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The impact of isolated lesions on white-matter fiber tracts in multiple sclerosis patients

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ABSTRACT

Infratentorial lesions have been assigned an equivalent weighting to supratentorial plaques in the new McDonald criteria for diagnosing multiple sclerosis. Moreover, their presence has been shown to have prognostic value for disability. However, their spatial distribution and impact on network damage is not well understood. As a preliminary step in this study, we mapped the overall infratentorial lesion pattern in relapsing–remitting multiple sclerosis patients ($N = 317$) using MRI, finding the pons (lesion density, 14.25/cm^3) and peduncles (13.38/cm^3) to be predilection sites for infratentorial lesions. Based on these results, 118 fiber bundles from 15 healthy controls and a subgroup of 23 patients showing lesions unilaterally at the predilection sites were compared using diffusion tensor imaging to analyze the impact of an isolated infratentorial lesion on the affected fiber tracts. Fractional anisotropy, mean diffusion as well as axial and radial diffusivity were investigated at the lesion site and along the entire fiber tract. Infratentorial lesions were found to have an impact on the fractional anisotropy and radial diffusivity not only at the lesion site itself but also along the entire affected fiber tract. As previously found in animal experiments, inflammatory attack in the posterior fossa in multiple sclerosis impacts the whole affected fiber tract. Here, this damaging effect, reflected by changes in diffusivity measures, was detected in vivo in multiple sclerosis patients in early stages of the disease, thus demonstrating the influence of a focal immune attack on more distant networks, and emphasizing the pathophysiological role of Wallerian degeneration in multiple sclerosis.

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1. Introduction

In the revised McDonald criteria, the dissemination of lesions in infratentorial regions has been assigned an equal weighting to those in the supratentorial region and spinal cord, emphasizing their significance in the diagnosis of multiple sclerosis (MS) (Polman et al., 2011). Such lesions are thought to be specific to MS (Miller et al., 1987) and their detection using magnetic resonance imaging (MRI) has been found to be a predictor for long-term disability (Minneboo et al., 2004), and indeed, the presence of at least one brainstem lesion has been found to represent an increased risk of disability (Tintore et al., 2010). These studies investigating infratentorial lesions in MS have focused on their prevalence and effects on clinical outcome (Minneboo et al., 2004; Tintore et al., 2010); however, the pathophysiological effects of infratentorial lesions on white matter (WM) tracts in MS remain unclear. Using the experimental autoimmune encephalomyelitis (EAE) model, it has been demonstrated that MS lesions lead to axonal dissection and damage in sites distant to the autoimmune attack itself (Siffrin et al., 2010a). Local damage resulting from MS lesions has been reported in MS patients (Ciccarelli et al., 2008; Filippi et al., 2001; Rovaris et al., 2005), but their impact along WM fibers prior to complete transection is not well understood.

White-matter tissue can be specifically visualized using diffusion tensor imaging (DTI) (Beaulieu, 2002) and brain pathways can then be traced in vivo via fiber tractography (Ciccarelli et al., 2008; Mori and van Zijl, 2002). In DTI, MS lesions typically manifest as a local

Abbreviations: AD, axial diffusivity; EAE, experimental autoimmune encephalomyelitis; FA, fractional anisotropy; ICP, inferior cerebellar peduncle; LD, lesion density; LSAF, left superior arcuate fasciculus; MD, mean diffusivity; NAWM, normal-appearing white matter; RD, radial diffusivity.

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reduction in fractional anisotropy (FA) and increase in mean diffusivity (MD) within the lesioned area (Ciccarelli et al., 2008; Filippi et al., 2001). By exploiting directional diffusivities, it has been demonstrated in mouse models of WM pathology that decreased axial diffusivity (AD) can be associated with axonal injury and increased radial diffusivity (RD) with demyelination (Song et al., 2003; Song et al., 2005). Furthermore, patients with relapsing–remitting MS (RRMS) (Pagani et al., 2005) and clinically isolated syndrome (CIS) (Lin et al., 2007) were shown to have abnormal diffusion indices in the corticospinal tract that correlated with lesion load, which was interpreted as being associated with ongoing pathologic processes such as Wallerian degeneration and diffuse inflammation (Ciccarelli et al., 2008). Previous in vivo studies using DTI and tractography in MS patients have demonstrated changes in DTI measures along fibers affected by MS lesions; however, these changes were not associated with the effects of an isolated lesion (Bammer et al., 2000; Rocca et al., 2013; Walsh et al., 2011). In a combined post-mortem histology and MRI study, Kolasinski et al. were able to demonstrate diffuse WM damage as a result of a focal MS lesion reflected by DTI measures. This was found to correlate with histological measures of myelin integrity (Kolasinski et al., 2012).

In this work, we aimed to investigate the impact of MS lesions in vivo on WM fibers in RRMS patients using DTI measures. Due to a lack of reports regarding the predilection sites of lesions in the brain stem, a preliminary lesion mapping study was performed on a large patient cohort in order to identify regions of interest for the subsequent DTI analysis. Then, the main focus of this work was to investigate the impact that an isolated lesion has on diffusivity measures in affected WM fiber tracts by comparison to corresponding contralateral non-lesioned fibers in those patients and to healthy controls. We could show that diffusivity measures are not only affected locally at the lesion site but along the entire fiber tract.

2. Method

This study was approved by the local ethical committee and was conducted in accordance with the declaration of Helsinki. All participants gave their informed consent for participating in this study.

2.1. Subjects

In total 317 patients with RRMS were examined using MRI (215 using a 1.5-T scanner and 102 with a 3-T scanner). All patients were diagnosed according to the revised McDonald criteria (Polman et al., 2011). In the 1.5- and 3-T cohorts, 106 (49%) and 68 (67%) patients, respectively, showed infratentorial lesions in T2-weighted MRI. The mean age of these patients was 35 y (SD = ± 10 y), with a mean disease duration of 6.1 y (± 5.8 y) and median expanded disability status scale (EDSS) score of 1.5 (range 0–6.5).

2.2. Magnetic resonance acquisition

For the lesion mapping study (see details below), data were collected on either a 1.5 or 3-T scanner. Data for the fiber tractography analysis was collected on the 3-T scanner only. T2-weighted images were obtained using a 1.5-T whole-body MR scanner with the standard head coil. The measurement parameters for the turbo spin echo (TSE) sequence were: TR = 3000 ms, TE = 175 ms, 160 sagittal slices with slice thickness 1 mm, and FOV = 256 × 208 mm^2. Data were also recorded using a 3-T MR scanner (Magnetom TimTrio©, Siemens, Germany) with a 32-channel head coil and using the following protocol: 3D T1-weighted MP-RAGE sequence (TI = 900 ms, TR = 1900 ms, TE = 2.52 ms, FOV = 256 × 265 mm^2, flip angle = 9°, voxel size = 1 × 1 × 1 mm^3, 192 slices). 3D T2-weighted TSE sequence (TR = 500 ms, TE = 79 ms, FOV = 256 × 256 mm^2, flip angle = 120°, voxel size = 1 × 1 × 1 mm^3, 192 slices); and 2D T2-FLAIR sequence (TR = 9000 ms, TE = 79 ms, FOV = 210 × 210 mm^2, flip angle = 150°, voxel size = 1 × 1 mm^2, 45 slices, slice thickness = 3 mm, slice gap = 2 mm). The diffusion data were obtained using a single-shot DW EPI sequence (TR = 9000 ms, TE = 102 ms, 30 directions, $b = 0$ and 900 s/mm^2, FOV = 256 × 256 mm^2, matrix size = 128 × 128, flip angle = 90°, 62 slices slice thickness = 2 mm and gap = 0.5 mm, voxel size = 2 × 2 mm^2, number of averages = 1).

2.3. Lesion mapping

The preliminary lesion mapping study, conducted retrospectively to select regions of interest in the brain stem to be used in the subsequent DTI analysis, included all 317 patients. To define regional vulnerability to MS lesions, a lesion density (LD) map was calculated by relating the probability of plaques to the volume of the corresponding region using the MRIcroN software (Baier et al., 2012; Rorden et al., 2007) (https://www.nitrc.org/projects/mricron). To create the lesion overlay map, T2-weighted WM lesion boundaries were firstly delineated on the T1-weighted images and then transposed onto a T1 Montreal Neurological Institute (MNI) template by an experienced operator (VF). The extension and location of the lesion shapes was controlled by a second experienced operator (AD).

2.4. Post-processing of diffusion data and tractography

Building on the preliminary lesion-mapping study, DTI data were selected from the 3-T cohort only for tractography analysis based on lesions being found unilaterally at the inferior cerebellar peduncle (ICP; $N = 21$), or for comparison, at the left superior arcuate fasciculus (LSAF) fiber tracts ($N = 23$), which are commonly affected by MS lesions (Rossi et al., 2012). Fifteen age-matched healthy controls (HC) were also sampled on the same MR system. The ICP was located using a DTI atlas (Wakana et al., 2004). All DTI data were post-processed using the SPM8 diffusion toolbox (http://www.sourceforge.net/projects/spmtools/). Images were co-registered and re-sliced to the b0 image for motion correction. FA and MD maps were calculated. For the tractography, the lesion mask was used to define the seed points, which were determined individually in native space. Contralesional fibers were also extracted and considered as normal-appearing white matter (NAWM) fibers. The affected fibers were screened by an experienced operator to ensure the presence of only one single lesion along the fibers, and in the case of NAWM fibers that no lesion was present. Seed points were marked in HCs in order to extract corresponding fibers.

Tensor estimation and fiber tracking was performed using the MedINRIA DTI Track software (http://www-sop.inria.fr/asclepios/software/MedINRIA/) employing the streamline approach for tractography using angle and anisotropy thresholds of 0.2 and 0.3, respectively. Additional steps such as controlling the volume, length, and angulation, as well as employing Hausdorff mean gravity in order to remove outliers of the retraced fibers were taken to minimize possible inherent artifacts, particularly in brainstem regions.

2.5. Fiber tract-oriented statistics

After extracting target fibers from MedINRIA, they were normalized and bundled by volume and length using the built-in length, center of mass-based fiber gravity, and Hausdorff distance-based fiber-set clustering algorithms in the Fiberviewer© software (Corouge et al., 2006). The DTI indices were plotted along the entire tract arc length as a function of the geodesic distance from the lesion site center in patients or the corresponding site in NAWM and HC groups. The distribution function of each diffusion component was compared using the Kolmogorov–Smirnov test.

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