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Brain white matter abnormalities and correlation with severity in amyotrophic lateral sclerosis: An atlas-based diffusion tensor imaging study

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ABSTRACT

Objectives: To assess microstructural alterations in white matter (WM) in amyotrophic lateral sclerosis (ALS) using diffusion tensor imaging (DTI).

Methods: DTI data were collected from 34 subjects (18 patients with ALS and 16 healthy controls). The atlas-based region of interest (ROI) analysis was conducted to assess WM microstructure in ALS by combining intra-voxel metrics, which included fractional anisotropy (FA) and mean diffusivity (MD), and an inter-voxel metric, i.e., local diffusion homogeneity (LDH). Correlation analysis of diffusion values and clinical factors was also performed.

Results: ALS group showed a significant FA reduction in bilateral corticospinal tract (CST) as well as right uncinate fasciculus (RUF). The areas with higher MD were situated in right corticospinal tract (RCST), left cingulum hippocampus (LCH), RUF, and right superior longitudinal fasciculus (RSLF). Additionally, ALS patients showed decreased LDH in bilateral anterior thalamic radiation (ATR), bilateral CST and left inferior frontal-occipital fasciculus (LIFOF). Significant correlations were observed between ALSFRS-R (revised ALS Functional Rating Scale) scores or progression rate and FA in bilateral CST, as well as between disease duration and LDH in right CST. Receiver operating characteristic (ROC) analysis revealed the feasibility of employing diffusion metrics along the CST to distinguish two groups (AUC = 0.792–0.868, $p < .005$ for all).

Conclusions: WM microstructural alteration is a common pathology in ALS, which can be detected by both intra- and inter-voxel diffusion metrics. The extent of abnormalities in several WM tracts such as ATR and LIFOF may be better assessed through the inter-voxel diffusion measurement.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that mainly involves the upper and lower motor neurons, resulting in disability in bulbar and limb function. It has a relatively short mean survival time (i.e., 3–5 years from onset of symptoms). The pathogenesis of ALS remains unclear, and heterogeneity in clinical symptoms and disease progression further complicates its diagnosis [1]. Furthermore, no curative treatment is available for ALS and > 40% patients undergo inappropriate medical treatment, including surgery currently [2]. ALS has been regarded as a disease involving the gray matter, although pathological changes involving WM such as axonal loss or demyelination and oligodendrocyte death may also occur in ALS patients [3].

Post-mortem analyses of ALS brains has indicated that large areas of the WM, such as the CST, the corpus callosum and fibers in the globus pallidus, the ansa lenticularis, and the fasciculus lenticularis, may be affected by the disease [4,5]. Furthermore, neuroimaging studies have also revealed the involvement of WM in ALS in vivo [6]. One study using voxel-based intensitometry (VBI) based on T1-weighted images

Abbreviations: ALS, Amyotrophic lateral sclerosis; ALSFRS-R, Revised ALS functional rating scale; AUC, Area under the receiver operating characteristic curve; DTI, Diffusion tensor imaging; FA, Fractional anisotropy; LDH, Local diffusion homogeneity; MD, Mean diffusivity; ROC, Receiver operating characteristic; ROI, Region of interest; WM, White matter

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Table 1
Patient demographics and clinical features.

	Healthy controls (n = 16)	ALS patients (n = 18)	P value
Age (year)	52.7 ± 6.5 (45–61)	55.5 ± 4.9 (48–63)	0.17
Sex (male/female)	10/6	12/6	0.80
Education (year)	8.0 ± 3.5 (4–15)	6.3 ± 3.0 (4–12)	0.14
Site of onset (Bulbar/cervical/thoracic/lumbosacral)	–	1/9/1/7	–
Diagnostic category (Definite/probable/possible)	–	6/4/8	–
ALSFRS-R score	–	40.0 ± 7.8 (22–47)	–
Disease duration (months)	–	18.1 ± 14.5 (2–48)	–
Disease progression rate	–	0.86 ± 0.95 (0.03–2.00)	–

ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS Functional Rating Scale. Disease Progression Rate was calculated as (48-ALSFRS-R)/disease duration. "-" denotes no data available. The range of variables is shown in bracket.

showed widespread WM changes in ALS [7], which is correlated to disease severity. In addition, patterns of cerebral involvement varied between bulbar- and limb-onset ALS [8–11]. Spectroscopic measurement of NAA/Cr in the SWM (subcortical white matter) and PV (periventricular WM) were significantly different in ALS patients [12], which mean neuronal loss or neuronal metabolism abnormity in patients suffering from ALS. Positron emission tomography (PET) indicated an increase in ^{18}F-FDG uptake in affected motor neurons as well as descending WM tracts of ALS patients, which is related to astrocyte and microglial proliferation, as glial cells serve as sites for glycolytic metabolism upon brain activation [13]. Taken together, in vitro and in vivo studies have revealed WM damage in ALS patients. Studies have also revealed the topographical changes in WM, which extending from the motor to the extra-motor tracts in ALS [14]. In addition, these may be utilized in classifying patients based on disease stage [15,16].

Diffusion MRI is considered as a promising and non-invasive approach in assessing the extent of fiber damage in a range of disease processes that influence WM. DTI has been employed in assessing UMN pathology in ALS patients [17–23] and investigations have shown that it is a sensitive tool for the detection of WM microstructural abnormalities based on fractional anisotropy (FA) and mean (MD), axial (AD), and radial (RD) diffusivity features [24–26]. FA represents fraction anisotropy of water molecular diffusion and is sensitive to fibers that are aligned over a significant area such as the corpus callosum, corticospinal tract, or optic tract [8,27]. MD is a measure for the mean molecular motion that is independent of tissue directionality [27,28]. AD, which is the primary eigenvector, has been used for assessing water diffusivity that runs in the direction of the fiber tract and allows evaluation of axonal functions or degeneration [29]. RD represents diffusivity that is perpendicular to the axonal fibers and shows higher sensitivity to myelin abnormalities [29,30]. Above all are used intra-voxel diffusion measurements to observe WM damage, whereas another inter-voxel diffusion metric has been recently proposed, called local diffusion homogeneity (LDH), which never been used for evaluating microstructural changes of WM in ALS. A previous study has demonstrated that LDH can represent the local coherence of water molecule diffusion, which is defined as the similarity in water diffusion profile between voxels and their neighbors [31]. It is speculative that LDH measurement can reflect the specific microstructural properties (such as fiber orientations, myelination, diameter and density) along WM fibers [31,32]. LDH has been utilized in assessing distinct changes in particular WM regions in the elderly or individuals diagnosed with vascular cognitive impairment, diabetes mellitus, temporal lobe epilepsy and schizophrenia [31–35]. LDH thus generates important information that could complement conventional DTI data. Hence, this study simultaneously utilized both intra- and inter-voxel diffusion metrics to more extensively assess microstructural changes in the WM of ALS patients, as well as analyze their correlation with clinical parameters.

2. Materials and methods

2.1. Subjects

The 18 patients with ALS (1 familial, 17 sporadic) and 16 healthy controls were included in this study. Participants with ALS were recruited through physician referrals in our hospital. ALS was diagnosed using the El Escorial criteria [36], and disease severity was assessed using the revised ALS Functional Rating Scale (ALSFRS-R). Of ALS patients, 5 subjects were undergoing the treatment of Riluzole, when they were recruited. The healthy controls were recruited through community advertisements. The clinical and demographic data are provided in Table 1. No significant differences in terms of age, sex, or education level were observed among the patients and control groups. The exclusion criteria were as follows: (1) other neuropsychiatric disorders, including Alzheimer's disease, Parkinson's disease, depression, or epilepsy; (2) taking psychotropic medications; (3) suffering from respiratory failure or other serious disorders such as angiocardiopathy and cancer; or (4) contraindication of MRI examination. This study was approved by the Research Ethics Committee of Fujian Medical University Union Hospital, China. All study participants provided their written informed consent.

2.2. MRI data acquisition

A 3 T MRI scanner (Prisma, Siemens Medical Systems, Erlangen, Germany) was employed to acquire images. The DTI data were generated using a spin-echo single-shot echo-planar imaging sequence using the following parameters: b = 1000 s/mm^2 and 64 encoding diffusion directions; one non-diffusion-weighted image (b = 0 s/mm^2); repetition time = 2500 ms; echo time = 81 ms; number of averages = 1; slice thickness = 2 mm without gap; field of view = 260 mm × 260 mm; matrix = 130 × 130; flip angle = 90°; 72 axial slices; multiband factor = 4.

2.3. DTI data processing

Diffusion data preprocessing was performed using the Pipeline for Analyzing Brain Diffusion Images toolkit (PANDA [37]; http://www.nitrc.org/projects/panda/). Geometric correction of individual diffusion images was performed using an unweighted B0 image (b = 0 s/mm^2) and a filed map, which was then co-registered to the B0 image using the linear least-squares fitting method to reduce effect of head movements. Diffusion-tensor models were calculated at each voxel. After that, the FA, MD, and LDH maps can be computed for each subject. The LDH images (pre-defined neighborhood = 26 voxels) were calculated, referring to [31]. All of the procedures about these metrics calculation have been implemented in the PANDA toolbox [37].

The atlas-based ROI (region of interest) analysis was performed to investigate the between-group difference in DTI measurements. The FA images of all subjects were aligned onto a FMRIB-58 FA template in the

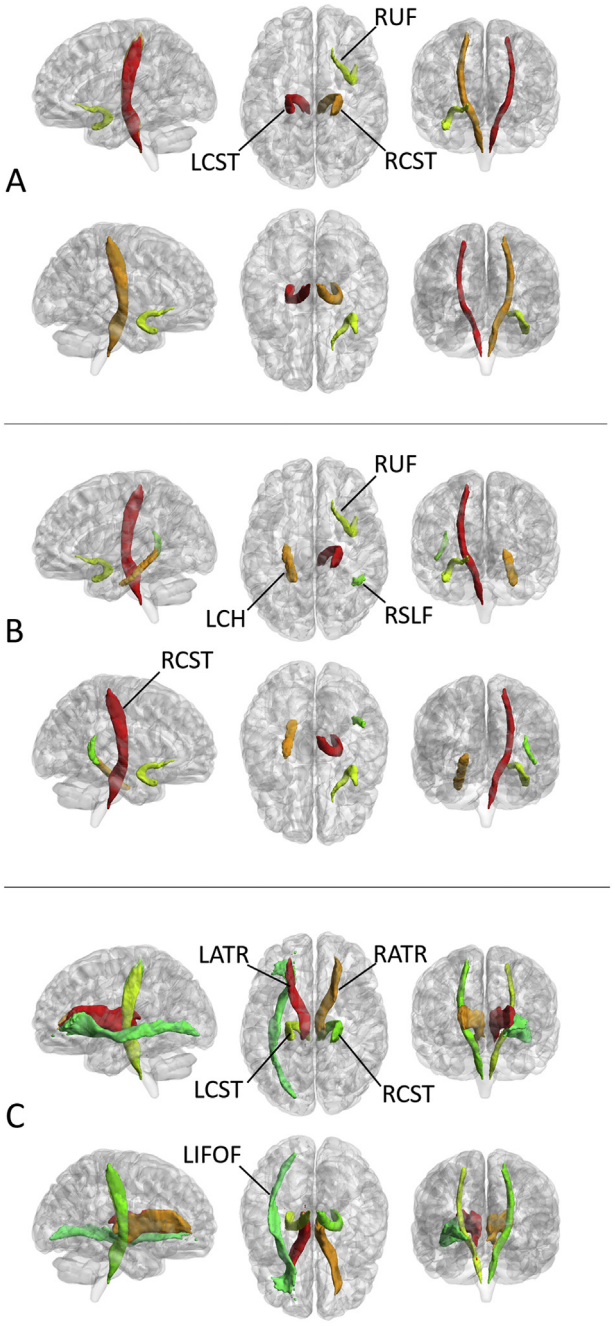

Fig. 1. The white matter (WM) tracts with significant between-group differences in FA (A), MD (B) and LDH (C), respectively. "R" and "L" indicate right and left side, respectively. RUF, right uncinate fasciculus; RCST, right corticospinal tract; LCST, left corticospinal tract; LCH, left cingulum hippocampus; RSLF, right superior longitudinal fasciculus (temporal part); LATR, left anterior thalamic radiation; RATR, right anterior thalamic radiation; LIFOF, left inferior frontal-occipital fasciculus. These tracts were defined by the JHU ICBMDTI-81 white matter atlas (Johns Hopkins University International Consortium for Brain Mapping; http://cmrm.med.jhmi.edu/).

Montreal Neurological Institute (MNI) space with a non-linear registration algorithm. The resulting spatial normalization information obtained by FA analysis was also employed in the MD and LDH images. Then, all images were smoothened using a 6-mm FWHM (Full Width at Half Maximum) Gaussian kernel. After that, the mean DTI metric values were extracted for each ROI that was defined by the JHU ICBMDTI-81 white matter atlas (Johns Hopkins University International Consortium for Brain Mapping; http://cmrm.med.jhmi.edu/).

2.4. Statistical analysis

The two-sample *t*-test was used to examine the between-group difference in every DTI measurement; statistical significance was set at $P < .05$, following correction for multiple comparisons using the False Discovery Rate (FDR) method. Spearman correlation coefficients were computed to assess the correlation of clinical variables to the mean values of diffusivity parameters of the regions that survived between-group comparisons, using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA); and FDR-corrected *P*-values < .05 were deemed statistically significant. We conducted ROC analysis to assess the discrimination performance of various diffusion metrics between the two groups; and the area under the ROC curve (AUC) was estimated using SPSS software.

3. Results

WM regions with diffusion metrics exhibiting significant between-group differences are presented in Fig. 1. Relative to the control group, the ALS group showed significantly lower FA values in the bilateral corticospinal tract and right uncinate fasciculus. The areas with higher MD were located in right corticospinal tract, left cingulum hippocampus, right uncinate fasciculus, and right superior longitudinal fasciculus (temporal part). In addition, ALS patients showed decreased LDH in bilateral anterior thalamic radiation, bilateral corticospinal tract, and left inferior frontal-occipital fasciculus.

Correlation analysis revealed a positive correlation between the mean FA values along the bilateral corticospinal tracts and the ALSFRS-R scores and a negative correlation between the mean FA values along the bilateral corticospinal tracts and the progression rate of the ASL patients (Fig. 2). Meanwhile, the LDH value along right corticospinal tract was negatively correlated with disease duration. No significant correlation was detected between various clinical measures and the MD values along the fiber tracts showing significant between-group differences.

Furthermore, the WM tracts whose diffusion metrics exhibited significant correlations with clinical parameters were utilized as target tracts for ROC analysis (Fig. 3). FA value along right corticospinal tract (AUC = 0.868, $p = .003$) and left corticospinal tract (AUC = 0.802, $p = .0003$) showed moderate discrimination potential. Meanwhile, LDH values along right corticospinal tract (AUC = 0.792, $p = .004$) also exhibited moderate potential in distinguishing the two groups.

4. Discussion

The present study employed an atlas-based DTI method to identify alterations in the microstructural properties of WM tracts of ALS patients. We found WM abnormalities extending from the motor to the extra-motor regions in ALS. We have also observed a correlation between distinct diffusion metrics and various clinical variables. These findings support the contention that WM damage is a common pathology in ALS [3,11,38–41], which may contribute to clinical syndromes and cognitive dysfunction [41,42], and DTI metrics may be utilized as the diagnostic biomarker of ALS. Meanwhile, it was noted that the extent of WM abnormalities in several tracts (e.g. ATR and LIFOF) were better revealed by LDH measurement, suggesting the supplementary role of inter-voxel diffusion evaluation to the intra-voxel ones in reflecting ALS-related pathological process.

Both intra- and inter-voxel diffusion metrics were simultaneously assessed to comprehensively evaluate WM microstructural alterations in ALS. FA is a normalized ratio of diffusion directionality that reflects the extent of alignment of cellular structures of fiber tracts and thus provides an indirect measure of pathological alterations in the axons or myelin in the brain WM [38]. MD measures the bulk mobility of water molecules that reveals changes in water diffusion in the extracellular space due to axonal loss [43]. Neuropathological alterations of the WM,

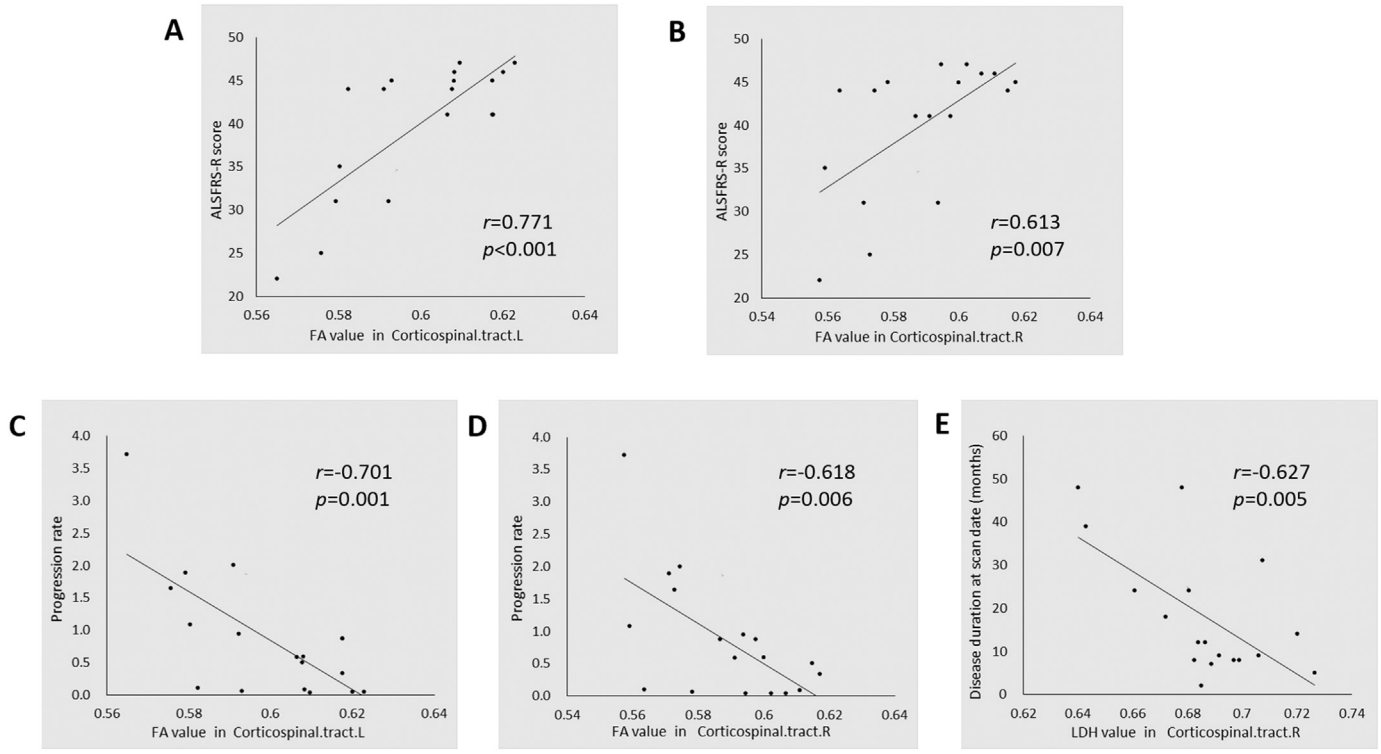

Fig. 2. Correlations between the diffusion measurements and the clinical parameters. A-D show FA value along bilateral corticospinal tract correlated significantly with both ALSFRS-R score and progression rate. E shows that there is significant correlation between LDH in right corticospinal tracts and disease duration.

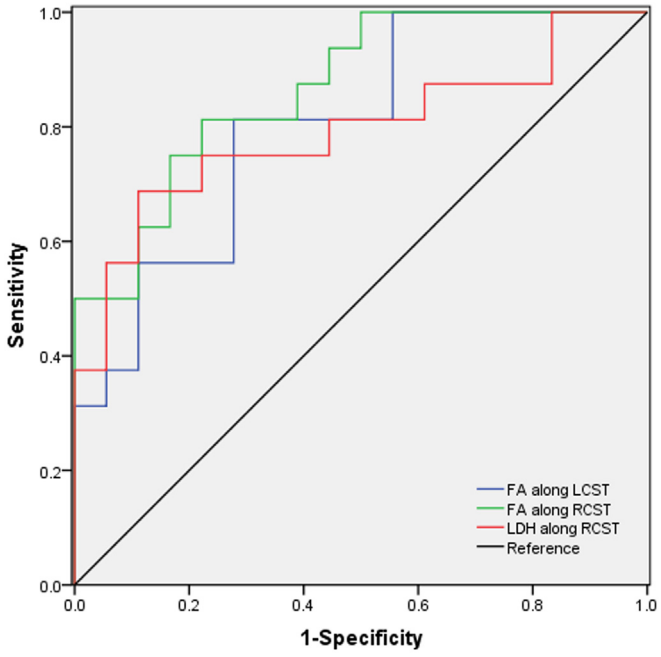

Fig. 3. The results of receiver operating characteristic (ROC) curve analysis.

including axonal degeneration and myelin breakdown [44,45], have been reported in postmortem and ALS animal models. Therefore, the observation of lower FA and higher MD may be attributable to loss of axonal fibers as well as demyelination, which is similar to the findings of earlier studies [19,43,46]. In addition to FA and MD, the inter-voxel diffusion metric-LDH, which measures local coherence of water molecule diffusion in the immediate environment and reflects microstructural coherence of the associated WM fibers, was also assessed between groups. We hypothesize that the decrease in LDH represents loss of local coherence in relation to fiber orientation, myelination, diameter, or density of the WM tracts that are affected by ALS. In this study, we found some other regions with significantly changes, such as ATR and IFOF, beyond that detected by FA and MD. Thus, we propose that LDH may be employed to generate additional information to better understand pathological processes occurring in WM tracts as well as a complementary indicator of neurological disease [31,32].

The CST is a WM motor pathway that originates from the somatosensory and motor regions and terminates at motor neurons and interneurons of the spinal cord, thereby controlling movements of the limbs and trunk [47,48]. Here, a significant decrease in FA and LDH, as well as an increase in MD were observed along the CST. Consistently, the earlier DTI studies have also shown significant abnormalities in the CST of ALS patients relative to healthy volunteers, which coincides with pathological findings [49–53]. For example, one study reported longitudinal FA decline along the cranial CST in ALS [54], while another study described a significant DTI-metric change over time in the CST of the spinal cords [43], thereby suggesting a progressive CST degeneration in ALS. In this study, we found FA was significantly correlated with the ALSFRS-R score and the progression rate among ASL along bilateral corticospinal tracts, similar to previous studies [23,24,53,55]. Meanwhile, LDH along right corticospinal tract was significantly correlated with disease duration. These findings suggest that the CST is specifically vulnerable to the disease and could serve as the imaging target for diagnosis and monitoring of ALS, keeping in line with previous study [56].

In addition to the motor regions, this study also observed microstructural alterations in various extra-motor areas such as the frontal areas as well as frontal-temporal association fibers (e.g., ATR, IFOF, SLF, and UF) that may be associated with symptoms of cognitive decline, which can range from mild executive impairment to behavioral variant frontotemporal dementia (bvFTD) [57,58]. This finding represents a profile for WM microarchitectural alterations in ALS patients as well as evidence showing that neuronal degeneration is not restricted to the CST but also involves extra-motor areas, thereby supporting the

concept that ALS is a multisystem degenerative condition [59]. The selective involvement of frontotemporal tracts reveals neural substrates that are responsible for one component of ALS (e.g., semantic deficits), which is proposed by previous studies through the clinical observations [60,61]. For instance, the UF is a WM fiber tract that links the anterior temporal lobe to the medial and lateral orbitofrontal cortex [62,63] and apparently plays a role in episodic memory, language, semantic activities, and social emotional processing [64]. Furthermore, the ILF and IFOF fiber pathways are two extensive association pathways that have been proposed to link the occipital lobe to the anterior temporal and the frontal lobes. An earlier study has shown that the IFOF possibly has a larger contribution to semantic processing, and the ILF is more related to visual-orthographic processing [65]. Previous research has established that semantic deficits are common in ALS [61], and these imply the underlying correlation between structure and function changes.

This study has a number of limitations. First, only a limited number of ALS pertains were included in this investigation. Future studies involving more subjects and multi-center researches are thus warranted to confirm our findings. Second, we evaluated microstructural changes only in the WM and the ALS is a multisystem disorder that involved WM and the gray matter (GM), thus it is possible to later combine both WM and GM to analyze the disorder. Third, we can use subgroup analysis to evaluate the disease according to more detailed clinical characteristics or disease stages in the future, in consideration of the intrinsic heterogeneity of the pathologic process in ALS. Forth, we cannot directly evaluate the effect of WM damage on patients' cognitive function, due to the lack of cognition assessment in this study. Fifth, although several studies have demonstrated the usefulness of LDH for serving as a complementary marker to investigate WM abnormalities in various neuropsychological diseases such as stroke [66] and schizophrenia [32], the precise biological relevance of LDH metric is still not well understood. Further studies should be recommended to help provide better biophysical interpretation for the information reflected by the LDH measurement.

5. Conclusion

Taken together, this study showed that ALS involves both intra-voxel and inter-voxel diffusion alterations across major tracts of the WM, which in turn is indicative of the contribution of WM microstructural changes to its pathogenesis. The findings of the present study indicate that DTI metrics may be utilized as indicators of neuropathological symptoms of ALS. In addition, the extent of abnormalities in several WM tracts such as ATR and LIFOF could be better assessed using the inter-voxel diffusion measurement; thereby, LDH can provide valuable information complementary to those obtained by conventional DTI metrics, when exploring WM alterations in ALS. Future studies should be performed to further clarify the pathophysiology processes related to diffusion measurement changes in ALS and to better evaluate the correlation between the diffusion parameters and the clinical symptoms or scales.

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Declarations of Competing Interest

None.

References

[1] O. Hardiman, A. Al-Chalabi, A. Chio, E.M. Corr, G. Logroscino, W. Robberecht, P.J. Shaw, Z. Simmons, L.H. van den Berg, Amyotrophic lateral sclerosis, Nat Rev Dis Primers 3 (2017) 17071.
[2] M. Kraemer, M. Buerger, P. Berlit, Diagnostic problems and delay of diagnosis in amyotrophic lateral sclerosis, Clin. Neurol. Neurosurg. 112 (2) (2010) 103–105.
[3] T. Zhou, T.K. Ahmad, K. Gozda, J. Truong, J. Kong, M. Namaka, Implications of white matter damage in amyotrophic lateral sclerosis (review), Mol. Med. Rep. 16 (4) (2017) 4379–4392.
[4] M.C. Smith, Nerve fibre degeneration in the brain in amyotrophic lateral sclerosis, J. Neurol. Neurosurg. Psychiatry 23 (4) (1960) 269–282.
[5] C.M. Lloyd, M.P. Richardson, D.J. Brooks, A. Al-Chalabi, P.N. Leigh, Extramotor involvement in ALS: PET studies with the GABA(a) ligand [(11)C]flumazenil, Brain 123 (Pt 11) (2000) 2289–2296.
[6] S. Basaia, M. Filippi, E.G. Spinelli, F. Agosta, White matter microstructure breakdown in the motor neuron disease spectrum: recent advances using diffusion magnetic resonance imaging, Front. Neurol. 10 (2019) 193.
[7] V. Hartung, T. Prell, C. Gaser, M.R. Turner, F. Tietz, B. Ilse, M. Bokemeyer, O.W. Witte, J. Grosskreutz, Voxel-based MRI intensitometry reveals extent of cerebral white matter pathology in amyotrophic lateral sclerosis, PLoS One 9 (8) (2014) e104894.
[8] T. Prell, T. Peschel, V. Hartung, J. Kaufmann, R. Klauschies, N. Bodammer, K. Kollewe, R. Dengler, J. Grosskreutz, Diffusion tensor imaging patterns differ in bulbar and limb onset amyotrophic lateral sclerosis, Clin. Neurol. Neurosurg. 115 (8) (2013) 1281–1287.
[9] M. Vora, S. Kumar, S. Sharma, S. Sharma, S. Makhaik, R.G. Sood, Advanced magnetic resonance neuroimaging in bulbar and limb onset early amyotrophic lateral sclerosis, J Neurosci Rural Pract 7 (1) (2016) 102–108.
[10] H.J. Kim, M. de Leon, X. Wang, H.Y. Kim, Y.J. Lee, Y.H. Kim, S.H. Kim, Relationship between clinical parameters and brain structure in sporadic amyotrophic lateral sclerosis patients according to onset type: a voxel-based morphometric study, PLoS One 12 (1) (2017) e0168424.
[11] S.M. Smith, M. Jenkinson, H. Johansen-Berg, D. Rueckert, T.E. Nichols, C.E. Mackay, K.E. Watkins, O. Ciccarelli, M.Z. Cader, P.M. Matthews, T.E. Behrens, Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data, Neuroimage 31 (4) (2006) 1487–1505.
[12] H. Yin, C.C. Lim, L. Ma, Y. Gao, Y. Cai, D. Li, Y. Liang, X. Guo, Combined MR spectroscopic imaging and diffusion tensor MRI visualizes corticospinal tract degeneration in amyotrophic lateral sclerosis, J. Neurol. 251 (10) (2004) 1249–1254.
[13] M. Pagani, A. Chio, M.C. Valentini, J. Oberg, F. Nobili, A. Calvo, C. Moglia, D. Bertuzzo, S. Morbelli, F. De Carli, P. Fania, A. Cistaro, Functional pattern of brain FDG-PET in amyotrophic lateral sclerosis, Neurology 83 (12) (2014) 1067–1074.
[14] F. Christidi, E. Karavasilis, M. Rentzos, N. Kelekis, I. Evdokimidis, P. Bede, Clinical and radiological markers of extra-motor deficits in amyotrophic lateral sclerosis, Front. Neurol. 9 (2018) 1005.
[15] J. Kassubek, H.P. Muller, K. Del Tredici, J. Brettschneider, E.H. Pinkhardt, D. Lule, S. Bohm, H. Braak, A.C. Ludolph, Diffusion tensor imaging analysis of sequential spreading of disease in amyotrophic lateral sclerosis confirms patterns of TDP-43 pathology, Brain 137 (Pt 6) (2014) 1733–1740.
[16] J. Brettschneider, K. Del Tredici, J.B. Toledo, J.L. Robinson, D.J. Irwin, M. Grossman, E. Suh, V.M. Van Deerlin, E.M. Wood, Y. Baek, L. Kwong, E.B. Lee, L. Elman, L. McCluskey, L. Fang, S. Feldengut, A.C. Ludolph, V.M. Lee, H. Braak, J.Q. Trojanowski, Stages of pTDP-43 pathology in amyotrophic lateral sclerosis, Ann. Neurol. 74 (1) (2013) 20–38.
[17] C.M. Ellis, A. Simmons, D.K. Jones, J. Bland, J.M. Dawson, M.A. Horsfield, S.C. Williams, P.N. Leigh, Diffusion tensor MRI assesses corticospinal tract damage in ALS, Neurology 53 (5) (1999) 1051–1058.
[18] A.T. Toosy, D.J. Werring, R.W. Orrell, R.S. Howard, M.D. King, G.J. Barker, D.H. Miller, A.J. Thompson, Diffusion tensor imaging detects corticospinal tract involvement at multiple levels in amyotrophic lateral sclerosis, J. Neurol. Neurosurg. Psychiatry 74 (9) (2003) 1250–1257.
[19] J.M. Graham, N. Papadakis, J. Evans, E. Widjaja, C.A. Romanowski, M.N. Paley, L.I. Wallis, I.D. Wilkinson, P.J. Shaw, P.D. Griffiths, Diffusion tensor imaging for the assessment of upper motor neuron integrity in ALS, Neurology 63 (11) (2004) 2111–2119.
[20] M. Sach, G. Winkler, V. Glauche, J. Liepert, B. Heimbach, M.A. Koch, C. Buchel, C. Weiller, Diffusion tensor MRI of early upper motor neuron involvement in amyotrophic lateral sclerosis, Brain 127 (Pt 2) (2004) 340–350.
[21] N.K. Iwata, S. Aoki, S. Okabe, N. Arai, Y. Terao, S. Kwak, O. Abe, I. Kanazawa, S. Tsuji, Y. Ugawa, Evaluation of corticospinal tracts in ALS with diffusion tensor MRI and brainstem stimulation, Neurology 70 (7) (2008) 528–532.
[22] N.S. Metwalli, M. Benatar, G. Nair, S. Usher, X. Hu, J.D. Carew, Utility of axial and radial diffusivity from diffusion tensor MRI as markers of neurodegeneration in amyotrophic lateral sclerosis, Brain Res. 1348 (2010) 156–164.
[23] F. Agosta, E. Pagani, M. Petrolini, D. Caputo, M. Perini, A. Prelle, F. Salvi, M. Filippi, Assessment of white matter tract damage in patients with amyotrophic lateral sclerosis: a diffusion tensor MR imaging tractography study, AJNR Am. J. Neuroradiol. 31 (8) (2010) 1457–1461.
[24] C. Keil, T. Prell, T. Peschel, V. Hartung, R. Dengler, J. Grosskreutz, Longitudinal diffusion tensor imaging in amyotrophic lateral sclerosis, BMC Neurosci. 13 (2012) 141.
[25] A.R. Martin, I. Aleksanderek, J. Cohen-Adad, Z. Tarmohamed, L. Tetreault, N. Smith, D.W. Cadotte, A. Crawley, H. Ginsberg, D.J. Mikulis, M.G. Fehlings, Translating state-of-the-art spinal cord MRI techniques to clinical use: a systematic

review of clinical studies utilizing DTIMT, MWF, MRS, and fMRI, Neuroimage. Clin 10 (2016) 192–238.
[26] A. Cardenas-Blanco, J. Machts, J. Acosta-Cabronero, J. Kaufmann, S. Abdulla, K. Kollewe, S. Petri, S. Schreiber, H.J. Heinze, R. Dengler, S. Vielhaber, P.J. Nestor, Structural and diffusion imaging versus clinical assessment to monitor amyotrophic lateral sclerosis, Neuroimage. Clin 11 (2016) 408–414.
[27] D. Le Bihan, J.F. Mangin, C. Poupon, C.A. Clark, S. Pappata, N. Molko, H. Chabriat, Diffusion tensor imaging: concepts and applications, J. Magn. Reson. Imaging 13 (4) (2001) 534–546.
[28] S.B. Vos, D.K. Jones, B. Jeurissen, M.A. Viergever, A. Leemans, The influence of complex white matter architecture on the mean diffusivity in diffusion tensor MRI of the human brain, Neuroimage 59 (3) (2012) 2208–2216.
[29] P.J. Basser, Inferring microstructural features and the physiological state of tissues from diffusion-weighted images, NMR Biomed. 8 (7–8) (1995) 333–344.
[30] P.J. Basser, S. Pajevic, C. Pierpaoli, J. Duda, A. Aldroubi, In vivo fiber tractography using DT-MRI data, Magn. Reson. Med. 44 (4) (2000) 625–632.
[31] G. Gong, Local diffusion homogeneity (LDH): an inter-voxel diffusion MRI metric for assessing inter-subject white matter variability, PLoS One 8 (6) (2013) e66366.
[32] C. Zhuo, X. Ma, H. Qu, L. Wang, F. Jia, C. Wang, Schizophrenia patients demonstrate both inter-voxel level and intra-voxel level white matter alterations, PLoS One 11 (9) (2016) e0162656.
[33] H.H. Liu, J. Wang, X.M. Chen, J.P. Li, W. Ye, J. Zheng, Reduced local diffusion homogeneity as a biomarker for temporal lobe epilepsy, Medicine (Baltimore) 95 (30) (2016) e4032.
[34] H.J. Chen, Y.Q. Gao, C.H. Che, H. Lin, X.L. Ruan, Diffusion tensor imaging with tract-based spatial statistics reveals white matter abnormalities in patients with vascular cognitive impairment, Front. Neuroanat. 12 (2018) 53.
[35] Y. Liang, H. Zhang, X. Tan, J. Liu, C. Qin, H. Zeng, Y. Zheng, Y. Liu, J. Chen, X. Leng, S. Qiu, D. Shen, Local diffusion homogeneity provides supplementary information in T2DM-related WM microstructural abnormality detection, Front. Neurosci. 13 (2019) 63.
[36] B.R. Brooks, R.G. Miller, M. Swash, T.L. Munsat, D. World Federation of Neurology Research Group on Motor Neuron, El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis, Amyotroph Lateral Scler Other Motor Neuron Disord. 1 (5) (2000) 293–299.
[37] Z. Cui, S. Zhong, P. Xu, Y. He, G. Gong, PANDA: a pipeline toolbox for analyzing brain diffusion images, Front. Hum. Neurosci. 7 (2013) 42.
[38] F. Zhang, G. Chen, M. He, J. Dai, H. Shang, Q. Gong, Z. Jia, Altered white matter microarchitecture in amyotrophic lateral sclerosis: a voxel-based meta-analysis of diffusion tensor imaging, NeuroImage. Clinical 19 (2018) 122–129.
[39] G. Chen, B. Zhou, H. Zhu, W. Kuang, F. Bi, H. Ai, Z. Gu, X. Huang, S. Lui, Q. Gong, White matter volume loss in amyotrophic lateral sclerosis: a meta-analysis of voxel-based morphometry studies, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 83 (2018) 110–117.
[40] A. Chio, M. Pagani, F. Agosta, A. Calvo, A. Cistaro, M. Filippi, Neuroimaging in amyotrophic lateral sclerosis: insights into structural and functional changes, The Lancet. Neurol 13 (12) (2014) 1228–1240.
[41] M. Cirillo, F. Esposito, G. Tedeschi, G. Caiazzo, A. Sagnelli, G. Piccirillo, R. Conforti, F. Tortora, M.R. Monsurro, S. Cirillo, F. Trojsi, Widespread microstructural white matter involvement in amyotrophic lateral sclerosis: a whole-brain DTI study, AJNR Am. J. Neuroradiol. 33 (6) (2012) 1102–1108.
[42] M. Chaves, M. Bettini, M.C. Fernandez, M.J.G. Basalo, J.I. Rojas, C. Besada, E. Cristiano, A. Golimstok, M. Rugiero, Usefulness of diffusion tensor imaging in amyotrophic lateral sclerosis: potential biomarker and association with the cognitive profile, Arq. Neuropsiquiatr. 75 (5) (2017) 272–276.
[43] F. Agosta, M.A. Rocca, P. Valsasina, S. Sala, D. Caputo, M. Perini, F. Salvi, A. Prelle, M. Filippi, A longitudinal diffusion tensor MRI study of the cervical cord and brain in amyotrophic lateral sclerosis patients, J. Neurol. Neurosurg. Psychiatry 80 (1) (2009) 53–55.
[44] L.R. Fischer, D.G. Culver, P. Tennant, A.A. Davis, M. Wang, A. Castellano-Sanchez, J. Khan, M.A. Polak, J.D. Glass, Amyotrophic lateral sclerosis is a distal axonopathy: evidence in mice and man, Exp. Neurol. 185 (2) (2004) 232–240.
[45] A. Nonneman, W. Robberecht, L. Van Den Bosch, The role of oligodendroglial dysfunction in amyotrophic lateral sclerosis, Neurodegener Dis Manag 4 (3) (2014) 223–239.
[46] M. Cosottini, M. Giannelli, G. Siciliano, G. Lazzarotti, M.C. Michelassi, A. Del Corona, C. Bartolozzi, L. Murri, Diffusion-tensor MR imaging of corticospinal tract in amyotrophic lateral sclerosis and progressive muscular atrophy, Radiology 237 (1) (2005) 258–264.
[47] Q. Welniarz, I. Dusart, E. Roze, The corticospinal tract: evolution, development, and human disorders, Dev Neurobiol 77 (7) (2017) 810–829.
[48] J.P. Seo, S.H. Jang, Different characteristics of the corticospinal tract according to the cerebral origin: DTI study, AJNR Am. J. Neuroradiol. 34 (7) (2013) 1359–1363.
[49] P. Lillo, E. Mioshi, J.R. Burrell, M.C. Kiernan, J.R. Hodges, M. Hornberger, Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum, PLoS One 7 (8) (2012) e43993.
[50] Y. Zhang, N. Schuff, S.C. Woolley, G.C. Chiang, L. Boreta, J. Laxamana, J.S. Katz, M.W. Weiner, Progression of white matter degeneration in amyotrophic lateral sclerosis: a diffusion tensor imaging study, Amyotroph. Lateral Scler. 12 (6) (2011) 421–429.
[51] M.E. Bastin, L.D. Pettit, T.H. Bak, T.H. Gillingwater, C. Smith, S. Abrahams, Quantitative tractography and tract shape modeling in amyotrophic lateral sclerosis, J. Magn. Reson. Imaging 38 (5) (2013) 1140–1145.
[52] A. Sarica, A. Cerasa, R. Vasta, P. Perrotta, P. Valentino, G. Mangone, P.H. Guzzi, F. Rocca, M. Nonnis, M. Cannataro, A. Quattrone, Tractography in amyotrophic lateral sclerosis using a novel probabilistic tool: a study with tract-based reconstruction compared to voxel-based approach, J. Neurosci. Methods 224 (2014) 79–87.
[53] C.A. Sage, R.R. Peeters, A. Gorner, W. Robberecht, S. Sunaert, Quantitative diffusion tensor imaging in amyotrophic lateral sclerosis, Neuroimage 34 (2) (2007) 486–499.
[54] J.P. Nickerson, C.J. Koski, A.C. Boyer, H.N. Burbank, R. Tandan, C.G. Filippi, Linear longitudinal decline in fractional anisotropy in patients with amyotrophic lateral sclerosis: preliminary results, Klin. Neuroradiol. 19 (2) (2009) 129–134.
[55] B.R. Stanton, D. Shinhmar, M.R. Turner, V.C. Williams, S.C. Williams, C.R. Blain, V.P. Giampietro, M. Catani, P.N. Leigh, P.M. Andersen, A. Simmons, Diffusion tensor imaging in sporadic and familial (D90A SOD1) forms of amyotrophic lateral sclerosis, Arch. Neurol. 66 (1) (2009) 109–115.
[56] W. Sako, T. Abe, Y. Izumi, M. Harada, R. Kaji, Deterministic-tractography-based approach for diagnosis and disease monitoring of amyotrophic lateral sclerosis, Clin. Neurol. Neurosurg. 181 (2019) 73–75.
[57] S. Byrne, M. Heverin, M. Elamin, P. Bede, C. Lynch, K. Kenna, R. MacLaughlin, C. Walsh, A. Al Chalabi, O. Hardiman, Aggregation of neurologic and neuropsychiatric disease in amyotrophic lateral sclerosis kindreds: a population-based case-control cohort study of familial and sporadic amyotrophic lateral sclerosis, Ann. Neurol. 74 (5) (2013) 699–708.
[58] M. Elamin, M. Pinto-Grau, T. Burke, P. Bede, J. Rooney, M. O'Sullivan, K. Lonergan, E. Kirby, E. Quinlan, N. Breen, A. Vajda, M. Heverin, N. Pender, O. Hardiman, Identifying behavioural changes in ALS: validation of the Beaumont Behavioural Inventory (BBI), Amyotroph Lateral Scler Frontotemporal Degener 18 (1–2) (2017) 68–73.
[59] F. Trojsi, G. Caiazzo, M. Siciliano, C. Femiano, C. Passaniti, A. Russo, A. Bisecco, M.R. Monsurro, M. Cirillo, F. Esposito, G. Tedeschi, G. Santangelo, Microstructural correlates of Edinburgh cognitive and behavioural ALS screen (ECAS) changes in amyotrophic lateral sclerosis, Psychiatry Res. Neuroimaging 288 (2019) 67–75.
[60] J.A. Saxon, J.M. Harris, J.C. Thompson, M. Jones, A.M.T. Richardson, T. Langheinrich, D. Neary, D.M.A. Mann, J.S. Snowden, Semantic dementia, progressive non-fluent aphasia and their association with amyotrophic lateral sclerosis, J. Neurol. Neurosurg. Psychiatry 88 (8) (2017) 711–712.
[61] F.V. Leslie, S. Hsieh, J. Caga, S.A. Savage, E. Mioshi, M. Hornberger, M.C. Kiernan, J.R. Hodges, J.R. Burrell, Semantic deficits in amyotrophic lateral sclerosis, Amyotroph Lateral Scler Frontotemporal Degener 16 (1–2) (2015) 46–53.
[62] L.G. Ungerleider, D. Gaffan, V.S. Pelak, Projections from inferior temporal cortex to prefrontal cortex via the uncinate fascicle in rhesus monkeys, Exp. Brain Res. 76 (3) (1989) 473–484.
[63] M. Catani, M. Thiebaut de Schotten, A diffusion tensor imaging tractography atlas for virtual in vivo dissections, Cortex 44 (8) (2008) 1105–1132.
[64] R.J. Von Der Heide, L.M. Skipper, E. Klobusicky, I.R. Olson, Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis, Brain 136 (Pt 6) (2013) 1692–1707.
[65] A.S. Dick, B. Bernal, P. Tremblay, The language connectome: new pathways, new concepts, Neuroscientist 20 (5) (2014) 453–467.
[66] G. Liu, S. Tan, C. Dang, K. Peng, C. Xie, S. Xing, J. Zeng, Motor recovery prediction with clinical assessment and local diffusion homogeneity after acute subcortical infarction, Stroke 48 (8) (2017) 2121–2128.