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Multiple white matter tract abnormalities underlie cognitive impairment in RRMS

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ABSTRACT

Diffusion tensor imaging (DTI) is a sensitive tool for detecting microstructural tissue damage *in vivo*. In this study, we investigated DTI abnormalities in individuals with relapsing remitting multiple sclerosis (RRMS) and examined the relations between imaging-based measures of white matter injury and cognitive impairment. DTI-derived metrics using tract-based spatial statistics (TBSS) were compared between 37 individuals with RRMS and 20 healthy controls. Cognitive impairment was assessed with three standard tests: the Symbol Digit Modalities Test (SDMT), which measures cognitive processing speed and visual working memory, the Rey Auditory Verbal Learning Test (RAVLT), which examines verbal memory, and the Paced Auditory Serial Addition Test (PASAT), which assesses sustained attention and working memory. Correlations between DTI-metrics and cognition were explored in regions demonstrating significant differences between the RRMS patients and the control group. Lower fractional anisotropy (FA) was found in RRMS participants compared to controls across the tract skeleton (0.40 ± 0.03 *vs.* 0.43 ± 0.01, $p < 0.01$). In areas of reduced FA, mean diffusivity was increased and was dominated by increased radial diffusivity with no significant change in axial diffusivity, an indication of the role of damage to CNS myelin in MS pathology. In the RRMS group, voxelwise correlations were found between FA reduction and cognitive impairment in cognitively-relevant tracts, predominantly in the posterior thalamic radiation, the sagittal stratum, and the corpus callosum; the strongest correlations were with SDMT measures, with contributions to these associations from both lesion and normal-appearing white matter. Moreover, results using threshold-free cluster enhancement (TFCE) showed more widespread white matter involvement compared to cluster-based thresholding. These findings indicate the important role for DTI in delineating mechanisms underlying MS-associated cognitive impairment and suggest that DTI could play a critical role in monitoring the clinical and cognitive effects of the disease.

Introduction

Multiple sclerosis (MS) is the most common acquired inflammatory demyelinating disorder of the central nervous system (CNS), predominantly affecting young and middle-aged adults (Keegan and Noseworthy, 2002). It is associated with axonal damage and characterized by neurological and cognitive impairments (Keegan and Noseworthy, 2002). Given its prevalence and progressive disability, a major effort over the past decade has been devoted to noninvasively measuring subtle changes in white matter (WM) fiber structure in order to understand disease progression and potentially predict clinical outcome. One of the imaging modalities that can be

Abbreviations: AD, Axial Diffusivity; BPF, Brain Parenchymal Fraction; CNS, Central Nervous System; CVLT, California Verbal Learning Test; DTI, Diffusion Tensor Imaging; EDSS, Expanded Disability Status Scale; EPI, Echo Planar Imaging; FA, Fractional Anisotropy; FLAIR, Fluid Attenuated Inversion Recovery; MRI, Magnetic Resonance Imaging; MD, Mean Diffusivity; NAWM, Normal-Appearing White Matter; RAVLT, Rey Auditory Verbal Learning Test; PASAT, Paced Auditory Serial Addition Test; RRMS, Relapsing Remitting Multiple Sclerosis; RD, Radial Diffusivity; SDMT, Symbol Digit Modalities Test; SRT, Selective Reminding Test; SPGR, Spoiled Gradient Recalled; TBSS, Tract-Based Spatial Statistics; MS, Multiple Sclerosis; TFCE, Threshold Free Cluster Enhancement; WM, White Matter.

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used to achieve this goal is diffusion tensor imaging (DTI). DTI is a magnetic resonance imaging (MRI) technique that enables the measurement of restricted diffusion of water in tissue (Dong et al., 2004), a unique property of tissue water within myelinated WM axons, and can provide quantitative metrics related to WM fiber structural integrity. This technique has been applied increasingly in MS research over the last few years (Ge et al., 2005; Goldberg-Zimring et al., 2005; Rovaris and Filippi, 2007), and has helped better delineate the mechanisms underlying tissue injury thought to be responsible for neurological dysfunction.

Cognitive impairment is a major disabling feature of MS, affecting approximately 50% or more of individuals (Chiaravalloti and DeLuca, 2008; Patti et al., 2009). The impairment is characterized primarily by memory impairment, attention deficits, slowed information processing and deficits in executive function (Chiaravalloti and DeLuca, 2008; Winkelmann et al., 2007). Exploration of the damage to WM pathways associated with cognitive impairments has been a focus of MS studies (Benedict et al., 2007; Chiaravalloti and DeLuca, 2008; Kern et al., 2010; Lin et al., 2008). Among the various neuroimaging methodologies available, DTI might be a method of choice for examining the association between cognition and tissue pathology because of its potential to examine tissue injury-related changes in normal appearing white matter (NAWM) and to quantify pathway-specific disease activity (Filippi et al., 2000; Guo et al., 2002; Miller et al., 2003), in contrast to past studies focused primarily on lesion burden or atrophy.

This study utilized a recently developed DTI analysis method, tract-based spatial statistics (TBSS), which has improved sensitivity to identify areas of disrupted WM tract integrity in RRMS. TBSS is a non-hypothesis driven technique that enables DTI data analysis in a voxelwise fashion (Smith et al., 2006), minimizing multi-subject registration errors by carrying out the analysis in a common skeleton of major WM structures. TBSS has been applied to a few MS DTI studies; however, prior studies utilized cluster-based thresholding for identifying regions with significant cognitive associations (Dineen et al., 2009; Roosendaal et al., 2009). In contrast, this study used a new, threshold-free technique (TFCE) which does not require an (arbitrarily chosen) cluster size threshold or spatial smoothing of the data. We examined DTI abnormalities and their associations with cognitive impairment in individuals with RRMS compared to healthy controls using the TBSS-TFCE approach.

Methods

Subjects and clinical assessments

Thirty-seven individuals with RRMS and 20 healthy controls participated in this study. The MS participants were a convenience sample who all underwent neurological assessment using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) at the time of participation. All 37 MS subjects and 15 of the healthy controls underwent cognitive assessments exploring commonly affected cognitive domains in MS as assessed with the Symbol Digit Modalities Test (SDMT), a measure of cognitive processing speed and visual working memory (Rao and Society, 1990; Smith, 1982), the Rey Auditory Verbal Learning Test (RAVLT), a measure of short term auditory-verbal learning and memory (Strauss et al., 2006), and the three-second version of the Paced Auditory Serial Attention Test (PASAT), a timed task that assesses sustained attention and verbal working memory (Gronwall, 1977; Rao and Society, 1990). All three tests are reliable and sensitive measures of cognitive function in MS (Zakzanis, 2000). Due to logistic issues, 9 of the 37 RRMS participants received the Selective Reminding Test (SRT) (Buschke and Fuld, 1974; Rao and Society, 1990; Scherl et al., 2004) rather than the RAVLT as a measure of verbal memory; since both tasks assess the same domain (Strauss et al., 2006), the SRT scores were used to estimate RAVLT scores via a Z score transformation using scores from a separate MS sample who received both tasks (Krupp et al., 2011). Due to significant differences between the age of patients and healthy controls ($p<0.05$), age was treated as a covariate in all analyses. The study was approved by the Stony Brook University Institutional Review Board and written informed consent was obtained from all participants.

MR data acquisition

All scans were conducted on a 3T Phillips Achieva MR Scanner (Philips Medical Systems, Best, The Netherlands) with an 8-channel SENSE head coil. DTI scans were collected using an echo planar imaging (EPI) spin echo sequence with a SENSE factor of 2.4 (TE/TR = 62/5400 ms, $2\times2\times3$ mm resolution), a b factor of 800 s/mm^2 and 15 encoding directions. A 3D T1-weighted, inversion-recovery-prepared spoiled gradient recalled (SPGR) image (TE/TR/TI = 4.6/8.0/400 ms, flip angle 18°, 1 mm isotropic resolution) was used for tissue segmentation and volumetrics, and T2-weighted fluid-attenuation inversion recovery (FLAIR) images (fast spin echo, TE/TR/TI = 125/7600/2320 ms, 15 ETL, $1\times1\times3$ mm resolution) were used for lesion quantification.

MR data analysis

Volumetric analysis was performed in SPM 8.0 (available at http://www.fil.ion.ucl.ac.uk/spm) on white matter, gray matter (GM) and cerebrospinal fluid (CSF) tissue maps, segmented from SPGR images using the standard SPM segmentation protocol (Ashburner and Friston, 2005). Whole brain parenchymal fraction (BPF) was calculated by normalization of total gray and white matter volumes to total intracranial volume.

An in-house developed algorithm was implemented under Matlab R2007b (The Mathworks, Natick, MA) for lesion segmentation and quantification. The algorithm used both T1-weighted SPGR and the co-registered T2-weighted FLAIR images to segment out the hyperintense lesions. First, the skull-stripped FLAIR images were enhanced by an image median filter for noise reduction, and an erosion/dilation process for shape/border enhancement. FLAIR images were then thresholded at two standard deviations above mean intensity of GM on FLAIR (*i.e.*, voxels defined as GM by SPM segmentation). The initial lesion masks were "cleaned" by filling holes and removing spurious voxels. Since hyperintensities on FLAIR can also come from bone and flow artifacts, the lesion masks were then further refined by morphological criteria including eccentricity and area (>6 mm in one dimension). The final lesion masks were overlaid on FLAIR images and visually inspected; the algorithm parameters could be manually adjusted if needed. Lesion maps were superimposed on SPGR white matter maps to manually correct for occasional misidentification of hypointense white matter lesions as gray matter. Lesion load was finally calculated as the sum of all mask voxels (for region-specific lesion load, the sum was calculated within a given region, as defined by the JHU-ICBM-DTI-81 WM atlas (Mori et al., 2008)). Mean lesion probability maps were created by first registering the SPGR images to MNI 152 space (Mazziotta et al., 2001), and then applying the transformation matrix to each of the co-registered binarized lesion masks. Lesion maps were then averaged to create a single lesion probability map. The threshold for lesions in overlay figures was set at 30%, identifying those voxels demonstrating lesions in at least 30% of patients.

All DTI images were processed following the TBSS pipeline, part of FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl). Briefly, images were preprocessed to correct for motion and eddy current distortion, and the diffusion tensors were then fitted to each voxel. The four primary quantitative DTI measures, fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), were then derived voxelwise. The TBSS registration then nonlinearly transformed the FA images using the FMRIB58_FA standard