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Original Article

Early and Persistent White Matter Damage in Severe Traumatic Brain Injury: A Longitudinal Diffusion Tensor Imaging Analysis

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Abstract

Objective: This study aims to identify early and longitudinal microstructural changes in white matter tracts in patients with severe traumatic brain injury (TBI) using tract-based spatial statistics (TBSS) and fully automated tractographic methods.
Methods: Participants were 16 adult TBI patients with a Glasgow Coma Scale (GCS) score <7 and 16 age- and gender-matched healthy controls. Magnetic resonance imaging (MRI) scans were performed using a 3 Tesla scanner, following the high-angular resolution diffusion imaging (HARDI) protocol. Diffusion tensor imaging (DTI) parameters [fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD)] were calculated. TractSeg was used for automated segmentation of white matter tracts, including the arcuate fasciculus (AF), anterior thalamic radiation (ATR), corpus callosum, cingulum, corticospinal tract (CST), superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus (ILF). Statistical comparisons between groups and longitudinal analyses within the patient group were conducted using *t*-tests and Wilcoxon signed-rank tests, with significance thresholds adjusted for multiple comparisons.
Results: In the acute phase, TBSS revealed widespread decreases in FA and AD, and increases in MD and RD in several white matter tracts including the ATR, CST, cingulum, and corpus callosum. Tractography also showed decreased FA and increased RD and MD in several tracts. Longitudinal analysis indicated persistent decreases in FA and increases in RD over time, while tractography did not show significant longitudinal changes.
Conclusion: The study demonstrates significant early white matter damage in severe TBI patients, with continued microstructural changes observed longitudinally.
Keywords: Diffusion tensor imaging (DTI), longitudinal analysis, tract-based spatial statistics (TBSS), traumatic brain injury (TBI), white matter microstructure

INTRODUCTION

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality in young patients.[1] Diffuse axonal injury involves axonal disruptions in trauma patients and may not be visible on computed tomography or conventional magnetic resonance imaging (MRI) sequences if there is no accompanying hemorrhage. Diffusion-weighted imaging (DWI) has become widely used in recent years for its ability to demonstrate microstructural changes in tissues not detectable on conventional MRI.[2] Diffusion tensor imaging (DTI) allows for the visualization of white matter tracts by altering diffusion gradients in specific directions. Fractional anisotropy (FA) is 1 of the key parameters of DTI, providing highly sensitive information about the integrity of white matter tracts. The literature indicates that DTI can detect microstructural abnormalities in TBI that are not apparent on conventional MRI sequences, with studies spanning at least 20 years. These studies have shown decreases in FA and increases in mean diffusivity (MD) in these patients, particularly in commissural fibers such as the corpus callosum.[3] Diffusion tensor imaging has successfully revealed microstructural changes in mild, moderate, and severe TBI.[4,5]

Trauma is a process that triggers neuroinflammation. Encephalomalacia and gliosis develop in these patients, and increased neuroinflammation can exacerbate the existing brain injury. Therefore, identifying microstructural changes in the chronic phase of TBI is crucial for patient management.[6] However, there are very few longitudinal studies investigating microstructural changes in TBI. In the existing studies, the focus has primarily been on mild TBI.[7] Furthermore, the degree of neuroinflammation in mild TBI is not the same as in severe TBI.[8] Thus, studying longitudinal changes in severe TBI is of significant importance.

Several methods exist to investigate microstructural changes in tissues using DTI. The traditional region of interest (ROI) method involves marking specific areas using certain atlases and examining the average DTI parameters in these regions. Studies using this method in TBI have found widespread decreases in FA and increases in MD, particularly in areas where commissural fibers pass.[9,10] However, this method is dependent on the observer and only includes measurements from specific white matter regions.[11] Another method, tract-based spatial statistics (TBSS), is largely user-independent and allows for voxel-wise group comparisons across the entire brain by automatically transferring white

matter tracts onto a white matter skeleton and taking local maxima.[12] Tract-based spatial statistics has become a popular alternative to the ROI method because it mitigates some of the subjective elements involved in manual ROI selection. By projecting all participants' white matter tracts onto a common skeleton, TBSS enables a more standardized comparison across subjects, facilitating voxel-wise statistical analyses of the entire brain. Many studies have shown microstructural changes throughout the brain in TBI using TBSS.[13] However, TBSS can introduce bias through statistical measurements taken at local maxima and may produce incorrect calculations in crossing fibers.[14]

Another advantage of DTI is its non-invasive ability to visualize white matter tracts, which is particularly useful in preoperative planning for tumor patients. Traditional DTI typically employs a maximum b-value between 800 and 1000 s/mm². However, this b-value range has limitations, particularly when it comes to accurately depicting complex fiber configurations such as crossing or kissing fibers. Lower b-values may result in a loss of directional information in regions with complex fiber architecture, leading to inaccuracies in tractography, especially in areas like the centrum semiovale where multiple fiber bundles intersect.[15] Recently, the use of high-angular resolution diffusion imaging (HARDI) with higher b-values and constrained spherical deconvolution (CSD) has been shown to produce better results compared to classical tractography using lower b-values.[16] Identifying white matter tracts traditionally involves a labor-intensive process requiring manual selection of multiple parameters, including start and end points and voxel transition angles, which depends heavily on the operator's experience. Recently developed deep learning-based algorithms, such as TractSeg using CSD, can automatically segment white matter tracts.[17] There are a lot of studies in the literature investigating tractographic changes in TBI, and most of these studies have utilized classical DTI techniques.[18] A recent study demonstrated that tractography using CSD might better reveal changes in TBI compared to classical tractography methods.[19] However, the number of studies investigating tractographic changes in TBI using CSD-based tractography is quite limited.

Our study has several objectives. First, the aim is to reveal early microstructural changes in the white matter of patients with severe TBI (Glasgow Coma Scale [GCS] < 7) using TBSS and fully automatic tractographic methods. Our second objective is to identify longitudinal microstructural changes in these patients.

MAIN POINTS

- This study reveals significant early microstructural damage in the white matter tracts of severe TBI patients, with notable decreases in fractional anisotropy (FA) and axial diffusivity (AD), and increases in mean diffusivity (MD) and radial diffusivity (RD).
- Longitudinal analysis indicates persistent and progressive white matter damage over time, characterized by continued decreases in FA and increases in RD, underscoring the chronic nature of brain injury in severe TBI patients.
- Tract-based spatial statistics (TBSS) effectively detected both acute and chronic microstructural changes, while constrained spherical deconvolution (CSD)-based tractography proved more sensitive to acute damage, highlighting the importance of advanced imaging techniques for comprehensive TBI assessment.

MATERIAL AND METHODS

Participants

This observational study utilized clinical and MRI images licensed under the Creative Commons Attribution 4.0 International (CC-BY 4.0) from a public dataset (https://openneuro.org/datasets/ds003367).[20] Ethics committee approval was received from the "blinded for review" Ondokuz Mayıs University Clinical Research Ethics Committee (Approval No: OMUKAEK 2024295 Date: 5/7/2024). The cohort included 16 adult patients with TBI, a GCS score of less than 7, who did not open their eyes and completely recovered from this coma state after 6 months (Age [Median: 27.5; Inter Quantile Range (IQR): 21.5-33], Gender [12 Male, 4 Female]), and 16 age- and gender-matched healthy controls (Age [Median: 27; IQR: 21-35], Gender [12 Male, 4 Female]). Follow-up MRI examinations were available for 9 of these patients (Median: 206 [190-370] days). All subjects consisted of individuals who did not have a pre-existing neurodegenerative disease or a history of TBI.[20,21] Informed consent was obtained from participants by researchers while collecting data within the scope of the open science project. The findings are presented in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.[22]

MRI Acquisition and Preprocessing

Magnetic resonance imaging scans were performed using a Siemens 3 Tesla Skyra device with a 32-channel head coil. Following the HARDI protocol, 60 slices (b=2000 s/mm²) and 10 slices with b=0 were acquired with a thickness of 2 mm. Other sequence parameters were defined as per previous literature.[21]

Initially, an average b=0 image was generated from the diffusion images, and a brain tissue mask was created using SynthStrip.[23] Eddy current artifact and motion artifact corrections were applied using FMRIB Software Library (FSL) eddy.[24] Images were aligned to the Montreal Neurological Institute (MNI-152) template, and FA, MD, radial diffusivity (RD), and axial diffusivity (AD) maps were generated using FSL dti_fit. All FA and MD images were evaluated by a radiologist with 8 years of experience.

Preprocessed diffusion-weighted images were analyzed using TractSeg, which performed fully automated segmentation of key white matter tracts, including the arcuate fasciculus (AF), anterior thalamic radiation (ATR), corpus callosum, cingulum, corticospinal tract (CST), superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus (ILF) (Figure 1).[17] For each segmented tract, the average values of FA, MD, AD, and RD were automatically calculated using the fslstats tool.[25]

Statistical Analysis

Tract-Specific Analysis

For the comparison of FA, MD, RD, and AD values in the tracts segmented by TractSeg between the early period of the patient group and the control group, either the *t*-Test or the Mann–Whitney *U* test was used, depending on the normality of the distribution. For the comparison of early and late findings within the patient group, either the paired *t*-test or the Wilcoxon signed-rank test was employed based on the distribution. Given that 32 parameters were investigated for each individual, the alpha threshold was set at 0.05/32, which is approximately 0.0016.

Tract-Based Spatial Statistics

In accordance with the main TBSS pipeline (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide),[12] FA images were aligned to the MNI

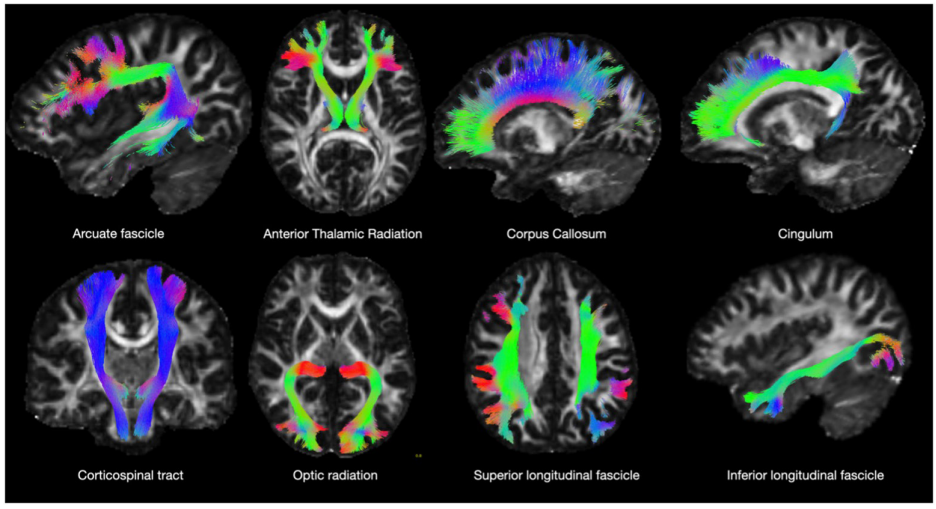

Figure 1. White matter tracts segmented using TractSeg (images from sub-TCRc007).

template and subsequently to the FMRIB-58 FA template. Average FA skeleton images were then created. Differences between the patient and control groups were assessed using a *t*-test, and longitudinal changes were evaluated using a paired *t*-test. To determine the significance of threshold-free cluster enhancement, a Monte Carlo simulation with n = 5000 iterations was performed.[26] A *P*-value of less than .05 was considered statistically significant. Tracts showing significant differences were identified using the Johns Hopkins University (JHU) white matter atlas Tractography Atlas within FSL's autoaq.[27]

RESULTS

Cross-Sectional Analysis

Tract-Based Spatial Statistics (TBSS)

Our TBSS results indicate widespread decreases in FA (Minimum $P = .002$) and AD (Minimum $P = .002$), along with increases in MD (Minimum $P = .004$) and RD (Minimum $P = .002$) in traumatic coma patients. These changes were observed bilaterally in the ATR, CST, cingulum, forceps major and minor, OR, ILF, SLF, and UF (Figure 2).

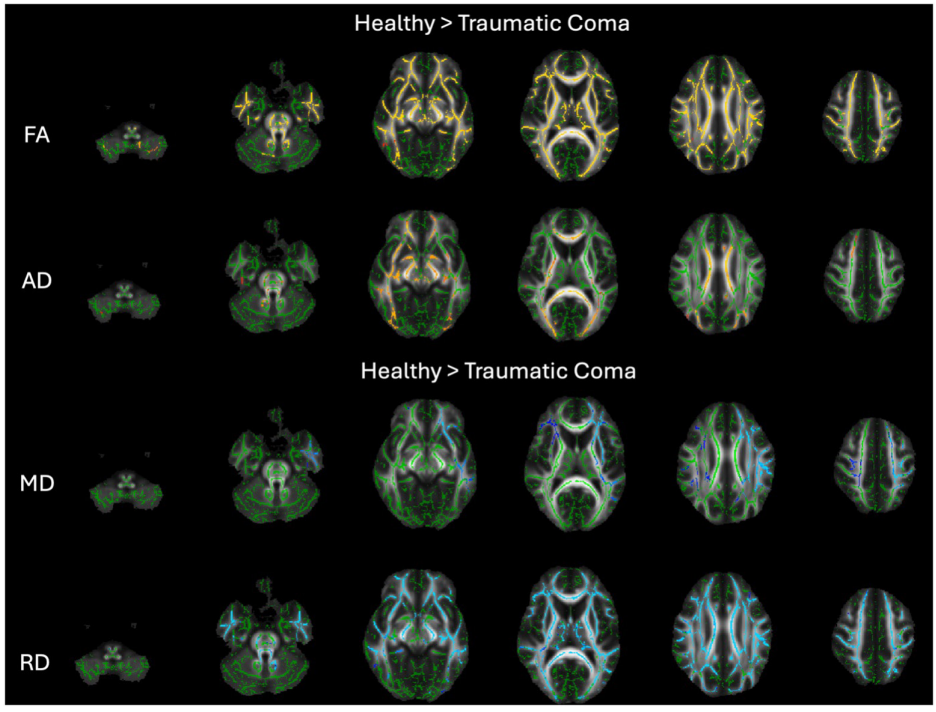

Figure 2. White matter tracts showing changes in early post-traumatic brain injury patients compared to healthy controls according to TBSS ($P < .05$). AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; TBSS, tract-based spatial statistics.

Tractography Findings

According to the tractography results, there was a decrease in FA observed in the bilateral AF, CST, ATR, cingulum, SLF, UF, and corpus callosum fibers. An increase in MD was found in the left AF, bilateral ATR, and left UF fibers. Additionally, there was an increase in RD detected in the bilateral AF, bilateral ATR, bilateral cingulum, corpus callosum, and bilateral UF fibers ($P < .0016$). No significant changes in AD were observed between the groups in the identified white matter tracts (Figure 3).

Longitudinal Analysis

Tract-Based Spatial Statistics

In the longitudinal analysis, over time, there was a decrease in FA (minimum $P = .026$) and an increase in RD (minimum $P = .022$) observed in the white matter tracts, including the bilateral ATR, bilateral CST, bilateral cingulum, forceps major and minor, bilateral Inferior Frontoccipital Fasciculus (IFOF), bilateral ILF, and bilateral SLF fibers (Figure 4). A more limited area showed an increase in MD (minimum $P = .028$). Axial diffusivity did not show any changes over time.

Longitudinal Analysis

Tractography Findings

In the longitudinal analysis, no significant differences were observed in the white matter tracts.

DISCUSSION

This study investigated the acute and chronic changes in the brains of patients in comas with severe TBI. Our findings demonstrate widespread decreases in FA and AD, and increases in MD and RD in white matter areas in the acute phase of severe traumatic coma, as revealed by TBSS analysis. Tractography analysis also indicated reduced FA and increased RD and MD along white matter tracts in these patients. Longitudinal analysis revealed that this white matter damage continued progressively even after the patients regained consciousness.

Diffusion tensor imaging changes in TBI have been a subject of research for many years.[3] Previous studies have similarly shown that DTI is a sensitive method for detecting TBI. Fractional anisotropy, the most commonly used parameter in DTI, showed widespread reduction in the acute phase in our study, consistent with the literature.[28,29] The non-specific decrease in FA can be due to myelin loss, axonal loss, or crossing fibers.[30] Experimental studies in rats have suggested that RD could be a specific indicator of myelin integrity.[31] As myelin integrity decreases, water molecules diffuse more in directions other than the primary fiber orientation. Studies have shown that an increase in RD, consistent with myelin damage, has been present since the early stages of trauma, and these findings are consistent with our study.[32,33] Mean diffusivity is also a non-specific parameter affected by many factors disrupting fiber integrity. Similar to the literature, our study found widespread increases in MD in TBI, indicating early axonal and myelin loss.[3]

Traumatic brain injury is not just an acute process. A study in mice showed early post-trauma axonal damage, microglia and astrocyte activation, and early axonal damage associated with decreased AD, consistent with our study.[34] In the chronic phase, neuroinflammation increases, leading to axonal degeneration, more pronounced demyelination, and gliosis.[34] Palacios et al's[7] study in patients with mild TBI found widespread FA decreases and MD increases early after trauma, similar to our study, but no FA and MD changes in longitudinal analysis. However, that study showed longitudinal increases in neurite density index and free water fraction from Neurite Orientation Dispersion and Density Imaging (NODDI) parameters. NODDI is more sensitive to microstructural changes than conventional DTI.[35] In the study conducted by Veeramuthu and colleagues on patients with mild TBI, a decrease in FA along with an increase in MD and RD was detected in the early stages of TBI. Similar to our study, the longitudinal analysis demonstrated that the progressive decrease in FA and the increase in MD and RD continued.[33] A recent study shows that there

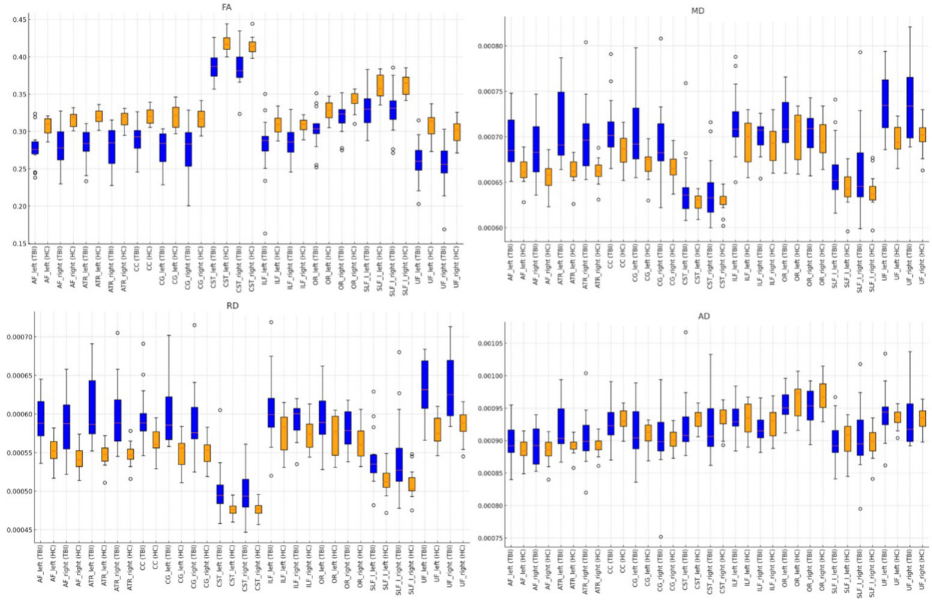

Figure 3. Box-plot representation of changes in FA, MD, RD, and AD in white matter tracts segmented by tract-specific statistics in the early period of trauma. AD, axial diffusivity; AF, arcuate fasciculus; CG, cingulum; CST, corticospinal tract; FA, fractional anisotropy; HC, healthy control; ILF, inferior longitudinal fasciculus; MD, mean diffusivity; OR, optic radiation; RD, radial diffusivity; SLF, superior longitudinal fasciculus; TBI, traumatic brain injury; UF, uncinate fasciculus.

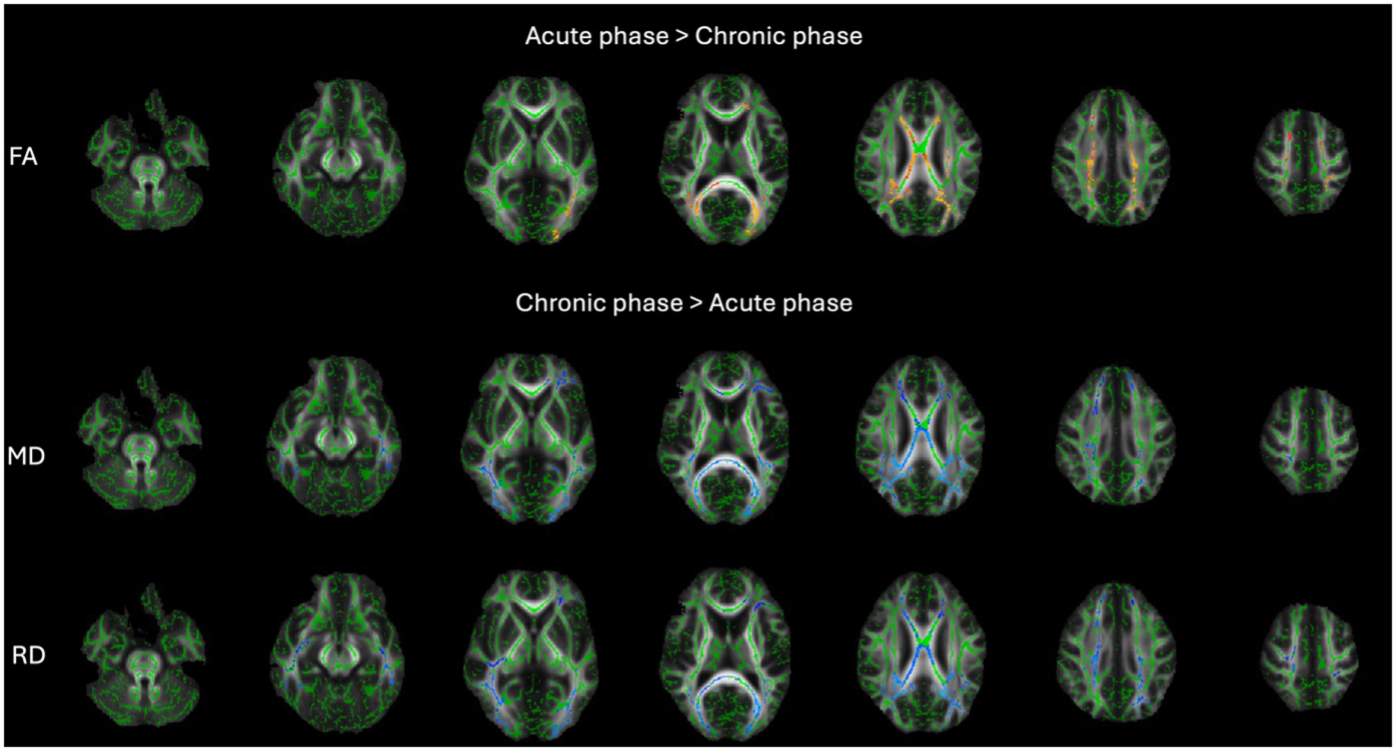

Figure 4. White matter tracts showing changes longitudinally in longitudinally post-traumatic brain injury patients according to TBSS ($P < .05$). AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; TBSS, tract-based spatial statistics.

is a longitudinal increase in enlarged perivascular spaces in patients with TBI, along with a longitudinal increase in the DTI-ALPS index.[36] These combined findings indicate that microstructural changes in trauma patients continue longitudinally.

The optimal tractographic algorithm for investigating microstructural changes in TBI is not yet clearly established.[37] Tallus et al's[19] study showed that using CSD-based tractographic methods, as in our study, rather than classical tractographic methods, is more successful in revealing tractographic changes in TBI. However, that study did not use b-values compatible with HARDI. Our study used a tractographic algorithm with b-values compatible with HARDI. Therefore, CSD-based tractography using high b-values is useful in detecting acute traumatic injury. However, AD decreases, an indicator of acute traumatic axonal injury, were not shown with CSD-based tractography, but were detected with TBSS. Additionally, longitudinal changes detected with TBSS were not shown with CSD-based tractography. Future studies using multi-shell multi-tissue spherical convolution tractography may address these limitations.

Most studies to date have focused on microstructural changes in mild TBI. However, our study shows that progressive white matter damage continues in severe head trauma. Despite clinical improvement, progressive demyelinating processes and gliosis continue, and voxel-based analysis methods like TBSS may be useful in tracking these processes.

Our study has several limitations. First, it is based on data shared for use by all scientists through the open science project, leading to limited patient data. Clinical examination findings of the patients were not available, so DTI findings could not be correlated with cognitive data. The small number of patients makes it difficult to generalize these findings. However, our study may pave the way for large-scale multicenter studies in the future. Despite using DTI-based tractography, incorporating multi-shell b-values, NODDI, diffusion kurtosis, and other advanced DTI methods could deepen our findings.

In conclusion, our study shows that early axonal loss and changes consistent with myelin damage occur in TBI. Even after patients regain consciousness, gliotic processes, neuroinflammation, and demyelinating processes in the brain continue in the long term. While CSD-based tractography methods are useful for assessing acute damage, TBSS is successful in evaluating both acute and chronic damage.

Data Availability Statement: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: This study was approved by the Ondokuz Mayıs University Clinical Research Ethics Committee (Approval No: OMUKAEK 2024295 Date: 5/7/2024).

Informed Consent: Written consent was obtained from individuals while acquiring images for the database.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.G.; Design – B.G.; Supervision – K.A.; Resources – B.G.; Materials – B.G.; Data Collection and/orProcessing – B.G.; Analysis and/or Interpretation – B.G.; LiteratureSearch – K.A.; Writing Manuscript – B.G.; Critical Review – K.A., L.I; Other – L.I.

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