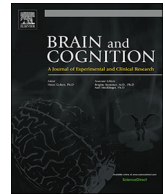




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## Thalamic and hippocampal volume associated with memory functions in multiple sclerosis



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## ABSTRACT

**Objectives:** Although multiple sclerosis (MS) has long been considered to primarily affect white matter, it is now recognized that cognitive deficits in MS are also related to neocortical, thalamic and hippocampal damage. However, the association between damage to these structures and memory deficits in MS is unclear. This study examines whether MS patients with cognitive impairment have a reduction of hippocampal and/or thalamic volumes compared to cognitively intact patients, and whether these volume reductions correlate with various aspects of memory function.

**Methodology:** Volumetric MRI measures of thalamus and hippocampus of forty-one patients with MS were performed. The patients were divided in two groups depending on the presence or absence of cognitive impairment, based on their neuropsychological tests scores.

**Results:** Right hippocampal volume was found to be associated with learning, and the left thalamic volume was found to predict performance in verbal memory. Cognitively impaired patients had a tendency to have a reduced left thalamic volume compared to cognitively intact patients.

**Conclusions:** This study does not support a direct relationship between hippocampal atrophy and verbal memory. These results add to the growing evidence of the involvement of thalamus in cognitive impairment in MS and its association with verbal memory deficits.

### 1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system, characterized by the formation of plaques (lesions) (Chiaravalloti & DeLuca, 2008). This chronic disease primarily affects the myelin sheath, a protective layer that facilitates propagation of nerve impulses (Chiaravalloti & DeLuca, 2008). Although this disease has long been considered to primarily affect white matter, neuro-imaging and pathological studies have shown that MS is also characterized by cortical and subcortical gray matter involvement, including hippocampus and thalamus (Benedict, Ramasamy, Munschauer, Weinstock-Guttman, & Zivadinov, 2009; Calabrese, Filippi, & Gallo, 2010; Cifelli et al., 2002; De Stefano et al., 2003). These gray matter lesions are more closely associated to cognitive impairment found in 54–65% of MS patients, than white matter lesions (Defer, Brochet, & Pelletier, 2010;

Rao, Leo, Bernardin, & Unverzagt, 1991). Cognitive impairment may be present in the early stages of the disease and impairs the patient's functional autonomy and quality of life (Amato et al., 1995). Verbal and visuospatial memory impairments are common in MS and are one of the main clinical complaints (Amato et al., 1995; Chiaravalloti & DeLuca, 2008). Several authors claim that memory deficits in MS are related to encoding and retrieval difficulties that would significantly alter the learning of new information (Chiaravalloti & DeLuca, 2008; Defer et al., 2010). Memory deficits in MS have been associated with other cognitive impairments; such as executive function, information processing speed and strategy development (Chiaravalloti & DeLuca, 2008; Deluca, Barbieri-Berger, & Johnson, 1994). Thalamus is a gray matter structure that plays an important role in several cerebral circuits involved in executive function (Batista et al., 2012; Jurado & Rosselli, 2007; Rao et al., 2014). Hence, it is logical to envision an association between

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memory difficulties in MS and the presence of thalamic damage. Indeed, a study measuring total lesion volume, third ventricle width, corpus callosum volume and thalamic volume demonstrated that the best predictor of memory and executive deficits in patients with relapsing-remitting (RR) MS was the total volume of the thalamus (Papathanasiou et al., 2015). However, this study did not distinguish between verbal and visuospatial memory performances, and only one global memory score was created. In addition, a study by Houtchens et al. (2007) demonstrated thalamic atrophy in a group of MS patients, compared to a control group. These authors reported a significant positive association between total thalamic volume and verbal and visuospatial memory (total score and delayed recall; California Verbal Learning Tests-II and Brief Visuospatial Memory Test-R). To our knowledge, the association between thalamic atrophy and verbal memory in MS has been frequently reported in the literature. However, the results remain contradictory for the association between thalamus and visuospatial memory. The results of recent studies suggest that memory impairment may also be associated with hippocampal atrophy. This gray matter structure plays an important role in the acquisition, and especially in the consolidation of new information (Ceccom, 2011; Zatorre, Fields, & Johansen-Berg, 2012). Sicotte et al. (2008) are one of the first teams to demonstrate an association between the loss of right and left hippocampal volumes and a reduction in a verbal memory task performance requiring encoding and retrieval of unrelated pairs of words in a combined group of RRMS and secondary progressive (SP) MS patients (Sicotte et al., 2008). Subsequently, other researchers have also shown hippocampal involvement in memory performance. Sacco et al. (2015) also demonstrated a reduction of right and left hippocampal volumes in patients with RRMS compared to control subjects. They reported an association between a decrease in verbal memory performance and left hippocampal atrophy. Some studies have also examined the association between memory performance of patients with MS and the volumes of thalamic and hippocampal structures simultaneously. Damjanovic et al. (2017), suggested that atrophy of hippocampus and deep gray matter nuclei, including thalamus, would be the best correlates of a global cognitive score in MS, compared to white matter measurements. Their results showed an association between visuospatial memory and thalamic volume but the association was not statistically significant between this cognitive domain and hippocampal volume. In addition, none of their MRI measurements were associated with verbal memory (Damjanovic et al., 2017). These results contrast with those from a recent study by Koenig et al. (2018) that showed a predictive role of hippocampal volume on immediate recall and of the left thalamic volume on delayed recall for a visuospatial episodic memory task. Benedict et al. (2009) examined the relative importance of the medial temporal lobe (hippocampus and amygdala) and deep gray structures (thalamus and caudate nucleus) in predicting verbal and visuospatial memory performance of MS patients. The results demonstrated that atrophy of target regions of deep gray matter was associated with lower performance in verbal and visuospatial memory tasks and was a strong predictor of learning performance. Moreover, medial temporal lobe volumes strongly predicted recognition measures (Benedict et al., 2009). In addition, Dineen, Bradshaw, Constantinescu, and Auer (2012) examined the total volume of hippocampus and thalamus in patients with RRMS and reported no associations between verbal and visuospatial memory measurements and hippocampal volume. The results revealed that the total volume of thalamus would be a positive predictor of performance in a word list recall task but not in visuospatial memory. As demonstrated above, there are currently inconsistencies in the literature on the exact role of hippocampal and thalamic atrophy in verbal and visuospatial memory deficits in MS.

The first objective of our study is to examine whether cognitively impaired patients with MS have significantly reduced hippocampal and/or thalamic volumes compared to cognitively intact patients. Secondly, associations between the right and left volumes of these structures and the measures of learning, verbal memory and

visuospatial memory are evaluated. An additional objective is to evaluate the link between these specific regions and executive and attentional functions since they are closely linked to memory.

We hypothesized that cognitively impaired patients with MS will have reduced hippocampal and thalamic volumes compared to cognitively intact patients. Hence, hippocampal volumes should be positively associated with memory measurements and thalamic volumes should predict attentional, executive and memory performances in these patients.

## 2. Materials and methods

### 2.1. Subjects

Forty-one MS patients were recruited. The sample consisted of 12 men and 29 women, aged between 28 and 56 years ( $M = 44.49$ ;  $SD = 7.43$ ). Women are more affected by this condition than men (ratio of 3:1), which explains the gender distribution in this sample (Brassat, 2010; Jobin, Larochelle, Parpal, Coyle, & Duquette, 2010). To be included, patients had to meet the following criteria: (1) be between 18 and 55 years of age; (2) have RR or SP MS according to McDonald's revised diagnostic criteria (Polman et al., 2005); (3) have a maximum score of 7 in the Expanded Disability Status Scale (EDSS); (4) be fluent in French; (5) have completed high school; and (6) be able to give informed consent. Patients with the following criteria were excluded: (1) neurological disorders other than MS; (2) psychiatric or medical condition that may interfere with cognitive functioning; (3) significant depressive symptoms (score greater than 4 in the Beck Depression Inventory); (4) developmental disorders; (5) drug or alcohol abuse; and (6) a recent MS relapse (in the past 6 months). Psychostimulant use was not an exclusion criterion, if the dose was stable.

### 2.2. Measures

#### 2.2.1. Questionnaires

Several questionnaires and scales were administered at recruitment to ensure eligibility and to control for the effect of the following confounding variables that could influence the participants' cognition; the Beck Depression Index Fast Screen (BDI-FS) was completed to rule out the presence of depressive symptoms; the Pittsburgh Sleep Quality Index (PSQI) was used for assessment of sleep quality; the Modified Fatigue Impact Scale (MFIS) was used to document the level of subjective fatigue; and the Expanded Disability Status Scale (EDSS) was used to examine the level of any neurological impairment. These questionnaires are commonly used in clinical and research settings and possess good psychometric properties (Lezak, Howieson, & Loring, 2012; Meyer-Moock, Feng, Maeurer, Dippel, & Kohlmann, 2014).

#### 2.2.2. Neuropsychological evaluation

The selection of neuropsychological tests was based on their validity and reliability for the evaluation of cognition in MS patients (Benedict et al., 2006; Dusankova, Kalincik, Havrdova, & Benedict, 2012). The French version of each test was administered and appropriate norms for age and, if available, sex and education were used. Verbal memory was evaluated by the Rey Auditory Verbal Learning Test (RAVLT: validated for Quebec francophone population by Lavoie et al., 2018) and by two subtests of the Wechsler Memory Scale-III (Logical Memory Subtest and Paired Associates subtest: Wechsler, 2001). Immediate and delayed recall of the Rey-Osterrieth Complex Figure and the Brief Visual Memory Test (BVMT-R) as well as the delayed recall of the 10/36 Spatial Recall Test were used to examine visuospatial memory. Executive functions and attention were evaluated by the Paced Auditory Serial Addition Test (PASAT-3), the Symbol Digit Modality Test (SDMT), the execution time of the Trail Making Test A and B, the D-KEFS sorting test and inhibition and flexibility conditions of the D-KEFS Color-Word Interference test. The Controlled Oral Word Association

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