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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.

1. 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.

2. 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 T scanner (Siemens Medical Solutions, Erlangen, Germany) with a

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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. 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. 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 = 1000 s/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/s; x-slice thickness = 1 mm; 144 slices; FOV = 256 mm^2; matrix = 256 × 256, frequency offset = 1250Hz.

2.1. 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).

2.2. 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 (Fig. 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 (Fig. 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.

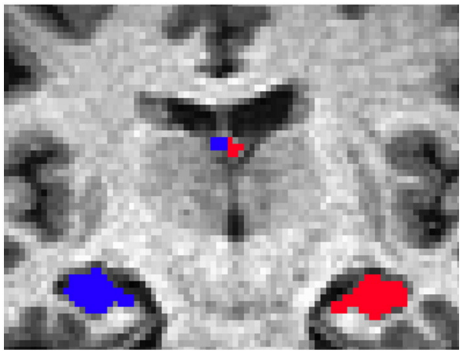

Fig. 1. Representative example of hippocampal and fornicial ROIs.

2.3. 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.

2.4. 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-s 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].

3. Results

3.1. 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