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Patterns of white matter damage are non-random and associated with cognitive function in secondary progressive multiple sclerosis

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ABSTRACT

In multiple sclerosis (MS), white matter damage is thought to contribute to cognitive dysfunction, which is especially prominent in secondary progressive MS (SPMS). While studies in healthy subjects have revealed patterns of correlated fractional anisotropy (FA) across white matter tracts, little is known about the underlying patterns of white matter damage in MS. In the present study, we aimed to map the SPMS-related covariance patterns of microstructural white matter changes, and investigated whether or not these patterns were associated with cognitive dysfunction.

Diffusion MRI was acquired from 30 SPMS patients and 32 healthy controls (HC). A tensor model was fitted and FA maps were processed using tract-based spatial statistics (TBSS) in order to obtain a skeletonised map for each subject. The skeletonised FA maps of patients only were decomposed into 18 spatially independent components (ICs) using independent component analysis. Comprehensive cognitive assessment was conducted to evaluate five cognitive domains. Correlations between cognitive performance and (1) severity of FA abnormalities of the extracted ICs (i.e. *z*-scores relative to FA values of HC) and (2) IC load (i.e. FA covariance of a particular IC) were examined.

SPMS patients showed lower FA values of all examined patterns of correlated FA (i.e. spatially independent components) than HC ($p < 0.01$). Tracts visually assigned to the supratentorial commissural class were most severely damaged ($z = -3.54$; $p < 0.001$). Reduced FA was significantly correlated with reduced IC load (i.e. FA covariance) ($r = 0.441$; $p < 0.05$). Lower mean FA and component load of the supratentorial projection tracts and limbic association tracts classes were associated with worse cognitive function, including executive function, working memory and verbal memory.

Despite the presence of white matter damage, it was possible to reveal patterns of FA covariance across SPMS patients. This could indicate that white matter tracts belonging to the same cluster, and thus with similar characteristics, tend to follow similar trends during neurodegeneration. Furthermore, these underlying FA patterns might help to explain cognitive dysfunction in SPMS.

1. Introduction

Multiple sclerosis (MS) is a progressive, inflammatory demyelinating and neurodegenerative disease of the central nervous system, which is commonly diagnosed in young adults (Lublin et al., 2014). Although the clinical course of MS patients is characterised by heterogeneous symptoms, the majority of MS patients develop a progressive phase of the disease (i.e. secondary progressive (SP) MS), after an initial relapsing-remitting course (i.e. relapsing remitting (RR) MS) (Lublin et al., 2014). Cognitive impairment is observed in 40 to 65% of the MS patients and occurs in all types of MS (Chiaravalloti and DeLuca, 2008).

Cognitive dysfunction might, in part, arise from damage to white matter tracts that connect distant brain regions (Dineen et al., 2009). In MS, transected axons due to focal white matter lesions and diffuse white matter injury might eventually lead to less dense and efficient connections between regions. Using diffusion tensor imaging (DTI),

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white matter abnormalities have been consistently observed in MS patients with diverse disease courses (Roosendaal et al., 2009; Hulst et al., 2013; Bodini et al., 2009). DTI parameters, including fractional anisotropy (FA), reflect the integrity of white matter tracts (Pierpaoli et al., 1996) and provide in vivo information about white matter alterations in neurodegenerative disease (Basser et al., 1994).

Recent studies have demonstrated that independent component analysis (ICA) applied to DTI data reveals specific patterns of covariance between FA values (i.e. correlated FA) across white matter tracts in the healthy population (Li et al., 2012). Such covariance is believed to result from underlying phylogenetic and/or functional relationships between white matter tracts (Wahl et al., 2010; Dubois et al., 2008). Although loss of white matter integrity is observed in MS patients, little is known about the underlying patterns of white matter damage. It might be that white matter tract damage occurs in a random fashion, however, it could also be that white matter tracts with similar morphological characteristics show similar degrees of white matter damage.

We hypothesise that (1) white matter pathology, as reflected by reduced FA values, is non-random, (i.e., pathology in MS tends to distribute according to the patterns of covariance); and (2) that patterns of microstructural pathology in part explain cognitive dysfunction. Therefore, the aim of the present study was to identify whether or not specific patterns of microstructural changes occur across white matter tracts in SPMS, and to investigate whether or not these patterns of FA covariance were associated with cognitive performance.

2. Methods

2.1. Participants

Thirty SPMS patients (20 women; mean age = 53 years (range 36–65)) attending the MS clinics at the National Hospital of Neurosurgery and Neurology and 32 healthy controls (HC) (20 women; mean age = 41 years (range 21–65)), who did not have any neurological or neuropsychiatric disorders, were recruited (Table 1). These patients were diagnosed according to the Lublin and Reingold criteria (Lublin and Reingold, 1996). None had a clinical relapse within three months of their clinical examination and magnetic resonance imaging (MRI) scans.

Table 1
Demographic, clinical, neuropsychological and MRI characteristics.

	SPMS	Healthy controls	*P*-values
Demographic and clinical characteristics			
N	30	32	
Age (years)	53 (36–65)	41 (21–65)	<0.01
Sex (M/F)	10/20	10/22	0.86
Time walked test (seconds)	81.7 (4.7–180.00)	5.0 (3.2–7.3)	<0.001
9HPT (seconds)	59.3 (20.6–300.00)	19.3 (16.1–25.0)	<0.001
PASAT-3 (seconds)	32.9 (14–59)	49.3 (21-60)	<0.001
Disease duration (years)	20 (8–48)		
EDSS	6.5 (4.0–8.5)		
Neuropsychological characteristics			
Processing speed (*z*-score)	−2.1 (1.1)	0 (0.9)	<0.001
Verbal memory (*z*-score)	−1.4 (1.2)	0 (0.8)	<0.001
Visual memory (z-score)	−1.4 (1.1)	0 (0.7)	<0.001
Executive function (z-score)	−2.2 (2.5)	0 (0.7)	<0.01
Working memory (z-score)	−0.7 (0.9)	0 (1.0)	0.02
MRI characteristics			
NBV (mL)	1.19 (1.2)	1.32 (0.12)	<0.001
NGMV (mL)	0.69 (0.7)	0.77 (0.7)	<0.001
Lesion volume (mL)	7.26 (0.80–32.04)		

For demographic and clinical characteristics mean scores (range) were provided. Neuropsychological characteristics are expressed as mean z-scores (standard deviation (SD)). Mean z-scores were obtained by using cognitive scores of controls as reference. MRI characteristics are expressed as mean (SD). SPMS: secondary progressive multiple sclerosis; HC: healthy controls; EDSS: Expanded disability status scale; PASAT-3: Paced auditory serial attention test-3 seconds; TWT: Timed walk test; 9HPT: Nine-hole peg test.

The joint Medical Ethics Committee of the National Hospital for Neurology and Neurosurgery and the UCL Institute of Neurology approved the study. Written and informed consent was obtained from all participants.

2.2. Neuropsychological and physical evaluation

On the day of scanning, all patients and a subset of the HC ($N = 23$) underwent neuropsychological evaluation of cognitive domains often impaired in MS. Processing speed was assessed using the Paced Auditory Serial Addition Test-3 seconds (PASAT-3) (Gronwall, 1974) and Symbol Digit Modalities Test (SDMT) (Smith, 1982). Verbal memory was assessed using the immediate and 30-minute delayed Story Recall Test (SRT) from the adult memory and information processing battery (AMIPB, Coughlan and Hollows, 1985) and the Recognition Memory Test (RMT) for words (Warrington, 1984). Visuospatial memory was measured using the immediate and 30-minute delayed complex Figure Recall Test (FRT) from the AMIPB and RMT for faces (Warrington, 1984). Executive function was assessed using the Stroop colour-word interference test (Stroop, 1935) and Hayling Sentence Completion Test (Burgess and Shallice, 1997). Working memory was assessed with the Digit-Span, a subtest of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997). For each cognitive domain, single test scores were transformed into *z*-scores and averaged. The *z*-scores were computed based on the cognitive performance of the HC. In addition, MS participants underwent neurological assessment, including the Expanded Disability Status Scale (EDSS) to assess disease severity (Kurtzke, 1983) and Multiple Sclerosis Functional Composite (MSFC) subtests (Cutter et al., 1999).

2.3. MRI and DTI acquisition

Magnetic resonance imaging (MRI) scanning was performed on a Philips Achieva 3T system (Philips Healthcare, Best, The Netherlands) using a 32-channel receive-only head-coil. All subjects underwent a whole-brain, cardiac gated, spin-echo diffusion-weighted sequence (TR = 24.000 ms; TE = 68 ms; 72 axial slices with an isotropic 2 mm resolution) with 61 volumes with non-collinear diffusion gradients (b-value of 1200 s mm^{-2}) and 7 volumes without directional weighting. For white matter lesion detection, turbo spin-echo dual-echo proton density- and T2-weighted images were obtained (TR = 3500 ms; TE = 19/85 and 50 axial slices, $1 \times 1 \times 3$ mm^3; FOV 240×180 mm^2). Lesion marking was carried out by an experienced rater (VS) using JIM version 5 (Xinapse Systems, Northants). Additionally, a three-dimensional inversion-prepared fast spoiled gradient recall (3D FSPGR) T1-weighted sequence of the brain was conducted (TR = 13.3 ms; TE = 4.2 ms; inversion time = 450 ms; 124 contiguous axial slices; slice thickness of 1.5 mm; FOV 300×225 mm; matrix size 256×160 (reconstructed to 256×256 for a final in plane resolution of 1.17 mm)). Normalised grey matter volume (NGMV) was computed from segmented lesion filled T1-weighted images (Chard et al., 2010) using SIENAX software.

2.4. DTI pre-processing and tract-based spatial statistics (TBSS)

After correction of motion and eddy-current distortions using FMRIB's Linear Image Registration Tool, a diffusion tensor model was fitted on a voxel-by-voxel basis to the DTI of all subjects using DTIFIT from the FMRIB's Diffusion Toolbox (FSL, FMRIB Image Analysis Group, Oxford, UK). FA images were derived from this tensor. The default tract-based spatial statistics (TBSS) pipeline (FSL version 5.0.2) was used to align all FA images to a common target and to create a mean 'skeletonised' FA image. For each subject the maximum FA value perpendicular to each voxel of the skeleton was projected onto the skeleton (Smith et al., 2006).