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The nature of memory failure in mild cognitive impairment: examining association with neurobiological markers and effect of progression

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Abstract

The main goal of this study was to assess vulnerability to proactive interference and memory binding capacity, the ability to combine different information into a single coherent memory event, in persons with mild cognitive impairment (MCI). We also examined whether hippocampal atrophy and vascular burden were differentially related to these memory capacities in MCI. We further assessed whether memory performance and brain changes differ as a function of later development (or not) of dementia and whether they can predict progression to dementia. The study included 77 participants, 49 meeting the criteria for MCI and 28 healthy older adults. Results showed binding deficits and greater vulnerability to proactive interference in persons with MCI compared with healthy older adults. Hippocampal volume was associated with binding capacity, whereas vascular burden was associated with resistance to interference in persons with MCI. Follow-up analyses indicated that binding deficits predict progression from MCI to dementia. In conclusion, binding deficits and vulnerability to proactive interference are present in persons with MCI and are associated with different brain markers. However, only binding deficits predict progression to dementia.

Keywords: Mild cognitive impairment; Episodic memory; Binding; Proactive interference; Hippocampal volume; Vascular burden

1. Introduction

A major research goal is the identification of specific and sensitive markers for the early diagnosis of neurodegenerative diseases. The presence of episodic memory deficits is one of the defining symptoms of dementia, and has been shown to characterize persons with mild cognitive impairment (MCI) who are at risk of developing Alzheimer's disease (AD) (Gauthier et al., 2006; Petersen, 1999). Binding capacity and sensitivity to proactive interference play a prominent role in episodic memory and are impaired in individuals with AD and MCI (Collie et al., 2002; De Jager et al., 2005; Ebert and Anderson, 2009; Hanseeuw et al., 2010; Loewenstein et al., 2007). In this study we assessed these features in individuals with MCI. We also examined whether binding and interference deficits in MCI are related to hippocampal volume and white matter lesions (WML). Those brain changes are prevalent in MCI (Apostolova et al., 2006; Bombois et al., 2008; Calvini et al., 2009; Jack et al., 1999) and have been associated with different memory deficit patterns (Nordahl et al., 2005; Nordlund et al., 2007; Villeneuve et al., 2011). Therefore, they may cause different memory changes in MCI and contribute to cognitive heterogeneity. As not all MCIs progress to dementia, we investigated whether binding and interference—as well as their hypothesized brain correlates—vary as a function of future progression to dementia, and whether they can predict future decline.

We used the AB/AC paired-associate paradigm, a classical paradigm for evaluating proactive interference that can also be used to measure binding difficulty. In the AB/AC paired-associate paradigm, the person first studies a list of paired lexical items (AB portion, e.g., bottle-rock), which

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are then retrieved by using the first word of the pair as a retrieval cue (for the above example: bottle-?). Memorizing the word pairs requires binding capacity, that is, the ability to form integrated memory traces, particularly when the word pairs are unrelated items. When the same procedure is repeated with a new list constructed by associating the first words from the preceding list with new words (AC portion; for the above example: bottle-sky), performance declines due to proactive interference (also known as negative transfer). Increasing the semantic relationship between the paired words in the AB portion (e.g., bottle-glass) results in more interference than when unrelated words are used (Anderson and Neely, 1996; see also Winocur and Moscovitch, 1983). These results are informative because they show that the semantic relationships between word pairs can be manipulated in order to assess binding capacity and vulnerability to proactive interference. A condition using semantically related word pairs should be more sensitive to interference than binding problems. In contrast, the use of pairs of semantically unrelated words should reveal binding deficits and be less sensitive to interference problems.

Binding capacity and resistance to proactive interference appear to depend on hippocampal and prefrontal regions, which are critical neurobiological markers in aging, and have been associated with different memory impairment patterns in MCI (Nordahl et al., 2005). Henson et al. (2002) associated the prefrontal lobe regions to proactive interference in a neuroimaging study based on the AB/AC paradigm using semantically related words. Many studies have shown that WML result in decreased functioning of the prefrontal regions (Cummings, 1994; McPherson and Cummings, 1996; Román et al., 2002; Tullberg et al., 2004). WML are frequent in MCI, and have been related to executive deficits (Nordahl et al., 2005; Nordlund et al., 2007). Through their effect on the prefrontal lobe, WML might therefore account for the interference deficit previously reported in MCI (Meyer et al., 2000; Posner et al., 2002). It has been suggested in turn that binding deficits in MCI are caused by hippocampal dysfunction (Collie et al., 2002). This hypothesis is based on the fact that the hippocampus is essential for binding new information in memory (Dolan and Fletcher, 1997; Moscovitch, 1989; Nadel and Moscovitch, 1997) and that hippocampal atrophy is frequent in MCI (Jack et al., 1999; Striepens et al., 2010). Because cognition is known to be heterogeneous in MCI, we examined whether binding and interference deficits in MCI are related to vascular burden and hippocampal volume.

Another goal of this study was to assess these features as a function of future progression to dementia. It is generally agreed that MCI is a risk state for dementia, but that not all persons meeting the current criteria will actually progress to dementia. Indeed, a proportion of these persons remain stable, and some revert to normal (Mitchell and Shiri-Feshki, 2009; Ritchie, 2004). There are many reasons for this, including the presence of depression or adverse life events associated with transient cognitive decifits, nonevolutive underlying causes (e.g., diabetes), fluctuation around the psychometric cutoff, measurement unreliability, or regression to the mean. Thus, although finding that a marker is sensitive to MCI status is significant and informative, it does not mean that the marker is sensitive to the prodromal phase of dementia. This can be determined only by following patients over time and isolating performance in those who later progress to dementia. Many studies have reported that MCIs who later progressed to dementia had higher forgetting and lower learning and recognition abilities than those who did not progress to dementia (Landau et al., 2010; Luis et al., 2004; Perri et al., 2007). Some studies have reported that hippocampal volume is smaller in MCIs who later progressed to dementia than in MCIs who remained stable (Apostolova et al., 2006; Jack et al., 1999). Others have reported that memory was a better predictor of future decline than hippocampal volume (Landau et al., 2010). It remains unclear whether the presence of WML increases the risk of progression to dementia. The process appears to depend on the severity of the lesions (Frisoni et al., 2007). Thus, a few studies have found that neuropsychological and brain measures vary as a function of whether or not MCIs progress to dementia. However, very few studies have examined both neurobiological and memory markers, and none have used specific measures of binding and interference. Combining those different measures in a single study could contribute to identifying the optimal marker or combination of markers that predict progression to dementia (Landau et al., 2010).

The present study had 3 goals: (1) to assess binding capacity and sensitivity to proactive interference in individuals with MCI; (2) to assess whether binding and interference deficits in MCI are related to hippocampal volume and vascular burden, respectively; and (3) to investigate whether binding and interference vary as a function of future progression to dementia, and to identify which memory deficits predict future progression to dementia independently or in combination with brain markers. To address these goals, episodic memory was assessed using 2 versions of the paired-associate paradigm: one that increased binding requirements and minimized interference effects by using pairs of semantically unrelated words, and one that increased the likelihood of proactive interference and reduced binding requirements by using pairs of semantically related words. A binding deficit would be reflected in a slower learning rate across trials in the AB/AC paired-associate task with semantically unrelated words. Interference would manifest as worse performance in the first trial of the AC portion than in the first trial of the AB portion. Hence, interference would be particularly significant in the AB/AC paired-associate task with semantically related words. This impairment should be coherently related to brain anomalies. More precisely, hippocampal volume was expected to be associated with binding deficits, whereas vascular burden

was expected to be associated with higher interference. To serve as an appropriate marker of future progression, performance on memory tasks should differ when directly comparing MCIs who progressed to dementia with those who remained stable. This would indicate that memory measures are valid predictors of future decline. However, given that the brain markers used here have been identified as predictors of dementia in at least some of the reviewed studies, it was expected that combined memory and brain markers would be the best set of predictors for future progression to dementia. Furthermore, because the literature on progression rarely distinguishes between different memory processes, it was unclear whether interference and binding or binding impairment alone would be related to progression to dementia.

2. Methods

2.1. Participants

The study included 77 participants, 49 meeting criteria for MCI and 28 older adults with no cognitive deficit or complaint. All participants gave their written informed consent and the Institutional Research Ethics Committee approved the project. Participants with MCI were recruited from memory clinics in Montreal and referred by neurologists or geriatricians. Healthy controls were recruited from a pool of volunteers living in the same community as the MCIs. MCIs met the following clinical criteria: (1) subjective complaint, preferably corroborated by an informant; (2) performance below 1.5 standard deviations (SD) for age and education on at least one cognitive domain based on a neuropsychological assessment; (3) essentially preserved activities of daily living; and (4) no dementia (Petersen and Morris, 2005). MCIs were not excluded based on type of cognitive deficit because we wanted to account for some of the heterogeneity of the syndrome. Thus, 11 individuals with MCI showed memory deficits only, meeting the criteria for single domain amnestic MCI. Thirty-five MCIs showed memory deficits plus impairment in at least one other cognitive domain, meeting the criteria for multiple domain amnestic MCI. Three MCIs showed deficits in one domain other than memory (single domain nonamnestic MCI). Note that none of our results changed when the 3 nonamnestic MCIs were removed from our sample.

All participants, including healthy controls, underwent a clinical, neuropsychological, and neuroradiological examination. The Questionnaire d'auto-évaluation de la mémoire (Van der Linden et al., 1989), the Mini Mental State Examination (MMSE; Folstein et al., 1975), and the Mattis Dementia Rating Scale (MDRS, Mattis, 1976) were used to assess cognitive compliance and global cognitive functioning. We also computed a nonvascular disease burden using a modified version of the Charlson scale (Charlson et al., 1987) and measured functional autonomy using the Functional Autonomy Measurement System (SMAF, Desrosiers et al., 1995). The neuropsychological assessment included measures of memory (Text Memory of the Batterie d'efficience mnésique-144 (BEM), Signoret, 1991; immediate and delayed word recall task (Rappel Libre/Rappel Indicé, RL/RI), Van der Linden et al., 2004; immediate and delayed recall of the Rey Figure, Rey, 1959), executive functions (Stroop-Victoria Modification, Regard, 1981; Code subtest of the WAIS-III, Wechsler, 1997), apraxia (Rey Figure Copy, Rey, 1959), language (Boston Naming Test, Kaplan et al., 1983), and perception (Benton judgment of line orientation test, Benton et al., 1983).

Exclusion criteria for all participants included dementia, alcoholism, presence of a stroke or large vessel disease on the magnetic resonance (MR) image, history of stroke, traumatic brain injury, and general anesthesia in the past 6 months. All participants spoke French and had normal or corrected hearing and vision.

2.2. Measures of vascular burden and hippocampal volume

2.2.1. MRI acquisition

Participants compatible with magnetic resonance imaging (MRI) (MCI, $n = 46$; healthy older controls, $n = 19$) underwent a structural MRI scan to assess the presence of WML and measure hippocampal volume (note that the subgroup of MRI-compatible participants did not differ from the larger group of participants on demographic or clinical variables). Three sequences were obtained: (1) 3-dimensional magnetization prepared rapid gradient echo (MPRage) (Time repetition (TR) = 3000 ms, Time echo (TE) = 2.98 ms, Time inversion (TI) = 900 ms, flip angle = 9°, field of view = 256 mm, 240 × 256 matrix, 160 contiguous slices, slice thickness = 1.2 mm), with images acquired from right to left, parallel to the mid-sagittal plane (interhemispheric fissure); (2) axial proton density (PD)/T2-weighted (TR = 3000 ms, TE = 11 ms, TI = 101 ms, field of view = 240 mm, 228 × 256 matrix, 48 slices, slice thickness = 3 mm, interslice gap = 0 mm); and (3) fluid-attenuated inversion recovery (FLAIR) (TR = 9000 ms, TE = 107 ms, TI = 2500 ms, field of view = 220 mm, 256 × 256 matrix, slice thickness = 4 mm, interslice gap = 0.8). The structural MRI was performed at the Unité de neuroimagerie fonctionnelle of the Institut universitaire de gériatrie de Montréal on a Siemens 3T Magnetom TRIO MRI system (Siemens Medical Solutions, Erlangen, Germany).

2.2.2. Hippocampal volume

We used Anatomist/BrainVISA 3.1 package (http://brainvisa.info/) to analyze hippocampal volume. Four reference points were first positioned (anterior commissure, posterior commissure, interhemispheric plan, and left hemisphere) to allow volume reorientation and to generate a transformation referenced to the Talairach atlas. This transformation was used to reduce the volumes of different subjects to the same reference volume without altering the

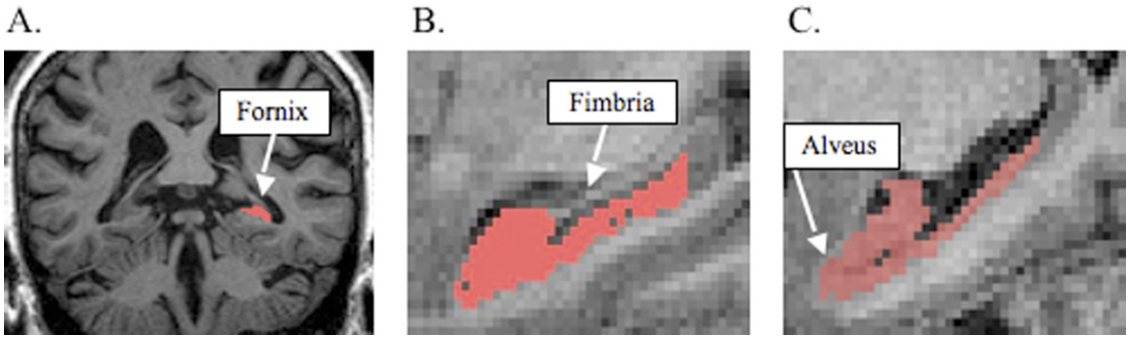

Fig. 1. Example of hippocampal delimitation. (A) Caudal limitation; (B) how fimbria is excluded from measurement; (C) hippocampus is distinguished from the overlying amygdala by the alveus.

data. Included in our hippocampus measurements were the cornu ammonis (CA1–CA4), the dentate gyrus, the subiculum, and the alveus, based on the protocol described in Wu et al. (2002). Rostrally, the portion of the uncus connecting to the amygdala was included. Caudally, the fimbria (white matter fibers connecting the hippocampus to the fornix) was excluded from the measurements. The sagittal orientation was initially used, and subsequent corrections were made to the coronal orientation as necessary. Left and right volumes were calculated separately. Intracranial volume (ICV) was measured following the procedure of Eritaia et al. (2000). Hippocampal volumes were normalized to head size using the formula: (Hippocampal volume/ICV). All volumes were measured by a single experienced rater, blind to participant diagnosis, whose reliability had been previously determined in a related study in older adults (intraclass correlation coefficient on random measurements of 28 hippocampi separated by 4 months = 0.90) and for whom we obtained very good interrater reliability (0.91 for 20 hippocampi) (Belleville, Mellah, and Tisserand, unpublished data). See Fig. 1 for an example of hippocampal measurement.

2.2.3. Vascular burden

White matter lesion (WML) volumes were measured using a FLAIR sequence. The FLAIR parameters were adjusted for the 3T scanner according to Lu et al. (2005), and we ensured that WML ratings were comparable with those obtained from 1.5T images (Bocti et al., 2005). WML were assessed by an experienced radiologist, blind to participant diagnosis, and quantified using the age-related white matter changes (ARWMC) Wahlund scale (Wahlund et al., 2001) rated on a 4-point scale (0, no lesion; 1, focal lesions; 2, beginning confluence of lesions; 3, diffuse involvement of entire region) for 4 brain areas (frontal, parieto-occipital, temporal, infratentorial/cerebellum, and basal ganglia). See Fig. 2 for an example of WML quantification.

In addition, clinical vascular burden was assessed using an index that computes the number of vascular risk factors rated on an 8-point scale (hypertension, hypotension, dyslipidemia, diabetes mellitus, carotid stenosis, history of coronary artery disease, transient cerebral ischemia, and cardiac arrhythmia) (Villeneuve et al., 2009). Vascular risk factors were assessed as patients were enrolled in the study based on information in clinical records and provided by participants or proxies during the medical interview.

2.3. Identification of progressors

Participants with MCI were monitored yearly for progression to dementia over a 3-year follow-up period. Three patients were lost to follow-up. In the remaining 46 patients, we determined whether they later progressed to dementia (progressor MCIs) or remained stable (stable MCIs). Progression to dementia was determined by meeting the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria for dementia (American Psychiatric Association, 1994) following a clinical assessment by an experienced neurologist or geriatri-

Fig. 2. Magnetic resonance imaging (MRI) images of a mild cognitive impairment (MCI) patient with white matter lesions (WML). White arrow indicates a confluence of WML.

cian blind to the experimental memory measures used in this study. We did not analyze progression as a function of type of dementia, because this information was not available for all patients, and when it was available, we had no autopsy reports to confirm the diagnosis.

2.4. AB/AC procedure

2.4.1. AB/AC paired-associate task with semantically unrelated words

Four lists of 12 pairs of semantically unrelated words were used to construct 2 versions of the task with semantically unrelated words. The words were mono- or bisyllabic and were of frequent occurrence (New et al., 2004). Words were matched across lists in terms of frequency of occurrence. Word frequency was also matched to the semantically related task described below. In both the AB and AC portions, the first word of the pairs was the same, whereas the second word was different (e.g., if the pair nez-trésor was used in the AB portion, the pair nez-boîte was used in the AC portion). For each version, the lists in the AB and AC portions were counterbalanced between participants to control for a potential list effect. The 2 task versions were also counterbalanced between participants.

During the learning phase of the AB portion of the task, 12 word pairs were presented visually on a computer screen at a rate of 1 pair every 5 seconds. Participants were asked to read the 2 words and memorize them as a pair. They were informed that in the test phase, the first word would be shown and they would be asked to recall the associated word (the second word). In the test phase, the first word of each pair was presented visually at the center of the screen for a maximum of 10 seconds, and the participant was asked to recall the word with which it had been paired. After the participant responded, the complete pair was presented visually and read aloud by the examiner. Pairs were presented in random order, with order differing between the learning and test phases. Immediately after completion of the first learning trial, 2 further learning and test trials were administered using the same procedure, but in a different presentation order. At least 4 pairs were presented between pair learning and retrieval in order to reduce the contribution of short-term memory to retrieval. Immediately after the end of the 3 learning and test trials of the AB portion of the task, a second list (AC portion) composed of 12 new pairs of words was presented using the same procedure. As described above, the first word of the pair was the same as in the first learning list, but the associated word was different (e.g., nez-trésor vs. nez-boîte).

2.4.2. AB/AC paired-associate task with semantically related words

The materials and procedure used in this task were similar to those described above for the semantically unrelated words, except that the word pairs were semantically related words (Freibergs, 1968).

Two test sessions were run, separated by a 1-week interval. The unrelated words task was always presented in the first session, with the related words task presented in the second session. A fixed order was used to prevent participants from making associations between word pairs in the unrelated task.

2.5. Statistical analyses

We used *t* tests and analyses of variance (ANOVAs) to assess group differences on the variables of interest. We first analyzed data on the entire group of MCIs and then separated progressor MCIs from stable MCIs. Correlations between memory scores and brain markers were then computed separately for progressor MCIs and stable MCIs. Next, a logistic regression was used to weight and quantify memory and brain markers as predictors of dementia. Analytical procedures are described below.

2.5.1. Group comparisons: MCIs versus healthy older adults

Independent sample *t* tests were conducted to assess group differences on demographic variables, clinical characteristics, index of vascular burden, index of ARWMC, and right and left hippocampal volumes obtained on the entire group of MCIs and healthy older adults. A χ^2 test was used to assess gender differences. Separate ANOVAs were used to assess group differences on the 2 memory tasks (AB/AC with unrelated words; AB/AC with related words). For the AB/AC task with semantically unrelated words, a 2 (Group: MCIs, controls) $\times$ 2 (Portion: AB, AC) $\times$ 3 (Trial: trial 1, trial 2, trial 3) mixed-design ANOVA was conducted. A 2 (Group: MCIs, controls) $\times$ 2 (Portion: AB, AC) mixed-design ANOVA was used to analyze data on the AB/AC task with semantically related words. In this case, we analyzed performance on Trial 1 only, due to a ceiling effect on the other trials. Post hoc comparisons using Bonferroni tests were used to assess significant main effects and interactions.

2.5.2. Group comparisons: progressor MCIs versus stable MCIs

As a second step, ANOVAs were used to compare progressor MCIs with stable MCIs and healthy older adults. Separate ANOVAs were conducted to determine whether groups differed on demographic variables, clinical characteristics, index of vascular burden, index of ARWMC, and right and left hippocampal volumes. A χ^2 test was used to assess gender differences. A 3 (Group: progressor MCIs, stable MCIs, controls) $\times$ 2 (Portion: AB, AC) $\times$ 3 (Trial: trial 1, trial 2, trial 3) mixed-design ANOVA was conducted to analyze performance on the semantically unrelated word task and a 3 (Group: progressor MCIs, stable MCIs, controls) $\times$ 2 (Portion: AB, AC) mixed-design ANOVA was conducted on the semantically related word task. Again, in the semantically related word task, only the first trials of the AB and AC portions were included in the analysis due to a ceiling effect on other trials.

2.5.3. Correlational analyses

To assess the relationship between memory processes, vascular burden, and hippocampal volumes, we created a

memory score to reflect binding capacity ([trial 3 AB + trial 3 AC] − [trial 1 AB + trial 1 AC]) and another memory score to reflect vulnerability to interference [(trial 1 AB − trial 1 AC)/trial 1 AB]. Pearson's correlations were computed between memory scores and right and left hippocampal volumes. Kendall rank correlations were computed between memory scores and the vascular burden and ARWMC indices. Nonparametric correlations were performed on the vascular measures because their distributions were abnormal (Field, 2005).

2.5.4. Logistic regression analysis

The ANOVA comparing performance in progressor and stable MCIs provides valuable information on group differences and allows examining interaction terms. However, it does not determine the relative strength of these predictors, nor can it be used to quantify their ability to predict progression to dementia. Logistic regression can be used to determine the effect of memory decrement on the percent risk of dementia. To assess the power of these markers to predicatively discriminate progressor MCIs from stable MCIs, a multivariate logistic regression with forced entry selection was performed on the MCI data. Clinical status after the 3-year follow-up (dementia vs. stable) was used as a binary outcome. Five predictors were included in the analysis: binding memory score, proactive interference memory score, number of vascular risk factors, WML severity (ARWMC score), and left hippocampal volume. We used left hippocampal volume only due to the strong correlation between left and right hippocampal volumes.

3. Results

3.1. Group comparisons: MCIs versus healthy older adults

3.1.1. Sociodemographic data

Demographic and clinical information for the entire group of MCIs and healthy controls are presented in Table 1. Results indicated that MCIs and controls were compara-

Table 1
Demographic and clinical cognitive tests of MCIs and controls (SD in parentheses)

	Controls (n = 28)	MCIs (n = 49)	Stable MCIs (n = 24)	Progressor MCIs (n = 22)
Age	70.6 (6.1)	71.6 (7.1)	69.8 (7.3)	72.9 (6.8)
Sex	M 8, F 20	M 24, F 25	M 11, F 11	M 13, F 11
Education	12.9 (3.7)	13.3 (4.9)	13.7 (5.1)	12.9 (4.6)
Vascular burden				
Vascular diseases	1.04 (1.00)	1.71 (1.54)[a]	1.88 (1.48)	1.64 (1.71)
WML	4.21 (3.34)	6.66 (4.11)[a]	6.81 (4.20)	6.10 (4.18)
Hippocampal volume				
Left (vol/ICV)	1.63 (0.21)[E-03]	1.50 (0.29)[E-03a]	1.48 (0.17)[E-03]	1.52 (0.24)[E-03]
Right (vol/ICV)	1.65 (0.26)[E-03]	1.57 (0.21)[E-03]	1.58 (0.21)[E-03]	1.54 (0.22)[E-03]
Memory scores				
Binding	13.43 (4.37)	7.98 (6.18)[a]	10.08 (6.07)	5.05 (5.35)[a,b]
Interference	−0.11 (1.99)	1.39 (2.81)[a]	1.25 (3.18)	1.59 (2.57)
General functioning				
MMSE	29.6 (0.6)	27.8 (1.6)[a]	28.3 (1.2)[a]	27.2 (1.8)[a,b]
MDRS	140.5 (3.0)	133.9 (7.3)[a]	137.2 (5.2)	129.6 (7.1)[a,b]
Memory				
RL/RI-16 immediate	11.9 (2.1)	8.0 (3.5)[a]	9.7 (2.8)[a]	5.9 (3.4)[a,b]
RL/RI-16 delay	12.1 (2.2)	8.6 (3.7)[a]	10.1 (2.9)[a]	6.6 (3.7)[a,b]
BEM immediate	9.8 (1.2)	7.0 (2.5)[a]	7.6 (2.5)[a]	6.3 (2.5)[a]
BEM delay	9.3 (1.5)	6.1 (2.7)[a]	7.1 (2.4)[a]	4.8 (2.8)[a,b]
Rey immediate	15.9 (5.8)	11.4 (6.5)[a]	13.9 (6.8)	8.4 (5.4)[a,b]
Rey delayed	15.7 (5.5)	11.6 (6.2)[a]	14.2 (6.3)	8.6 (5.0)[a,b]
Executive functions				
Coding	62.0 (15.1)	45.6 (12.7)[a]	46.7 (12.5)[a]	45.4 (13.7)[a]
Stroop	28.1 (8.4)	39.3 (14.4)[a]	37.8 (12.7)[a]	41.7 (17.2)[a]
Apraxia				
Rey copy	32.8 (2.6)	29.3 (4.7)[a]	29.7 (4.7)[a]	28.5 (4.9)[a]
Language				
Boston	13.6 (1.4)	12.8 (1.7)[a]	13.4 (1.2)	11.9 (1.9)[a,b]
Visual perception				
Benton	24.2 (3.8)	23.4 (3.7)	23.6 (4.0)	23.0 (3.5)

The number of subjects for neuroimaging data are n = 19 for controls, n = 44 for MCIs, n = 21 for stable MCIs, and n = 20 for progressor MCIs. Significant p values ($p \leq 0.05$).

Key: BEM, Batterie d'efficience mnésique; E-03, multiplied by 10^{-3}; F, female; M, male; MCI, mild cognitive impairment; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental State Examination; RL/RI, Immediate and delayed recall of the Rey Figure; vol/ICV, hippocampal volume/intracranial volume; WML, white matter lesions.

[a] Difference from control.

[b] Difference from stable MCI.

ble for age ($t(75) = 0.62$; $p = 0.54$) and education ($t(75) = 0.45$; $p = 0.65$). The χ^2 test assessing group differences in gender distribution revealed more men in the MCI than control group: $\chi^2(1) = 3.1$; $p = 0.08$. Healthy controls had fewer vascular risk factors ($t(75) = -2.46$; $p < 0.05$) and less WML than MCIs ($t(61) = -2.48$; $p < 0.05$). MCIs had smaller left hippocampal volume then healthy controls ($t(61) = -0.04$; $p < 0.05$), but no group difference was found for right hippocampal volume ($t(61) = 0.64$; $p = 0.52$). As expected, MCIs performed worse than healthy controls on all neuropsychological tests except for the Benton judgment of line orientation test.

3.1.2. Semantically unrelated words

The ANOVA indicated a main Group effect, $F(1,67) = 26.67$; $p < 0.0001$; $\eta^2 = 995.72$, a main Trial effect, $F(2,67) = 276.88$; $p < 0.0001$; $\eta^2 = 1679.18$, and a Group-by-Trial interaction, $F(2,67) = 12.60$; $p < 0.0001$; $\eta^2 = 76.43$. No other significant interactions were found ($p < 0.05$). Decomposition of the Group-by-Trial interaction indicated that MCIs were impaired relative to controls on all trials ($p < 0.0001$ for all trials). In addition, MCIs had a slower learning rate than healthy controls (mean difference between trial 1 and trial 3 was 4.77 for MCIs and 6.91 for controls), which supports lower binding capacity in MCIs.

3.1.3. Semantically related words

The ANOVA indicated a main Group effect, $F(1,75) = 31.91$; $p < 0.0001$; $\eta^2 = 427.05$, a main Portion effect, $F(1,75) = 4.51$; $p < 0.05$; $\eta^2 = 14.61$, and a Group-by-Portion interaction, $F(1,75) = 6.14$; $p < 0.05$; $\eta^2 = 19.91$. Decomposition of the Group-by-Portion interaction indicated that MCIs performed worse than healthy controls on both portions of the task ($p < 0.0001$ for both portions), but only MCIs performed worse on the AC portion than on the AB portion ($p < 0.0001$), suggesting that only MCIs are vulnerable to proactive interference.

3.2. Group comparisons: progressor MCIs versus stable MCIs

3.2.1. Sociodemographic data

Twenty-two patients (48.0%) with MCI showed progression to dementia over the 3-year follow-up. Four of these (18%) initially met the criteria for single domain amnestic MCI, 17 (77%) initially met the criteria for multiple domain amnestic MCI, and 1 (5%) initially met the criteria for single domain nonamnestic MCI. Demographic and clinical information for progressor MCIs, stable MCIs, and healthy controls are presented in Table 1. The ANOVAs indicated that progressor MCIs, stable MCIs, and controls were comparable in terms of age, education, gender distribution, amount of WML, vascular diseases, and hippocampal volumes. Progressor MCIs were impaired when compared with healthy controls on all neuropsychological tasks except for the Benton judgment of line orientation test. Stable MCIs were impaired relative to controls on general cognitive functioning (MMSE), memory (immediate and delayed recall of the RL/RI and immediate and delayed recall of the BEM), executive functions (Coding and Stroop) and praxia (copy of the Rey complex figure). Progressor MCIs scored lower than stable MCIs on measures of general cognitive functioning (MMSE and MDRS), memory (immediate and delayed recall of the RL/RI, delayed recall of the BEM, immediate and delayed recall of the Rey complex figure), and language (Boston Naming Test).

3.2.2. Semantically unrelated words

The ANOVA indicated a main Group effect, $F(2,63) = 20.63$; $p < 0.0001$; $\eta^2 = 682.10$; a main Trial effect, $F(2,63) = 216.23$; $p < 0.0001$; $\eta^2 = 1301.78$; and a Group-by-Trial interaction, $F(2,63) = 8.28$; $p < 0.0001$; $\eta^2 = 49.83$. Decomposition of the Group-by-Trial interaction indicated that, on trial 1, progressor MCIs were impaired relative to stable MCIs ($p = 0.05$) and controls ($p < 0.0001$), but no difference was found between stable MCIs and controls ($p = 0.27$). On trials 2 and 3, progressor MCIs were impaired relative to stable MCIs ($p < 0.01$ for both trials) and controls ($p < 0.01$ on trial 2, $p < 0.0001$ on trial 3) and stable MCIs were impaired relative to controls ($p < 0.01$ on both trials). Furthermore, as can be seen in Fig. 3A, the Trial effect was larger in controls than in both MCI groups, and was larger in stable than in progressor MCIs (mean difference between trial 1 and trial 3 was 3.53 for progressor MCIs, 5.04 for stable MCIs, and 6.91 for controls), suggesting that progressor MCIs had less binding capacity than both stable MCIs and controls, and that stable MCIs had less binding capacity than controls. No other significant interactions were found ($p < 0.05$).

3.2.3. Semantically related words

The ANOVA indicated a main Group effect, $F(2,71) = 29.19$; $p < 0.0001$; $\eta^2 = 315.93$, a main Portion effect, $F(2,71) = 9.02$; $p < 0.001$; $\eta^2 = 30.42$, and a Group-by-Portion interaction, $F(2,71) = 3.08$; $p = 0.05$; $\eta^2 = 10.39$. Decomposition of the Group-by-Portion interaction indicated that progressor MCIs performed worse than both healthy controls and stable MCIs on the first trial of both portions of the task ($p < 0.001$ for both portions for both groups). When stable MCIs were compared with healthy controls, no difference was found on the first trial of the AB portion ($p = 0.34$), but stable MCIs performed worse than controls on the first trial of the AC portion ($p = 0.001$). Furthermore, both progressor and stable MCIs performed worse on the first trial of the AC portion than on the first trial of the AB portion ($p < 0.01$ for progressor MCIs and $p < 0.05$ for stable MCIs), in contrast to controls, who performed equally well on the first trial of both portions of the task ($p = 0.83$) (Fig. 3B).

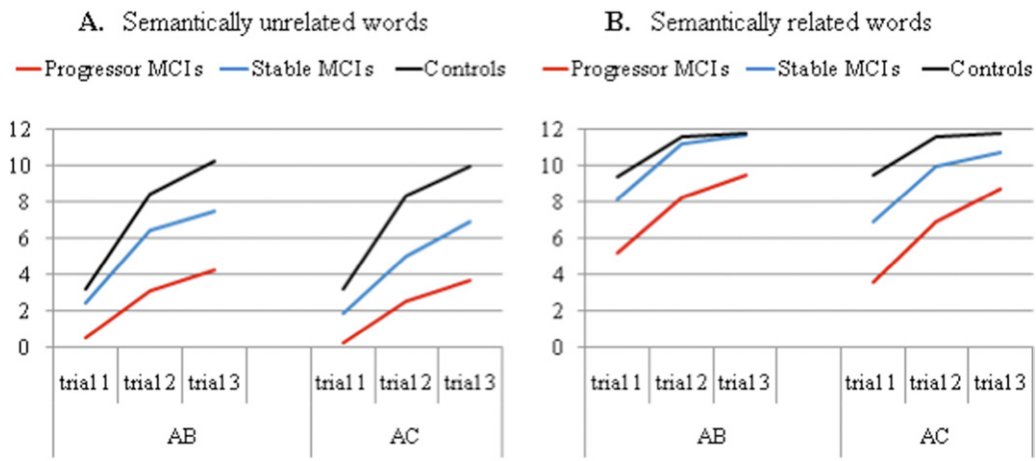

Fig. 3. Performance by progressor mild cognitive impairment patients (MCIs), stable MCIs, and healthy older adults on the AB/AC paired-associate tasks. (A) Both groups of MCIs have a slower learning rate than controls and progressor MCIs have a slower learning rate than stable MCIs, suggesting that both MCI groups have binding impairment and that this impairment is greater in progressor MCIs than in stable MCIs. (B) Both MCI groups performed worse on the first trial of the AC portion than on the first trial of the AB portion, in contrast to controls, who performed equally well on the first trial of both portions of the task, suggesting that both MCI groups are vulnerable to proactive interference.

3.2.4. Correlations between memory scores, hippocampal volume, and vascular burden

A positive correlation was found between binding memory score and right hippocampal volume in progressor MCIs ($r = 0.38$; $p < 0.05$, 1-tailed) (Table 2, see Fig. 4 for scatterplots), indicating that smaller right hippocampal volume is associated with worse binding capacity in progressor MCIs. In stable MCIs, binding memory score correlated with both right ($r = 0.51$; $p < 0.01$, 1-tailed) and left ($r = 0.62$; $p = 0.001$, 1-tailed) hippocampal volume, indicating that smaller right and left hippocampal volume is associated with worse binding capacity in stable MCIs. The interference score correlated positively with the number of WML in progressor MCIs ($\tau = 0.34$; $p < 0.05$, 1-tailed) and with the number of vascular diseases in stable MCIs ($\tau = 0.32$; $p < 0.05$, 1-tailed). The positive correlation in progressor MCIs indicates that a larger WML burden is associated with increased vulnerability to proactive interference in progressor MCIs, whereas the positive correlation in stable MCIs indicates that a larger clinical vascular burden is associated with increased vulnerability to proactive interference in stable MCIs.

Table 2
Correlations between memory and MRI scores for MCIs and controls

	Vascular burden		Hippocampal volume	
	Vascular diseases	WML	Left	Right
Binding				
Controls	−0.08	0.09	−0.14	0.04
Stable MCIs	0.07	0.06	0.62**	0.51**
Progressor MCIs	−0.03	−0.10	0.26	0.38*
Interference				
Controls	−0.05	−0.19	0.12	0.04
Stable MCIs	0.32*	−0.20	0.03	0.12
Progressor MCIs	0.05	0.34*	−0.07	−0.06

See Methods for details. See Fig. 4 for scatterplots of progressors.
Key: MCI, mild cognitive impairment; MRI, magnetic resonance imaging; WML, white matter lesions.
* $p \leq 0.05$.
** $p \leq 0.01$.

3.2.5. Predictors of progression to dementia

Multivariate logistic regression results indicated that testing the full model against a constant-only model provided statically reliable results, $\chi^2 = 17.67$; $p < 0.01$, and allowed correct classification of 71% of patients (70% of progressors and 71% of stable MCIs). Only binding capacity showed a significant effect on predicting progression to dementia (odds ratio = 1.35, confidence interval: 1.12–1.64; $p < 0.01$]. The odds ratio indicated that each point lost on the binding memory score increased by 35% the likelihood of developing dementia. No other variable significantly predicted progression to dementia. Note that the results remained unchanged when the predictors were entered individually.

4. Discussion

This study indicates that MCIs have binding and interference difficulties, and that the AB/AC paired-associate paradigm is a valid task to assess these difficulties. Difficulty in binding unrelated information is revealed by the slower learning rate in MCIs on semantically unrelated words relative to healthy controls. This result is in line with those of previous studies indicating that MCIs show impairment when asked to associate unrelated items or to associate items with a context (Collie et al., 2002; Dudas et al., 2005; Nordahl et al., 2005). Importantly, the deficit was associated

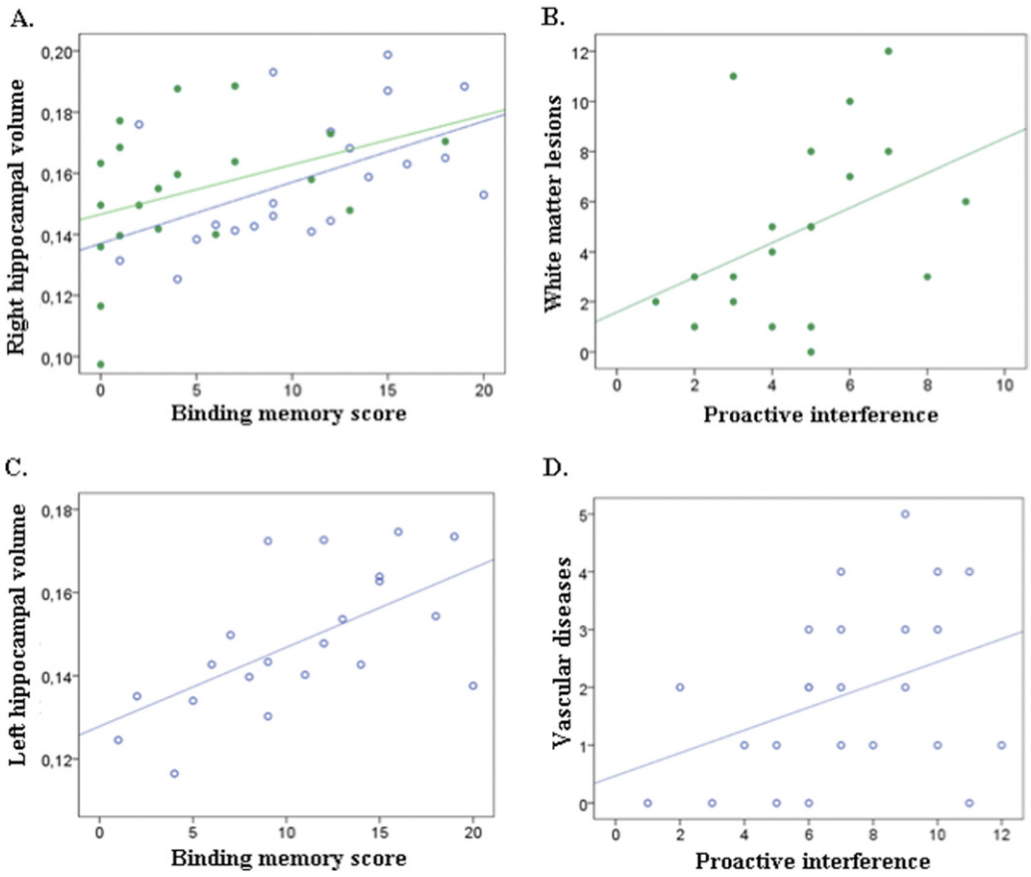

Fig. 4. Scatterplots between memory, magnetic resonance imaging (MRI) scores, and vascular diseases for mild cognitive impairment patients (MCIs). (A) The correlation between binding memory score and right hippocampal volume in progressor MCIs (filled dots) and stable MCIs (empty dots). (B) The correlation between proactive interference and the severity of white matter lesions in progressor MCIs. (C) The correlation between binding memory score and left hippocampal volume in stable MCIs. (D) The correlation between proactive interference and the number of vascular diseases in stable MCIs.

with a coherent brain marker: persons with MCI who had smaller hippocampal volume showed less binding capacity than MCIs with larger hippocampal volume. In theoretical terms, this finding supports memory models that propose that the hippocampal formation is essential for binding new information (Moscovitch, 1989). It is also coherent with the data reported by Winocur et al. (1996) showing that persons with left temporal lobectomy have difficulty learning new word pairs in the AB/AC task.

Our study also revealed that the AB/AC task with semantically related word pairs is appropriate for measuring sensitivity to proactive interference in MCIs (see Winocur and Moscovitch, 1983 for similar results in institutionalized older adults). In this condition, persons with MCI had difficulty learning new associations following a previous learning phase, indicating heightened vulnerability to proactive interference. Similar results were found using different paradigms (Bélanger et al., 2010; Ebert and Anderson, 2009; Loewenstein et al., 2007), which suggests that susceptibility to interference could be ubiquitous in MCIs. A novel finding in this study is the relationship between vulnerability to proactive interference and the severity of vascular burden. Many studies have found that vascular burden impairs frontal lobe functions (e.g., Tullberg et al., 2004). Hence, our data suggest that by impairing functioning of the frontal lobe, vascular burden diminishes resistance to proactive interference (Dolan and Fletcher, 1997; Henson et al., 2002; Shimamura et al., 1995).

Binding capacity and resistance to interference were associated with different brain markers: hippocampal volume and vascular burden, respectively. This relationship between binding and vulnerability to proactive interference in MCIs and distinct brain indicators shows that resistances to interference and binding capacity are independent, which constitutes a novel finding of this study. It also indicates that memory deficits in MCI are probably related to a constellation of brain changes. These would include damage to the mediotemporal areas as well as disruption of the frontal lobe functions. Because they reflect independent processes, these changes might not be equally valid predictors of progression to dementia, as revealed by our follow-up findings.

Over the 3-year follow-up, 48% of MCIs had progressed to dementia, which is consistent with other studies that also included a longitudinal component (Landau et al., 2010;

Loewenstein et al., 2007; Petersen, 1999). Identifying markers that can discriminate progressor MCIs from stable MCIs would be useful in clinical decision-making as it may help selecting candidates for clinical trials and eventual therapeutic interventions. The comparison of memory impairment patterns in MCIs who progressed to dementia with those in stable MCIs showed that both groups had binding deficits and were vulnerable to interference. However, MCIs who progressed to dementia showed greater binding difficulty than those who remained stable. The two groups did not differ on any other target variables. In line with these results, binding deficit was a strong predictor for progression to dementia, and the addition of other variables to the model did not increase prediction accuracy. It was found that each point drop in the binding score resulted in a 35% increase in the risk of progression to dementia over the next 3 years.

The fact that interference was not a significant predictor of future decline provides relevant information for clinicians. First, it underscores the fact that not all memory tasks have the same power to predict progression, and that care should be taken to select appropriate testing conditions. A related point was put forward by Balota et al. (2010). Using a variety of standard clinical tests, they also found that not all tasks were equivalent in predicting further progression.

In this study, hippocampal volume was not a marker of neurodegenerative disease in MCI. This was determined by comparing progressor and stable MCIs and by regression analysis. In support of our results, Landau and collaborators (Landau et al., 2010) found that episodic memory deficit was superior to hippocampal volume in predicting progression to dementia. However, this result is at odds with studies indicating that hippocampal atrophy predicts progression from MCI to Alzheimer's disease (Apostolova et al., 2006; Jack et al., 1999). Variations in sample size and characteristics as well as data acquisition methods (e.g., manual versus automatic) may explain these conflicting results (Jak et al., 2009; Landau et al., 2010; Pruessner et al., 2010). This finding on hippocampal volume is also surprising because there was a strong relationship between binding deficits (which predicted dementia) and hippocampal volume. Because the measures were correlated, both would be expected to predict dementia. There are many reasons for this finding. One lies in the fact that hippocampal volume was equally correlated with binding in stable and progressor MCIs. This result is consistent with the fact that binding is governed by the hippocampus in normal individuals. Our data therefore indicate that older adults with smaller hippocampus, whether caused or not by a neurodegenerative disease, have lower binding capacity. Therefore, whereas hippocampal volume measured at entry is sensitive to dementia, it may not have been specific enough to predict dementia in this small sample size. The large variability in volume size in MCIs may also explain why hippocampal volume was not a strong predictor of progression. One way to circumvent this problem might be to use hippocampal volume change as a predictor rather than volume size at entry. In a recent study using different MRI techniques, the Alzheimer's Disease Neuroimaging Initiative suggested using annual changes in medial temporal lobe volumes rather than baseline hippocampal volumes to discriminate progressor from stable MCIs (Risacher et al., 2010). More research is needed to clarify the role of brain markers in predicting MCI progression.

Some limitations of this study should be mentioned. First, the number of participants was small, particularly in the control group. Nevertheless, our results were highly significant and the surprising results were consistently corroborated by other studies, providing external validity for our findings. Another limitation was the ceiling effect in healthy controls on the AB/AC task with semantically related words. Note, however, that this task was designed to assess interference capacity, which was not affected by the ceiling effect when only the first trial of each task portion was considered. Furthermore, we did not assess the predictive value of nonmemory cognitive functions, which could be considered a limitation. Note that our goal was to compare the contribution of memory processes typically associated with hippocampal versus frontal lobe regions, although recent work suggests that tasks assessing attentional control could be particularly useful for predicting subsequent decline (Balota et al., 2010; Bélanger and Belleville, 2009; Belleville et al., 2007).

In summary, we used two versions of the AB/AC paired-associate paradigm to assess binding and interference deficits in MCI, which led to some novel findings. First, we found impaired binding capacity and greater vulnerability to interference in MCI. These impairments were related to different neurobiological markers: binding capacity was related to hippocampal volume, and resistance to interference was related to vascular burden. In addition, we found that binding deficits predicted progression to dementia. In sum, our data shed light on impaired memory processes in MCIs and factors that could be useful for identifying progressive disease in MCIs.

Disclosure statement

The authors report no conflict of interest.

All participants gave written informed consent and the Institutional Research Ethics Committee approved the project.

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