NeuroImage 55 (2011) 1169–1177

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Corpus callosal diffusivity predicts motor impairment in relapsing–remitting multiple sclerosis: A TBSS and tractography study

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ARTICLE INFO

Article history:
Received 28 June 2010
Revised 26 October 2010
Accepted 27 October 2010
Available online 5 November 2010

Keywords:
Multiple sclerosis
Diffusion tensor imaging
Tract-based spatial statistics
Nine hole peg test
Transcallosal motor pathway

ABSTRACT

Motor deficits in relapsing remitting multiple sclerosis (RRMS) patients are monitored using standard measures of disability that assess performance ranging from walking ability to hand function, thus reflecting involvement of a variety of motor pathways. We investigated the relative contributions of diffuse white matter damage and focal lesions using diffusion tensor imaging (DTI), in predicting future worsening of hand function in RRMS. The nine hole peg test (NHPT), a test of fine hand motor control, was used to measure baseline upper limb function in 16 controls and 25 RRMS patients, and then performed at follow-up on 22 of these patients at 6 and 12 months. Tract-based spatial statistics (TBSS) were used across the whole brain as a non-hypothesis driven method for localizing white matter changes associated with motor deficits. Subsequently, we used probabilistic fiber tractography in the corticospinal tracts (CST) and the transcallosal hand motor (TCHM) fibers to assess the predictive power of diffusion metrics and/or functionally relevant visible lesion volumes on the decline of hand motor function over the next 12 months. While fractional anisotropy (FA) and radial diffusivity (RD) of both pathways were strongly associated with NHPT performance at baseline, only RD of the TCHM fibers was predictive of NHPT decline over the next 12 months. Neither total visible lesion load nor pathway specific lesion loads were indicative of NHPT performance or progression. The TCHM fibers may play an important role in modifying the effects of MS pathology on fine motor control, and RD in these fibers may be a sensitive biomarker for future disability.

Introduction

Motor deficits are characteristic of multiple sclerosis (MS) and can have a tremendous effect on patient quality of life (Paltamaa et al., 2007). As evidence of this, mobility and motor control are the principal measures for disease severity scales and are the primary outcome measures for therapeutic intervention (Kurtzke, 1983). While ambulatory dysfunction is commonly seen in later stage MS, loss of fine motor control is evident even in the earliest disease stages (Kurtzke et al., 1972; Martin et al., 2006). The nine hole peg test (NHPT) is a measure of upper extremity function (Goodkin et al., 1988) that has been adopted as a primary component of the Multiple Sclerosis Functional Composite measure (MSFC) (Fischer et al., 1999). This test is very sensitive to early motor deficits in multiple sclerosis, and investigating the anatomical changes underlying these deficits may provide insight into disease progression.

Electrophysiological studies of MS patients have demonstrated delayed conduction in primary motor pathways suggesting white matter damage (Mills and Murray, 1985; Hess et al., 1987; Ingram et al., 1988; Kidd et al., 1998). However, T2 lesion volumes only weakly correlate with disability (Nijeholt et al., 1998; Miki et al., 1999). While including only functionally relevant lesions improves these associations (Riahi et al., 1998), there is evidence that disability results from demyelination and axonal loss in these pathways distal to lesions (Lee et al., 2000; De Stefano et al., 2001). More advanced imaging techniques further support the idea that diffuse tissue damage also contributes to clinical deficits. Among these techniques are magnetization transfer imaging (Wolff and Balaban, 1989), magnetic resonance spectroscopy (Frahm et al., 1989) and diffusion tensor imaging (DTI) (Basser and Pierpaoli, 1996).

DTI has the power to identify anatomical connectivity as well as microstructural integrity in brain tissue. DTI is sensitive to subtle changes in both the magnitude and direction of water diffusion on the cellular level and is used to derive metrics that reflect MS disease related effects. White matter damage in MS is reflected by a reduction in fractional anisotropy (FA) and increased overall diffusion (Filippi et al.,

Abbreviations: RRMS, relapsing remitting multiple sclerosis; 25FTW, 25 foot timed walk; AD, axial diffusivity; CST, corticospinal tract; DTI, diffusion tensor imaging; EDSS, expanded disability severity scale; FA, fractional anisotropy; FLAIR, fluid attenuated inversion recovery; MSFC, multiple sclerosis functional composite; NHPT, nine hole peg test; PASAT, paced auditory serial addition task; RD, radial diffusivity; TBSS, tract-based spatial statistics; TCHM, transcallosal hand motor.

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doi:10.1016/j.neuroimage.2010.10.077

2001). Diffusion components that contribute to changes in fractional anisotropy are axial diffusivity (AD), diffusion along the primary component of the tensor, and radial diffusivity (RD), or diffusion perpendicular to the to the primary tensor component (Pierpaoli and Basser, 1996). While decreased AD has been detected in association with acute axonal injury and Wallerian degeneration in both human and animal models (Pierpaoli et al., 2001, Song et al., 2002), recent work indicates that increases in AD and RD are sensitive, but pathologically non-specific, markers of tissue disruption that may be altered in varying degrees depending on the type of fibers involved and the extent of tissue damage (Wheeler-Kingshott and Cercignani, 2009). While axonal damage is likely to be involved in ultimate loss of motor function, early increases in RD may reflect subtle damage that could affect the fine motor skills required for the NHPT. Understanding how changes in these metrics are associated with motor performance may reveal the pathological mechanisms that contribute to the loss of motor function.

One application of DTI is to assess tract specific metrics using a region of interest approach. Tractography studies of the pyramidal tracts in MS patients have shown that reduced FA and increased diffusion in this region are associated with disability and poor motor function (Wilson et al., 2003). However, tract-based spatial statistics (TBSS) is a non-hypothesis-driven technique that allows for voxel-wise assessment of changes in diffusion metrics without identifying a specific anatomical target (Smith et al., 2006). This method has been used previously to assess white matter changes associated with cognition (Dineen et al., 2009; Roosendaal et al., 2009) and disability (Cader et al., 2007; Bodini et al., 2009) in a range of MS disease subgroups. We used TBSS to localize white matter diffusion changes that were most highly associated with motor deficits in a group of right-handed, early relapsing–remitting MS patients (RRMS). Furthermore, we investigated the relationship between diffusion metrics and progressive loss of fine motor skills. Finally, we extended our results by investigating motor-specific pathways to assess the relative contribution of visible white matter lesions.

Methods

Subjects

Subjects were recruited from the UCLA Multiple Sclerosis clinic and the community and informed consent was obtained. The UCLA Human Subjects Protection Committee approved the research protocol. Subjects were all right-handed and included 16 healthy, age-matched controls and 25 clinically definite RRMS patients as defined by both Poser and McDonald criteria (McDonald et al., 2001; Poser and Brinar, 2001). RRMS patients had disease duration less than 6 years at baseline and had not had a relapse nor received steroids within the previous 3 months.

Clinical testing

The Multiple Sclerosis Functional Composite (MSFC) was administered to all subjects on the day of scanning (Cutter et al., 1999). The battery consists of the right and left hand NHPT to measure upper extremity fine motor skills, the 25-foot timed walk (25FTW) to assess lower extremities, and the two-second Paced Auditory Serial Addition Task (PASAT), a working memory task used to assess cognitive function. All subjects performed each test weekly for 3 sessions prior to baseline testing in an attempt to reduce practice effects. Patients were also evaluated based on the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). To calculate the MSFC score, the inverse of the NHPT was used to improve the distribution of scores. Subcomponent scores were converted into Z-scores using the mean and standard deviation of the control group at baseline. In calculating the upper extremity Z-score of the MSFC, we used the mean of the right and left inverse NHPT scores to create Z-arm (Fischer et al., 1999). However, we also assessed a Z-score for the right (Z-Rhand) and left (Z-Lhand) separately. To combine the subcomponent Z-scores into an overall Z-MSFC, we used the following equation adopted by the National MS Society Outcomes Assessment Task Force (Fischer et al., 1999):

$$Z - MSFC = (Z - arm - Z - 25FTW + Z - PASAT) / 3.$$

We also conducted follow-up clinic visits for 22 of the 25 patients at 6 months and 12 months after baseline. The same tests were administered, and the same baseline scores of the control group were used to calculate a mean and standard deviation for Z-scores.

MRI acquisition

At baseline for all subjects, standard structural scans were acquired on a Siemens 1.5 T Sonata scanner. A T1 weighted MPRAGE scan with an isotropic 1 mm resolution was used for the identification of structural landmarks and as a registration target (see below) (TR = 1900 ms, TE = 4.38 ms, TI = 1100 ms, Matrix = 256 × 256, FOV = 256 mm, 160 1 mm axial slices). A fluid attenuated inversion recovery (FLAIR) scan was acquired to quantify visible white matter lesion volumes (TR = 9000 ms, TI = 2400 ms, TE = 82 ms, Matrix = 256 × 256, FOV = 240 mm, 50 3 mm axial slices, final resolution = 1.3 × 0.9 × 3.0 mm). These studies were done as part of an ongoing longitudinal natural history study.

DTI was collected at baseline using a Siemens 3 T Allegra scanner optimized for multi-direction DTI acquisition (TR = 10200 ms, TE = 84 ms, Matrix = 128 × 128, FOV = 256 mm). One b0 image with no diffusion weighting and 12 non-collinear diffusion encoded spin echo EPI images were acquired with a single b-value of 900 s/mm^2. Seventy-five 2 mm thick contiguous axial slices were acquired permitting a final resolution of 2 mm isotropic. The scan was administered twice for each subject and the images were averaged to increase signal to noise ratio.

DTI processing and tract-based spatial statistics

Every DTI volume of both acquisitions was rigid-body aligned to the b0 image from the first acquisition to correct for head motion using Automated Image Registration software (Woods et al., 1998), and the diffusion gradient tables were adjusted for this realignment using custom software. Eddy current distortions were corrected using a nonlinear, 2D registration of each slice to the b0 image (Woods et al., 1998). Both acquisitions and the corrected gradient tables were used to calculate the tensor image and determine the eigenvalues, L1, L2, and L3 at each voxel. Fractional anisotropy (FA), axial diffusivity (L1) and radial diffusivity ((L2 + L3)/2) were derived from these values (Basser and Pierpaoli, 1996).

The standard TBSS procedure (Smith et al., 2006) was applied to this study as summarized below. In order to align all subjects into a common space, the most representative subject of the group was identified and served as a registration target. FA images from all subjects were nonlinearly aligned to this subject, and this individual was registered to the MNI152 atlas template (Evans et al., 2003) using a linear registration approach. Subsequently, the combined nonlinear/linear transformation was used to align all subjects' FA images into MNI152 space, which were then averaged to create a study-specific FA atlas. This atlas is used to display results and report stereotaxic coordinates. To derive the FA skeleton, the 2nd and 3rd derivatives of the mean FA image are used to find the central points of maximal intensity within each fiber tract. For each subject, a perpendicular search is made from each point on the group skeleton to find individual maximal FA values. An advantage of the TBSS approach is that maximal FA values for each subject can be directly compared at each point on the skeleton even if the fiber centers are not perfectly