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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).

2.5. DTI independent component analysis

Following the procedure described by Li et al. (2012), independent component analysis (ICA) was applied to the "skeletonised" FA maps of the SPMS patients only to estimate patterns of covariance between voxel-based FA values of white matter tracts after spatial normalisation using TBSS (Li et al., 2012). The aligned individual FA skeletons of the SPMS patients were concatenated across subjects to create a single 4D data set. Using ICA implemented in the Group ICA fMRI Toolbox (GIFT) and the FastICA algorithm, it was possible to decompose this concatenated dataset into 18 independent components (ICs) in total (Fig. 1). The resulting 18 spatial maps of the ICs show voxels for which the FA values within each map co-vary across individuals and represent clusters of white matter tracts that were spatially independent. For the

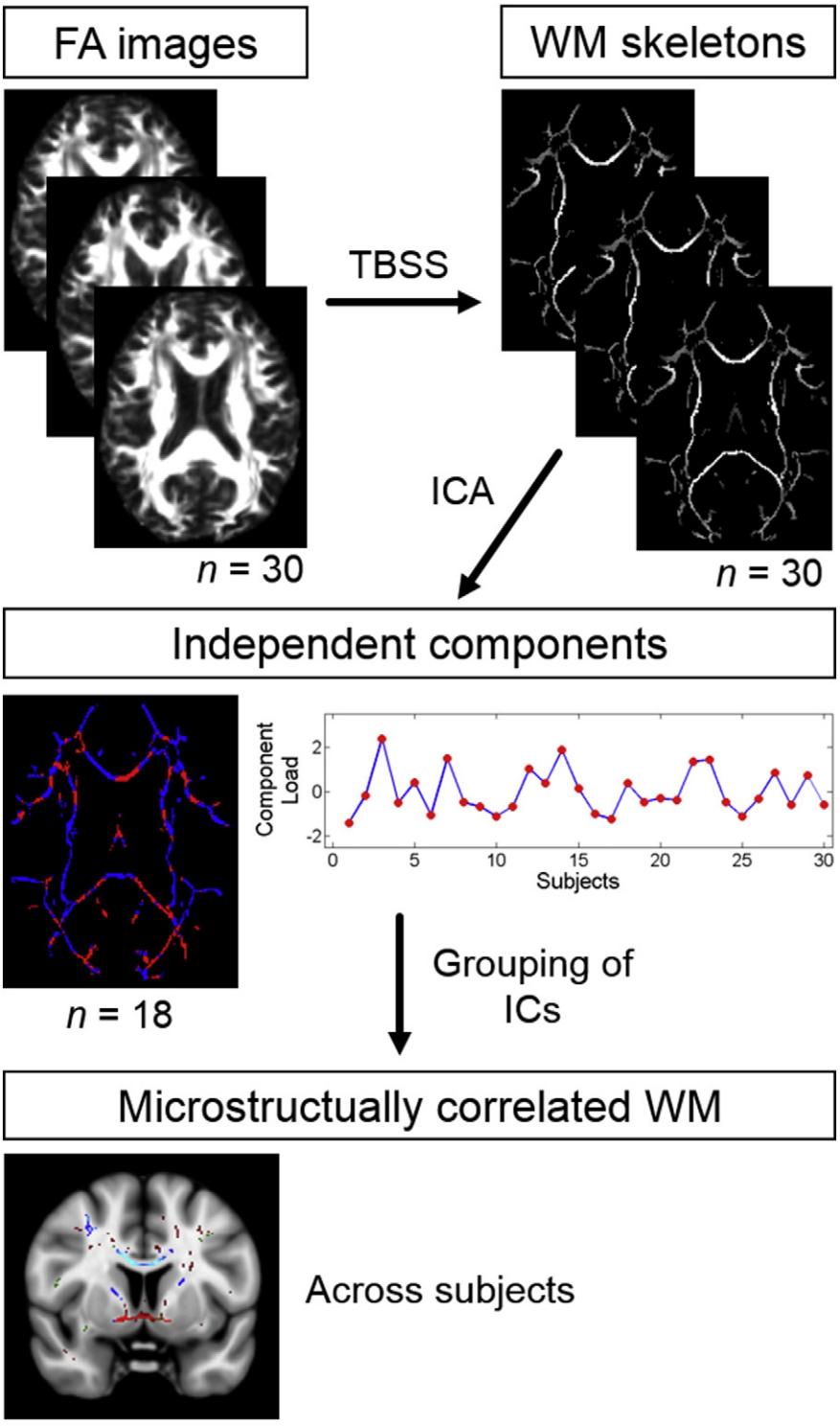

Fig. 1. Data analysis flow chart: Subjects' FA values were projected onto a common white matter skeleton using TBSS (top row). Independent component analysis (ICA) decomposes the group of FA skeleton maps into 18 spatially independent components (ICs) (middle row). ICA returns for each component a spatial map and component loading, which corresponds in this context to the across subject variation in FA values for that particular IC. High variance in FA of a particular component, results in a low component load. The resulting spatial maps of the ICs (i.e. IC1 in red and IC2 in blue) show voxels for which the FA values within each map co-vary across individuals (bottom row).

anatomical localization of white matter tracts associated with the ICs the John Hopkins University white matter tractography atlas was used (Mori et al., 2005). Additionally, following the classification suggested by Li et al. (2012), ICs were assigned to six distinct classes by visual inspection, based on their dominant anatomic features. These anatomically familiar classes of white matter tracts included the supratentorial commissural tracts (class I), supratentorial projection tracts (class II), neocortical association tracts (class III), limbic association tracts (class IV), thalamus, brainstem and cerebellum (class V) and an undefined class (class VI). ICs assigned to the same classes were depicted in one spatial map. ICA returns for each IC the corresponding component loading per subject, which corresponds in this context to the FA covariance of a particular IC. Higher values reflect a higher degree of FA covariance, whereas lower values reflect a lower degree of FA covariance within an IC. For analysis and illustration purpose an index number was assigned to each IC (Fig. 1). A composite score was computed from the mean component loads of all ICs assigned to the same class. Additionally, binary masks were created by thresholding the obtained ICs at the significance level in order to extract FA values. After that, severity of white matter damage of each IC was quantified by converting FA values to *z*-scores, based on the mean and standard deviations of FA values of healthy controls (Schoonheim et al., 2014). A composite score was computed from the mean FA *z*-scores of all ICs assigned to the same class.

2.6. Statistical analysis

Statistical analyses were performed using SPSS software, version 21 (Chicago, Illinois, USA). All variables were checked for normality using Kolmogorov-Smirnov testing and histogram inspection. FA *z*-scores for each class and cognitive test scores were compared between SPMS patients and HC using a one-way between group analysis of covariance (ANCOVA) including age and sex as covariates.

Two different approaches were applied in order to investigate the association between cognitive performance and white matter patterns by using Pearson's product moment correlations: 1) correlations between FA *z*-scores of each white matter class, which corresponds to the degree of white matter damage within patterns belonging to the same class, and test scores for the different cognitive domains were assessed; and 2) correlations between IC load (i.e. degree of FA covariance), which corresponds in this context to the FA covariance of a particular IC per subject, and cognitive test scores were assessed. Additionally, correlations between IC load and conventional MRI measures (i.e. log-transformed whole brain lesion load, whole brain FA and normalised grey matter volume) were examined.

For correlations between mean FA *z*-scores for the different classes and cognitive performance p values <0.05 were considered as significant, whereas a more stringent alpha level of $p < 0.01$ was considered as significant for correlations between single IC scores and cognitive test scores to compensate for the number of tests.

3. Results

3.1. SPMS-related white matter patterns

In SPMS, 16 out of 18 extracted ICs were associated with anatomically recognisable white matter tracts. The components were visually grouped into separate classes depending on the tract anatomy (as done by Li et al., 2012) (Table 2).

Out of the five classes previously proposed (Li et al., 2012), we identified four classes, including the supratentorial commissural tracts, supratentorial projection tracts, neocortical association tracts and limbic association tracts. Although ICs belonging to the thalamus were not identified, ICs belonging to the brainstem and cerebellum were observed, which partly represented the fifth class as described by Li et al. (2012). Two components were not obviously associated to specific white matter tracts (i.e. IC13 and IC16) and were assigned to a separate 'undefined' sixth class.

Table 2
Extracted independent components were assigned to six different white matter classes.

Class	Independent component	Prominent WM structures
I. Supratentorial commissural tracts	IC1	Anterior commissure
	IC2	Splenium of corpus callosum
		Genu of corpus callosum
	IC5	Body of corpus callosum
II. Supratentorial projection tracts	IC6	Optic radiations
	IC10	Anterior thalamic radiation
	IC14	Posterior limb of internal capsule
	IC18	Corticospinal tract
III. Neocortical association tracts	IC4	Inferior fronto-occipital fasciculus
	IC11	Superior longitudinal fasciculus
IV. Limbic association tracts	IC3; IC12; IC17	Cingulum
	IC 7; IC15	Uncinate fasciculus
	IC15	Fornix
V. Brainstem and Cerebellum	IC8	Superior cerebellar peduncle
	IC9	Middle cerebellar peduncle
VI. Undefined WM tracts	IC13; IC16	

WM: white matter; IC: independent component.

3.1.1. Class I: The supratentorial commissural tracts

ICs maps predominantly corresponding to supratentorial commissural tracts were assigned to the first class. The first class included 3 components (IC1, IC2 and IC5) and was mainly represented by the anterior commissure and the body, splenium and genu of the corpus callosum (Fig. 2A).

3.1.2. Class II: The supratentorial projection tracts

The second class contained four IC maps (IC6, IC10, IC14 and IC18) predominantly corresponding to the supratentorial projection tracts. This second class showed bilateral symmetry, encompassing the corticospinal tract, optic radiations and anterior thalamic radiations (Fig. 2B).

3.1.3. Class III: The neocortical association tracts

The third class, the neocortical association tracts, included 2 components (IC4 and IC11), corresponding to the superior longitudinal fasciculus, inferior fronto-occipital fasciculus and inferior longitudinal fasciculus (Fig. 2C). For these IC maps bilateral symmetry was observed as well.

3.1.4. Class IV: The limbic association tracts

Five IC maps (IC3, IC7, IC12, IC15 and IC17) in which the dominant anatomical features corresponded to the limbic association tracts were assigned to the fourth class. These IC maps predominantly represent represented the fornix, uncinate fasciculus, dorsal and ventral part of the cingulum (Fig. 2D).

3.1.5. Class V: Cerebellum and brainstem

The fifth class consisted of two IC maps (IC8 and IC9) that were largely overlapped with the middle and superior cerebellar peduncles (Fig. 2E).

3.1.6. Class VI: Undefined white matter

The sixth class consisted of two components (IC13 and IC16) that showed non-localised patterns and were therefore not clearly associated with specific tracts.

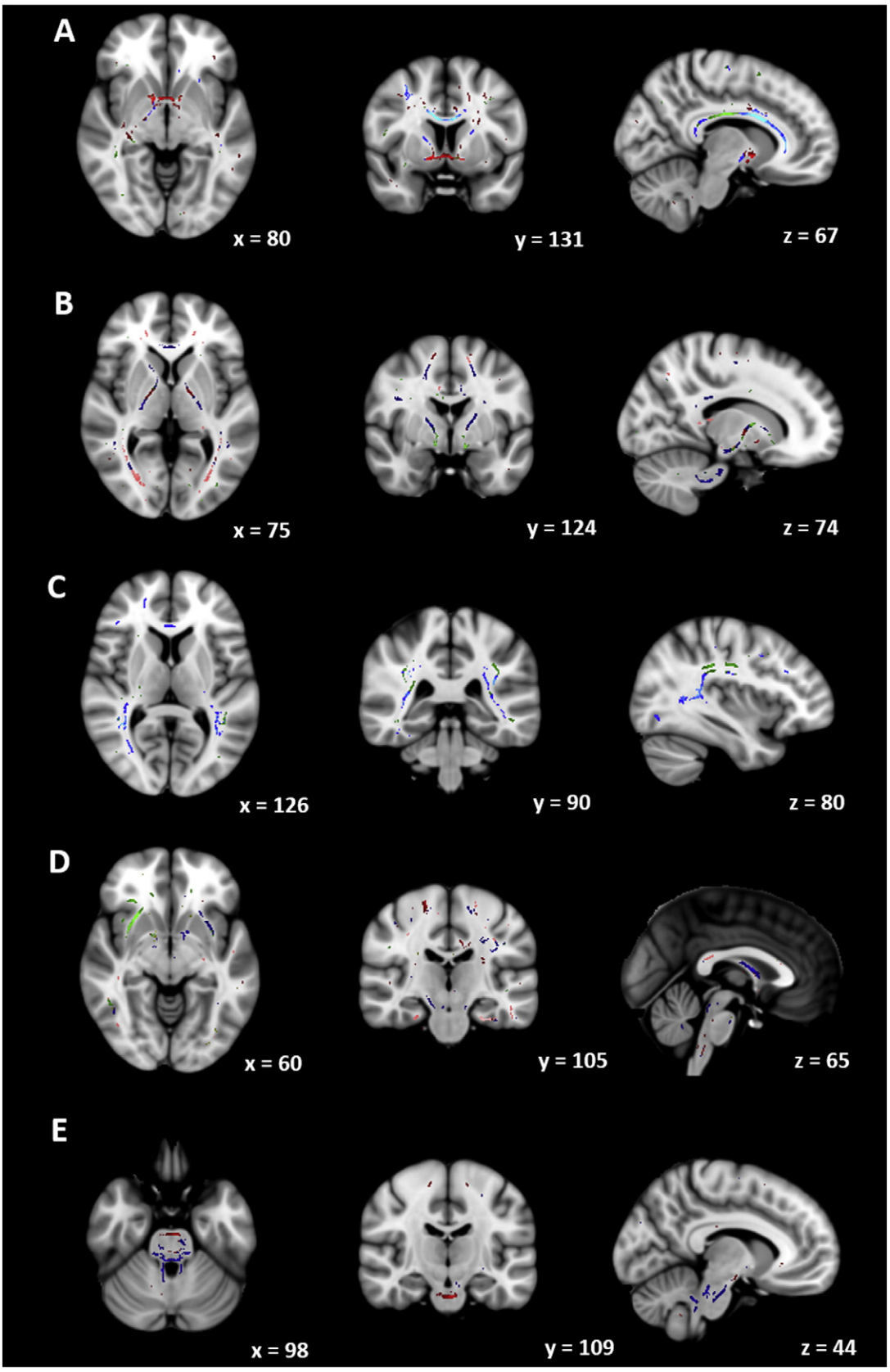

Fig. 2. Spatial maps of the different white matter classes: (A) supratentorial commissural tracts consisting of IC1 (red), IC2 (blue) and IC5 (green); (B) supratentorial projection tracts consisting of IC6 (light blue), IC10 (green), IC14 (red) and IC18 (blue); (C) neocortical association tracts consisting of IC4 (blue) and IC11 (green); (D) limbic association tracts consisting of IC3 (pink), IC7 (green), IC15 (blue) and IC17 (red); (E) brainstem and cerebellum consisting of IC8 (red) and IC9 (blue).

3.2. Severity of white matter class specific damage

When looking at the FA z-scores of the different white matter classes (i.e. FA z-scores of ICs belonging to the same white matter class were averaged), significantly lower FA values were observed for all examined classes in SPMS patients relative to HC. The 'supratentorial commissural tracts' class was the most abnormal (z-score = −3.54; $F = 45.06$; $p < 0.001$), followed by the 'cerebellum and brainstem' class (class V) (z-score = −3.24; $F = 33.46$; $p < 0.001$), whereas the 'neocortical association tracts' class (class III) was the least severely affected (z-score = −1.68; $F = 8.74$; $p < 0.01$).

3.3. Association between classes' specific white matter integrity and cognitive performance

Lower FA averaged across the 'supratentorial projection tracts' class was associated with worse averaged cognition ($r = 0.413$; $p = 0.03$). Additionally, lower mean FA of this class was also associated with worse executive function ($r = 0.399$; $p = 0.03$), whereas lower mean FA of the 'limbic association tracts' class was significantly correlated with worse visuospatial memory ($r = 0.364$; $p = 0.04$).

3.4. Associations between component load and cognitive performance

When looking at the association between IC load (i.e. FA covariance of a particular IC) for the different white matter classes (i.e. component load scores of ICs belonging to the same white matter class were averaged) and cognitive performance of several domains, a significant correlation was observed between IC load for the 'supratentorial projection tracts' class and executive function ($r = 0.368$; $p = 0.02$) and IC load for the 'limbic association tracts' and visuospatial memory ($r = 0.409$; $p = 0.03$).

When looking at the association between IC load of single ICs and cognitive performance, the load for IC1 was significantly correlated with verbal memory ($r = 0.523$; $p < 0.01$), working memory ($r = 0.663$; $p < 0.001$), executive function ($r = 0.469$; $p \leq 0.01$) and averaged cognition ($r = 0.590$; $p < 0.001$) (Fig. 3). The load for IC6 was correlated with processing speed ($r = 0.479$; $p < 0.001$). All these correlations indicated that a lower degree of FA covariance was associated with worse performance on several cognitive domains.

3.5. Associations between component load, white matter damage and lesion load

FA values of the different white matter classes were strongly correlated with the IC load of their corresponding class. Mean FA values of class I ($r = 0.740$; $p < 0.001$), class II ($r = 0.485$; $p < 0.01$), class III ($r = 0.665$; $p < 0.001$), class IV ($r = 0.441$; $p = 0.02$) and class V ($r = 0.583$; $p < 0.01$) were correlated with IC load of the corresponding classes; in particular, lower mean FA values were correlated with lower component loadings (i.e. lower FA covariance). Additionally, lesion load was significantly correlated with the component load corresponding to IC1 ($r = -0.591$; $p < 0.001$) meaning a higher lesion load was associated with lower FA covariance.

4. Discussion

By using ICA applied to skeletonised FA maps of SPMS patients, we have found that pathology in white matter tracts does not occur in a random fashion, and instead occurs in more regional patterns. In addition, both white matter integrity and microstructural covariance of IC regions were of relevance for cognitive function.

4.1. Patterns of covariance between white matter tracts

A recent study by Li and colleagues has demonstrated that FA values of white matter tracts, tracts segments and group of tracts co-vary in healthy subjects (Li et al., 2012). Furthermore, these patterns of correlated FA were grouped by location (Li et al., 2012). In our study, despite the presence of white matter pathology, patterns of FA covariance were observed in SPMS patients and appeared to visually overlap, at least partially, with the findings in healthy controls (Li et al., 2012). The ICs were

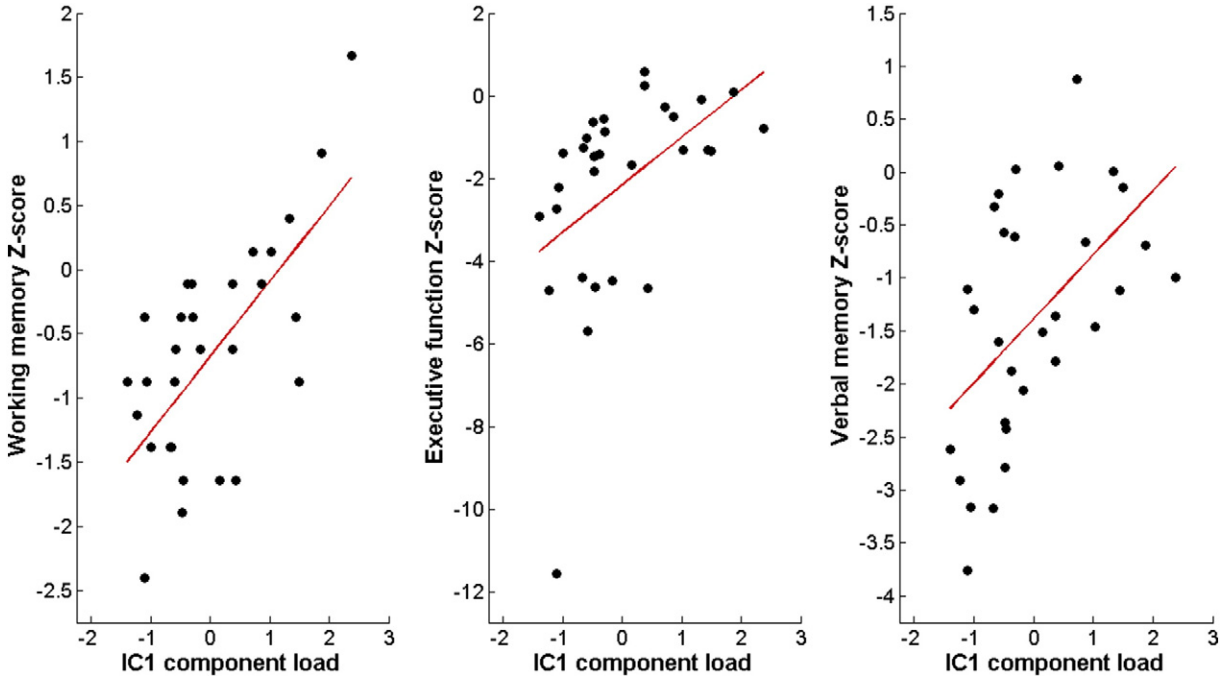

Fig. 3. The independent component load (i.e. FA covariance of a particular independent component) was associated with cognitive performance. Correlations between across-subject load for the first independent component, predominantly represented by the anterior commissure and cognitive z-scores, were significant for (A) working memory, (B) executive function and (C) verbal memory.

visually assigned to six different classes and localised substantial segments of white matter tracts rather than single voxels. This suggests that white matter tracts belonging to the same IC tend to follow similar trends during neurodegeneration.

Significant loss of white matter integrity was observed in all examined IC classes, with the supratentorial commissural class being most abnormal. Segments of the corpus callosum and anterior commissure were assigned to this particular class. Diffuse and focal white matter pathology is commonly observed in MS. However, most of the in vivo imaging studies examined samples primarily or solely compromising patients with relapsing remitting (RR) MS (Dineen et al., 2009; Roosendaal et al., 2009; Schoonheim et al., 2014; Yu et al., 2012; Hulst et al., 2013). In the progressive phase of the disease the extent and severity of diffuse white matter injury of the so-called normal-appearing white matter is increasing (Kutzelnigg et al., 2005). The degree of white matter damage in SPMS patients became especially apparent in post mortem studies, in which SPMS patients were predominantly included (Schmierer et al., 2007; Kolasinski et al., 2012). Although these studies thoroughly examined the degree of white matter abnormalities in MS, they did not take into account that specific patterns of correlations exist in DTI parameters. However, a few studies have attempted to investigate spatial characteristics of grey matter pathology in MS (Audoin et al., 2006; Battaglini et al., 2009; Pagani et al., 2005). A recent study demonstrated that cortical atrophy occurs largely in a non-random fashion as well (Steenwijk et al., 2016).

For other neurodegenerative disorders than MS, only a few studies have examined patterns of white matter damage. A recent study applied ICA on skeletonised FA images of Alzheimer's patients and healthy controls and found reduced FA of several ICs as well (Ouyang et al., 2015). Additionally, in our study loss of white matter integrity (i.e. reduced FA) was associated with less covariance in FA (i.e. lower IC loads) of the corresponding IC.

4.2. Underlying mechanisms of microstructural correlations

The biological basis of microstructural correlations in the white matter is not fully understood, there are several possible explanations for this. In health, the variation in the rate of development of myelin might underlie the interdependence of several white matter tracts (Lebel et al., 2008; Dean et al., 2015; Cohen et al., 2016). For example, frontotemporal connections seemed to mature relatively slow, whereas left-right hemispheric connections show the most rapid development (Lebel et al., 2008). It might be that the spatial variation in the development of white matter tracts results in tracts with different microstructural characteristics (Lebel et al., 2012; Yeatman et al., 2014). Thereby it is thought that anatomical connectivity patterns might be the underlying mechanism of these correlations (Li et al., 2012). Therefore, loss of structural network integrity might explain the less coherent ICs observed in SPMS patients than previously observed in healthy controls. Since the strongest correlations for FA values have been observed between homologous tracts in healthy subjects (Wahl et al., 2010), it is likely to observe a certain degree of symmetry in ICs. However, in SPMS the symmetry of the ICS appears to be only marginal. This could because of the involvement of commissural tracts in the pathogenesis of MS (Cader et al., 2007; Kern et al., 2011), which makes it less likely that FA values of bilateral white matter tracts were strongly related in SPMS.

However, despite the presence of less symmetrical and coherent correlated segments of white matter tracts, the identified patterns of correlated FA indicated that white matter damage still occurs predominantly in a more non-random fashion. This might correspond to the finding that the effect of focal white matter damage could disseminate throughout white matter tracts by means of both anterograde (e.g. towards the end point of a tract) and retrograde (e.g. towards the source of a tract) axonal degeneration (Trapp and Stys, 2009).

4.3. Cognition and changes in FA patterns

Cognition depends not on the function of single brain regions, but can be assigned to several brain regions that interact and exchange information (Bressler and Menon, 2010). Although previous studies have mainly investigated how the integrity of single white matter tracts, or a cluster of voxels, contributes to cognitive decline in MS (Dineen et al., 2009; Roosendaal et al., 2009; Yu et al., 2012), in this study we investigated whether patterns of white matter integrity underlie cognitive functions in MS patients. Two different approaches were applied to examine the relationship between FA patterns and cognitive function. First, we extracted FA values from the obtained ICs and correlated mean FA z-scores of the different classes with scores for the cognitive domains. Loss of white matter integrity (i.e. reduced FA) of ICs assigned to the 'supratentorial projection tracts' class and 'limbic association tracts' class were correlated with worse performance on several cognitive domains. Although earlier studies did not examined patterns of white matter damage, similar trends were observed previously. More extensive WM abnormalities were associated with worse performance on several cognitive domains in those with secondary progressive MS (Francis et al., 2014; Meijer et al., 2016). Second, the mean IC load for each class and single component loads were correlated with scores for the different cognitive domains. These results indicated that both a greater severity of white matter damage (i.e. reduced FA) and a lower degree of FA covariance (i.e. IC load) were associated with worse cognitive performance. Our results suggest that the loss of underlying FA patterns is associated with cognitive dysfunction. A lower degree of FA covariance could indirectly reflect that structural network integrity is compromised. The strongest correlation between cognitive performance and co-varying FA patterns was observed for the first IC assigned to the "supratentorial commissural tracts" class, consisting of tracts connecting the two hemispheres. It is, however, important to note that the composite score for the component loadings of all ICs assigned to this class were not significantly correlated with cognitive performance. Nevertheless, the importance of commissural tracts for cognitive function in MS has been previously reported. Several studies pointed out the relevance of reduced white matter integrity of tracts connecting the right and left hemispheres for cognitive dysfunction in MS (Dineen et al., 2009; Roosendaal et al., 2009; Schoonheim et al., 2014). Since FA values were correlated with ICs loads, the different approaches resulted in overlapping findings. However, the correlations between cognitive scores and ICs loads were slightly higher than those with FA values.

4.4. Limitations, future directions and conclusion

ICA applied to DTI parameters is an automated extraction method and requires no a priori hypothesis since it is fully data-driven. In this study, the ICs derived from the diffusion data of SPMS patients were visually compared to previously published data from healthy participants (Li et al., 2012). Recently, ICA was applied to concatenated diffusion data from both healthy controls and Alzheimer's patients (Ouyang et al., 2015). However, this approach was based on the assumption that subjects from different groups have common ICs and thus the same underlying pattern of white matter integrity. For future studies it would be interesting to statistically compare differences in white matter patterns without assuming that ICs are similar between groups. Additionally, studies with a larger sample size are needed to investigate factors that potentially influence the microstructural correlations, such as age, sex and level of education. Given the innovative character and the limited number of subjects included, this should be considered an exploratory study. Nevertheless, considering the number of statistical tests, there may be an increased risk of type I errors, which should be taken into account in the interpretation of our results. However, for an alpha level of 0.05 one would expect on average 1 out of 20 false positive results which makes it unlikely that type I errors account for all our significant

results. For the correlation analyses between specific components and cognitive performance a more stringent alpha level of 0.01 was used. In this study we only explored the covariance of FA in SPMS patients, but more microstructural information might be obtained by using other diffusion measures as well. In addition, between patient differences regarding pathology, such as differences in lesion location and the presence of more destructive lesions may influence the observed white matter patterns of FA covariance and should be explicitly taken into account. Last, future studies including a broader range of people with MS can help us to examine exactly how white matter patterns change along the disease course. Here, we studied only SPMS patients with advanced disease progression. Since more severe loss of white matter integrity was associated with loss of FA covariance, we expect that the patterns of FA covariance will be more pronounced and similar to healthy controls in earlier phases of the disease.

In conclusion, this study has shown non-random patterns of white matter FA in MS patients, and the integrity and coherence of these patterns - as measured using FA - were positively associated with executive function, working memory and verbal memory. The structural substrates of these patterns, and the pathological processes that disrupt them, are not known yet. However, our results suggest that they are clinically relevant in people with MS, and therefore may usefully be the subject of further investigation.

Disclosures

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