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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-