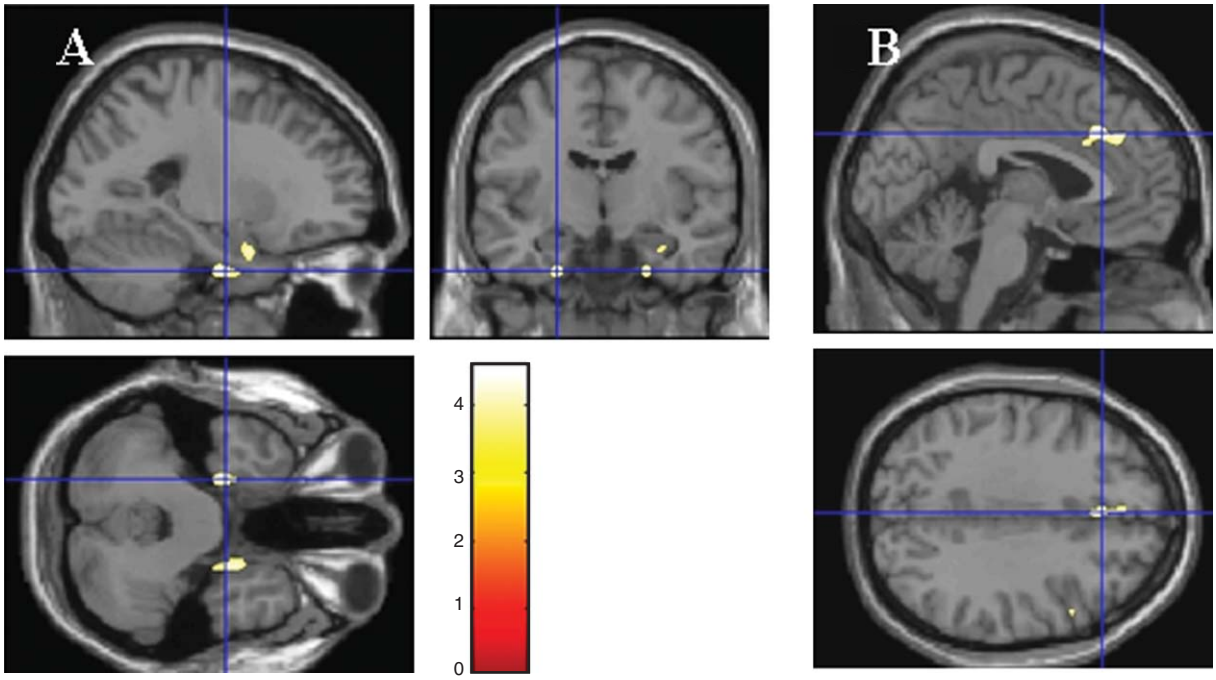

Fig. 6. A) Correlations within medial temporal lobe structures between the semantic memory composite Z-score and grey matter intensities for each voxel within the group of patients. B) Correlations with the left anterior cingulate.

Table 4
Regions showing a significant correlation between the semantic memory composite Z-score and grey matter intensities within the group of patients. x, y, z = Talairach coordinates. BA: Brodmann Area. MFG: Middle frontal gyrus, MTG: Middle temporal gyrus, STG: superior frontal gyrus, L: left, R: Right

t-score	Talairach coordinates			Localization	
	X	y	Z		
4.57	−2	29	31	L anterior cingulate	BA 32
4.5	−22	−13	−28	L entorhinal/ perirhinal	BA 28/36
4.24	24	−6	−30	R perirhinal	BA 36
4.13	30	−25	−6	R entorhinal	BA 28
4.1	−22	2	−21	L entorhinal	BA 28
4.05	51	13	32	R MFG	BA 9
3.09	29	−2	−38	R Uncus	BA 20
3.08	33	−13	−19	R entorhinal	BA 28
3.7	38	6	−17	R STG	BA 38
3.7	−35	13	−25	L STG	BA 38

All analyses that were performed on semantic tasks were carried out again and performance of converters was compared with that of non-converter. Virtually no difference was found. Direct comparisons of the semantic memory composite Z-score between both groups did not yield any significant difference (non-converters' mean = −1.38, SD = 1.03; converters' mean = −1.87, SD = 1.03, $p = 0.24$). Neuroimaging correlation analyses were also carried out within each group, but no correlations were found, probably because of reduced sample size.

DISCUSSION

In this study, we found that the defining feature of MCI, impaired anterograde memory, is accompanied by an extensive impairment in the realm of semantic memory, affecting various areas of knowledge (famous faces, cultural knowledge, historical facts, geographical facts, famous public events). This suggests that the semantic memory disorder is more widespread and severe than previously documented. In addition, the lack of a temporal gradient in the semantic memory loss suggests that all periods of knowledge are affected, not only the more recent ones. This makes it unlikely that anterograde amnesia underlies the semantic deficits, since this would have lead to a gradient with better knowledge on remote compared with more recent decades. Neuroimaging analyses using grey matter density and blood-flow measures suggest that impaired semantic knowledge in these patients is related to dysfunction within anterior, extra-hippocampal, temporal lobe structures (entorhinal and perirhinal cortices) and the hippocampus.

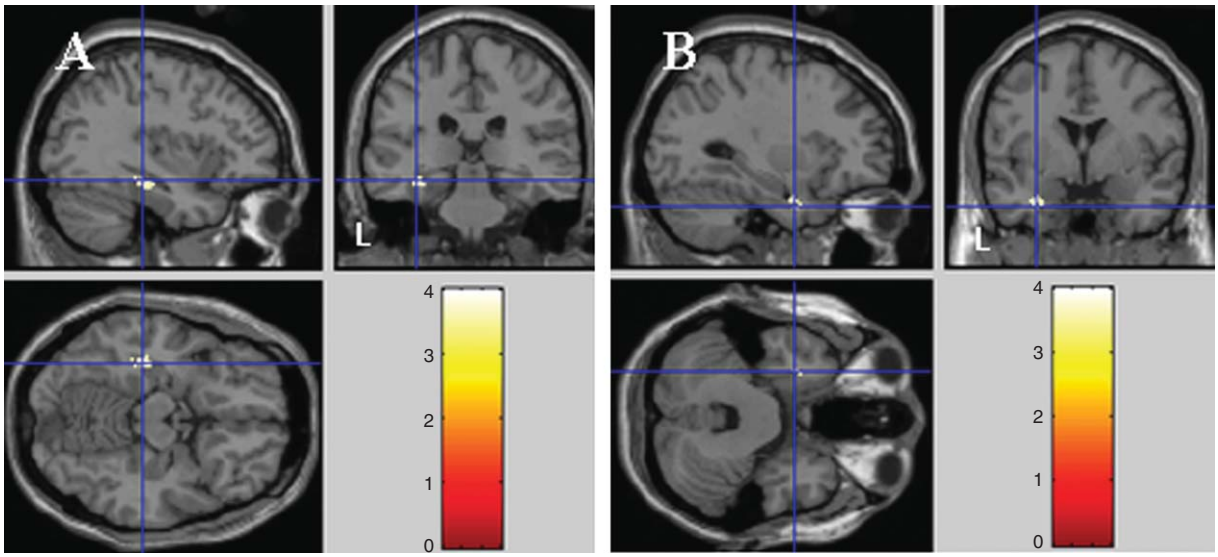

Fig. 7. Correlations between the semantic memory composite Z-score and peaks of significant SPECT rCBF ($p < 0.001$ uncorrected) within the group of patients. A) Correlation with the hippocampus. B) correlation with the medial temporal pole (BA28/BA36). L: left hemisphere.

Table 5
Talairach coordinates of significant SPECT rCBF findings (p-voxel < 0.001, uncorrected) within the group of patients. x, y and z are the Talairach coordinates (mm). BA = Brodmann area

t-score	Talairach coordinates			Localization
	x	y	Z	
3.83	−30	−1	−27	Left Perirhinal/ Entorhinal Cortex (BA36/BA28)
3.60	−36	−20	−12	Left Hippocampus

Table 6
Neuropsychological performance on standard tests of converters vs. non-converters (mean, SD in brackets)

	Non-converters	Converters	p
MMSE	27.18 (1.19)	27.25 (1.14)	$P = 0.84$
Lexical fluency "P" in 2 min	20.88 (5.00)	16.08 (5.85)	$P = 0.03$
FCSR test-delayed free recall	5.00 (3.12)	3.58 (2.43)	$P = 0.13$
FCSR test-delayed cued recall	7.82 (2.38)	7.25 (2.67)	$P = 0.64$
WAIS-III digit span	9.53 (2.79)	10.00 (3.44)	$P = 0.75$
WAIS-III Matrix reasonning	10.12 (2.34)	9.67 (1.87)	$P = 0.68$
Confrontation naming (DO80)	79.35 (1.17)	79.42 (1.38)	$P = 0.69$

Evidence for a widespread semantic impairment in MCI

The present study confirms previous findings that MCI patients are impaired on tests of naming famous faces and famous person knowledge (e.g., [8, 10, 12, 13, 15, 17, 24, 35, 39, 40]). The current study additionally indicates that other domains of semantic memory are impaired. This is the case for general factual knowledge, as assessed with the standard Information subtest of the WAIS-III [34]. Such knowledge is largely context-free and does not rely on episodic memory. Individuals are regularly exposed to this type of culturally-shared knowledge in everyday conversations in the context of their social and professional activities, media exposure, or hobbies. However, MCI patients were impaired on most questions, even the easy ones. We also found MCI patients to have impaired knowledge about history and geography. Since all subjects were exposed to this type of knowledge under similar conditions during formal education at school, the period of acquisition of this knowledge can clearly be dated and dates back several decades before the assessment (acquired during childhood), suggesting that even remote knowledge is affected, confirming the findings of a previous study [14]. A further domain of semantic memory that was impaired in MCI patients was knowledge concerning famous public events. Such knowledge is shared by many people and repeatedly presented in newspapers, TV news, and in some instances, in ensuing TV documentaries or movies. Knowledge about such events was impaired in MCI regardless of test format, using free recall, closed questions, recognition or dating, supporting recent preliminary data [15]. In summary, the semantic memory impairment in MCI patients covers

multiple domains of knowledge, multiple periods, and is severe, such as indicated by effect sizes that were well above 1 (Cohen's d).

It is noteworthy that the MCI patients were impaired at the recognition subtest of the public event task, which does not rely on recall (Fig. 4B). In addition, all subjects were systematically told the correct answer following this procedure, even if they had answered correctly. Despite this cue, MCI patients performed poorly compared to control subjects on the subsequent questions (Cohen's d = 1.84). Such results are usually interpreted as a genuine memory impairment [41]. Also, the lack of correlation between the composite semantic Z-score and lexical fluency or delayed free recall on the FCSRT suggests that the semantic impairment found in the current study is unlikely to be related to impaired recall. Taken together, these results provide converging evidence to support the notion that the semantic memory impairment in MCI patients may be due to impairment at the level of the semantic store.

Finally, it is worth mentioning that findings from previous studies suggest that semantic aspects of autobiographical memory, (e.g., one's own teacher's names) are preserved in MCI patients for both childhood and early adulthood [42, 43]. While this may appear to be in contradiction with the findings of the present study, this could alternatively be related to a dissociation between semantic memory for personal facts (also depending on representations from episodic memory), and semantic memory for general facts, which may not rely on the same neural systems (e.g., [44]).

Is there a temporal gradient in the semantic memory impairment?

Although a gradient for autobiographical episodic memory has been reported at the dementia stage of AD [6, 45], there is evidence that there may be no gradient for semantic memory [7, 8]. For example, Greene and Hodges [7], did not find a gradient for knowledge about famous faces at the dementia stage of AD, since all periods of knowledge (over five decades) were impaired.

This issue has rarely been investigated in MCI patients. Seidenberg et al. [46] emphasized that MCI patients show impaired naming, reaction time, and knowledge about names of people who became famous recently (in the 1990–2003 period). Although this was attributed to impaired anterograde memory, it is noteworthy that knowledge for people who had been famous at a more remote period of time (during the 1950–1965 period) and whose fame did not last afterward was also impaired in this study. This absence of a gradient for retrograde knowledge would therefore be consistent with what is found at the dementia stage of AD. Likewise, no temporal gradient for either the "famous faces" or the "public events" task in MCI patients was found in the present study, as all periods of knowledge up to the most remote ones were impaired, compared to controls. Even the most remote knowledge acquired at school was impaired as assessed with tasks assessing knowledge on history and geography. Of note, control subjects did not show any gradient in our study (i.e., they showed a rather flat curve), as has previously been reported for either famous faces or public events [16, 47]. Taken together, these results support the idea that there is no gradient in semantic memory in MCI patients. The only exception was for the most recent decade (90 s-00 s) of public events, which was more severely impaired, possibly as a result of an anterograde memory impairment, as has been previously suggested [46].

The standard Consolidation theory and the Multiple Trace Theory [48] both predict that the hippocampus plays a crucial role for the acquisition of new semantic information during a limited period of time, after which semantic knowledge increasingly depends on adjacent neocortical structures acting as semantic memory stores. Consequently, lesions of the hippocampus should lead to a temporal gradient, while lesions of the hippocampus and the adjacent neocortex should lead to an impairment of all periods of time. The findings of the present study may therefore provide additional evidence that the impairment of semantic memory stores may be independent from hippocampal dysfunction in MCI patients.

What is the neural substrate of the semantic impairment in MCI?

Using correlations of a semantic memory composite Z-score with grey matter density on MRI, as well as regional blood flow using SPECT, we found that the neural substrate of semantic memory loss involves anterior mesiotemporal areas, including the anterior portion of the hippocampus as well as adjacent structures. Precisely, on MRI the correlations were bilateral for the perirhinal/entorhinal cortices but only concerned the right hippocampus. On PET, only a correlation with the left perirhinal/entorhinal cortices and the left hippocampus was found. These areas are part of a ventral mesiotemporal pathway interlinking the anterior hippocampus with extra-hippocampal areas

recently identified in high resolution functional connectivity studies in the human brain using fMRI [49]. Moreover, this network has recently been shown to have a functional relationship with context-free object-based memory [50]. This network includes the rhinal region (perirhinal/entorhinal cortices), the anterior lateral temporal lobe, the middle temporal gyrus, and the head of the hippocampus. Therefore, the findings of a correlation with cortical areas adjacent to the hippocampus appear consistently related to a functional network. These areas are located anterior and under the head of the hippocampus [51]. In addition, the composite Z-score correlated with grey matter density in the left anterior cingulate (BA32) and in the right dorso-lateral prefrontal cortex (BA9).

These results are consistent with recent imaging studies of healthy individuals which report hippocampal activation using fMRI during semantic retrieval [52, 53], particularly on the left. Interestingly, a right dorso-medial area (BA8), adjacent to the area BA9 reported in our study, was also involved in semantic retrieval [52]. Burianova and colleagues [54] tried to identify the network of brain areas that was common to autobiographical, episodic (lab tests), and semantic memory retrieval. The anterior cingulate was identified as one of these regions and its activity was found to correlate with that of the hippocampus. Overall, the brain areas that were correlated with performance on the semantic memory composite Z-score appear to be involved in a network of brain areas engaged in declarative memory.

We also found correlations between semantic memory and the perirhinal/entorhinal cortices. Only two previous studies investigated such correlations. A result implying a region more lateral to the one found in our study has been reported recently in patients with MCI using grey matter density and ROI analyses [13]. A study in patients with very mild AD (MMSE = 23) likewise identified correlations with anterior temporal lobe structures along the parahippocampal gyrus using a detailed analysis of a lexical fluency task [55]. Overall, there is therefore converging evidence that changes within anterior mesial temporal areas, adjacent to the hippocampus, contribute to impaired semantic memory in MCI patients.

These structures, i.e., the temporal pole, regions within the anterior collateral sulcus and the anterior fusiform gyrus, have repeatedly been suggested to be a crucial site for the representation of semantic representations at an abstract and amodal level [56–59]. A region slightly more lateral to that reported in the present study has been identified as a critical node among three regions that appear to be consistently involved in semantic retrieval [25]. Among these three regions, this temporal area is proposed to be involved in semantic knowledge storage. The present findings are also consistent with previous studies that explored the neural basis of context-free memory or long-term knowledge representations in patients with semantic dementia, which suggested that the rhinal region may be a central area for the storage of long-term knowledge representations [33, 60]. Interestingly, a recent study which investigated the neural correlate of semantic impairment in patients with semantic dementia identified areas in the anterior (bilateral) fusiform gyrus "subjacent to the head and body of the hippocampus", a pattern that closely resembles the changes reported in the present study [51]. This same region has also been shown to be involved in context-free and single-item memory in MCI [61–63]. Importantly, this region is consistently affected by neuropathological lesions in patients with MCI who display AD [64, 65].

Overall, our findings of a semantic impairment related to anterior subhippocampal structures thus appear remarkably convergent with previous studies in MCI and with studies on semantic memory in healthy subjects. While it was suggested that the interaction between the rhinal region and the temporopolar cortex is the main target of pathology in semantic dementia [60], the main target of neurofibrillary tangles in AD is thought to be the interaction between the rhinal region and the hippocampus in the so-called transentorhinal cortex [19, 66]. We here provide evidence that impaired interaction between the hippocampus and the rhinal region in MCI patients not only plays a role in the acquisition of new knowledge, but also in long-term representation of such knowledge.

Semantic impairment in converters versus non-converters

There was no clear difference between patients who converted to AD over the 36 months follow-up period and patients who did not convert over this period of time on the neuropsychological assessment, suggesting that the population of MCI patients was overall homogenous. It is likely that many patients who did not convert over the comparatively short follow-up period may in fact have AD, and will convert to dementia later. The rate of progression from MCI to dementia of 41% over 36 month appears comparable to that of other studies, but some MCI patients have been shown to convert over longer periods of up to 72 month or more [67]. In addition, the

inclusion of patients mainly meeting criteria for amnestic MCI could lead to an overrepresentation of patients with AD due to focal mesial temporal lobe dysfunction [68] and pure progressive amnesia [69–71], with very slow progression. This may explain why there was little difference between converters and non-converters regarding semantic tasks, but also regarding other neuropsychological tests including those that assess episodic memory.

CONCLUSION

To sum up, we found a significant and widespread impairment in the realm of semantic memory in a group of patients with MCI, related to dysfunction of brain areas beyond the classic limbic-diencephalic network involved in episodic memory. The memory impairment at the predementia stage of AD is therefore not limited to episodic memory and the limbic-diencephalic system as sometimes assumed. Furthermore, the relative severity of the semantic memory impairment observed in this group of patients at an early stage of MCI (slow conversion) suggests, in accordance with other studies [72], that this impairment began insidiously many years before patients first consulted, and possibly during the transentorhinal stage in preclinical AD [73]. Semantic memory impairment may therefore be a defining characteristic of very early AD, in addition to the episodic memory impairment.

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