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ORIGINAL ARTICLE

Investigation of Neurodegenerative Processes in Amyotrophic Lateral Sclerosis Using White Matter Fiber Density

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Abstract

In the current work two novel parameters, fiber density (FD) and mean diffusion signal (MDS) are investigated for evaluating neurodegenerative processes in amyotrophic lateral sclerosis (ALS). The MDS provides a measure of the FD but is derived directly from the diffusion signal. Using tract-based spatial statistics (TBSS), pathological changes across the entire white matter and changes in the parameters over time were evaluated. The results were related to those obtained using the fractional anisotropy (FA) value. A widespread pattern of significantly decreased FD and MDS values was observed. A strong trend towards statistical significance was seen in similar white matter structures using TBSS analysis based on the FA value. Longitudinal analysis of the FD values demonstrated continuing deterioration of the same fiber tracts that were shown to be impaired in the group analysis. The findings suggest that MDS and in particular FD show great promise for evaluating microstructural white matter changes in ALS and may be more sensitive than the more commonly used FA value.

Keywords Amyotrophic lateral sclerosis · Diffusion-weighted imaging · Longitudinal analysis · Mean diffusion signal · Tract-based spatial statistics

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive upper and lower motor signs with a markedly heterogeneous clinical presentation and course [1].

Diffusion magnetic resonance imaging (MRI) has proven to be a reliable method for assessing pathological abnormalities in ALS [2–5]. A commonly assessed parameter is diffusion tensor imaging (DTI) based fractional anisotropy (FA). A reduction in FA is believed to reflect axonal degeneration and demyelination [6–9]. Compared to healthy controls, decreasing FA values in the corticospinal tract (CST) of ALS patients were consistently observed using region of interest analysis and spatial profiling [10–22]. Further-

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more, it has been demonstrated that ALS is a multisystem degenerative disorder [2, 23] that extends beyond the motor system [18, 19, 24–33]. Nevertheless, in areas with complex fiber configurations and multiple fiber populations the FA has been shown to inadequately characterize the underlying tissue structure [34–39] which may reduce sensitivity to ALS-induced neuronal degeneration.

In recent years, a large number of advanced models have been proposed to infer microstructural features of the neuronal tissue from diffusion-weighted imaging (DWI) data, such as axonal diameter and fiber density (FD). Comprehensive overviews have been published [40, 41]. In particular, the FD may be more sensitive than the FA to the neurodegenerative processes that occur in ALS since it more closely represents the underlying anatomy. Until recently the techniques suffered either from long acquisition times or computationally intensive fitting procedures. By combining the estimation of local microstructure properties of the tissue with the versatility of fiber tracking, convex optimization modelling for microstructure informed tractography (COMMIT) overcomes these drawbacks [42]. As a result, intracellular compartment maps are generated, which are a direct measure of and correspond to the FD used in this work. Using numerical simulations, it was in addition shown that under certain experimental conditions the FD in a given direction is proportional to the DWI signal arising from the tissue aligned in that orientation [43]. Thus, the mean diffusion signal (MDS) averaged across a large number of diffusion directions poses a measure of the local FD (for details, see supplementary material Sect. 3). The main advantage of this approach is that it is fast and that the MDS is derived directly from the acquired diffusion signal. Thereby, potentially error-prone post-processing steps such as the fitting of a diffusion model or the reconstruction of stream lines are eliminated.

The present work aimed at investigating the potential of the FD and the MDS for evaluating neurodegenerative processes in ALS using tract-based spatial statistics (TBSS) analysis methods [44] by comparing ALS patients with healthy age-matched controls and by evaluating longitudinal changes in the parameters. The novel parameters may prove to be more sensitive to the microstructural changes in brain white matter than the more commonly used FA value. The FD and the MDS values are compared in 21 ALS patients (mean age = 62.9 years, range = 48–84 years) and 12 healthy controls (mean age = 60.4 years, range = 51–69 years) using TBSS and the results are related to those obtained using the FA value. Correlations of the parameters with disease severity were also calculated. Finally, changes in the parameters over time were investigated in a subset of 17 ALS patients (mean age = 63.1 years, range = 48–84 years).

Material and Methods

Patients and Control Subjects

Patients and age-matched healthy controls were recruited at the Neuromuscular Disease Unit/ALS Clinic of the Cantonal Hospital St. Gallen (St. Gallen, Switzerland). Recruitment took place as part of the European project for sampling and biomarker optimization and harmonization in ALS and other motor neuron diseases (SOPHIA). The study was approved by the Cantonal Research Ethics Committee of St. Gallen (St. Gallen, Switzerland). All participants received written and oral descriptions of the study procedures and provided written informed consent statements in accordance with the declaration of Helsinki before participation in the study.

The initial patient sample consisted of 23 ALS patients (mean age = 62.9 years, range = 48–84 years, 13 female, 10 male, 8 bulbar and 15 limb onset). Of the patients two had to be secondarily excluded due to insufficient data quality caused by extensive head motion (see section on data quality assessment). Thus, 21 ALS patients (mean age = 64.1 years, range = 48–84 years, 12 female, 9 male, 8 bulbar and 13 limb onset) were included in the TBSS analysis. Among these, two had definite, six probable, nine probable laboratory-supported, and four possible ALS according to the revised El Escorial criteria [45]. Beyond that, longitudinal data were acquired 3–6 months (5.55 months ± 1.03 months) after the baseline measurement. Of the patients four were lost to follow-up: one patient died after the baseline measurement, two patients could not further participate in the study after rapid deterioration of respiratory function, and one patient had to be secondarily excluded due to insufficient data quality (see section on data quality assessment). Thus, 17 ALS patients (mean age = 63.1 years, range = 48–84 years) were included in the longitudinal analysis of parameter changes over time. For the control group, 13 age-matched healthy controls (mean age = 61.3 years, range = 51–72 years, 8 female, 5 male) were recruited. Of the control subjects one had to be secondarily excluded due to insufficient data quality so that the control group during data analysis was comprised of 12 healthy subjects (mean age = 60.4 years, range = 51–69 years, 8 female, 4 male).

In the ALS patients, disease severity was assessed at each measurement time point using the revised ALS functional rating scale (ALSFRS-R, maximum score = 48) [46]. In the patient group which was compared to healthy controls, the mean ALSFRS-R score was 39.3 (standard deviation = 5.0, range = 22–44). In the patient group whose data were analyzed longitudinally, the mean ALSFRS-R score was 39.9 (standard deviation = 3.5, range = 30–44) at

baseline and 36.4 at follow-up (standard deviation = 4.3, range = 27–43).

Acquisition of MRI Data

Acquisition of MRI data was performed on a 3 T whole-body scanner (Achieva, Philips Healthcare, Best, the Netherlands, release 5.1.7), equipped with 80 mT/m gradients and an 8-element receive-only head coil array. The DWI data were acquired using a diffusion-weighted single-shot spin-echo echo-planar imaging sequence with the following parameters: repetition time (TR) = 8.565 s, echo time (TE) = 49 ms, field of view (FOV) = 224 × 224 mm^2, 48 contiguous transversal slices, slice thickness = 2.5 mm, acquisition matrix = 96 × 96, Sensitivity Encoding (SENSE) factor = 2.1, partial Fourier encoding = 60%. The slices were positioned parallel to a line bisecting the anterior and posterior commissure defined on a T1-weighted midline sagittal survey image. The DWI acquisition was performed along 64 directions distributed uniformly on a half-sphere [47] with a b-value of 1000 s/mm^2. Additionally, six non-diffusion-weighted b = 0 s/mm^2 scans were acquired resulting in a scan time of 10 min 8 s. For structural reference and anatomical priors for the tracking algorithm, T1-weighted images were recorded using a three-dimensional magnetization prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: TR = 8.2 ms, TE = 3.8 ms, FOV = 240 × 240 × 160 mm^3, voxel size = 1 × 1 × 1 mm^3, flip angle = 8°.

Data Quality Assessment

First the quality of all DWI data was assessed based on several criteria. To this end, the brain extraction tool [48] from FSL (*FMRIB Software Library*, Analysis Group, FMRIB, Oxford, UK, version 5.0.6) [49] was applied to remove non-brain tissue from the diffusion data and to estimate the inner and outer skull surfaces. Thereafter, the DWI data were corrected for eddy current-induced image distortions and subject motion using the eddy tool in FSL [50]. Diffusion tensor residuals were calculated for every acquired diffusion direction and the nine slices in the whole diffusion dataset with the highest residuals were identified for visual inspection. Furthermore, the MRtrix3 software package (Brain Research Institute, Melbourne, Australia, version 0.3.12) was applied to estimate the voxel-wise noise level using the residuals from a truncated spherical harmonics fit. Plots were generated depicting the 12 slices with the highest noise level, 4 in sagittal, 4 in axial, and 4 in coronal direction. In addition, mean signal intensity plots for every diffusion direction and the non-DWI were derived and plotted slice by slice in sagittal, axial, and coronal directions. Peaks in these signal courses often indicate head motion. Based on a subject-wise visual inspection of these signal courses and fitting residuals, a rating was performed on a Likert-type scale by two trained MR physicists. Beyond that, the DWI data were visually inspected for artifacts. As noted above, two patients and one healthy control subject had to be secondarily excluded in the group comparison and another patient in the longitudinal study based on this quality assessment.

DWI Data Analysis and Parameter Calculation

FD Computation

Fiber orientation distribution (FOD) reconstruction and fiber tractography using the default iFOD2 probabilistic tracking algorithm was performed in MRtrix3 [51]. The resulting streamlines were optimized using the COMMIT framework [42] to derive the FD for every subject and measurement time point. Full details of the diffusion data

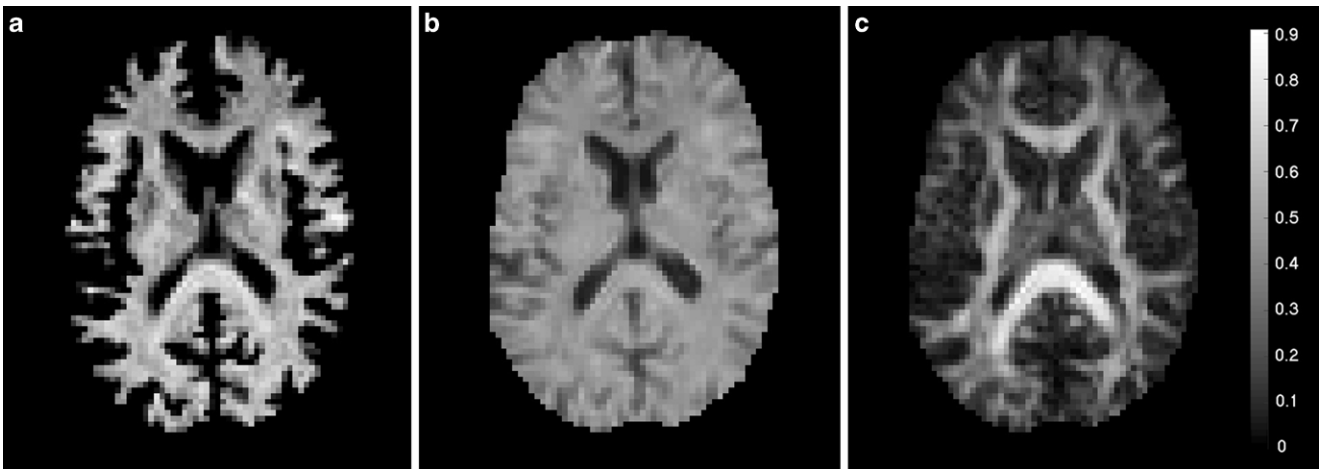

Fig. 1 **a** FD, **b** MDS, **c** FA maps of a single transversal slice in a healthy volunteer for visual comparison

processing can be found in the supplementary material (Sect. 1).

MDS and FA Computation

The FA maps of every dataset were calculated with FSL and the normalized mean diffusion signal (MDS) was derived using the following formula:

$$MDS = \frac{\sum_{i=1}^{n} \frac{S_i}{S_0}}{n},$$

thereby S_i corresponds to the diffusion-weighted images, S_0 to the non-diffusion weighted ($b = 0 s/mm^2$) image and n refers to the total number of directions on the shell.

By way of example, Fig. 1 depicts FD, MDS, and FA maps of a single axial slice in a healthy volunteer for visual comparison.

TBSS Analysis

The TBSS analysis was performed firstly to assess differences between ALS patients and healthy controls and secondly to investigate changes in the diffusion parameters over time in the ALS patients. Thereby, the standard processing steps as described in [44] were used. Full details of the TBSS analysis processing steps can be found in the supplementary material (Sect. 2).

In each case two contrasts were computed, testing for positive and negative differences of the parameters in the ALS patients compared to healthy controls and across two points in time, respectively. Furthermore, for the ALS patients, voxel-wise correlations between disease severity (measured by the ALSFRS-R score) and the FD, the MDS, and the FA values were computed by TBSS regression analysis using the ALSFRS-R score as the predictor variable. For all TBSS analyses, the randomize tool implemented in FSL [52] was applied with 5000 permutations to correct for multiple comparisons, and a p-value <0.05 was considered statistically significant.

Results

ALS Patients Versus Healthy Controls and Correlation with Disease Severity

Fig. 2 depicts the results of the TBSS analysis based on the FD (Fig. 2a) and the MDS (Fig. 2b) values whereas Fig. 3 illustrates the results based on the FA values in ALS patients versus age-matched healthy controls. A significant deterioration of the white matter integrity in the patient group, as reflected by reduced FD and MDS values, was found in several white matter regions (see Fig. 2a, b). A high agreement of the results derived based on the FD and the MDS values was observed. Significant decreases of both parameters were found along the projection fibers, including the right and left parts of the CST and the thalamic radiation. Furthermore, significantly reduced FD and MDS values were detected along the commissural fibers, namely the body of the corpus callosum (CC) as well as the forceps major and minor. Beyond that, TBSS analysis revealed significantly decreased values of both parameters in the association fibers, including the uncinated fasciculus, the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF), and the inferior fronto-occipital fasciculus (IFOF). With respect to the SLF and the ILF, decreased FD values were observed in both hemispheres while reduced MDS values were observed only in the right parts of the fiber tracts. Finally, reduced parameter values were detected in the limbic system tracts, namely the cingulum.

No statistically significant changes in the FA values could be detected but a strong trend towards a statistically significant decrease was observed especially in the CC as illustrated in Fig. 3a which shows significant clusters at a p-value of <0.10. With increasing p-values (see Fig. 3b for a p-value of 0.20), similar patterns of clusters as derived using TBSS analysis based on the FD and the MDS values showed up.

Finally, TBSS analysis did not reveal significant correlations of the diffusion parameters with disease severity as measured by the ALSFRS-R.

Parameter Changes over Time

The TBSS analysis revealed statistically significant changes in the FD and the FA values over time in various anatomical locations. In contrast, no significant differences of the MDS values were observed between time points ($p < 0.05$).

Fig. 4 depicts significant changes in the FD values over time. With disease progression, significant decreases in the FD values were observed in the left hemisphere. The FD values decreased in parts of the CST, the thalamic radiation, the body of the CC, the arcuate fasciculus, the uncinate fasciculus and in various association fibers, namely the SLF, the ILF, and the IFOF.

Fig. 5 illustrates significant changes in the FA values over time. Surprisingly, an increase in the FA values was found in several regions in the right hemisphere. These included parts of the CST, the splenium of the CC, the SLF, the ILF, the IFOF, the thalamic radiation, the arcuate, and the uncinate fasciculus.

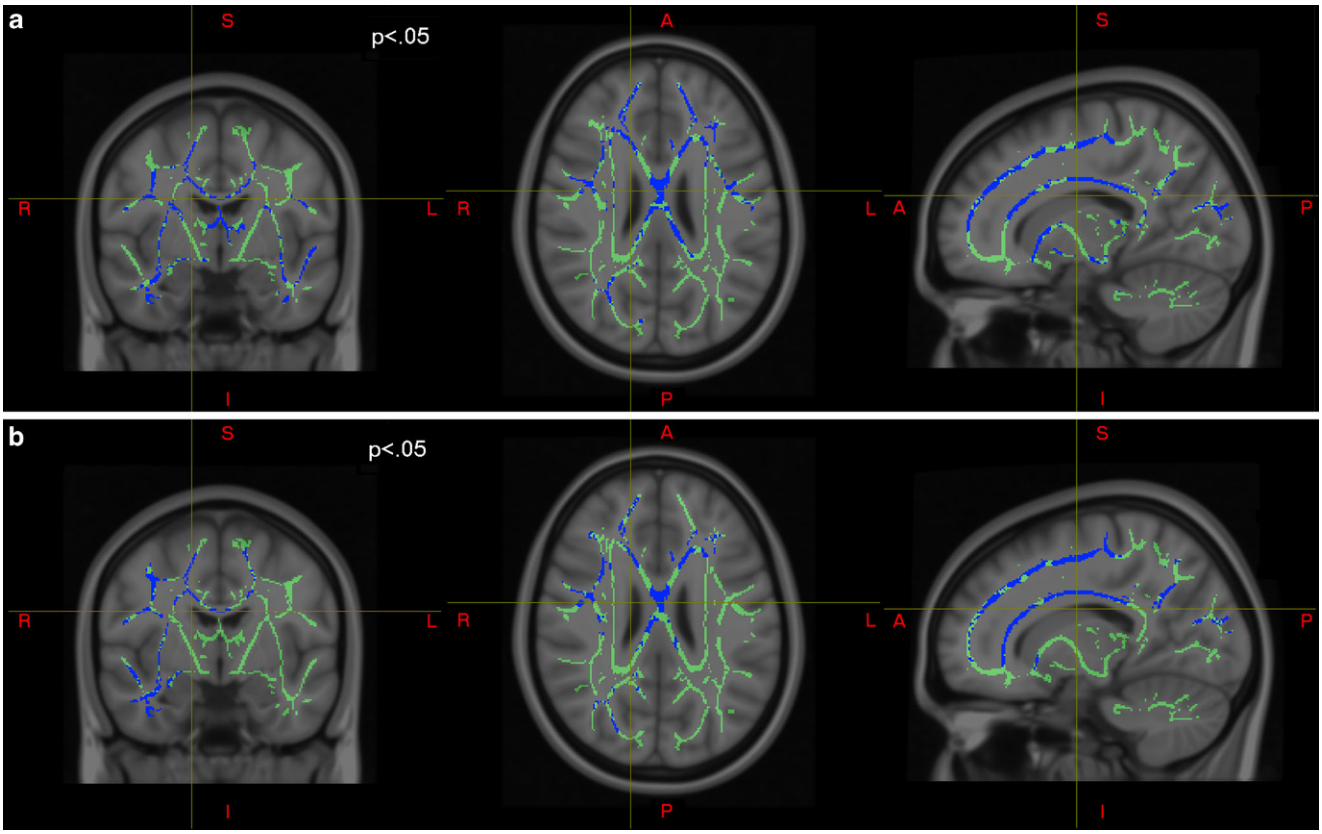

Fig. 2 Tract-based spatial statistics (TBSS) results of the comparison of (**a**) the fiber density (FD) and (**b**) the mean diffusion signal (MDS) values between amyotrophic lateral sclerosis (ALS) patients and age-matched healthy controls on coronal, axial, and sagittal views (from *left* to *right*). Clusters exhibiting statistically significant decreases ($p < 0.05$) in the diffusion parameters are shown in *blue* on the *green* TBSS fractional anisotropy (FA) skeleton. There is a high anatomical agreement between the clusters derived based on the FD and the MDS values (*R* Right, *L* Left, *S* Superior, *I* Inferior, *A* Anterior, *P* Posterior)

Discussion

In the present work, the benefit of the FD and the MDS for evaluating neurodegenerative processes in ALS patients was investigated using TBSS. The findings demonstrate that the MDS and in particular the FD may be more sensitive to white matter changes than the FA value and may permit evaluating pathological processes at an earlier stage of the disease. Data of 21 ALS patients were compared to those of 12 healthy controls. Beyond that, changes in the parameters over time were evaluated in a subset of 17 ALS patients. The TBSS results were compared to those obtained based on the FA value, a parameter that has been evaluated in numerous clinical studies as a potential indicator for pathological changes in ALS [53–55]. Compared to healthy controls, the FD and the MDS were significantly reduced in various white matter structures throughout the brain. Although no statistically significant changes in the FA values were observed, a similar trend as for the FD and the MDS values was observed. Furthermore, based on the FD value, continuing deterioration of the previously identified impaired fiber tracts was found in the ALS patients. The results indicate that the FD and the MDS may be more sensitive to the neurodegenerative changes that occur in ALS than the commonly used FA value.

The TBSS analysis of the FD and the MDS revealed a widespread pattern of white matter impairment affecting both motor and extra-motor fiber tracts which is in agreement with previous results [13, 18, 19, 26–28, 30, 33, 56–58] confirming the view of ALS being a multisystem degenerative disorder [2, 23]. Significantly reduced values of the FD and the MDS in ALS patients relative to healthy controls were observed in the projection fibers, the commissural fibers, the association fibers, and the limbic system tracts. The observed pattern of white matter changes is in close agreement with a previous TBBS analysis based on the FA value [33] but the present findings suggest that the FD and the MDS may be more sensitive parameters for the evaluation of microstructural changes in ALS. The pyramidal cells of the precentral gyrus are also called upper motor neurons. The fibers of the upper motor neurons project out of the precentral gyrus ending in the lower medulla oblongata to form the lateral corticospinal tract on each side of the spinal cord. A lesion or degeneration of these neurons

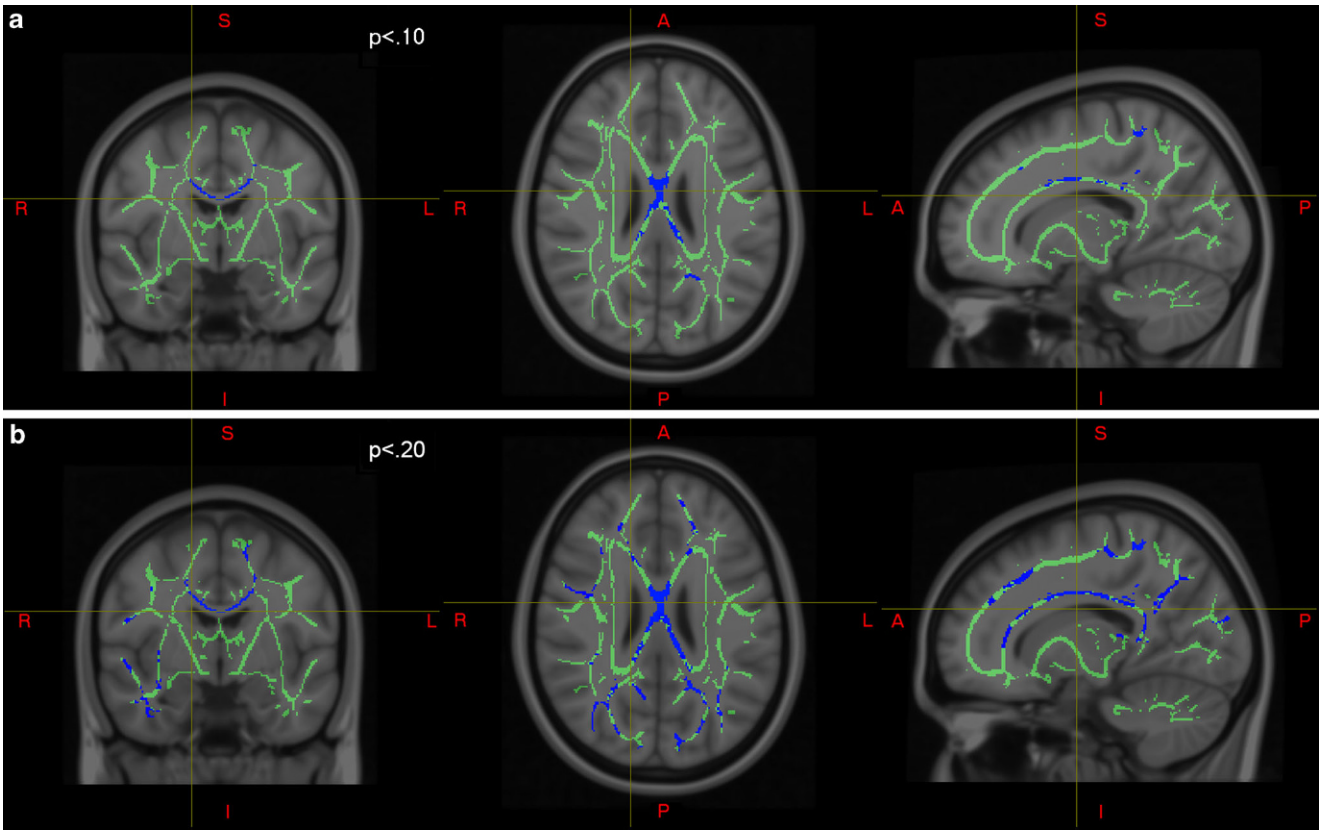

Fig. 3 Tract-based spatial statistics (TBSS) results of the comparison of fractional anisotropy (FA) values between amyotrophic lateral sclerosis (ALS) patients and age-matched healthy controls on coronal, axial, and sagittal views (from *left* to *right*). Clusters exhibiting a strong trend towards a statistically significant decrease in FA values are shown in *blue* on the *green* TBSS FA skeleton: (**a**) clusters at a *p*-value of <0.10 and (**b**) clusters at *p*-value of <0.20. There is a high anatomical agreement between the clusters derived based on the FA values and the findings based on the fiber density (FD) and the mean diffusion signal (MDS) values (*R* Right, *L* Left, *S* Superior, *I* Inferior, *A* Anterior, *P* Posterior)

result in a paresis, loss of fine motor skills and spasticity of the upper and lower extremities as typical clinical signs of an upper motor dysfunction or loss [59].

In line with expectations, significantly decreasing values of the FD were observed over time in various white matter structures, especially in the left hemisphere. The fiber tracts affected by continuing deterioration agreed with those that had already shown decreased FD values in the group analysis of ALS patients versus healthy controls. The lateralization of decreased FD values in the left hemisphere over time might be explained by a high occurrence of disease onset in the right (vs. left) limbs of the patient population. No significant changes of the MDS over time were observed. Since DWI data were acquired as part of the European project SOPHIA, DWI was performed with a maximum b-value of 1000 s/mm^2. Higher b-values, however, are required to ensure the proportionality of the FD to the diffusion-weighted signal [43, 60] (see also Sect. 3 of the supplementary material) and may increase sensitivity of the MDS to pathological processes in ALS. Thus, further studies incorporating higher b-values are needed to corroborate the benefit of the MDS for investigating neurodegenerative processes in ALS. Contrary to expectations, increasing FA values were observed in several white matter structures over time in the right hemisphere. This finding may be explained by the degeneration of minor fiber bundles perpendicular to the dominant fiber bundle in the respective voxel which would artificially increase the FA value despite the occurrence of axonal loss. In musicians, significantly increased FA values were observed in the right arcuate fasciculus after music-cued left-handed motor training [61]. Similarly, the more intensive use of the unaffected limbs in ALS patients might lead to increasing FA values in the hemisphere contralateral to the affected hand. Due to this bias in disease onset lateralization in the patient group, the right limbs are more affected in the early stage of the disease and thus the left limbs (predominately controlled by the right hemisphere) might compensate these deficits. So far, relatively few studies have investigated FA changes in white matter structures of ALS patients over time and these studies have yielded inconsistent results. Some observed significantly decreased FA values over time [29, 62, 63] while others found no significant changes in the FA values [19, 64, 65].

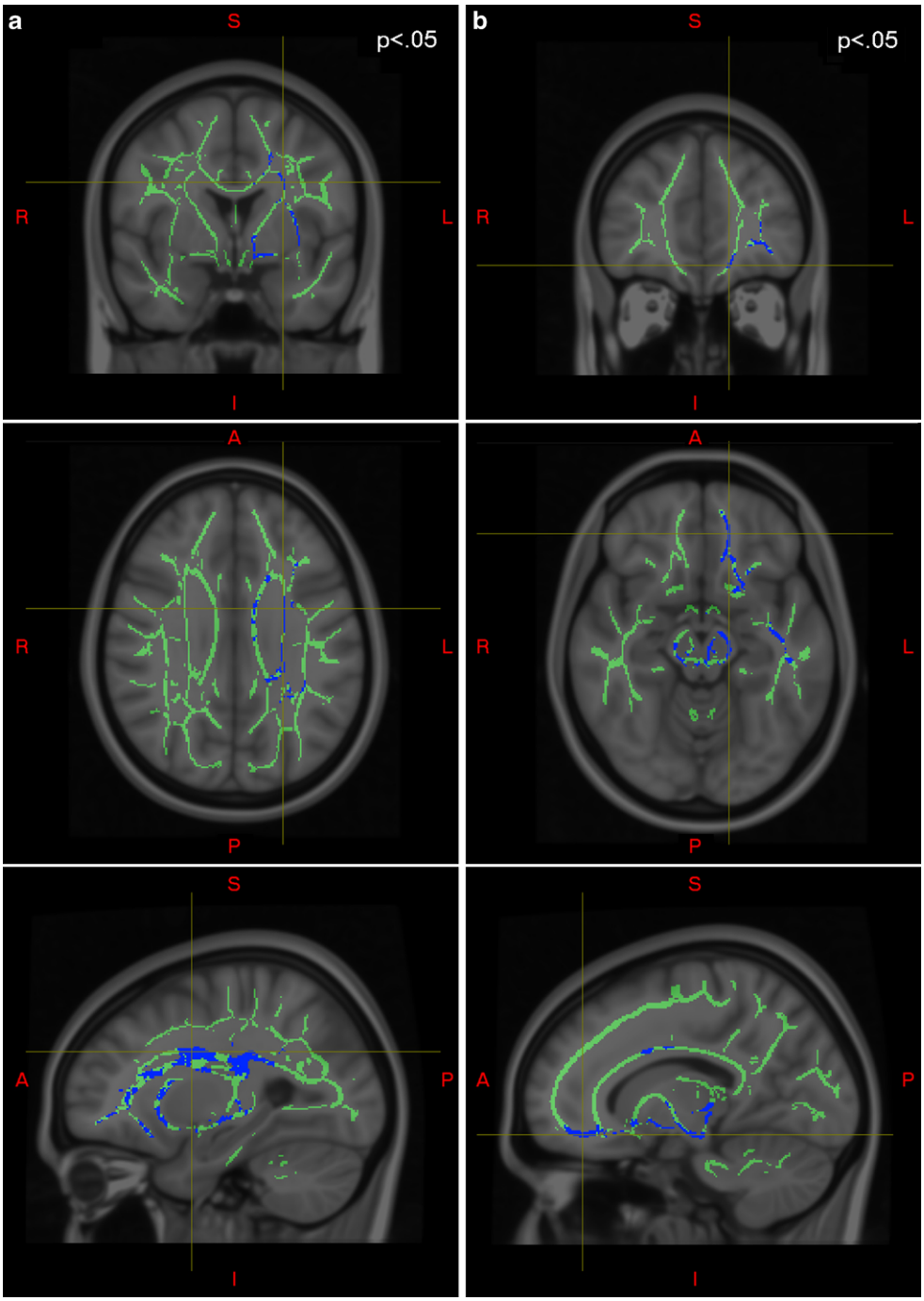

Fig. 4 Tract-based spatial statistics (TBSS) results of the changes in the fiber density (FD) values in the amyotrophic lateral sclerosis (ALS) patients over time on coronal, axial, and sagittal views (from *top* to *bottom*). Clusters exhibiting statistically significant decreases in the FD values are shown in *blue* on the *green* TBSS fractional anisotropy (FA) skeleton. The two columns (**a**) and (**b**) depict different anatomical locations (*R* Right, *L* Left, *S* Superior, *I* Inferior, *A* Anterior, *P* Posterior)

Compared to the FD and the FA, it should be stressed that the MDS is derived directly from the acquired diffusion signal and thus does not rely on potentially error-prone post-processing steps. Furthermore, the simplicity of its computation facilitates applicability in the clinical setting. The MDS is closely related to the mean diffusivity derived from the diffusion tensor (by a logarithmic transform) but the MDS is not coupled to a tensor model and therefore does not rely on the Gaussian assumption. As noted before, the FD in a given direction is proportional to the diffusion-weighted signal arising from the tissue aligned in that orientation [43]. Thus, the MDS constitutes a measure of the local FD. For this reason, a high correspondence between FD and the MDS findings is expected and was confirmed in the present study.

No significant correlations of the parameters with disease severity have been observed. This may have been caused by the relatively low number of study participants, the composition of the patient group which featured a relatively narrow range of the ALSFRS-R scores or the relative lack of

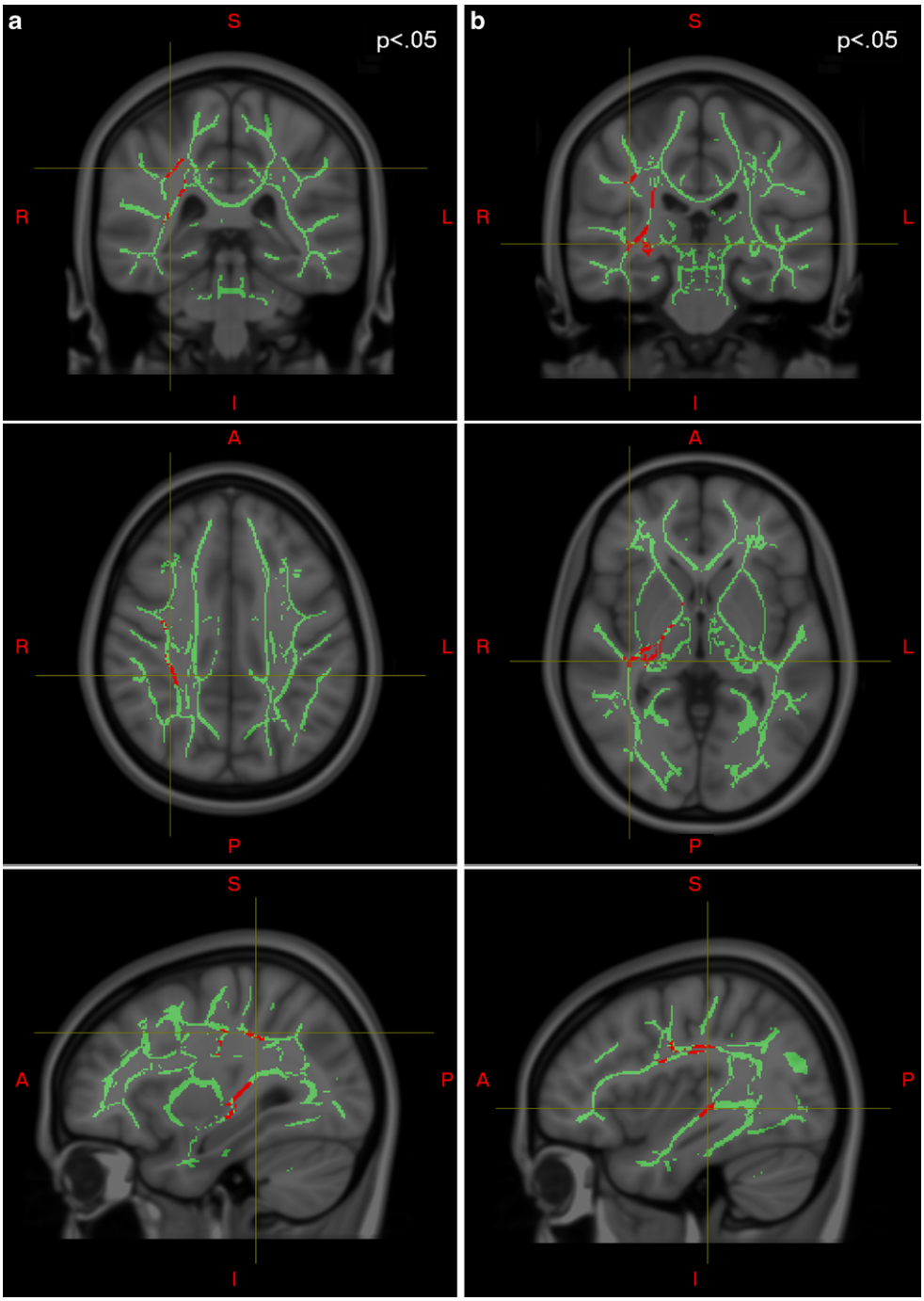

Fig. 5 Tract-based spatial statistics (TBSS) results of the changes in the fractional anisotropy (FA) values in the amyotrophic lateral sclerosis (ALS) patients over time on coronal, axial and sagittal views (from *top* to *bottom*). Clusters exhibiting statistically significant increases in the FA values are shown in *red* on the *green* TBSS FA skeleton. The two columns (**a**) and (**b**) depict different anatomical locations (*R* Right, *L* Left, *S* Superior, *I* Inferior, *A* Anterior, *P* Posterior)

the ALSFRS-R to upper motor neuron involvement; however, inconsistent results have been reported in previous studies with some studies observing correlations of the FA values with the ALSFRS-R [11, 12, 19, 26, 31, 33, 62, 66, 67] while others found that it does not relate to disease severity [15, 21, 32, 57, 68–70].

When comparing ALS patients to healthy controls, changes in the parameters were predominantly observed in the right hemisphere. Similarly, asymmetry was observed when changes in the parameters over time were evaluated. These findings are in agreement with previous studies in ALS [19, 30, 70] and with the report of asymmetry in motor neuron pathology [71].

A limitation of the present work is the already noted relatively small patient population and in addition, three patients had to be secondarily excluded from data analysis due to severe motion-induced artifacts, two in the group analysis and one in the longitudinal study. This might be the reason why only a trend towards statistically reduced FA values was observed in ALS patients relative to healthy controls.

Due to the limited number of patients, the population was not subdivided into patients with bulbar versus limb onset. Furthermore, the disease onset predominantly occurred in the right limbs. Additionally, the relatively short follow-up period of 3–6 months may be insufficient to reliably capture the full evolution of white matter changes in ALS; however, despite the relatively short interval, three patients were lost to follow-up, in one case since the patient died prior to the termination of the study and in two cases due to an acute deterioration in their health condition which made further participation in the study impossible. Since a wide range of survival times are observed in ALS ranging from a few months to several decades [1], it is difficult to determine the optimum follow-up period and larger patient cohorts are required to reliably evaluate white matter changes over time. Nevertheless, despite the relatively short follow-up period, changes in various white matter structures throughout the brain were detected using the FD values.

Conclusion

The present work showed that the MDS and in particular the FD show great promise for evaluating white matter integrity and neurodegenerative processes in ALS. The findings suggest that the parameters may be more sensitive to white matter changes than the FA value and may permit evaluating pathological processes at an earlier stage of the disease.

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Compliance with ethical guidelines

Conflict of interest P. Stämpfli, S. Sommer, D. Czell, S. Kozerke, C. Neuwirth, M. Weber, S. Sartoretti-Schefer, E. Seifritz, A. Gutzeit and C. Reischauer declare that they have no competing interests.

Ethical standards All procedures described in this article were carried out in accordance with national law and the Helsinki Declaration of 1964 (in its current revised form). Informed consent was obtained from all patients included in the study.

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