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The role of the thalamus and hippocampus in episodic memory performance in patients with multiple sclerosis

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Abstract

Background—Episodic memory loss is one of the most common cognitive symptoms in patients with multiple sclerosis (MS), but the pathophysiology of this symptom remains unclear. Both the hippocampus and thalamus have been implicated in episodic memory and show regional atrophy in patients with MS.

Objective—In this work, we used functional magnetic resonance imaging (fMRI) during a verbal episodic memory task, lesion load, and volumetric measures of the hippocampus and thalamus to assess the relative contributions to verbal and visual spatial episodic memory.

Methods—Functional activation, lesion load, and volumetric measures from 32 patients with MS and 16 healthy controls were used in a predictive analysis of episodic memory function.

Results—After adjusting for disease duration, immediate recall performance on a visual spatial episodic memory task was significantly predicted by hippocampal volume ($p < 0.003$). Delayed recall on the same task was significantly predicted by volume of the left thalamus ($p < 0.003$). For both memory measures, functional activation of the thalamus during encoding was more predictive than that of volume measures ($p < 0.002$).

Conclusion—Our results suggest that functional activation may be useful as a predictive measure of episodic memory loss in patients with MS.

Keywords

MRI; fMRI; multiple sclerosis; episodic memory; hippocampus; thalamus; atrophy

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Introduction

It is estimated that 40% to 65% of patients with multiple sclerosis (MS) experience cognitive impairment, with declines in processing speed and episodic memory loss commonly reported.^{1, 2} There is no consensus on the pathophysiology behind memory dysfunction in patients with MS, although early reports implicated both the hippocampus and thalamus.³ These and associated structures such as the fornix and cingulate comprise the Papez circuit, which is involved in both encoding and recall.⁴

The hippocampus is involved in the encoding of long-term memory and in organizing and linking information related to context and associations of episodic memories.⁵ Hippocampal atrophy and demyelination are common in MS,^{6, 7} and hippocampal volume loss has been associated with deficits in both verbal and visual spatial episodic memory.^{8–10} A recent functional magnetic resonance imaging (fMRI) study found that during encoding of visual stimuli, cognitively-preserved patients with MS showed increased activation in the hippocampus, parahippocampus, and anterior cingulate, whereas cognitively-impaired patients showed widespread decreases in activation, including in the hippocampus.¹¹ Evidence that functional changes precede memory impairment also comes from fMRI measures taken at rest, in which MS patients with intact memory function demonstrated a decrease in the strength of hippocampal connectivity with progressing atrophy.⁷

Specific thalamic nuclei have been linked to particular aspects of episodic memory function. The anterior thalamic nuclei are theorized to be involved in the selection of stimuli for encoding and encoding strategies, while the medial dorsal nucleus is involved in the selection of retrieval strategies.¹² Atrophy of the thalamus has been widely reported in patients with MS, and changes in thalamic volume have been linked to episodic memory performance and overall cognitive impairment.^{13–16} Functional changes have been related to cognitive measures and disease variables, with increased thalamic functional connectivity related to decreased cognitive function¹⁵ and functional activation of the medial dorsal and ventral lateral thalamic nuclei during performance of a verbal episodic memory recognition task positively related to total lesion volume.¹⁷

Here, we assess the relative contributions of volumetric and functional measures of the hippocampus and thalamus to episodic memory performance. Based on previous work showing that functional measures account for additional variance over volumetric measures in the prediction of cognitive function,^{15, 18} we hypothesized that volumetric measures would be most predictive of episodic memory function and that hippocampal activation during retrieval and thalamic activation during encoding would account for significant additional variance.

Materials and methods

Participants

Table 1 provides demographic and disease characteristics for the MS and healthy control groups. The groups showed no differences in age, sex, or education, and all participants were right handed. All data collection took place under an Institutional Review Board-

approved protocol and complied with the Declaration of Helsinki. MS-related inclusion criteria were as follows: 1. clinically definite MS,¹⁹ 2. No changes in disease-modifying drug treatment in the previous month, 3. Expanded Disability Status Scale (EDSS) score of seven or less, 4. No clinical relapse within the past 8 weeks. Exclusion criteria for both patients and healthy controls included 1. Neurologic history (other than MS for patients) such as head injury, stroke, or seizures, 2. History of substance abuse, major psychiatric disorder, or learning disability, 3. Exclusion criteria specific to MRI.

Behavioral testing

At the time of imaging, all participants completed a battery of behavioral tests and the MS patients were rated on the EDSS. Depression was assessed using the Beck Depression Inventory (BDI). Motor function was assessed using the 9-hole peg test and the 25-foot walk. As expected, MS patients had significantly higher BDI scores and poorer extremity motor performance (Table 1).

Verbal episodic memory was measured using the California Verbal Learning Test-Second Edition (total score: CVLT-T; delayed recall score: CVLT-DR), which involves the recollection and identification of a series of words.²⁰ Visual spatial episodic memory was measured using the Brief Visuospatial Memory Test-Revised (total score: BVMT-T; delayed recall score: BVMT-DR), which requires participants to recall and reproduce simple line drawings.²¹ Raw scores for each measure were corrected and standardized using published norms.^{20, 21} Motor function, disease characteristics, and memory performance were compared across groups using unpaired Student's t-tests.

MR imaging

The following scans were performed on a TIM Trio 3 Tesla scanner (Siemens Medical Solutions, Erlangen, Germany) with a standard 12-channel receive-only head coil and a bite bar to limit motion:

1. Whole-brain T1-weighted inversion recovery turboflash (MPRAGE); voxel size, $1 \times 1 \times 1.2 \text{ mm}^3$; scan time, 8:08.
2. Whole-brain FLAIR; voxel size $1.2 \times 1 \times 1 \text{ mm}^3$; scan time 5:14.
3. Whole-brain verbal memory encoding fMRI task; voxel size, $2 \times 2 \times 4 \text{ mm}^3$; scan time, 6:18.
4. Whole-brain verbal memory recognition fMRI task; voxel size, $2 \times 2 \times 4 \text{ mm}^3$; scan time, 6:40; 2 runs.

Episodic memory fMRI task

Patients with MS tend to show greater impairment in free recall than in recognition memory.²² To mitigate the effect of group differences in performance, we chose a verbal recognition memory task consisting of encoding and recognition phases. The encoding phase consisted of 60 words visually presented for 4.5 seconds each. Participants decided whether each word was "abstract" or "concrete" and responded with a button press. The recognition phase occurred after 20 minutes and consisted of 60 words seen during the encoding phase

(targets) and 60 new words (foils) visually presented for 4.5 seconds. Participants decided whether they had seen each word during the encoding task and responded “yes” or “no” with a button press. Performance was measured by the normalized percent correct recognition for target stimuli and for correct rejections of foil stimuli. Sensitivity (logistic d') and response bias (logistic β) were also calculated.

fMRI analysis

Data were retrospectively motion corrected using the AFNI²³ routine 3dvolreg and spatially filtered with a Gaussian filter. Response data from the recognition task were used to categorize target words as correctly or incorrectly recognized. Foils were categorized as correctly rejected or as false alarms. The two recognition scans were concatenated, and these categories, along with a category for “no response,” were used to create input timing files for a deconvolution analysis. The categorization of targets was also applied to the encoding task. The AFNI routine 3dDeconvolve was used to create individual Student’s t-maps for three conditions: 1. correctly recognized targets 2. correctly identified foils 3. correctly encoded targets. All maps were converted to z-scores.

Figure 1 shows the process used to create functional regions of interest (ROIs) in the left and right thalamus (L_THAL_ACT; R_THAL_ACT) and left and right hippocampus (L_HIP_ACT; R_HIP_ACT). For each condition, a whole-brain -average z-score map was calculated for each group, and thresholded to ensure activation within each of the anatomical areas. Significant activation within the thalamus was seen in both groups at a threshold of $p < 1 \times 10^{-4}$ (cluster size = 300), and within the hippocampus, at $p < 0.01$ (cluster size = 1000). Activation within each anatomical region was bounded using Eickhoff-Zilles defined masks.²⁴ For each condition, the masked, thresholded group average maps were added to create a functional mask. The result was four ROIs for each condition (Figure 2). The region of greatest overlap between each ROI and atlas-based parcellation is reported below.^{25, 26}

For each participant, the four ROIs for a given condition were applied to the activation map for that condition. The mean z-score within each ROI was calculated and used in subsequent statistical analysis. Unpaired Student’s t-tests compared between-group activation in. In patients, mean activation was correlated with neuropsychological and volumetric measures. The false discovery rate (FDR) was used as a correction for multiple comparisons.

Motion

Functional datasets were assessed for motion using visual inspection and mean and maximum peak-to-peak displacement.²⁷ Visual inspection focused on motion-related artifacts including rings of activation/correlation around the outside of the brain, activation/correlation in the ventricles, and rapid pattern changes from slice to slice. Group differences were tested using unpaired Student’s t-tests.

Volumetric analysis

Bilateral thalamus (L_THAL_VOL; R_THAL_VOL) and hippocampus (L_HIP_VOL; R_HIP_VOL) volumes were calculated from ROIs manually drawn by a trained expert (K.A.K.). Freesurfer v5.1.0 (<http://surfer.nmr.mgh.harvard.edu/>) was used to estimate

intracranial volume. Individual Freesurfer parcellations were manually inspected and corrected for accuracy. Corrected volumes were calculated as (ROI volume / intracranial volume)*100. Group differences were tested using unpaired Student's t-tests. Lesion volume was calculated using the Lesion Prediction Algorithm²⁸, as implemented in the LST toolbox version 2.0.15 (www.statistical-modelling.de/lst.html) for SPM 12.²⁹ Lesion volumes in the whole brain, hippocampus, and thalamus were calculated. Partial correlations were used to assess the relationship between volume measures and memory, using level of education as a covariate and applying the FDR correction.

Prediction of episodic memory

Our goal was to assess the predictive power of functional activation beyond clinical and structural variables. Linear stepwise regression assessed the relative importance of volumetric and activation to episodic memory performance in patients. Due to sample size limitations, dependent variables were limited to measures of episodic memory performance that showed a significant relationship to imaging measures. Predictors were identified by using Pearson correlations (FDR corrected) to measure relationships between episodic memory and demographic or imaging variables. For each memory measure, an initial regression included significant demographic variables. A second regression added significant volume measures. Finally, functional activation from significant ROIs was added. Predictors were added with $p < 0.05$ to enter and $p > 0.1$ to exit.

Results

Table 2 shows episodic memory performance reported as z-scores. The MS group performed worse than controls on both BVMT measures ($p < 0.016$) and on the CVLT-DR ($p < 0.025$), but showed no difference on the CVLT-T. Despite this, the MS group included a range of scores on the CVLT-T, with 7 participants scoring -1 or lower. In the MS group, disease duration (DDUR) showed a significant relationship to performance on both the BVMT-T and BVMT-DR (Table 3).

Motion

No participants were excluded because of motion. No significant differences in mean or maximum displacement were found for either encoding (mean: $p < 0.121$; maximum: $p < 0.231$) or recognition (mean: $p < 0.374$; maximum: $p < 0.570$).

Volumetrics

The MS group had significantly smaller left ($p < 0.006$) and right ($p < 0.001$) hippocampal volumes, with an average reduction of 20.4% as compared to controls (Table 2). Bilateral thalamic volumes were also smaller in patients ($p < 3.1 \times 10^{-5}$; average reduction 17.2%). DDUR was negatively related to all structural volumes ($p < 0.013$), and EDSS was negatively related to R_THAL_VOL ($p < 0.005$). Total lesion volume was related to both DDUR (0.655, $p < 4.7 \times 10^{-5}$) and EDSS (0.486, $p < 0.005$). All structural volumes were significantly related to BVMT-T ($p < 0.011$), and with the exception of R_HIP_VOL, were significantly related to BVMT-DR ($p < 0.027$; Table 3). Total lesion volume was related to

all four memory measures ($p < 0.008$). Lesion volumes for individual structures were not related to demographics or memory measures.

Verbal episodic memory

The MS group performed more poorly than the control group on the logistic β measure of response bias ($p < 0.019$), driven by a non-significant increase in the false alarm rate in the MS group ($p < 0.343$). No other measures of in-scanner task performance reached significance. Functional activation was not related to demographic or disease measures.

Correct encoding—During correct encoding, L_THAL_ACT was located primarily in the medial dorsal nucleus, whereas R_THAL_ACT spanned both the medial dorsal and ventral lateral nuclei (Figure 2A). Thalamic activation did not show group differences (Table 2). In the MS group, L_THAL_ACT was significantly related to performance on both BVMT-T (Figure 3; Table 3) and BVMT-DR (Table 3) and to L_THAL_VOL ($r = 0.477$, $p < 0.006$; Figure 4). Because L_THAL_ACT was related to atrophy, individual ROIs were double-checked to ensure they were located entirely in tissue. After partial correlations correcting for L_THAL_VOL, the relationship of activation to BVMT-T remained significant ($p < 0.013$), but the relationship to BVMT-DR did not ($p < 0.056$). There was no relationship between L_THAL_ACT and lesion measures. R_THAL_ACT was not significantly related to measures of interest.

The activation-based hippocampal ROIs were located in approximately CA 3 on the left and CA 1-3 and the dentate on the right (Figure 2A). L_HIP_ACT showed deactivation in the MS group as compared to controls (Table 2) but was not related to volume, lesion, or episodic memory measures. R_HIP_ACT did not show significant group differences and was not related to measures of interest.

Correct recognition—During correct recognition, L_THAL_ACT was located primarily in the ventral posterior lateral nucleus, whereas R_THAL_ACT was located in the ventral lateral nucleus (Figure 2B). The MS group showed increased activation bilaterally compared to the control group (Table 2), although activation was not related to measures of interest.

Both L_HIP_ACT and R_HIP_ACT were located primarily in the subiculum (Figure 2B). L_HIP_ACT did not show group differences, but the MS group showed decreased deactivation in R_HIP_ACT (Table 2). A negative relationship between R_HIP_ACT and performance on the BVMT-DR (Table 3) did not survive FDR correction. L_HIP_ACT and R_HIP_ACT were not related to other measures.

Correct rejection—During correct rejection of foils, both L_THAL_ACT and R_THAL_ACT spanned the medial dorsal and ventral lateral nuclei (Figure 2C). Thalamic activation did not show group differences (Table 2) and were not related to measures of interest.

L_HIP_ACT was located in primarily the subiculum, while R_HIP_ACT included the subiculum and CA 1-3 (Figure 2C). Neither region showed group differences (Table 2), nor were related to measures of interest.

Prediction of episodic memory

Table 4 shows the results of predictive modeling for the BVMT-T and BVMT-DR. CVLT-T and CVLT-DR were not included in this analysis, as the only demographic, volumetric, or functional variable to show a relationship to these measures was lesion volume. The “Demographics” column shows results for the initial models. DDUR significantly contributed to prediction for both BVMT measures and was included in all subsequent models. “Demographics + Volumetrics” shows the addition of significantly related volumetric measures. For BVMT-T, L_HIP_VOL (Model A3) and R_HIP_VOL (Model A4) significantly contributed to prediction. L_THAL_VOL was the only volumetric measure to significantly contribute to prediction of BVMT-DR (Model B1). “Demographics + Volumetrics + Activation” shows the addition of activation to each of the models that were significant for a volume measure. The only qualifying activation was L_THAL_ACT during correct encoding, which was included in the final models for both BVMT measures. No volume measures contributed significantly to the models after the inclusion of activation.

Discussion

This work examined the contributions of volumetric and functional measures of the hippocampus and thalamus to episodic memory performance in patients with MS. We hypothesized that volumetric measures would be most predictive of episodic memory function and that hippocampal activation during retrieval and thalamic activation during encoding would account for additional variance. We found that activation in the left thalamus during correct encoding was the strongest imaging predictor of visual spatial recall performance in MS, surpassing that of volumetric measures.

Both positive¹¹ and negative^{18, 30} relationships have been reported between cognitive function and task-based functional activation levels in MS. We found that thalamic activation was positively related to memory performance, accounting for added variance in prediction.^{15, 18} Thalamic activation was either higher or unchanged in MS patients as compared to controls, also in line with previous work.¹⁸ The positive relationship between activation and episodic memory is interesting in light of consistent reports of increased thalamic connectivity in patients with poor cognitive performance.^{15, 31, 32} As the thalamus becomes more strongly connected to other brain regions, typical function may be disrupted, leading to lower levels of activation during relevant tasks. Though we saw bilateral thalamic activation, only the left proved predictive. Given the strong right-handedness of our sample and the use of a verbal task, this may be related to reports of lateralization of thalamic function in relation to verbal memory.³³

In contrast to previous findings of increased activation in the hippocampus of patients with MS,¹¹ we found deactivation in the hippocampus in all conditions. Hippocampal activation is associated with both encoding and recognition,³⁴ and it is unclear why our sample showed only negative or non-significant activation in the hippocampus. Task timing files, registration of individual datasets to common space, and placement of ROIs were reviewed as potential causes, but did not seem to contribute to this issue.

Hippocampal and thalamic volumes and lesion load were related to memory measures, though neither thalamic^{13, 14} nor hippocampal⁹ volumes were related to verbal recall. However, results from our manually traced volume measures are generally in line with results from previous studies. Thalamic volume showed an overall reduction of 17.2% in patients,¹³ and both the thalamus and hippocampus were related to changes in neuropsychological and disease measures. Previous studies in MS find that thalamic volume is predictive of verbal memory performance, but that visual spatial memory is better predicted by white matter diffusion.^{16, 35} Dineen et al¹⁶ found that fractional anisotropy of the fornix contributes to prediction of visual spatial memory, and previous work has linked both functional and structural measures of the hippocampus to fornix diffusion.⁸ It should be noted, however, that Dineen et al¹⁶ observed no relationship between fornix fractional anisotropy and hippocampal volume in their sample.

This study had a number of limitations. Although the method used to select ROIs for the analysis of regional activation included regions of significant functional change in any group, merging group-based ROIs may mask subtle group differences in spatial extent and location of activation. The use of whole-structure volumes rather than anatomical subfield analysis may conceal more predictive volumetric measures,⁹ though an analysis investigating differences in hippocampal and thalamic subfield activation would be difficult given our scan resolution.

In this work we show that functional activation of the thalamus during encoding is related to visual spatial episodic memory and is more predictive of episodic memory than volumes of the hippocampus and thalamus or lesion load. Both the hippocampus and thalamus have been implicated in memory loss in MS, and this comparison suggests that targeted investigation of the thalamus is warranted. High resolution functional imaging would be optimal, allowing more precise identification of involved nuclei.

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MS Journal Appendix for MRI methodology

Hardware	
Field strength	3 tesla
Manufacturer	Siemens
Model	Trio
Coil type (e.g. head, surface)	Head coil
Number of coil channels	12

Acquisition sequence	
Type (e.g. FLAIR, DIR, DTI, fMRI)	MPRAGE

Acquisition sequence	
Acquisition time	8:08
Orientation	Axial
Alignment (e.g. anterior commissure/poster commissure line)	
Voxel size	$1 \times 1 \times 1.2\text{mm}^3$
TR	1900ms
TE	1.71
TI	900
Flip angle	8
NEX	1
Field of view	256×256
Matrix size	256×128
Parallel imaging	No
If used, parallel imaging method: (e.g. SENSE, GRAPPA)	
Cardiac gating	No
If used, cardiac gating method: (e.g. PPU or ECG)	
Contrast enhancement	No
If used, provide name of contrast agent, dose and timing of scan post-contrast administration	NA
Other parameters:	
Type (e.g. FLAIR, DIR, DTI, fMRI)	fMRI
Acquisition time	6:18 encoding / 6:40 recognition
Orientation	Axial
Alignment (e.g. anterior commissure/poster commissure line)	
Voxel size	$2 \times 2 \times 4\text{mm}^3$
TR	2800ms
TE	29
TI	
Flip angle	80
NEX	1
Field of view	256×256
Matrix size	128×128
Parallel imaging	No
If used, parallel imaging method: (e.g. SENSE, GRAPPA)	
Cardiac gating	No
If used, cardiac gating method: (e.g. PPU or ECG)	
Contrast enhancement	No
If used, provide name of contrast agent, dose and timing of scan post-contrast administration	NA
Other parameters:	

Image analysis methods and outputs	
Lesions	
Type (e.g. Gd-enhancing, T2-hyperintense, T1-hypointense)	NA
Analysis method	NA
Analysis software	NA
Output measure (e.g. count or volume [ml])	NA
Tissue volumes	
Type (e.g. whole brain, grey matter, white matter, spinal cord)	Hippocampus, thalamus; intracranial volume
Analysis method	Manual tracing; Freesurfer
Analysis software	AFNI; Freesurfer
Output measure (e.g. absolute tissue volume in ml, tissue volume as a fraction of intracranial volume, percentage change in tissue volumes)	Tissue volume as fraction of intracranial volume
Tissue measures (e.g. MTR, DTI, T1-RT, T2-RT, T2*, T2', ¹H-MRS, perfusion, Na)	
Type (e.g. whole brain, grey matter, white matter, spinal cord, normal-appearing grey matter or white matter)	NA
Analysis method	NA
Analysis software	NA
Output measure	
Other MRI measures (e.g. functional MRI)	
Type (e.g. whole brain, grey matter, white matter, spinal cord, normal-appearing grey matter or white matter)	Functional MRI
Analysis method	AFNI 3dDeconvolve
Analysis software	AFNI, Matlab
Output measure	fMRI Student's t-maps

Other analysis details:

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Figure 1.

Creating functional regions of interest from verbal episodic memory fMRI data. Thalamic ROIs for the correct encoding condition are shown. A. Z-scored activation maps are averaged within groups and thresholded. B. Group maps are anatomically bound. C. Group maps are added to produce a final functional mask for subsequent analysis.

Figure 2. Activation-based thalamic and hippocampal regions of interest from the (A) correct encoding, (B) correct recognition, and (C) correct rejection conditions.

Figure 3. Relationship between activation of the left thalamus during correct encoding and performance on the Brief Visuospatial Memory Test-Revised (total score) (BVMT-T) in 32 participants with multiple sclerosis.

Figure 4. Relationship between activation of the left thalamus during correct encoding and left thalamic volume in 32 participants with multiple sclerosis.

Table 1

Participant demographics and disease characteristics.

	Control group (n = 16)	MS group (n = 32)	P value ^a
Demographics			
Mean age, years (SD)	43.25 (9.9)	42.91 (9.4)	0.907
Mean education, years (SD)	15.56 (1.6)	15.03 (1.8)	0.323
Sex, % male	18.80	28.12	0.484
Disease characteristics			
Disease type	NA	27 RR; 5 SP	NA
Mean DDUR, years (SD)	NA	12.81 (9.3)	NA
Mean EDSS (range)	NA	2.56 (0–6.5)	NA
Mean BDI (SD)	3.47 (3.5)	12.81 (9.6)	0.001
Motor function, seconds			
Mean 9-hole peg score, dominant (SD)	18.41 (2.4)	21.15 (4.0)	0.016
Mean 9-hole peg score, non-dominant (SD)	18.55 (1.4)	22.37 (3.8)	3.2×10^{-4}
Mean 25-foot walk score (SD)	4.26 (0.59)	5.73 (3.5)	0.104

MS: multiple sclerosis; SD: standard deviation; NA: not applicable; RR: relapsing-remitting; SP: secondary progressive; DDUR: disease duration; EDSS: Expanded Disability Status Scale; BDI: Beck Depression Inventory.

^a *p* values and post hoc values were derived from unpaired Student's *t*-tests for continuous variables and Kruskal-Wallis for categorical variables.

Table 2

Neuropsychological and volumetric measures and functional activation.

	Control group <i>n</i> = 16	MS group <i>n</i> = 32	<i>P</i> value ^a
Neuropsychological measures, mean (SD)			
CVLT-T	0.81 (0.95)	−0.12 (1.11)	0.147
CVLT-DR	0.31 (0.91)	−0.16 (1.10)	0.025
BVMT-T	0.49 (0.79)	−0.40 (1.29)	0.006
BVMT-DR	0.50 (0.55)	−0.33 (1.38)	0.016
Volumetric measures, mean (SD)			
Lesion volume (mL)	–	10.26 (11.75)	–
L_THAL_VOL ^b	0.490 (0.04)	0.412 (0.06)	3.1 × 10^{−5}
R_THAL_VOL ^b	0.515 (0.05)	0.420 (0.07)	6.7 × 10^{−6}
L_HIP_VOL ^b	0.243 (0.06)	0.196 (0.05)	0.006
R_HIP_VOL ^b	0.262 (0.05)	0.205 (0.06)	0.001
Functional activation ^c , mean (SD)			
Encoding, correct			
L_THAL_ACT	1.62 (0.81)	1.49 (0.96)	0.645
R_THAL_ACT	0.786 (0.49)	0.575 (0.49)	0.165
L_HIP_ACT	0.031 (0.35)	−0.282 (0.45)	0.019
R_HIP_ACT	−0.182 (0.35)	−0.242 (0.29)	0.528
Recognition, correct			
L_THAL_ACT	0.124 (0.34)	0.568 (0.29)	2.4 × 10^{−5}
R_THAL_ACT	0.353 (0.55)	0.784 (0.38)	0.003
L_HIP_ACT	−0.393 (0.30)	−0.205 (0.39)	0.096
R_HIP_ACT	−0.590 (0.42)	−0.265 (0.46)	0.022
Recognition, correct rejection			
L_THAL_ACT	0.957 (0.52)	0.912 (0.45)	0.757
R_THAL_ACT	0.591 (0.38)	0.726 (0.41)	0.278
L_HIP_ACT	−0.280 (0.51)	−0.326 (0.47)	0.756
R_HIP_ACT	−0.456 (0.30)	−0.316 (0.31)	0.148

^a *p* values and post hoc values were derived from Student's *t*-tests.

^b Thalamic and hippocampal volume measures are the fraction of ROI to intracranial volume.

^c Functional activation measures are the mean *z*-score within the functional ROI. MS: multiple sclerosis; SD: standard deviation; CVLT-T: California Verbal Learning Test-Second Edition, total score; CVLT-DR: California Verbal Learning Test-Second Edition, delayed recall score; BVMT-T: Brief Visuospatial Memory Test-Revised, total score; BVMT-DR: Brief Visuospatial Memory Test-Revised, delayed recall score; L: left; THAL: thalamus; VOL: volume; R: right; HIP: hippocampus; ACT: activation.

Table 3

Relationship between demographics, volumetric, functional, and neuropsychological measures in 32 participants with MS.

	Neuropsychological measures			
	CVLT-T	CVLT-DR	BVMT-T	BVMT-DR
Demographic/clinical characteristics				
Age	0.057	0.047	−0.346	−0.369 ^a
Education	0.233	0.174	0.282	0.413 ^a
DDUR	−0.270	−0.255	−0.457^b	−0.422^a
EDSS	−0.234	−0.219	−0.383 ^a	−0.213
BDI	−0.063	0.048	−0.189	−0.273
Volumetric measures				
Total lesion volume	−0.463^b	−0.493^b	−0.492^b	−0.516^b
L_THAL_VOL	0.401 ^a	0.394 ^a	0.444^a	0.501^b
R_THAL_VOL	0.384 ^a	0.392 ^a	0.442^a	0.402^a
L_HIP_VOL	0.370	0.387 ^a	0.515^b	0.390^a
R_HIP_VOL	0.255	0.319	0.566^b	0.348
Functional activation				
Encoding, correct				
L_THAL_ACT	0.207	0.195	0.560^b	0.505^b
R_THAL_ACT	−0.034	0.003	0.289	0.308
L_HIP_ACT	−0.181	−0.145	−0.052	−0.099
R_HIP_ACT	−0.101	0.111	−0.275	−0.321
Recognition, correct				
L_THAL_ACT	−0.112	0.030	0.004	−0.160
R_THAL_ACT	−0.049	0.138	−0.180	−0.023
L_HIP_ACT	0.006	−0.022	0.099	−0.800
R_HIP_ACT	−0.171	−0.176	−0.242	−0.373 ^a
Recognition, correct rejection				
L_THAL_ACT	−0.051	0.046	−0.002	0.002
R_THAL_ACT	−0.152	−0.084	−0.100	−0.017
L_HIP_ACT	−0.130	−0.276	−0.115	−0.152
R_HIP_ACT	−0.063	−0.118	−0.143	−0.132

MS: multiple sclerosis; CVLT-T: California Verbal Learning Test-Second Edition, total score; CVLT-DR: California Verbal Learning Test-Second Edition, delayed recall score; BVMT-T: Brief Visuospatial Memory Test-Revised, total score; BVMT-DR: Brief Visuospatial Memory Test-Revised, delayed recall score; L: left; THAL: thalamus; VOL: volume; R: right; HIP: hippocampus; ACT: activation.

Partial correlation coefficients using education as a covariate are shown. Values in bold survived false discovery rate correction.

^a $p < 0.05$

^b
 $p < 0.01$

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Table 4

Regression results for the prediction of BVMT-T and BVMT-DR.

Demographics		Demographics + Volumetrics					Demographics + Volumetrics + Activation				
Model A		Model A1	Model A2	Model A3	Model A4	Model A5	Model A3.1	Model A4.1			
BVMT-T	Variable 1	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR
	Variable 2	-	L_THAL_VOL	R_THAL_VOL	L_HTP_VOL	R_HTP_VOL	LES_VOL	L_HIP_VOL	L_THAL_ACT	R_HIP_VOL	L_THAL_ACT
	Variable 3	-	-	-	-	-	-	-	-	-	-
	Model F	7.938	7.938	7.938	10.806	14.131	7.938	10.546	10.546	10.546	10.546
	Model <i>p</i>	0.008	0.008	0.008	0.003	7.4×10^{-4}	0.008	3.6×10^{-4}	3.6×10^{-4}	3.6×10^{-4}	3.6×10^{-4}
	R-square	0.209	0.209	0.209	0.265	0.320	0.209	0.421	0.421	0.421	0.421
	Adjusted r-square	0.183	0.183	0.183	0.240	0.298	0.183	0.381	0.381	0.381	0.381
Demographics		Demographics + Volumetrics					Demographics + Volumetrics + Activation				
Model B		Model B1	Model B2	Model B3	Model B4	Model B1.1					
BVMT-DR	Variable 1	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR	DDUR
	Variable 2	-	L_THAL_VOL	R_THAL_VOL	L_HIP_VOL	LES_VOL	L_THAL_VOL	L_THAL_VOL	L_THAL_VOL	L_THAL_VOL	L_THAL_VOL
	Variable 3	-	-	-	-	-	-	-	-	-	-
	Model F	6.507	10.543	6.507	6.507	6.507	6.507	7.751	7.751	7.751	7.751
	Model <i>p</i>	0.016	0.003	0.016	0.016	0.016	0.016	0.002	0.002	0.002	0.002
	R-square	0.178	0.260	0.178	0.178	0.178	0.178	0.348	0.348	0.348	0.348
	Adjusted r-square	0.151	0.235	0.151	0.151	0.151	0.151	0.303	0.303	0.303	0.303

Variables in bold significantly contributed to prediction for a given model. BVMT-T: Brief Visuospatial Memory Test-Revised, total score; BVMT-DR: Brief Visuospatial Memory Test-Revised, delayed recall score; DDUR: disease duration; L: left; THAL: thalamus; VOL: volume; R: right; HIP: hippocampus; ACT: activation; LES: lesion.