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High spatial and angular resolution diffusion-weighted imaging reveals forniceal damage related to memory impairment^{*}

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Abstract

Introduction—Diffusion tensor imaging (DTI) measures in patients with multiple sclerosis (MS), particularly those measures associated with a specific white matter pathway, have consistently shown correlations with function. This study sought to investigate correlations between DTI measures in the fornix and common cognitive deficits in MS patients, including episodic memory, working memory and attention.

Materials and Methods—Patients with MS and group age- and sex-matched controls underwent high-resolution diffusion scanning (1-mm isotropic voxels) and cognitive testing. Manually drawn forniceal regions of interest were applied to individual maps of tensor-derived measures, and mean values of transverse diffusivity (TD), mean diffusivity (MD), longitudinal diffusivity (LD) and fractional anisotropy (FA) were calculated.

Results—In 40 patients with MS [mean age±S.D.=42.55±9.1 years; Expanded Disability Status Scale (EDSS)=2.0±1.2; Multiple Sclerosis Functional Composite (MSFC) score=0.38±0.46] and 20 healthy controls (mean age±S.D.=41.35±9.7 years; EDSS=0.0±0; MSFC score=0.74±0.24), we found that FA, MD and TD values in the fornix were significantly different between groups ($P<.03$), and patient performance on the Brief Visuospatial Memory Test-Revised (BVM-T-R) was correlated with DTI measures ($P<.03$).

Discussion—These results are consistent with findings of axonal degeneration in MS and support the use of DTI as an indicator of disease progression.

Keywords

Multiple sclerosis; Fornix; Diffusion tensor imaging; High spatial resolution; BVM-T-R

1. Introduction

Loss of cognitive abilities is a common symptom in patients with multiple sclerosis (MS), occurring in more than 40% of patients [1]. These deficits are likely caused by a

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combination of ongoing inflammatory and neurodegenerative processes [2-7]. Although the specific deficits vary from patient to patient, episodic memory and visual processing speed are among the most commonly affected abilities [2,8]. Such memory impairments can affect the patient's ability to work and perform daily living skills [9]. However, there is currently no reliable imaging marker for cognitive deficit in MS; macroscopic lesion burden demonstrates only a modest correlation with cognitive abilities, perhaps because of the inclusion of lesions located outside of memory pathways or lesions in gray matter, which are not seen in routine MRI [10-12].

Episodic memory is particularly vulnerable among patients with MS [13]. Loss of episodic memory suggests injury of the hippocampus, which plays a central role in the consolidation of short-term memories into long-term memories [14]. Noninvasive imaging measures of hippocampal myelin integrity can therefore serve as candidate biomarkers for cognitive dysfunction in MS. Although previous research has found that diffusion tensor imaging (DTI) is an excellent measure of white matter damage [15,16], there are technical issues associated with applying this technique in the hippocampus. Specifically, the thin, interleaved layers of gray and white matter in the hippocampus lead to partial volume averaging of gray and white matter tissue within a given voxel, making it difficult to determine whether changes in DTI arise from changes in gray matter, white matter or both. Additionally, magnetic susceptibility produced by aerated temporal bones can potentially affect DTI measures in the hippocampus.

DTI of the fornix, the largest efferent pathway from the hippocampus, may serve as an indirect probe of the structural integrity of the hippocampus itself, thus overcoming the limitations involved in DTI of the hippocampus. The fornix projects from the posterior hippocampus to the septal area and hypothalamus [17]. Unlike the hippocampal white matter, the fornix can be readily differentiated from surrounding structures and contains axonal bundles of uniform orientation, making it amenable to analysis by DTI. White matter damage in the hippocampus may lead to injury to the fornix via Wallerian degeneration [18], and direct injury to the fornix may lead to deficits in episodic memory similar to those resulting from lesions in the hippocampus [19].

Although the fornix is an excellent candidate for assessment of potential hippocampal injury in terms of the uniformity and consistency of white matter tracts, its relatively small size makes it difficult to assess using the spatial resolution typical of most DTI studies [20]. In the present study, we address this through the use of high spatial resolution DTI imaging with 1-mm isotropic voxels to eliminate partial volume averaging. We assessed DTI measures and cognitive performance in patients with MS and controls, and hypothesized that DTI measures in patients with MS would show an increase in transverse diffusivity (TD, also known as radial diffusivity) and longitudinal diffusivity (LD, also known as axial diffusivity) in the crus of the fornix as compared to these measures in controls and that DTI measures would correlate with measures of memory, specifically performance on the California Verbal Learning Test (CVLT) and Brief Visuospatial Memory Test-Revised (BVM-T-R).

2. Materials and methods

All data were acquired under a protocol approved by the Cleveland Clinic Institutional Review Board. Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) scores were determined in 40 patients with MS and 20 group age- and gender-matched controls. All imaging was performed on a Siemens TIM Trio 3 Tesla scanner (Siemens Medical Solutions, Erlangen, Germany) with a standard 12-channel head

coil. Head motion was limited during the anatomical scans by a bite bar, but scanner vibrations necessitated removal of the bite bar for the DTI scans.

The following scans were performed in all study participants:

- Scan 1, whole brain T1-weighted inversion recovery turboflash (MPRAGE) with the following parameters: 120 axial slices; thickness=1.2 mm; field of view (FOV)=256×256 mm²; 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.
- Scan 2, SPACE 3D T2 with the following parameters: 144 sagittal slices; thickness=1.2 mm; FOV=256×224 mm²; matrix= 256×224; 6/8 partial Fourier acquisition; TE/TR=528/3200 ms; FA mode; GRAPPA factor=2; 24 reference lines; BW=434 Hz/pixel.
- Scan 3, SPACE 3D FLAIR with the following parameters: 144 sagittal slices; thickness=1.2 mm; FOV=256×224 mm²; matrix=256×224; 6/8 partial Fourier acquisition; TI/TE/TR=2000/395/6500 ms; GRAPPA factor=2; 24 reference lines; BW=698 Hz/pixel.
- Scan 4, whole brain field map. Axial gradient recalled echo with the following parameters: 32 axial slices; thickness=4 mm; FOV=256×256 mm²; matrix=64×64; TE1/TE2/TR/FA=4.89/7.35/388 ms/60°; BW=260 Hz/pixel.
- Scan 5, high angular resolution diffusion imaging (HARDI). Images were acquired at high spatial resolution with the following parameters: single-shot echo-planar imaging readout; FOV= 192×192 mm²; matrix=192×192; forty-five 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; 2 averages; 8 $b=0$ acquisitions per average.

The HARDI acquisition was designed to achieve high spatial resolution of 1-mm isotropic voxels with sufficient signal-to-noise ratio (SNR) to allow the resulting diffusion profiles to provide an accurate fit to the tensor model. SNR is approximately 6 in the regions of interest (ROIs). SNR was calculated by taking the ratio, on a voxel-by-voxel basis, of the mean and standard deviation across the 16 $b=0$ acquisitions. The maximum b value (750 s/mm²) was chosen to avoid the effects of Rician noise bias associated with the low SNR. For example, assuming a large diffusivity, for tissue, of $D=1.4 \times 10^{-3}$ mm²/s, the expected SNR of diffusion-weighted measurements would be expected to have a value of $\exp(-bD) \sim 2$. As shown by Gudbjartsson and Patz [21], Rician noise bias is difficult to detect for SNR of 2 or greater. Several aspects of the imaging techniques were designed to minimize TE and associated T2-related loss of signal; a so-called split-gradient scheme [22] limited the duration of the diffusion-weighting gradients, and partial Fourier reconstruction and GRAPPA limited the length of the readout gradients.

2.1. HARDI postprocessing

Motion correction was performed with an iterative algorithm [23]. At each voxel, the diffusion tensor was calculated using a standard log-linear fit [24], followed by unwarping of each image by a field map for image coregistration (gradient echo; FOV=256×256 mm²; matrix=64×64; thirty-two 4-mm-thick axial slices; TE1/TE2/TR=4.89/7.35/388 ms; BW=260 Hz/pixel) and FSL FUGUE [25]. A standard log-linear fit was then used to calculate the tensor at each voxel [24]. The tensors were then diagonalized to calculate eigenvalues that were subsequently used to calculate fractional anisotropy (FA), mean diffusivity (MD), LD and TD.

2.2. ROIs and group comparison

Fornix ROIs were drawn manually, using the high-resolution T1-weighted scan in Talairach space (Fig. 1). ROIs started at the posterior commissure and continued to the beginning of the fimbria. The T1-weighted image was coregistered to the unwarped mean $b=0$ image using FSL FLIRT [26], and the resultant transform was applied to the ROIs to isolate the fornix on the FA, MD, LD and TD images. Mean and S.D. values for FA, MD, LD and TD among voxels in the coregistered ROIs were then compared for patient and control groups using unpaired Student's t tests. In patients, measures of episodic memory (BVM-T-R and CVLT) were compared to diffusion values using a Pearson correlation.

2.3. Behavioral data

All participants completed a neuropsychological assessment and underwent several measures of cognitive function (Table 1), including the CVLT, the BVM-T-R, the Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modalities Test (SDMT). The CVLT is a standard test of verbal episodic memory, measuring both recall and recognition memory through the recollection and identification of a series of words [27]. The BVM-T-R is a test of visuospatial memory in which subjects must recall and reproduce six unique designs and their location on a page [28]. Both tests are commonly used in patients with MS and are part of the Minimal Assessment of Cognitive Functioning in MS (MACFIMS) battery [29]. The PASAT, which assesses working memory, calculation and speed of processing, is a component of the Multiple Sclerosis Functional Composite (MSFC) [30]. The SDMT also measures speed of processing and is commonly used in MS [31].

3. Results

A total of 40 patients with MS (38 relapse–remitting, 2 secondary progressive) and 20 healthy controls were scanned under the imaging protocol described above (Table 1). All participants were right handed (Edinburgh inventory >80) [32]. The fornix was identified in all participants (Fig. 1). The extent of the images in the inferior–superior direction was limited to allow for a tolerable scan time while ensuring coverage of the entire fornix.

In the bilateral fornices, MD and TD were significantly higher, while FA was significantly lower among patients compared with controls (Table 2). Table 1 shows the results of cognitive measures for both groups. No participants were considered outliers on these measures. Patients with MS scored significantly lower than controls on all tasks ($P<.05$), and patient scores on the BVM-T-R were significantly correlated with bilateral fornix TD and MD and with left fornix FA and LD (Table 3; Fig. 2).

4. Discussion

In this study, we found clear differences in diffusion measures between controls and patients with MS, which may reflect damage to the hippocampus or direct demyelination of the fornix. We also found that DTI measures were significantly correlated with the BVM-T-R, a test of episodic memory. These findings suggest that forniceal DTI measures may be a potential indicator of hippocampal and/or forniceal injury and subsequent memory deficit.

The DTI measures FA and MD have been used in previous studies of the fornix in healthy controls [33] and in patients with Alzheimer's disease (AD) or mild cognitive impairment (MCI) [19,34]. Animal studies have found that LD and TD may provide some additional specificity in understanding underlying histopathologic changes in white matter during neurodegenerative processes. Although many such changes may be occurring simultaneously, some studies have suggested that LD changes are associated with axonal loss, whereas TD changes are associated with demyelination [15,16]. Although these are

useful factors when discussing directional diffusivity in the context of MS, it should be noted that these are oversimplified characterizations of a complex biophysical process; for instance, Wallerian degeneration, which is not a clearly demyelinating process, also produces increased TD.

The present study differs from previous evaluations of DTI in the fornix in that this study used high spatial resolution DTI. DTI generally uses voxel sizes of at least 2 mm [20,35-37]. Given the size of the fornix (1.5–2 mm in diameter) [38], use of a 2-mm voxel size virtually guarantees partial volume averaging [20]. This would be exacerbated in the case of forniceal atrophy, as might be expected in MS disease progression. In our study, ultrahigh-resolution DTI with 1-mm isotropic voxels was used to eliminate partial volume averaging. A Student's *t* test of forniceal volume showed no significant difference between patients and controls.

The fornix has been implicated in a range of cognitive abilities. Animal studies of fornix transection have shown deficits in spatial cognition, particularly in the rapid acquisition of spatial relationships [39,40]. DTI measures in the fornix can also discriminate between healthy controls and patients with AD and MCI [34,41]. Mielke et al. [34] found that FA in the body of the fornix correlated with a wide range of cognitive measures in patients with AD and MCI, including performance on the CVLT and Clinical Dementia Rating (CDR). Sexton et al. [19] used tract-based spatial statistics to measure FA and MD in the body and crus of the fornix in patients with AD, those with MCI and healthy controls, and found that verbal and visuospatial episodic memory was associated with FA in the left crus of the fornix and with MD in the bilateral crura. Episodic memory was also found to correlate with fornix FA in healthy controls [33], and a recent study found that fornix FA was positively associated with verbal memory performance [36]. Fink et al. [42] found a significant correlation between TD in the fornix and performance on the CVLT in patients with MS. Interestingly, in this study, an increase in TD was associated with better performance on a recognition task.

Because of the relatively low level of cognitive dysfunction in our study, further research is needed to determine whether DTI could be useful as a predictor of cognitive decline. Additionally, it is unclear why diffusion tensor properties were not correlated with CVLT in our study. CVLT tests verbal episodic memory, whereas BVMT-R tests visuospatial memory; as the hippocampus plays a role in spatial navigation, the BVMT-R may be more relevant.

This study had several limitations. Although patients with MS scored lower on cognitive measures than control participants did, the sample still represents a relatively high-functioning subset of patients with MS. Additionally, at this spatial resolution, the time required to scan the entire brain is prohibitive. This led to limited brain coverage for this study.

This study examined the potential of using high spatial resolution diffusion imaging of the fornix as a biomarker for cognitive impairment. The results suggest that demyelination of the fornix is related to episodic memory in MS and that diffusion measures are sensitive to these changes. Importantly, the present study demonstrates the necessity of properly accounting for partial volume averaging. In this contribution, we have directly addressed the problem by matching spatial resolution to the structure of interest. In addition, our results suggest that the post hoc correction of Metzler-Baddeley et al. [20] is a viable alternative to our approach for the fornix. Although further work is required to deliver ultrahigh-resolution imaging in clinically relevant time frames, these results suggest that it may be possible to

detect cognitive impairment early with this method, thus allowing for the initiation of therapy that aims to spare cognition and improve quality of life.

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Fig. 1.
Color FA map with fornix regions of interest in red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 2. Correlation between left fornix transverse diffusivity and Brief Visuospatial Memory Test-Revised (BVMT-R) performance.

Table 1

Demographics and cognitive task results for patients with MS and controls.

	MS (n=40)	Control (n=20)
Demographics		
Males	11	7
Age	42.55±9.1	41.35±9.7
EDSS	2.0±1.2	0.0±0
MSFC	0.38±0.46	0.74±0.24
Disease duration	9.05±7.1	–
Cognitive tasks ^a		
SDMT	56.8±10.3	65.5±9.8
PASAT	48.6±10.0	53.9±6.0
CVLT	51.2±10.2	57.3±10.8
BVMT-R	25.9±4.9	29.2±3.9

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

^aPatients with MS scored significantly lower on all tasks ($P<.05$).

Table 2

Mean diffusion tensor imaging measures of the fornix in patients with MS and controls.

	TD (mm ² /s)	LD (mm ² /s)	MD (mm ² /s)	FA
Fornix, left				
MS	923.36±275.75 ^a	1474.03±250.61	1106.92±263.51 ^a	331.83±87.98 ^b
Control	627.12±115.19	1266.30±105.02	840.18±101.42	446.98±71.28
Fornix, right				
MS	1007.28±258.58 ^b	1532.21±238.76	1182.26±244.55 ^b	305.03±85.21 ^b
Control	677.87±170.12	1298.23±158.41	884.66±158.10	430.33±89.21

FA=Fractional anisotropy; LD=longitudinal diffusivity; MD=mean diffusivity; TD= transverse diffusivity.

^a Measures were significantly different in patients with MS ($P<.03$).

^b Measures were significantly different in patients with MS ($P<.003$).

Table 3

Pearson correlation between cognitive scores in patients with MS and DTI values in the fornix.

	TD (mm ² /s)	LD (mm ² /s)	MD (mm ² /s)	FA
BVMt-R				
Fornix, left	$r = -0.3800^a$	-0.4000^a	-0.3923^a	0.3355^b
Fornix, right	-0.3520^b	-0.2803	-0.3392^b	0.3065
CVLT				
Fornix, left	-0.0438	-0.0189	-0.0365	0.0408
Fornix, right	0.0544	0.0825	0.0652	-0.0297
SDMT				
Fornix, left	-0.3056	-0.2835	-0.3032	0.2925
Fornix, right	-0.1183	-0.0519	-0.1002	0.1477
PASAT				
Fornix, left	-0.1669	-0.1474	-0.1633	0.2080
Fornix, right	-0.0715	0.0030	-0.0494	0.1665

^aMeasures were significantly correlated ($P < .01$).

^bMeasures were significantly correlated ($P < .03$).