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Diffusion tensor imaging of the corticospinal tract and walking performance in multiple sclerosis

Elizabeth A. Hubbard [a], Nathan C. Wetter [b,c], Bradley P. Sutton [b,c], Lara A. Pilutti [a], Robert W. Motl [a,*]

[a] Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, United States
[b] Department of Bioengineering, University of Illinois at Urbana-Champaign, United States
[c] Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, United States

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ABSTRACT

Research has identified a significant relationship between DTI (Diffusion Tensor Imaging) indices in the Corticospinal Tract (CST) and disability status in persons with multiple sclerosis (MS). To date, there is little known about the association between DTI indices of the CST with walking and gait outcomes in MS. This study examined the associations among DTI indices [fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD)] of the CST with walking and gait outcomes in persons with MS. We enrolled 69 persons with MS who underwent 3 T brain magnetic resonance imaging (MRI) and examined white matter structural integrity in the CST in the brain with DTI. Participants completed three walking performance assessments: 6-minute walk (6MW), timed 25-foot walk (T25FW), and gait testing. We examined associations using Spearman (r_s) and partial Spearman correlation (pr_s) analyses, using the entire sample and stratifying by disability status after controlling for age and sex. After controlling for age, sex, and disease duration, RD was significantly correlated ($p < 0.05$) with step time ($pr_s = 0.30$). AD was significantly correlated ($p < 0.05$) with step length ($pr_s = -0.32$). MD was significantly associated ($p < 0.05$) with 6MW ($pr_s = -0.35$), T25FW ($pr_s = -0.34$), gait velocity ($pr_s = -0.31$), step time ($pr_s = 0.29$), and step length ($pr_s = -0.36$). FA was not significantly correlated with any of the walking parameters ($p > 0.05$). We provide novel evidence of possible motor pathway damage involved in walking performance in MS. There may be subtle differences in associations between MD, AD, and RD with walking outcomes, and these could be assessed in future longitudinal examinations and clinical trials of motor rehabilitation.

1. Introduction

Multiple sclerosis (MS) is a neurological disease that results in demyelination and transection of axons within the central nervous system (CNS) [1]. Walking dysfunction is common in MS and seemingly is a manifestation of the CNS damage [2], yet there is limited understanding of neural correlates of walking dysfunction in MS.

Diffusion tensor imaging (DTI) provides tract specificity for examining neural correlates of walking dysfunction that is not afforded by traditional magnetic resonance imaging (MRI). DTI identifies restrictions to diffusion of water within the white matter (WM) and can quantify disruptions and damage within WM tracts [3]. Quantitative biomarkers are obtained through DTI, including fractional anisotropy (FA, directionality of diffusion in an imaging voxel), mean diffusivity (MD, total diffusion within an imaging voxel), axial diffusivity (AD, diffusion along the white matter tract), and radial diffusivity (RD, diffusion perpendicular to the fiber tract). The basis of diffusion anisotropy is in the parallel organization of white matter bundles; the amount of anisotropy is modulated by myelin and less diffusion anisotropy is linked to axons that are less myelinated [4]. Myelin damage, axonal loss, cellular size and integrity influence MD [5,6]. AD and RD are modulated by myelin in white matter and axonal degeneration [4]. The decrease in overall diffusion anisotropy (measured by FA) caused by WM neuropathology may result from increased RD and/or decreased AD [4].

DTI is sensitive to changes in normal appearing white matter and lesions in MS [5–7] and can identify alterations in "normal-appearing" white matter that may go undetected by traditional MRI [8,9]. Indeed, barrier permeability reflected by increases in MD are associated with MRI-visible lesions and "normal-appearing" white matter in MS [6,10,11]. DTI further is a proposed biomarker of neurodegeneration and demyelination in axonal pathways in MS and experimental autoimmune encephalomyelitis [7,12–14], with it being proposed that more specific relationships to white matter pathology are demonstrated by RD and AD, rather than FA or MD [4]. Importantly, DTI improves pathological specificity in MS [3] and provides data linking anatomical damage and clinical disability in MS [7,15–17]. Accordingly, DTI of specific WM pathways can identify impairment of the pathway's associated function in targeted, functional system-specific research of MS [3,7,18].

* Corresponding author at: Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, 906 S. Goodwin Ave., Urbana, IL 61801, United States.
E-mail address: ehubbar2@illinois.edu (E.A. Hubbard).

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Researchers have reported significant relationships between DTI-related measures and overall disability status in MS [3,7,15–17,19]. One study established that DTI of the optic radiations had a stronger association with Expanded Disability Status Scale (EDSS) scores than more traditional MRI measures [7]. Of note, DTI indices in the optic radiation were more strongly related to disability status than cerebral volume. Low-contrast visual acuity was more strongly correlated with DTI indices of the corticospinal tract (CST) and optic radiations than both cerebral and lesion volumes. Significant, positive associations were identified between disability status via EDSS scores and MD and RD of the CST in relapsing-remitting MS [7]. Another study reported that persons with MS had significantly lower cerebrospinal tract FA than control participants [3]. Among persons with MS who ranged in disability between EDSS scores of 2–6, greater disability was significantly associated with lower connectivity, a DTI-related index, and approached significance with FA of the CST [3]. One additional study identified significant correlations between MD of the CST and the pyramidal function system score (FSS) of the EDSS in relapsing-remitting MS [18].

Missing from the literature are data specifically linking DTI metrics of the CST with walking parameters in MS. To that end, this study examined the associations of DTI metrics with walking and gait outcomes in MS. We expected that lower FA, higher MD, higher AD, and higher RD, representing an overall increase in isotropic diffusion, would be associated with shorter walking endurance, slower walking speed, and gait dysfunction.

2. Methods

2.1. Participants and procedures

A University Institutional Review Board approved the methods, and participants provided written informed consent. Participants were recruited through targeted advertisements dispersed in central Illinois. We enrolled 69 participants with clinically definite MS [20]. The inclusion criteria were confirmed diagnosis of MS, relapse-free within the past 30 days, not taking monthly medications for ongoing relapse, ambulatory with or without an assistive device, between the ages of 18 and 64, and willingness to undergo MRI. Participants who screened positive for MRI contraindications were excluded from the study. Participants underwent a neurological examination administered by Neurostatus certified research personnel for EDSS scoring, completed the walking outcomes, and then underwent an MRI within 14 days of the initial testing.

2.2. Walking performance

2.2.1. 6-minute walk (6MW)

Endurance walking performance was based on the 6MW [21]. Participants were instructed to walk as far and as fast as possible for a six-minute period in a single corridor that was 75 ft in length with two, 180-degree turns marked by plastic cones. Participants used an assistive device and took periods of rest within the 6-minute period, as needed. One researcher followed approximately 3 ft behind the participant with a measuring wheel (Stanley MW50, New Briton, CT) and recorded the total distance travelled (meters).

2.2.2. Timed 25-foot walk (T25FW)

The T25FW was administered to measure walking speed [22]. Participants were instructed to walk as fast and as safely as possible over a 25-foot course on a carpeted surface [23]. One researcher recorded the participant's time (s) over two trials. Scores were averaged and then converted into walking speed (ft/s) [24].

2.2.3. Gait-related measures

Participants completed two trials of walking at a self-selected pace on a 16-foot GAITRite™ (CIR Systems, Inc.) electronic walkway. Velocity (cm/s), cadence (steps/min), step time (s), step length (cm), base support (cm), and swing (s) were averaged for the two trials [25,26].

2.3. MRI & DTI acquisition and analysis

2.3.1. Whole-brain white matter and grey matter volumes

High resolution 3D T1-weighted structural brain images were acquired using a whole body Siemens Trio 3 Tesla MRI scanner (Erlange, Germany) using an MPRAGE sequence with the following parameters: 23 cm FOV, 256 × 256 × 192 matrix size with 0.9 mm isotropic resolution, echo time (TE)/repetition time (TR)/inversion time (TI) of 2.32/1900/900 ms, flip angle of 9°, GRAPPA accelerated factor of 2 [27,28]. To measure total brain volume, the brain was then extracted with the exclusion of the skull by removing non-brain tissue from the T1 whole-brain images using the Brain Extraction Tool (BET) [29] from FMRIB's Software Library (FSL). To ensure accurate brain extraction, we used the bias field correction option in BET. Using FSL's Linear Image Registration Tool (FLIRT), the volume scaling factor was computed by linear registration of the skull and brain masks to the template MNI152 space [30,31]. This enables normalization of the measured volumes to account for a subject's skull size using FSL's SIENAX [30–32]. We further computed whole brain WM and Grey Matter (GM) volumes using SIENAX. We then normalized all whole brain WM and GM volumes based on intracranial volume by multiplication with this volume scaling factor.

2.3.2. DTI acquisition and analysis of FA, RD, and AD

The DTI protocol utilized is based on one previously published in research identifying age-related changes in fine motor control and its associations with white matter integrity [27]. A single-shot echo planar (EPI) acquisition was utilized with the following specifications: 72 slices, 2 mm slick thickness, TR of 10 s, TE of 98 ms, GRAPPA accelerated factor of 2 with 38 reference lines [27,28]. The b-value was set at 1000 s/mm^2. The spatial resolution of the EPI diffusion acquisition was 1.9 × 1.9 × 2.0mm^3. The EPI diffusion acquisition also included 30 diffusion encoding directions and 2 volumes acquired without diffusion encoding. Next, FSL's DTIFit was used to fit a diffusion tensor to the data [27,33]. All diffusion data processing steps were performed in a subject's native DTI space

The CST was identified using probabilistic fiber tractography. The Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) and probabilistic tractography (PROBTRACKX) from FSL were utilized to execute the tractography [34]. The default parameters (e.g., a two fiber model for each voxel) for BEDPOSTX were used to calculate all potential fiber directions to yield a map of all directions. PROBTRACKX, which tracks all potential fibers from a seed mask in the motor cortex to the target mask in the brainstem by way of the internal capsule, used the following parameters: curvature threshold of 0.2, step length of 1.0 mm, 2000 steps per sample, 5000 samples per seed voxel. The motor cortex was identified by the use of the Harvard/Oxford cortical and subcortical structural atlases (http://www.cma.mgh.harvard.edu/) on the Montreal Neurological Institutes (MNI) space brain (http://www.bic.mni.mcgill.ca/ServicesAtlases/) and transformed to the participant-space DTI using FSL's FLIRT. The brainstem was identified using the same process from these atlases. In order to limit the tracking to only pathways that pass through the internal capsule, an internal capsule mask was created by transforming the JHU DTI-based white matter atlas (http://cmrm.med.jhmi.edu/) into the subject's native DTI space. Finally, an exclusion mask was created for the contralateral hemisphere to preclude tracks from crossing between hemispheres.

FA values were calculated by averaging the FA value for each voxel on the resulting tracts and weighting this value by the probability of a fiber tract passing through that voxel, which effectually yields a