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Hippocampal Volume Is Related to Cognitive Decline and Fornicial Diffusion Measures in Multiple Sclerosis

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Abstract

Purpose—To assess for associations between hippocampal atrophy and measures of cognitive function, hippocampal magnetization transfer ratio (MTR), and diffusion measures of the fornix, the largest efferent white matter tract from the hippocampus, in patients with multiple sclerosis (MS) and controls.

Materials and Methods—A total of 53 patients with MS and 20 age- and sex-matched healthy controls participated in cognitive testing and scanning including high spatial-resolution diffusion imaging and a T1-MPRAGE scan. Hippocampal volume and fornicial thickness measures were calculated and compared to mean values of fornicial transverse diffusivity, mean diffusivity, longitudinal diffusivity, fractional anisotropy, mean hippocampal MTR, and scores on measures of episodic memory, processing speed, and working memory tasks.

Results—In patients with MS, hippocampal volume was significantly related to fornicial diffusion measures ($P < 7 \times 10^{-4}$) and to measures of verbal ($P = 0.030$) and visual spatial ($P = 0.004$) episodic memory and a measure of information processing speed ($P < 0.037$).

Discussion—These results highlight the role of the hippocampus in cognitive dysfunction in patients with MS and suggest that measures of hippocampal atrophy could be used to capture aspects of disease progression.

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Keywords

Multiple Sclerosis; hippocampus; episodic memory; DTI; atrophy; fornix

INTRODUCTION

More than 40% of patients with the demyelinating disease multiple sclerosis (MS) suffer some form of cognitive decline[1]. Traditional imaging measures, such as assessment of macroscopic lesion burden, are weakly related to cognitive changes [2], leading some researchers to focus on the role of gray matter (GM) pathology in cognitive dysfunction [3, 4]. The hippocampus has emerged as a target for much of this research [5, 6].

The hippocampus plays an important role in episodic memory, one of the most frequently affected cognitive domains in MS [1, 7, 8]. Previous research has shown that hippocampal demyelination is common in postmortem MS and that demyelinated hippocampi show decreased expression of neuronal proteins involved in a number of biological processes, including learning and memory [9]. More recently, functional magnetic resonance imaging (MRI) studies have shown decreased functional connectivity to the hippocampus in patients with MS who have intact spatial memory [10], as well as functional activation changes in the hippocampal memory network during a visual spatial episodic memory task [11]. Even more straightforward measures such as hippocampal volume have been found to correlate with measures of verbal episodic memory [5, 12].

The current study assessed whether hippocampal volume is associated with cognitive performance and with imaging measures including hippocampal magnetization transfer ratio (MTR) and high spatial-resolution diffusion measures of the fornix, the largest efferent white matter (WM) tract from the hippocampus. We test the hypothesis that hippocampal volume in MS patients would be strongly related to fornicial diffusion measures and to MTR, and that damage to the hippocampus and fornix would correlate more strongly with episodic memory than other cognitive domains.

MATERIALS AND METHODS

A total of 53 patients with MS and 20 approximately age- and sex-matched controls were scanned using a Siemens TIM Trio 3 tesla scanner (Siemens Medical Solutions, Erlangen, Germany) with a standard 12-channel receive-only head coil. A bite bar was used to limit motion during anatomical scans but was removed during DTI scans because of scanner vibration. All data were acquired after informed consent was obtained, under a protocol approved by the Cleveland Clinic Institutional Review Board.

The following scans were performed for all study participants:

1. Whole-brain T1. T1-weighted inversion recovery turboflash (MPRAGE) with the following parameters: 120 axial slices; thickness = 1.2 mm; field-of-view (FOV) = 256 × 256 mm^2; inversion time (TI)/echo time (TE)/repetition time (TR)/flip angle (FA) = 900/1.71/1900 ms/8°; matrix = 256 × 128; receiver bandwidth (BW) = 62 kHz.

2. 2. Whole-brain field map. Axial gradient-recalled echo with the following parameters: 32 axial slices; thickness = 4 mm; FOV = 256 × 256 mm^2; matrix = 64 × 64; TE1/TE2/TR/FA = 4.89/7.35/388 ms/60°; BW = 260 Hz/pixel.

3. 3. High angular resolution diffusion imaging (HARDI). Single-shot echo-planar imaging readout; FOV = 192 × 192 mm^2; matrix = 192 × 192; 45 1-mm thick slices; TE/TR = 90/7700 ms; 6/8 partial Fourier factor with GRAPPA acceleration factor = 2; readout BW = 930 Hz/pixel; 71 directions with b = 1000sec/mm^2; 8 b = 0 acquisitions, 2 averages. High spatial resolution (1 mm isotropic) was used to avoid partial volume averaging between fornix and surrounding cerebrospinal fluid (CSF).

4. Repeat whole brain field map (scan 2)

In addition, all controls and a subset of 35 patients underwent two gradient-echo scans, one with (MT^+) and one without (MT^-) an off-resonance MT saturation pulse, with the following parameters: TR/TE = 3.81/24; 1 avg/sec; x–slice thickness = 1mm; 144 slices; FOV = 256mm^2; matrix = 256 × 256, frequency offset=1250Hz.

HARDI Postprocessing

A previously described iterative algorithm was used for motion correction [13]. FSL FUGUE was used for unwarping [14], and the diffusion tensor was calculated on a voxel-wise basis using a log-linear fit [15]. The tensors were diagonalized to determine eigenvalues used in the calculations of fractional anisotropy (FA), mean diffusivity (MD), longitudinal diffusivity (LD), and transverse diffusivity (TD).

ROIs and Volumetric Analysis

Fornix regions of interest (ROIs) were drawn manually. For the DTI analysis, the fornix was drawn in individual participants using the high-resolution T1-MPRAGE in Talairach space, starting at the posterior commissure and continuing to the fimbria. The ROIs were then warped into native space and checked for accuracy. The T1-MPRAGE was coregistered to the unwarped mean b = 0 image using FSL FLIRT [16], and the resultant transformation was applied to the ROIs to isolate the fornix on the FA, MD, LD, and TD images. Because the DTI images used a slightly smaller voxel size, ROIs were manually thinned in DTI space to ensure minimal effects of partial voluming. For the fornicial volume analysis, ROIs were manually drawn using the T1-MPRAGE in original space. Left and right fornix ROIs were drawn on five adjacent coronal slices, with the third slice approximately at the joining of the left and right crura (Figure 1).

Bilateral hippocampi were identified for each participant using the T1-MPRAGE and the automated program FSL FIRST [17]. ROIs were manually checked and corrected by a trained expert (Figure 1). Whole-brain WM and GM volumes were estimated using the FSL program SIENA [18-20]. SIENA uses an affine registration to MNI152 space to obtain a volumetric scaling factor, which is then used as a correction for head size [16, 21]. For each participant, the scaling factor was applied to GM, WM, hippocampal, and fornix volumes. Volume measures are defined as the number of voxels in the tissue mask multiplied by the scaling factor.

MTR Postprocessing

The MT^- and MT^+ scans were coregistered and the following formula was applied to each voxel:

$$MTR = \left((MT^-) - \left(MT^+ \right) \right) / (MT^-) * 100$$

Where MT^- is the MR signal intensity in a given voxel for the non-MT data and MT^+ is the signal in the data with the MT pulse. To exclude hippocampal WM, a trained expert manually drew bilateral fimbria ROIs on the T1-MPRAGE. Both fimbria and hippocampal ROIs as described above were registered to the MTR data using the AFNI program align_epi_anat.py [22]. For each participant, left and right hippocampal GM MTR values were histogrammed using 5% bins, with out-of-range values (MTR <0; MTR >100) excluded. Mean and mode MTR values were then calculated for each participant.

Behavioral Data

At the time of imaging, all participants were rated on the Expanded Disability Status Scale (EDSS) [23] and completed a variety of cognitive tests. The California Verbal Learning Test-II (CVLT-II) assesses verbal episodic memory and involves the recollection and identification of a series of words [24]. The Brief Visuospatial Memory Test, Revised (BVMT-R), is a measure of visual spatial episodic memory and requires participants to recall and reproduce simple line drawings [25]. Participants also completed the 3-second version of the Paced Auditory Serial Addition Test (PASAT), a measure of working memory, calculation, and speed of processing [26], and the oral version of the Symbol Digit Modalities Test (SDMT), also a measure of speed of processing and attention [27].

RESULTS

Demographics

All participants were right-handed (Edinburgh inventory > 80) [28]. The hippocampus and fornix were identified in all participants. One 49-year-old female patient was excluded from further analysis because of bilateral hippocampal volumes that were statistical outliers. Demographic information for the remaining participants is presented in Table 1. Unpaired Student's t-tests were used to compare patient and control groups with respect to age and years of education. Control participants had significantly more education than patients did ($P = 0.031$).

Behavioral Data

Raw scores for each cognitive measure were corrected using published norms. CVLT-II and BVMT-R total recall scores were converted to t-scores using age-corrected norms [24, 25], whereas SDMT scores were corrected for both age and level of education and converted to z-scores [29, 30]. PASAT scores were corrected for level of education and converted to z-scores [31]. Unpaired Student's t-tests were used to compare cognitive performance in patients and controls. Patients scored significantly lower than controls on the CVLT-II,

BVMT-R, and SDMT ($P < 0.007$) (Table 1). Uncorrected scores for all cognitive measures are reported in Table 1.

Volumetric Analysis and Imaging Measures

Unpaired t-tests were used to compare volumetric measures in patients and controls after correcting for head size. Corrected hippocampal volume was significantly lower in patients bilaterally ($P < 0.038$), whereas corrected fornix volume was significantly lower in patients only on the left ($P < 0.001$) (Table 2). Corrected GM and WM volumes were significantly lower in patients ($P < 0.004$). No sex differences were found after head size correction.

The relationship between imaging measures and hippocampal volumes was assessed with Pearson correlation. In patients, hippocampal volume was significantly related to all fornicial DTI measures. This relationship remained significant even after using a linear partial correlation to control for fornix volume (Table 3). Controls showed no correlation between hippocampal volumes and DTI measures. Bilaterally, patients showed significantly lower FA and significantly higher MD, TD, and LD than controls ($P < 7 \times 10^{-5}$).

All controls and a subset of 34 patients (13 men; mean age, 44.23 ± 9.1 years; mean MSFC, 0.32 ± 0.59; median EDSS, 1.75 [range, 1–6.5]; median disease duration, 7.5 years [range, 1–33]; 30 with relapse-remitting disease and 4 with secondary progressive disease) completed the MT scans. Neither patients nor controls showed a significant relationship between MTR and hippocampal volume. An unpaired t-test showed that patients had a significantly lower mean and mode MTR in the left hippocampus versus controls ($P < 0.039$).

Pearson correlations were used to assess the relationship between imaging and cognitive measures. In patients, hippocampal volume was significantly correlated with SDMT performance ($P < 0.037$) and EDSS ($p < 0.037$) bilaterally and with CVLT-II and BVMT-R performance on the left ($P < 0.030$) (Table 4). Bilateral fornicial DTI measures were strongly related to the BVMT-R and SDMT ($P < 0.006$) but showed no significant relationship to CVLT-II and PASAT. Fornicial MD, TD, and LD were related to EDSS ($P < 0.020$) on the right only. Mean hippocampal MTR was significantly related to performance on the CVLT-II ($P = 0.043$) and PASAT ($p = 0.034$) on the left and to the SDMT bilaterally ($P < 0.042$). MTR was not related to EDSS. Hippocampal volume, diffusion measures, and MTR were not significantly related to age or education level.

DISCUSSION

In this study, overall hippocampal volume was 6% to 7% smaller in patients than in controls. Measures of WM integrity in the fornix were strongly related to hippocampal volume in patients but not in controls. Measures of episodic memory were also related to hippocampal volume in patients, but only on the left, although a measure of attention and speed of processing was related to bilateral hippocampal volumes. These findings point to involvement of the hippocampus in cognitive decline in MS.

The finding of a relationship between hippocampal volume and fornicial DTI measures suggests that DTI measures of the fornix may be an indicator of hippocampal injury. The direction of this relationship is unclear, however; it is possible that injury of the fornicial WM results in subsequent damage to the hippocampus. In studies of anterior temporal lobectomy patients, long-term changes in fornicial DTI values were consistent with myelin degradation [32, 33], although acute measures were more variable [34]. Studies of hippocampal volume and fornicial integrity in patients with mild cognitive impairment have confirmed that hippocampal volume loss is related to reduced integrity of the fornix [35, 36], although fornicial abnormalities with no concurrent hippocampal atrophy have been found in patients with early mild cognitive impairment [37].

The current work did not demonstrate a relationship between MTR and hippocampal volume, although MTR was lower in the left hippocampus in patients with MS. Recent work has found that MTR is sensitive to cortical demyelination in patients with MS [38], and changes have been found in GM MTR and in the fornix specifically [39-41]. We did find modest positive correlations between MTR and performance on cognitive tasks, consistent with other studies that found associations between MTR and overall cognitive impairment [41-43].

We found clear relationships between cognition and both hippocampal volume and fornicial DTI measures in MS. Measures of verbal and visual spatial episodic memory were related to hippocampal volume only on the left, in contrast to results from a previous study that demonstrated a significant relationship between verbal episodic memory and hippocampal volume bilaterally [5], though Sicotte et. al found a much weaker correlation between verbal episodic memory and hippocampal volume on the right. The composition of the current sample may prevent us from detecting this relationship, as we have a more restricted EDSS and disease duration range. In our study, bilateral fornicial DTI measures were related to visual spatial memory but not verbal memory. This is in contrast to a previous study that demonstrated an association between verbal memory performance and FA in the fornix [44]. While we believe that the high spatial resolution in the current study leads to more accurate diffusion measurements, it is worth noting that both of the above studies used a similar test of verbal episodic memory, in contrast to our use of the CVLT-II.

We found a strong relationship between all imaging measures and performance on the SDMT, a measure of information processing speed and the task that showed the greatest difference between patients and controls in this sample. Although it is possible that the SDMT involves some element of working memory, SDMT performance is not thought to involve the hippocampal memory circuit [45]. This task is very sensitive to cognitive deterioration in MS [46], and the correlation with hippocampal volume suggests that hippocampal atrophy may be related to overall cognitive decline rather than a specific deficit in episodic memory.

A recent study showed a moderate relationship between fornicial MTR and diffusion imaging measures and performance on the PASAT [41]. While our fornicial diffusion measures showed no relationship to the PASAT, we did find a relationship between hippocampal MTR and PASAT performance on the left. Both studies found a relationship

between EDSS and fornicial diffusion measures, though in our case this measure was significant on the right only. It is possible that an increased number of participants and inclusion of patients with a higher EDSS and longer disease duration in the Syc et al. study resulted in a stronger relationship with imaging measures, though it does not appear that the samples differed substantially on PASAT performance.

The results of the current study draw a clear contrast between diffusion measures and MTR. Bilateral fornicial diffusion measures showed highly significant between-group differences and were related to hippocampal volume. Conversely, hippocampal MTR was not related to hippocampal volume, and showed group differences only on the left. A possible cause of these differences is the nature of pathology captured by DTI and MTR. Post-mortem studies confirm that lower MTR is sensitive to severe degrees of demyelination, but not intermediate levels [38]. DTI may be more sensitive to earlier and more subtle degeneration of nerve fibers [47]. As mentioned above, our low disease burden and small sample size may result in MTR changes that are insufficient for disease detection.

The SDMT has been shown to be one of the most sensitive measures for detecting cognitive decline in MS [46, 48]. Not surprisingly, the SDMT showed a bilateral and relatively strong relationship with MTR and DTI. The BVMT-R demonstrated strong, bilateral correlations with DTI, but not with MTR. In contrast, the PASAT and CVLT-II did not correlate with most MTR and DTI measures, the exception being their correlations with the left MTR. Further studies with a larger sample and a wider range of disease burden will be needed to determine if these differences in clinical-MRI correlations are meaningful with regard to specific cognitive processes or simply represent different degrees of sensitivity of the cognitive and MR measures.

This study had a number of limitations. The patient sample had relatively low disease burden; we expect that the addition of patients with a greater degree of cognitive impairment would reveal a relationship between hippocampal volume and MTR and greater differences between patients and controls in MTR measures. Additionally, because of the resolution of our anatomical scan, we were unable to reliably segment the hippocampus and measure regional volume loss.

We found that hippocampal volume is strongly related to fornicial diffusion measures but not to MTR. Hippocampal volume and MTR were correlated with episodic memory on the left only, whereas fornicial diffusion measures were strongly related to visual spatial episodic memory bilaterally. Most strikingly, all imaging measures showed a degree of correlation with performance on a speed of processing task. These results suggest that measurements of hippocampal atrophy can capture aspects of disease progression and that SDMT performance may be one of the more informative cognitive measures in MS.

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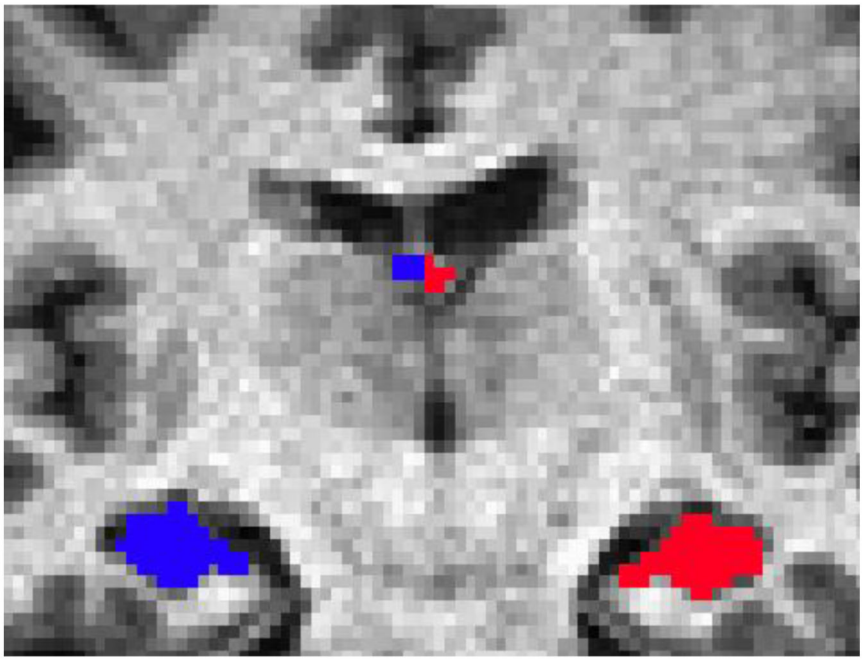

Figure 1.
Representative example of hippocampal and fornicial ROIs.

Table 1

Demographic characteristics

	Patients with MS (n = 52)	Controls (n = 20)	*P*
Men, n	16	7	–
Mean age, years (SD)	44.27 (8.9)	41.35 (9.7)	0.230
Mean education, years (SD)	15.09 (2.5)	16.65 (3.1)	0.032
Mean MSFC (SD)	0.31 (0.54)	0.74 (0.24)	0.001
Median EDSS (range)	1.5 (1–6.5)	–	–
Median disease duration (range)	8(1–33)	–	–
Disease phenotype	45 relapse remitting; 7 secondary progressive	–	–
Mean raw cognitive task scores (SD)			
SDMT	54.4 (11.8)	65.5 (13.5)	5×10^{-4}
PASAT	48.7 (9.9)	53.9 (6.0)	0.076
CVLT-II	49.5 (10.4)	58.3 (10.5)	0.002
BVMT-R	24.6 (5.9)	29.2 (3.9)	0.007

SDMT = Symbol Digit Modalities Test, PASAT = Paced Auditory Serial Addition Test, CVLT-II = California Verbal Learning Test-II, BVMT-R = Brief Visuospatial Memory Test-Revised

Table 2

Volumetric results

	Patients with MS (n = 52)	Controls (n = 20)	*P*
Volume measures, in voxels: mean (standard deviation)			
Right hippocampus, corrected	4192 (574)	4501 (527)	0.038
Left hippocampus, corrected	4040 (463)	4296 (431)	0.036
Right fornix, corrected	16.5 (6.9)	19.9 (6.0)	0.053
Left fornix, corrected	16.2 (6.4)	22.2 (7.2)	0.001
White matter, corrected	664,464 (48,658)	702,676 (48,117)	0.004
Gray matter, corrected	765,240 (39,773)	805,979 (37,916)	2×10^{-4}

Table 3
Correlation of hippocampal volume with fornicial DTI measures in patients with MS

			Corrected for fornix volume	
Right hippocampal volume	r	*P*	r	*P*
Fractional anisotropy	0.485	2×10^{-4}	0.462	6×10^{-4}
Mean diffusivity	−0.482	2×10^{-4}	−0.448	9×10^{-4}
Transverse diffusivity	−0.519	8×10^{-5}	−0.488	2×10^{-4}
Longitudinal diffusivity	−0.373	6×10^{-3}	−0.328	0.019
Left hippocampal volume				
Fractional anisotropy	0.538	3×10^{-5}	0.509	1×10^{-4}
Mean diffusivity	−0.522	7×10^{-5}	−330.492	2×10^{-4}
Transverse diffusivity	−0.555	1×10^{-5}	−0.529	6×10^{-5}
Longitudinal diffusivity	−0.425	1×10^{-3}	−0.383	5×10^{-3}

Table 4

Pearson's r for the correlation of cognitive measures with hippocampal volume, fornicial DTI measures, and MTR in patients with MS

	CVLT-II	BVMT-R	SDMT	PASAT	EDSS
Right					
Fractional anisotropy	0.132	0.431**	0.280*	0.164	−0.185
Mean diffusivity	−0.204	−0.439**	−0.295*	−0.181	0.334*
Transverse diffusivity	−0.206	−0.459***	−0.309*	−0.188	0.322*
Longitudinal diffusivity	−0.187	−0.370**	−0.246	−0.156	0.343*
Volume	0.123	0.249	0.290*	0.110	−0.289*
Mean MTR (n = 34)	0.161	0.158	0.350*	0.293	−0.196
Left					
Fractional anisotropy	0.166	0.484***	0.436**	0.235	−0.143
Mean diffusivity	−0.232	−0.531****	−0.469***	−0.245	0.223
Transverse diffusivity	−0.234	−0.533***	−0.478***	−0.243	0.215
Longitudinal diffusivity	−0.220	−0.504***	−0.429**	−0.237	0.231
Volume	0.301*	0.393**	0.456***	0.077	−0.289*
Mean MTR (n = 34)	0.349*	0.304	0.436**	0.365*	0.004

CVLT = California Verbal Learning Test-II, BVMT-R = Brief Visuospatial Memory Test-Revised, SDMT = Symbol Digit Modalities Test, PASAT = Paced Auditory Serial Addition Test

* $P < 0.05$,

** $P < 0.01$,

*** $P < 0.001$,

**** $P < 0.0001$