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# The nature of episodic memory deficits in MCI with and without vascular burden

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ABSTRACT

This study measured episodic memory deficits in individuals with mild cognitive impairment (MCI) as a function of their vascular burden. Vascular burden was determined clinically by computing the number of vascular risk factors and diseases and neuroradiologically by assessing the presence and severity of white matter lesions (WML). Strategic memory processes were measured with free recall and temporal contextual memory tasks requiring self-initiated retrieval. Nonstrategic memory retrieval processes were appraised with a five-choice recognition procedure. Results showed that MCI participants with high vascular burden displayed impairment of strategic memory processes, whereas MCI participants with no vascular burden showed impairment of both strategic and nonstrategic memory processes. A similar pattern was found whether vascular burden was measured using a clinical index of vascular risk profile or whether it was measured neuroradiologically by assessing the extent and severity of subcortical WML. However, the effect of WML on memory differed as function of level of education, used here as a proxy for cognitive reserve. Among participants with MCI, those who had higher education and no WML were the least memory impaired. The study also examined memory as a function of whether patients later progressed to dementia after a three-year follow-up. When examining progressors' performance, strategic and nonstrategic processes were both impaired in progressors with no concomitant vascular conditions, whereas progressors with a high vascular burden showed less impairment of nonstrategic than strategic processes. Overall, results indicate that the presence of vascular burden in MCI is associated with selective impairment of strategic memory processes.



## 1. Introduction

The concept of mild cognitive impairment (MCI) in older adults has been proposed as promising for identifying persons in an early phase of Alzheimer's disease (AD). However, it is increasingly recognized that MCI is a clinically heterogeneous syndrome that may include a range of slowly evolving age-related diseases (Gauthier et al., 2006; Petersen & Morris, 2005). Notably, recent evidence suggests that 60% of persons with MCI (herein referred to as MCIs) eventually progress to AD, whereas more than 30% of MCIs progress to vascular dementia, especially subcortical vascular dementia (SVD) (Solfrizzi et al., 2004). Similarly, the presence of vascular burden is a predictor for progression to SVD (Bombois et al., 2008; Nordlund et al., 2010). Those findings may account for some of the cognitive heterogeneity frequently reported in MCI (He et al., 2009). Gaining a better understanding of the nature and source of this heterogeneity is important, as it will help identify valid and reliable diagnosis criteria for diseases that lead to dementia before the threshold for dementia is crossed. Vascular health is an important potential source to account for heterogeneity, and memory is one component on which this heterogeneity is likely to have a substantial effect, as different types of dementia are characterized by different forms of memory deficits. Hence, the goal of this study was to assess whether the pattern of memory impairment in MCI with vascular burden can be differentiated from that found in MCI without vascular burden, and whether this pattern is coherent with what has been reported in SVD.

There is evidence that the pathology associated with SVD impairs the dorsolateral prefrontal-subcortical network (Cummings, 1994; McPherson & Cummings, 1996; Tullberg et al., 2004). As a result, SVD is characterized in the memory domain by difficulties in strategic learning and the retrieval of

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information (Cummings, 1994). Thus, patients with SVD typically show difficulties in free recall tasks—a condition that necessitates self-guided strategic retrieval—but have relatively preserved recognition; these findings are convergent whether SVD is defined with clinical–radiological (Tierney et al., 2001) or neuropathological analyses (Reed et al., 2007). By contrast, the medial temporal lesions that characterize AD cause a more pervasive amnesic syndrome in which both strategic and nonstrategic memory processes are impaired. This condition results in reduced recall and recognition (Deweer et al., 1995) and impaired contextual memory (Multhaup & Balota, 1997). Thus, comparing free recall with recognition has been suggested as a means of distinguishing AD from SVD (Lafosse, Reed, Mungas, Sterling, & Wahbeh, 1997; Tierney et al., 2001). As free recall requires strategic retrieval, patients with SVD show deficits on this task comparable to what is found in AD. However, because recognition does not require strategic retrieval, it is impaired only in AD.

A similar contrastive pattern is expected in individuals in a prodromal form of SVD (or vascular MCI). These persons should experience impairment of strategic memory processes, measured here with free recall and contextual memory, but not of nonstrategic memory processes, measured here with recognition. Few studies have investigated the memory functions in vascular MCI, and an even smaller number have contrasted strategic and nonstrategic tasks. As expected, studies that assessed strategic processes using free recall of word lists (Nordlund et al., 2007) or stories (Galluzzi, Sheu, Zanetti, & Frisoni, 2005), tasks of associative memory (Nordahl et al., 2005), or composite measures of trace decay (Villeneuve, Belleville, Massoud, Bocti, & Gauthier, 2009) reported impairment in vascular MCIs, and the impairment was of a similar magnitude to that found in nonvascular MCIs. In one study that compared strategic and nonstrategic tasks (Nordlund and collaborators, 2007), a slower learning rate was observed in vascular MCIs than in those without vascular burden, but the authors also reported the unexpected finding that MCIs with vascular burden actually showed impaired nonstrategic retrieval in a recognition task.

Among those studies, there was no consistency in how vascular MCI was defined. Whereas some studies relied on a definition of MCI based on the vascular risk profile in which vascular load is estimated by computing the number of vascular risk factors and diseases, others used neuroradiological criteria to distinguish vascular from nonvascular MCI. Differences in ways of defining vascular burden may explain some of the inconsistencies in the cognitive result reported by those studies. While it is generally accepted that the vascular risk profile is associated with the burden of WML (Jeerakathil et al., 2004), some studies have shown that this is not the case for all types of WML (Fazekas, Schmidt, & Scheltens, 1998), and it is unknown if vascular risk factors and WML impair memory processes in the same manner. In turn, some authors have proposed that WML affect brain function through impairment of brain plasticity, which results in a diminution of compensatory mechanisms while performing a cognitive task (Galluzzi, Lanni, Pantoni, Filippi, & Frisoni, 2008). From a somewhat related perspective, Dufouil, Alpérovich, and Tzouri (2003) reported that education, a typical proxy for brain reserve, modulated the impact of WML on cognition (Dufouil et al., 2003). Severe WML were associated with lower cognition in persons with low levels of education, but there was no association in persons with high education. Those results stress the importance of assessing whether vascular risk factors and WML impair memory performance in a similar manner and whether the impact of vascular burden on memory depends on reserve factors such as education.

In sum, there are good reasons to expect vascular burden to have an impact on memory impairment. There is also some indication that cognitive reserve may modulate the relationship between vascular burden and memory deficit in MCI. Thus, the main goal of this study was to assess if MCIs with vascular burden have a more severe episodic memory impairment than those without vascular burden or if they suffer from a qualitatively different pattern of deficit that impairs only or mostly strategic memory processes, leaving nonstrategic processes relatively intact. We measured vascular risk profile as well as the WML load using a magnetic resonance (MR) images to assess whether they provided a similar outcome, as suggested by Appelman, van der Graaf, Vincken, Mali, and Geerlings (2010). Because cognitive reserve may modulate the relationship between vascular burden and cognition in MCI, we also assessed the impact of education on this relationship. Finally, all MCIs were followed longitudinally to assess whether the effect of vascular burden on memory characterized in the same manner MCIs who progressed to dementia and those who remained stable. Through this comparison, the effect of vascular burden should distinguish whether affected individuals are engaged in a dementing process.

## 2. Method

### 2.1. Participants

This study included a total of 72 participants: 44 who met criteria for MCI and 28 healthy older adults. All participants underwent an extensive clinical, neuropsychological, and neurological evaluation. The clinical assessment included the Mini-Mental State Examination (MMSE, Folstein, Folstein, & McHugh, 1975) and the Mattis Dementia Rating Scale (MDRS, Mattis, 1976). We also used the nonvascular items of a modified version of the Charlson scale as a measure of health independent of vascular burden (Charlson, Pompei, Ales, & MacKenzie, 1987) and the Functional Autonomy Measurement System (SMAF, Desrosiers, Bravo, Hebert, & Dubuc, 1995) to measure functional autonomy. The neuropsychological evaluation included measures of memory (Text Memory of the BEM-144, Signoret, 1991; RL/RI word recall task, 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), praxia (Rey figure copy, Rey, 1959), language (Boston Naming Test, Kaplan, Goodglass, & Weintraub, 1983), and visual perception (Benton judgment of line orientation test, Benton, Hamsher, Varney, & Spreen, 1983).

Participants with MCI met the following criteria: (a) subjective complaint, preferably corroborated by an informant; (b) performance 1.5 standard deviations (SD) below the mean adjusted for age and education on at least one cognitive domain based on the neuropsychological assessment described above; (c) essentially preserved activities of daily living as measured with the SMAF and by means of a clinical interview with patients and proxies; and (d) no dementia (Petersen & Morris, 2005). The study included amnestic and nonamnestic single and multiple domain MCIs. Both amnestic and nonamnestic MCIs were included because we were interested in the prodrome of vascular dementia and did not want to exclude those whose memory deficit would be less severe on classical neuropsychological tests of memory. Exclusion criteria for all participants included dementia, history of temporal lobe epilepsy or other neurological disorders such as Parkinson's disease, alcoholism, major psychiatric disease, presence of a stroke or large vessel disease on the MR images or computed tomography scans, history of stroke, traumatic brain injury, and general anesthesia in the past six months. All participants were francophone and had normal or corrected hearing and vision. All participants gave written informed consent and the Institutional Research Ethics Committee approved the project.

### 2.2. Vascular burden

#### 2.2.1. Computation of the vascular risk profile

The vascular risk profile was assessed using an index that computed the number of vascular risk factors on a eight-point scale (hypertension, hypotension, dyslipidemia, diabetes mellitus, carotid stenosis, history of coronary artery disease, transient cerebral ischemia, and cardiac arrhythmia) (Villeneuve et al., 2009). This information was available for all participants included in the study and was assessed by relying on information in clinical records and on the medical interview with participants and proxies.

#### 2.2.2. Computation and localization of white matter changes

A subgroup of participants (MCI, $n = 43$; CA, $n = 19$) underwent a structural T2-weighted MR imaging examination with fluid-attenuated inversion recovery (FLAIR) to assess the presence of WML. The structural MRI examination was performed at the *Unité de neuroimagerie fonctionnelle* of the *Institut universitaire de gériatrie de Montréal* on a 3.0T Siemens TRIO. White matter lesions were assessed by an inde-

pendent experienced neuroradiologist and were quantified using the rating scale for age-related white matter changes (ARWMC) criteria proposed by Wahlund et al. (2001), a four-point scale (0: no lesion, 1: focal lesions, 2: beginning confluence of lesions, 4: diffuse involvement of entire region) rated on four brain areas (frontal, parieto-occipital, temporal, infratentorial/cerebellum and basal ganglia).

White matter lesions were predominant in the frontal (37% of MCIs) and the parieto-occipital (49% of MCIs) lobes, and WML in the temporal, infratentorial/cerebellum and basal ganglia regions were infrequent and generally not confluent. Correlations between WML in the frontal and parieto-occipital regions were all significant (all at $p < 0.001$), and both correlated with total WML (both at $p < 0.001$). Because of these high correlations and because localization did not impact our cognitive results, total WML scores were used in the analyses.

#### 2.2.3. Subclassification of MCI as a function of vascular burden

The MCI group was first divided as a function of their vascular risk profile. Participants with MCI were considered to have a high vascular risk profile (MCI-Vas) if they had two or more vascular risk factors ($n = 23$) and were considered to have a low vascular risk profile (MCI-NoVas) if they had less than two vascular risk factors ($n = 21$). This particular threshold was selected because it is the combined effect of risk factors that have been shown to impair cognition (Posner, Tang, Luchsinger, Lantigua, & Stern, 2002) and because our previous work with a larger cohort indicated that this threshold best distinguished those with and without executive deficits (Villeneuve et al., 2009). In addition, using categorical grouping allows the comparison of memory conditions by analyses of variance (ANOVAs), which is the method of choice in a design that manipulates testing conditions, as is the case here.

Of the MCI-Vas, 22 participants showed either isolated memory impairment (5 single domain amnestic MCI) or memory impairment plus impairment in another cognitive domain (17 multiple domain amnestic MCI), and 1 participant had no memory impairment (1 single domain nonamnestic MCI). Of the MCI-NoVas, 20 participants had memory impairment (5 single domain amnestic MCI, 15 multiple domain amnestic MCI), and 1 participant had no memory impairment (1 single domain nonamnestic MCI). None of our results were modified when the two participants with nonamnestic MCI were excluded from analyses.

As a second step, the MCI group was divided as a function of the presence (MCI-WML; $n = 21$) or absence (MCI-NoWML; $n = 22$) of significant WML, independently of the previous vascular risk profile score. Significant WML was defined as the presence of confluence on the MR image. This criterion was based on data suggesting that the presence of confluence is associated with cognitive deficits and progressive vascular neuropathology (Schmidt, Petrovic, Ropele, Enzinger, & Fazekas, 2007).

Among the 21 MCI-WML participants, 19 displayed memory impairment (2 single domain amnestic; 17 multiple domain amnestic), and 2 had impairment in a single nonmemory domain (single domain nonamnestic MCI). Among the 22 MCI-NoWML, 8 were single domain amnestic MCIs and 14 were multiple domain amnestic MCIs.

The two vascular indicators were consistent in 26 MCIs (60.5%; 13 positive and 13 negative). Nine MCIs had a clinically significant vascular risk profile without significant WML, and eight had significant WML without a significant vascular risk profile.

### 2.3. Cognitive reserve

Number of years of education was used as a proxy for cognitive reserve. In this study, participants below the median (median = 13 years of education) were considered to have a low cognitive reserve, and participants above the median were considered to have a high cognitive reserve.

### 2.4. Examination of progressors

Following the present experiment, participants with MCI underwent yearly clinical assessments over a three-year period. Therefore, for 41 MCIs, it was possible to determine whether they later progressed to dementia (progressor) or remained stable (stable). Progression to dementia was determined on the basis of patients meeting DSM-IV criteria for dementia (American Psychiatric Association, 1994) following a clinical assessment by an experienced neurologist or geriatrician blind to the experimental memory measures used in this experiment. We did not analyze progression as a function of type of dementia because it was not available in all patients and, where it was available, its etiology was not entirely independent of the vascular burden measures used to classify participants in this paper.

### 2.5. Memory tasks

#### 2.5.1. Free recall and recognition task

The free recall/recognition task was taken from the Mémoria computerized battery (Belleville et al., 2002). It can be used to compare strategic retrieval, reflected by free recall, with nonstrategic retrieval, measured by recognition. The task includes two 16-word study lists. The words included in each list are frequent and imageable substantives. Each list comprises two words taken from eight different natural (animals, fruits, insects, and vegetables) or artificial categories (furniture, tools, vehicles, and garments). Words in the two lists are matched in terms of category membership, typicality, and frequency of occurrence (Baudot, 1992) as well as in terms of number of letters and syllables. Half of the participants were tested with one list, and the other half were tested with the other list. In the recognition phase, each target is presented with four foils. The four foils include a phonological distractor (e.g., *lobe*, "lobe" in French, for the target word *robe*, "dress" in French), a semantic distractor (e.g., *chemise*, "shirt" in French), a semantic associate of the phonological distractor (e.g., *oreille*, "ear" in French, for the distractor *lobe*), and a phonological associate of the semantic distractor (e.g., *remise*, "storage room" in French, for the distractor *chemise*). Associated distractors are used to prevent participants from deducing the target by identifying the item similar to the two other items.

During the learning phase, each study word was presented visually on a computer screen at a rate of one item every 3 s. Participants were asked to read the words silently and to memorize them. They were then asked to recall as many words as possible in the order in which they came to mind. Following free recall, forced-choice recognition was tested. The target word and its four distractors were visually presented on the computer screen. Participants were asked to indicate which of the five words was part of the study list. Administering the test took approximately 15 min.

#### 2.5.2. Temporal contextual memory task

The temporal contextual memory task assessed strategic retrieval. It included two study lists, each comprising 12 words. The words included in the list were frequent substantives and members of 12 different semantic categories. Words in the lists were matched in terms of category membership (e.g., each list contained the name of a fruit), frequency of occurrence (New, Pallier, Brysbaert, & Ferrand, 2004), and number of letters and syllables.

During the learning phase, each study word from the first list was presented visually on a computer screen at a rate of one item every 3 s. Participants were asked to read the words silently and to memorize them. They were also asked to remember each word as belonging to list A. After the presentation of the first study list, participants were asked to count backwards for 45 s. Then, the second study list was presented in exactly the same manner except that participants were asked to remember the words as belonging to list B. After counting backwards for 45 s, recognition of the words from the two study lists was tested with a two-forced-choice procedure: Each target word was presented along with a distractor word. Distractors were matched to targets for frequency and semantic category. For each pair, participants were asked to indicate which of the two words had been studied in the learning phase and in which of the two lists (list A or list B) they had seen the target word. Study lists and distractor lists were counterbalanced across participants. Memory for temporal context was measured by dividing the number of correct answers for the temporal context by the number of words recognized correctly. Administering the test took approximately 20 min.

### 2.6. Statistical analysis

A chi-square test was used to assess gender distribution among groups. Analyses of variance (ANOVAs) were used to assess Group differences on sociodemographic characteristics, clinical measures, index of vascular risk factors, and the ARWMC score.

Mixed ANOVAs were used to assess Group differences on the experimental memory measures. As a first step, we included Cognitive reserve (high; low) in the ANOVA as a between-subject factor to determine if it interacted with vascular burden. When a critical interaction was found, Cognitive reserve was included in the model. If the Cognitive reserve factor had no effect, the data was pooled across reserve levels and the ANOVA was presented without this additional factor. This step was performed to optimize power and simplify data presentation. In all cases, post hoc comparisons using Bonferroni tests were used to assess the source of significant main effects or interactions in all ANOVAs.

These sets of analyses were first computed with the entire group of participants defining vascular MCI as a function of vascular diseases and risk factors (MCI-Vas) and as a function of the volume of WML (MCI-WML). Since the results were essentially unchanged when the analysis was restricted to regional WML (data not shown), we decided to use total WML volume instead of regional WML volume. This choice was supported by the high correlations between total WML and regional WML. The ANOVAs were then repeated, taking into account whether MCIs were stable or progressors. Because MCI defined as a function of vascular risk profile showed a clearer memory pattern than when defined as a function of WML in this study, only the former was used to assess the effect of progression.

## 3. Results

### 3.1. Memory impairment in MCI as a function of number of vascular diseases and risk factors

#### 3.1.1. Sociodemographic and clinical data

Table 1 presents demographic information and scores on the vascular risk factor index, nonvascular risk factor index, and ARWMC scale in healthy older adults, MCI-Vas, and MCI-NoVas. All groups were comparable on demographic characteristics. As

**Table 1**
Demographics, clinical characteristics, and MRI scores for MCIs and controls (SD in parentheses).

| | Controls | MCI-Vas | MCI-NoVas | MCI-WML | MCI-NoWML |
|---|---|---|---|---|---|
| Age | 71.0 (6.2) | 73.1 (6.4) | 70.1 (7.8) | 73.4 (5.1) | 69.7 (8.5) |
| Sex | M7, F20 | M13, F10 | M8, F13 | M11, F10 | M9, F13 |
| Education | 12.7 (3.7) | 13.6 (5.4) | 13.6 (4.7) | 12.4 (5.2) | 14.7 (4.8) |
| Vascular burden | 1.0 (1.0) | **3.1 (1.1)** | 0.5 (0.5) | **2.2 (1.5)** | 1.4 (1.4) |
| Nonvascular diseases | 0.6 (0.9) | 1.1 (1.5)[a] | 0.1 (0.4) | 0.7 (1.0) | 0.3 (0.8) |
| Wahlund scale | 4.4 (3.3) | **7.6 (4.2)** | 6.1 (4.1) | **10.0 (3.1)**[b] | 3.5 (1.8) |

*Note*: Bold indicates that the score is different from controls.
[a] The score is different from MCI-NoVas.
[b] The score is different from MCI-NoWML.
There was no significant difference between MCI-Vas and MCI-NoVas

expected, MCI-Vas suffered from more vascular diseases than both controls and MCI-NoVas. MCI-Vas also showed more WML than controls, but not more than MCI-NoVas. MCI-Vas also had more nonvascular diseases than MCI-NoVas. Table 2 presents scores on clinical measures. As expected, when compared with healthy older adults, MCI-Vas and MCI-NoVas had impaired general cognitive functioning, episodic memory, and executive functions. Only MCI-Vas showed impaired language. MCI-Vas and MCI-NoVas did not differ on language measures.

### 3.1.2. Free recall and recognition task

The preliminary analysis indicated no interaction implicating Cognitive reserve; therefore, the following is presented without this factor. A mixed ANOVA with Recall mode (two levels: Free-recall, Recognition) as a within-subject factor and Group (three levels: MCI-Vas, MCI-NoVas, controls) as between-subject factor was used to analyze performances (number of correct responses) on the memory task. The ANOVA indicated a Recall mode × Group interaction, $F(2,68) = 4.54$, $p < 0.05$, $\eta^2 = 0.12$ (Fig. 1). In the *free recall condition*, MCI-Vas and MCI-NoVas participants did not differ from one another, but both groups showed lower scores than healthy older adults ($p < 0.001$ for both groups). In the *recognition condition*, participants with MCI-NoVas showed lower scores than both MCI-Vas ($p < 0.05$) and healthy older adults ($p < 0.001$). Participants with MCI-Vas did not differ from healthy older adults.

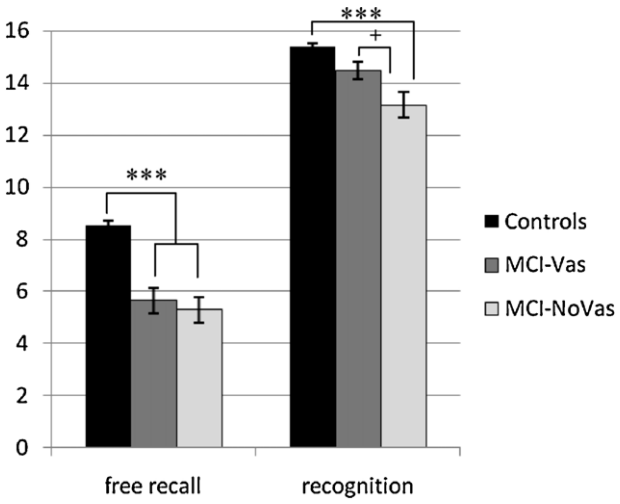


**Fig. 1.** Mean correct performance in the free recall and recognition conditions for MCIs and their controls when vascular burden is measured by assessing the vascular risk profile. *Note:* Different from controls at $^{***}p < 0.001$. Different from MCI-NoVas at $^{+}p < 0.05$.

### 3.1.3. Temporal contextual memory task

The preliminary analysis indicated no interaction implicating the Cognitive reserve factor; therefore, the following is presented by pooling data across education level. A one-way ANOVA with Group (MCI-Vas, MCI-NoVas, controls) as a between-subject factor was used to compare group performance (number of correct answers divided by the number of words recognized correctly) on the temporal contextual memory task. The ANOVA indicated a main Group effect, $F(2,68) = 8.46$, $p = 0.01$, $\eta^2 = 0.20$ (Table 5). MCI-Vas and MCI-NoVas participants showed lower temporal context recall than healthy older adults ($p < 0.01$). Performances of MCI-Vas and MCI-NoVas participants did not differ significantly.

**Table 2**
Mean and significance level on clinical cognitive tests for MCIs and controls (SD in parentheses).

| | Controls | MCI-Vas | MCI-NoVas | MCI-WML | MCI-NoWML |
|---|---|---|---|---|---|
| General functioning | | | | | |
| MMSE | 29.6 (0.6) | **27.9 (1.6)** | **27.4 (1.8)** | **27.5 (1.5)** | **27.7 (1.8)** |
| MDRS | 140.6 (3.1) | **133.1 (7.9)** | **134.0 (6.8)** | **132.6 (7.3)** | **134.5 (7.5)** |
| Memory | | | | | |
| RL/RI-16 imm | 11.8 (2.1) | **8.7 (3.7)** | **7.1 (3.4)** | **8.0 (3.9)** | **7.7 (3.5)** |
| RL/RI-16 delay | 12.2 (2.2) | **8.9 (3.4)** | **8.2 (3.9)** | **8.2 (3.9)** | **8.9 (3.4)** |
| BEM imm | 9.8 (1.2) | **7.5 (2.7)** | **6.3 (2.5)** | **6.9 (2.7)** | **6.8 (2.6)** |
| BEM delay | 9.3 (1.5) | **6.8 (2.9)** | **5.2 (2.9)** | **5.8 (3.0)** | **6.1 (2.9)** |
| Rey imm | 15.85 (5.9) | 11.7 (6.4) | 11.7 (7.2) | **10.2 (5.7)** | 13.3 (7.6) |
| Rey delayed | 15.7 (5.5) | 12.0 (6.2) | 11.9 (6.5) | **10.7 (5.8)** | 13.1 (6.7) |
| Executive functions | | | | | |
| Coding | 61.2 (14.9) | **42.9 (12.8)** | **48.1 (13.3)** | **41.1 (11.4)** | **50.0 (13.4)** |
| Stroop | 27.5 (7.9) | **39.9 (11.7)** | **36.0 (11.5)** | **38.3 (11.4)** | **37.6 (12.8)** |
| Apraxia | | | | | |
| Rey copy | 32.8 (2.6) | **29.9 (5.1)** | **29.2 (4.4)** | **29.2 (5.9)** | 30.0 (3.5) |
| Language | | | | | |
| Boston | 13.7 (1.4) | **12.6 (2.1)** | 12.8 (1.2) | **12.4 (1.5)** | 12.8 (1.9) |
| Visual perception | | | | | |
| Benton | 24.3 (3.8) | 23.1 (3.8) | 23.8 (3.7) | 22.9 (3.8) | 24.2 (3.5) |

*Note*: Bold indicates that the score is different from controls; there was no significant difference between MCI-Vas and MCI-NoVas or between MCI-WML and MCI-NoWML.

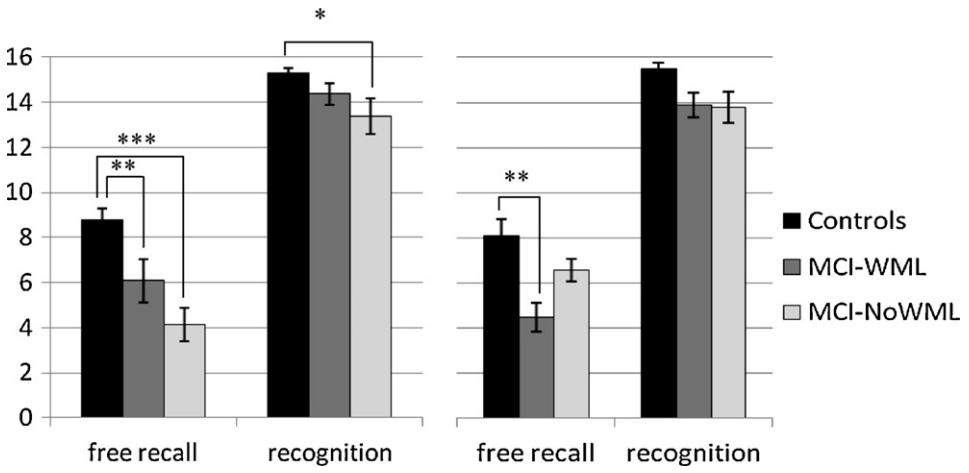


**Fig. 2.** Mean correct performance in the free recall and recognition conditions for MCIs and their controls when vascular burden is assessed neuroradiologically. Left panel presents data for those with a low cognitive reserve, right panel presents data for those with a high cognitive reserve. *Note:* Different from controls at $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

### 3.2. Memory impairment in MCI as a function of number of WML

#### 3.2.1. Sociodemographic and clinical data

Persons with MCI-WML, MCI-NoWML, and healthy older adults were comparable on demographic information, as shown in Table 1. As expected, MCI-WML had more WML than both controls and MCI-NoWML. MCI-WML also had more vascular diseases than controls, but not more than MCI-NoWML. On clinical measures, both MCI-WML and MCI-NoWML had impaired general cognitive functioning, verbal episodic memory, and executive functions when compared with healthy older adults. Only MCI-WML showed impaired visual episodic memory, language, and praxia. MCI-WML and MCI-NoWML were comparable on all clinical neuropsychological tasks.

#### 3.2.2. Free recall and recognition task

The preliminary analysis indicated an effect of Cognitive reserve; therefore, the following includes this factor. The ANOVA included Recall mode (Free recall, Recognition) as a within-subject factor, as well as Group (MCI-WML, MCI-NoWML, controls) and Cognitive Reserve (low, high) as between-subject factors. The ANOVA indicated a Recall mode × Group × Cognitive Reserve interaction, $F(2,64) = 16.23$, $p = 0.05$, $\eta^2 = 0.09$ (Fig. 2). When compared with controls, MCI-WML participants were impaired in free recall ($p < 0.01$) and normal in recognition whether low or high in cognitive reserve. By contrast, MCI-NoWML participants performed worse than controls in all conditions (free recall, $p < 0.01$; recognition, $p < 0.05$) when characterized by a low cognitive reserve, but were normal when characterized by a high cognitive reserve.

#### 3.2.3. Temporal contextual memory task

The preliminary analysis indicated no interaction implicating Cognitive reserve; therefore, the ANOVA is presented without this factor. A one-way ANOVA with Group (MCI-WML, MCI-NoWML, controls) as a between-subject factor was used to compare group performance on the temporal contextual memory task. The ANOVA indicated a main Group effect, $F(2,67) = 8.11$, $p = 0.01$, $\eta^2 = 0.20$. Both MCI-WML and MCI-NoWML participants showed lower temporal context recall than healthy older adults ($p < 0.01$). Performances of MCI-WML ($55.50 \pm 15.35$) and MCI-NoWML participants ($55.64 \pm 9.91$) did not differ significantly.

### 3.3. Follow-up examination of progressors

#### 3.3.1. Sociodemographic and clinical data

Twenty patients (49.0%) with MCI showed progression to dementia after a three-year follow-up. Of the progressors, 10 were initially in the MCI-Vas group (55.6%), and 10 were initially in the MCI-NoVas group (47.6%). Tables 3 and 4 present demographic and clinical information for the two subgroups of progressors and the two subgroups of stable MCIs. Overall, progressor MCI-Vas showed worse performance than stable MCI-Vas on most measures of cognition, including general cognitive functioning, memory, and language. By contrast, no difference was found between progressor MCI-NoVas and stable MCI-NoVas on clinical tasks. When compared with healthy controls, stable MCI-Vas showed impaired executive functioning, whereas stable MCI-NoVas showed impaired memory.

#### 3.3.2. Free recall and recognition task

On the free recall/recognition task, the ANOVA indicated a Recall mode × Group interaction, $F(4,63) = 4.79$, $p < 0.01$, $\eta^2 = 0.23$ (Fig. 3). In the *free recall condition*, both groups of progressor MCIs had lower scores than healthy older adults ($p < 0.001$ for both groups) and did not differ from one another. In addition, the two groups of progres-

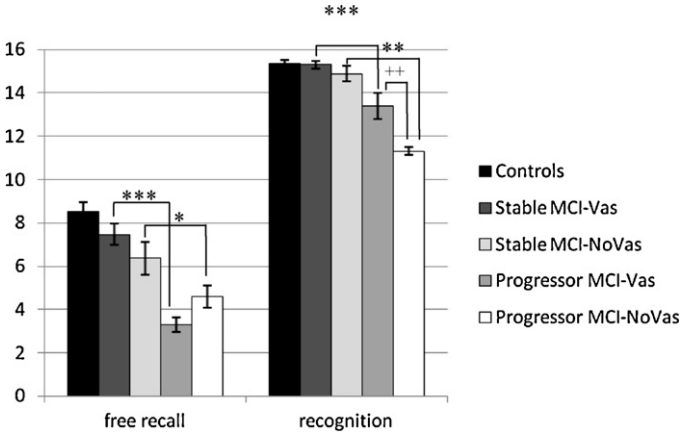


**Fig. 3.** Mean correct performance on the free recall and recognition conditions for progressor and stable MCIs (and their controls). *Note:* Different from controls or stable MCI at $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$. Different from progressor MCI-NoVas at $^{++}p < 0.05$. In the free recall and recognition procedures, both groups of progressor MCIs differed from controls at $^{***}p < 0.001$.

**Table 3**
Demographics, clinical characteristics, and MRI scores for progressor and stable MCIs (SD in parentheses).

| | Progressor | | Stable | |
|---|---|---|---|---|
| | MCI-Vas | MCI-NoVas | MCI-Vas | MCI-NoVas |
| Age | 76.9 (2.3) | 68.5 (7.8) | 70.2 (7.1) | 69.6 (8.4) |
| Sex | M6, F4 | M4, F6 | M7, F6 | M4, F4 |
| Education | 13.2 (4.8) | 13.2 (4.9) | 13.8 (6.0) | 13.8 (4.1) |
| Vascular burden | **3.3 (1.3)** | 0.2 (0.4) | **3.0 (1.0)** | 0.2 (0.4) |
| Nonvascular diseases | 1.3 (1.9) | 0.0 (0.0) | 0.9 (1.1) | 0.3 (0.5) |
| Wahlund scale | 8.1 (4.9) | 4.6 (2.8) | 7.3 (3.7) | 6.7 (5.5) |

*Note:* Performance of controls are in Table 1; bold indicates that the score is different from controls; there was no significant difference between progressor and stable MCI-Vas or between progressor and stable MCI-NoVas.

**Table 4**
Mean and significance level on clinical cognitive tests for progressor and stable MCIs (SD in parentheses).

| | Progressor | | Stable | |
|---|---|---|---|---|
| | MCI-Vas | MCI-NoVas | MCI-Vas | MCI-NoVas |
| General functioning | | | | |
| MMSE | **27.2 (1.7)** | **26.9 (2.0)** | 28.5 (1.3) | **28.0 (1.3)** |
| MDRS | **127.2 (7.7)**[a] | **131.3 (6.4)** | 137.6 (4.2) | 135.9 (7.1) |
| Memory | | | | |
| RL/RI-16 imm | **6.3 (3.2)**[a] | **5.1 (3.6)** | 10.5 (2.9) | 8.8 (2.3) |
| RL/RI-16 delay | **6.8 (3.4)**[a] | **6.2 (4.1)** | 10.5 (2.4) | 9.6 (3.1) |
| BEM imm | **6.1 (3.0)** | **5.8 (2.1)** | 8.8 (1.8) | **6.2 (3.2)** |
| BEM delay | **5.2 (3.0)** | **3.8 (2.8)** | 8.2 (1.9) | **5.5 (3.0)** |
| Rey imm | **8.3 (5.3)** | **8.6 (6.1)** | 14.5 (6.0) | 14.9 (8.5) |
| Rey delayed | **8.5 (4.9)** | **8.7 (5.3)** | 15.0 (5.9) | 15.4 (7.1) |
| Executive functions | | | | |
| Coding | **39.9 (12.8)** | 49.2 (14.2) | **45.2 (12.7)** | 50.4 (13.8) |
| Stroop | **43.8 (16.7)** | 37.6 (13.5) | 37.5 (9.1) | 34.0 (11.6) |
| Apraxia | | | | |
| Rey copy | 28.9 (6.1) | 28.9 (1.3) | 28.4 (1.5) | 28.4 (1.5) |
| Language | | | | |
| Boston | **11.3 (2.5)**[a] | 12.3 (1.1) | 13.5 (1.1) | 13.0 (1.4) |
| Visual perception | | | | |
| Benton | **24.0 (3.2)** | 22.4 (4.1) | 23.8 (3.6) | 23.8 (4.2) |

*Note:* Performance of controls are in Table 1; bold indicates that the score is different from controls.
[a] The score is different from stable MCIs.

sor MCIs had lower recall than their corresponding groups of stable MCIs ($p < 0.001$ and $p < 0.05$ for MCI-Vas and MCI-NoVas, respectively). By contrast, the two groups of stable MCIs were comparable to controls on free recall. The pattern of results was slightly different in the *recognition condition*. As for free recall, the two groups of stable MCIs were comparable to controls, and the two groups of progressors showed a lower recognition level than healthy older adults ($p < 0.001$ for both groups) and a lower recognition level than their corresponding groups of stable MCIs ($p < 0.01$ and $p < 0.001$ for MCI-Vas and MCI-NoVas, respectively). However, progressor MCI-Vas showed better recognition than progressor MCI-NoVas ($p < 0.01$).

### 3.3.3. Temporal contextual memory task

The ANOVA computed on the temporal contextual memory task indicated a main Group effect, $F(4,63) = 5.26$, $p = 0.001$, $\eta^2 = 0.25$ (Table 5). In this task, all groups of MCI showed impaired performance relative to controls ($p < 0.05$ for progressor and stable MCI-Vas, $p < 0.001$ for progressor MCI-NoVas) except for stable MCI-NoVas, in which no difference was found from controls.

**Table 5**
Performance (number of correct answers divided by the number of words recognized correctly) on the temporal contextual memory task for MCIs and their controls when vascular burden is measured by assessing the vascular risk profile.

| Temporal contextual memory task | Controls | MCI-Vas | MCI-NoVas |
|---|---|---|---|
| Initial group of MCIs ($n = 44$) | 68.2 (12.6) | 56.1 (13.8)** | 54.9 (11.6)** |
| Progressor MCIs ($n = 20$) | | 53.7 (12.3)* | 52.5 (7.1)** |
| Stable MCIs ($n = 21$) | | 55.9 (11.5)* | 61.2 (14.3) |

* Different from controls at $p < 0.05$.
** Different from controls at $p < 0.01$.

## 4. Discussion

The goal of this study was to assess memory processes in persons with MCI and to examine the effect of concomitant vascular burden and cognitive reserve as a source of cognitive heterogeneity. More precisely, our goal was to investigate whether the concomitant vascular burden in MCI is characterized by impaired strategic and preserved nonstrategic memory processes. Therefore, we relied on tasks that reflect either strategic (free recall and temporal contextual memory) or nonstrategic (recognition) memory processes. Results were consistent with our hypothesis. Persons with "pure" MCI, that is, those who do not exhibit concomitant vascular burden, showed impairment of both strategic and nonstrategic memory processes, which is a memory profile coherent with hippocampal and perirhinal/entorhinal dysfunctions (Wolk and Dickerson, 2011) and characteristic of early AD (Apostolova et al., 2006; Jack et al., 1999). By contrast, when MCI had a vascular component, it was characterized by impairment of strategic memory processes, with nonstrategic memory processes remaining relatively intact. These results suggest that the presence of vascular conditions in persons with MCI is associated with a characteristic pattern of memory deficit akin to that typically observed in SVD (Reed et al., 2007; Tierney et al., 2001) and frontal lobe dysfunction (Buckner,

2004; Fuster, 2001; Kramer, Rosen, Du, Schuff, & Hollnagel, 2005; Moscovitch, 1989).

One may argue that the selective difficulty of MCIs with vascular burden indicates a less severe memory deficit that affects only the most difficult tasks. Since the two groups of MCIs were equivalent in the classical memory tasks, we believe this is not the case and instead suggest that the nature of memory impairment in MCIs with vascular burden is qualitatively different from that characteristic of MCIs without vascular burden. This difference is in line with Moscovitch's (1989) theoretical model, which proposed that memory impairments caused by frontal dysfunctions are qualitatively different from memory impairments cause by temporal lesions.

Impaired strategic with normal nonstrategic memory processes were found in vascular MCI whether vascular burden was measured clinically by assessing the vascular risk profile or neuroradiologically on the basis of WML. Nonvascular MCIs showed both impaired strategic and nonstrategic memory processes when vascular burden was measured clinically. When vascular burden was measured neuroradiologically, the pattern was modulated by education (used here as a proxy of cognitive reserve; see Dufouil et al., 2003, for similar results). In this case, nonvascular MCIs with low cognitive reserve were impaired in both strategic and nonstrategic memory processes, but were normal when characterized by a high cognitive reserve. This finding suggests that older individuals exhibiting a high cognitive reserve and no significant amount of WML are the ones best maintaining their memory performances.

In this particular group of MCIs, WML were located predominantly in the frontal and the parieto-occipital lobes. Regional WML were highly correlated and correlated with total WML—a finding that may explain why WML localization did not influence the pattern of MCI memory deficits (data not shown). Some have suggested that the effect of WML on cognition does not result from localized lesions, but from a more widespread disconnection effect, which would be particularly detrimental to frontal lobe metabolism. In support of this idea, Tullberg and collaborators (2004) found that WML were associated with frontal hypometabolism, regardless of their location. Furthermore, Bombois et al. (2007) found that both periventricular and lobar WML were associated with executive dysfunctions. However, because all those studies used large regions of interest, we cannot exclude the possibility that looking at a specific white matter tract would have changed those results. Furthermore, we cannot discount the possibility that WML in regions that were not prevalent in MCI (i.e., the temporal lobe) could affect memory differently. In a recent study that targeted specific brain areas and included a large range of subjects with and without cognitive deficits, Smith and collaborators (2011) found that episodic memory was associated with bilateral temporal-occipital WML, right parietal periventricular WML, and lesions in the left anterior limb of the internal capsule, whereas executive functions were associated with bilateral inferior frontal WML, bilateral temporal-occipital WML, right parietal periventricular WML, and lesions in the anterior limb of the internal capsule bilaterally. Further work is needed to clarify the role of WML in cognition and to elucidate how WML localization contributes to those effects.

One critical aspect of this study was our following the MCIs longitudinally and assessing their progression to dementia. Our results show that, at a three-year follow-up, 49.0% of MCIs progressed to dementia and that this progression was quite similar across both subgroups of MCIs. This progression rate corresponds to what is generally reported in longitudinal studies that look at the rate of progression of amnestic MCI in clinic-based settings (Kluger, Ferris, Golomb, Mittelman, & Reisberg, 1999; Petersen et al., 1999) and indicates that our sample was quite comparable to other cohorts recruited from similar sources. Note that, in our relatively small sample, vascular burden, however measured, was not associated with a superior rate of progression to dementia, in contrast to what has been reported in other studies (Nordlund et al., 2010; Solfrizzi et al., 2009).

The memory profile of those MCIs who later progressed to dementia was qualitatively similar to that found in the entire group. That is, in progressors, a more important vascular risk profile was associated with a more severe impairment of strategic than of nonstrategic processes, whereas a less important vascular risk profile was associated with both strategic and nonstrategic memory impairment. By contrast, stable vascular and nonvascular MCIs showed normal performance in the free recall/recognition memory task. Thus, the contrast in effect of vascular burden on the pattern of memory impairment was driven by those persons who later developed dementia. Therefore, the memory profile of progressor MCIs with high vascular burden is qualitatively similar to what is usually reported in SVD, whereas the memory profile of progressor MCIs without vascular burden is qualitatively similar to that typically reported in AD. This pattern suggests that assessing the nature of memory impairment in MCI might help in understanding the etiology of the disease.

Interesting information was also gained when comparing the two memory tasks. Both groups of stable MCIs differed from their respective group of progressor MCIs on the free recall/recognition task. In turn, the contextual memory task was only useful for distinguishing stable from progressor nonvascular MCIs, since stable and progressor vascular MCIs were equally impaired on this task. These findings indicate that the free recall/recognition task might be more useful than the temporal contextual memory task for predicting progression from MCI to dementia, irrespective of vascular burden.

Close to half of our sample did not progress to dementia, and one issue that needs further exploration is the source and nature of memory deficits in nonprogressors. When looking at their performance on clinical tests, these participants showed less severe cognitive deficits overall than MCIs who later progressed to dementia. Stable nonvascular MCIs only showed deficits on the story recall task, whereas stable vascular MCIs only showed reduced performance on the coding task. Thus, their performance on clinical tests indicates that progressors tended to be of the multiple-domain subtype, and stable MCIs tended to be of the single-domain subtype (similar results have been reported by Nordlund et al., 2010). Stable MCIs also performed close to the normal range on the experimental memory tests, with the exception of those with vascular burden who showed poor performance on the contextual memory task.

Our study has some limitations. First, the lack of neuropathological confirmation makes it difficult to ascertain the etiology of dementia in progressors (Bombois et al., 2008). However, our study was not designed to address this question because our goal was to examine if vascular burden, when assessed with currently available measures, contributed to the memory symptomatology of MCI. Furthermore, we did not include an extensive evaluation of cognitive reserve, but used instead education as a proxy. Previous studies have shown that education is a valid proxy of cognitive reserve (Whalley, Deary, Appleton, & Starr, 2004) and that education contributes to the variance found in older adults verbal memory performances (Staff, Murray, Deary & Whalley, 2004). Studies like these suggest that this variable—though certainly not comprehensive—is a potentially valuable measure of cognitive reserve, particularly given its objectivity and easiness to evaluate. Some may also argue that using a semiquantitative rating scale to assess WML is less sensitive than relying on a quantitative measure of WML volume. Note, however, that we only retained patients with marked confluent WML, which is justified on the grounds that mild levels of WML are common in normal aging and not systematically associated with cognitive deficits (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2008). Furthermore, and

although there is a documented lower sensitivity when using visual rating scales, the correlation with volumetric measures of WML is usually good and allows for clinically meaningful analysis (Gouw et al., 2006). This result emphasizes the need for data to validate and ascertain measurement of vascular burden.

In summary, our results indicate that vascular burden modulates the pattern of memory deficit in MCI. Two subgroups defined as a function of their vascular load are characterized by different memory deficits: MCIs with no concomitant vascular burden show impairment of both strategic and nonstrategic processes. However, in the presence of vascular burden, MCI is characterized by a more selective memory deficit that impairs mostly strategic memory processes. This pattern of memory deficit is akin to that typically reported in Alzheimer's disease and subcortical vascular dementia respectively, and it is therefore likely that they represent prodromal symptoms corresponding to those dementia types. Half of our sample later developed dementia, and it was found that particular memory profiles were largely driven by those who later developed dementia. Consequently, in clinical practice, the pattern of memory deficit in older adults with MCI is expected to differ as a function of the presence or lack of vascular comorbidity and might predict further decline. Conceptually, our study indicates that the presence of vascular comorbidity in patients contributes to the cognitive heterogeneity of MCI and should be taken into account in studies that seek to identify the cognitive profile of persons with MCI.

## Contributions

SV collected and analyzed the data under the supervision of SB. SV and SB wrote the manuscript. SG, CB, and FM were involved in the patient characterization and recruitment, and they reviewed the manuscript. All authors read the final version of the article.

## Conflict of interest

The authors report no conflict of interest.

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