

High-definition fiber tracking for assessment of neurological deficit in a case of traumatic brain injury: finding, visualizing, and interpreting small sites of damage

Case report

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For patients with traumatic brain injury (TBI), current clinical imaging methods generally do not provide highly detailed information about the location of axonal injury, severity of injury, or expected recovery. In a case of severe TBI, the authors applied a novel high-definition fiber tracking (HDFT) to directly visualize and quantify the degree of axonal fiber damage and predict functional deficits due to traumatic axonal injury and loss of cortical projections.

This 32-year-old man sustained a severe TBI. Computed tomography and MRI revealed an area of hemorrhage in the basal ganglia with mass effect, but no specific information on the location of axonal injury could be obtained from these studies. Examinations of the patient at Week 3 and Week 8 after TBI revealed motor weaknesses of the left extremities. Four months postinjury, 257-direction diffusion spectrum imaging and HDFT analysis was performed to evaluate the degree of axonal damage in the motor pathway and quantify asymmetries in the left and right axonal pathways. High-definition fiber tracking was used to follow corticospinal and corona radiata pathways from the cortical surface to the midbrain and quantify projections from motor areas. Axonal damage was then localized by assessing the number of descending fibers at the level of the cortex, internal capsule, and midbrain. The motor deficit apparent in the clinical examinations correlated with the axonal losses visualized using HDFT. Fiber loss estimates at 4 months postinjury accurately predicted the nature of the motor deficits (severe, focal left-hand weakness) when other standard clinical imaging modalities did not. A repeat scan at 10 months postinjury, when edema and hemorrhage had receded, replicated the fiber loss.

Using HDFT, the authors accurately identified the presence and location of damage to the underlying white matter in this patient with TBI. Detailed information of injury provided by this novel technique holds future potential for precise neuroimaging assessment of TBI.

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KEY WORDS • axonal injury • diffusion tensor imaging • traumatic brain injury • high-definition fiber tracking

CURRENT imaging methods rarely provide definitive biological indicators of TBI.¹ Beyond the identification of mass lesions requiring evacuation, neuroimaging in TBI is generally of low clinical utility. The absence of a neuroimaging biomarker in TBI is also a major impediment to clinical care and research in the field. Recent developments in diffusion-weighted imaging have shown value in identifying axonal injury induced by trauma.^{4,6–8,11,12} However, the limitations of spatial resolution of current diffusion imaging methods and their sensitivity to signal loss from edema and hemorrhage makes it dif-

ficult to visualize the specific locations of axonal injury and isolate the affected pathways.

We have recently developed a novel white matter imaging approach, HDFT, which maps fiber pathways within the brain at a significantly advanced degree of resolution. We have previously used HDFT for surgical planning² and in vivo corticospinal pathway mapping.¹⁶ In addition, we have extensively analyzed white matter damage using the data generated by HDFT. In this paper, we report our initial application of HDFT in the assessment of TBI.

Case Report

This report centers on 1 patient and compares the results of HDFT in this patient to the results in healthy con-

Abbreviations used in this paper: DTI = diffusion tensor imaging; FA = fractional anisotropy; HDFT = high-definition fiber tracking; TBI = traumatic brain injury.

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trols. Institutional review board approval was obtained for review of the patient's medical records and imaging studies obtained in the patient and healthy volunteers.

This 32-year-old man sustained a severe TBI in an all-terrain vehicle accident (unhelmeted). The patient had a postresuscitation Glasgow Coma Scale score of 6 and had the following injuries: right subcortical intracerebral hemorrhage, T-8 and T-12 compression fractures, and left midface fractures. A CT scan of the head showed a $4.7 \times 3.1 \times 4$ -cm acute hemorrhage centered within the right basal ganglia resulting in local mass effect and 5 mm of right-to-left midline shift (Fig. 1 left).

After the patient underwent placement of a left external ventricular drain and brain tissue oxygen monitor, the severe TBI was managed medically. At 7 days postinjury, MRI scans showed a large right-sided basal ganglia hematoma with associated mass effect (Fig. 1 right). At 3 weeks postinjury, the patient followed commands with his right upper extremity, but had a dense left hemiparesis. He was subsequently transferred to inpatient TBI rehabilitation and returned for neurosurgical follow-up at 2 months postinjury.

At follow-up 8 weeks postinjury, the patient continued to have residual left upper- and lower-extremity weaknesses: hamstrings (3/5), quadriceps (4/5), biceps (2/5), triceps (3/5), and deltoid (4+/5). The strength at the wrist and in the hand intrinsic muscle groups was Grade 0 (0/5) according to the British Medical Research Council grading scale.

Based on the structural images, it might be assumed that the basal ganglia damage was the primary cause of the patient's motor impairments. However, the internal capsule is a white matter pathway immediately adjacent to the basal ganglia and contains all the descending corticospinal pathway fibers from the cortical motor areas. Therefore, at 4 months postinjury, 2 types of diffusion-weighted imaging scans were performed to measure white matter integrity in this descending fiber pathway. First, a standard 51-direction DTI sequence was acquired. Next, a novel 257-direction diffusion spectrum imaging scan was acquired. This second scan allows for the production of HDFT, which we have previously used to track corticospinal pathways, successfully tracking fibers from the cortical surface to midbrain with submillimeter resolution.¹⁶ The FA map from the 51-direction DTI sequence (Fig. 2) showed unconstrained diffusion in the basal ganglia, suggesting axonal breakage. Slight signal loss was also seen in the right anterior limb of the internal capsule that appeared to extend into portions of the posterior limb. However, the FA map did not provide specific information about which axonal pathway was injured, the degree of the injury, nor the projection field of the pathway.

To better visualize these white matter pathways, we used fiber tractography, a method that renders the fiber pathways in a 3D space. Our pilot analysis using DTI for fiber tracking provided poor-quality visualizations of fiber pathways that had anatomically inconsistent properties, such as false turns, false continuations, and random fiber trajectories (for example, "looping" [Fig. 3 left]).

We then used HDFT to provide 3D visualization of fibers. The HDFT data provided accurate mapping of

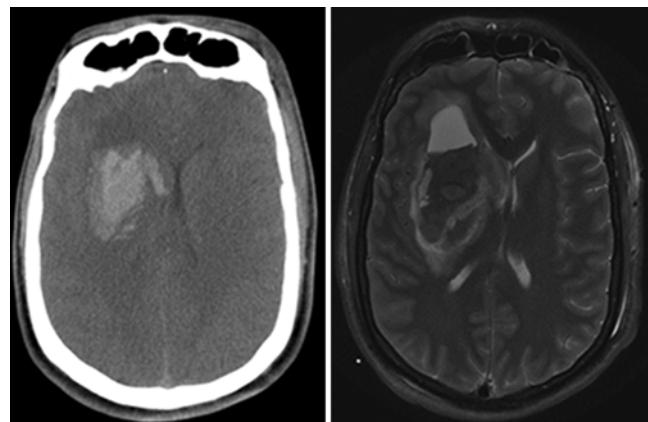


FIG. 1. Axial CT scan (left) obtained 5 days after severe TBI and T2-weighted FLAIR MR image (right) obtained 7 days after the injury showing acute hemorrhage in the basal ganglia with mass effect.

white matter pathways in healthy controls (Fig. 3 right) and in our patient (Fig. 4). Using HDFT, we were able to map several major pathways with specificity and quantify the degree of loss of connectivity as a result of axonal fiber damage. We reconstructed the corona radiata, cingulum, and superior longitudinal fasciculus. The HDFT data were then analyzed by comparing right and left fiber tracks, as well as by comparing the injured patient's fiber tracks to those of healthy controls.

Our first analysis mapped the corona radiata pathway, which contains fibers that pass through the anterior and posterior limbs of the internal capsule. Since fiber tracking involves a stochastic seeding process that has been reported to produce unstable results,⁵ we seeded the tracks 4 times using 70,000, 90,000, 110,000, and 130,000 random seeds to estimate the variability and significance of the method across random reseedings. The resampling variance was small (corona radiata SD 1.6%, cingulum SD 6.1%, and superior longitudinal fasciculus SD 6.4%). The volume estimates showed a $59.6 \pm 4.3 \text{ cm}^3$ loss on the left side compared with the right. There was a $62.8\% \pm 1.6\%$ difference (z score 38.3, $p < 0.0001$) between the left and right sides (Table 1, Video 1).

VIDEO 1. Comparison of the left and right sides of the corona radiata showing losses in the right side, with significant loss at the level of the midbrain. Click here to view with Media Player. Click here to view with Quicktime.

In contrast, volumetric analysis of the cingulum and superior longitudinal fasciculus found no significant differences ($p > 0.1$) between the left and right sides. Additional repeat reliability analysis performed by reseeding the corona radiata 10 times showed a similar mean volume loss of $67.4\% \pm 0.3\%$ (Table 2). The repeat analysis confirmed low variance (SD 0.3) and reliability of this method (z score > 200 , $p < 0.0001$), and both methods produced nearly the same proportion of loss (62.8% volume, 67.4% track counts).

After identification of the volumetric loss in the corona radiata, further analysis was performed by computing the number of fiber termination points, locations where diffusion signals for fiber tracks end. Fiber termination

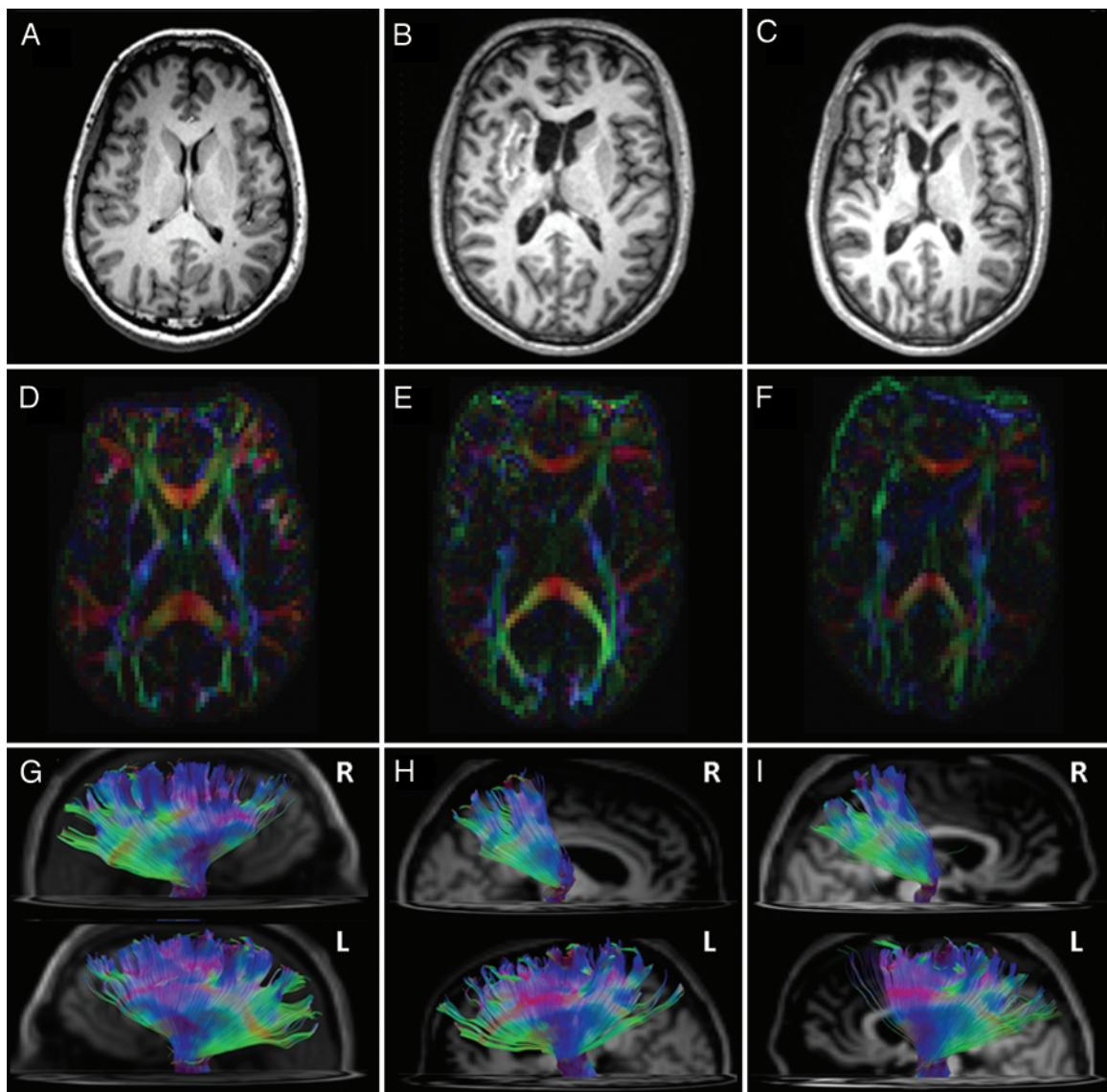


Fig. 2. Axial T1-weighted MR images (A–C), DTI FA maps (D–F), and HDFT fiber tracks (G–I) obtained in a healthy volunteer (A, D, and G), our TBI patient at 4 months postinjury (B, E, and H), and our patient at 10 months postinjury (C, F, and I). The T1-weighted MR image obtained 4 months postinjury (B) shows hyperintensity in the right basal ganglia, demonstrating edema and hemorrhage. The DTI FA map (E) from the same time point also shows loss of white matter pathways passing through the basal ganglia. Fiber streamlines obtained using HDFT (H) show major loss of the right anterior corona radiata at 4 months. A T1-weighted MR image obtained at 10 months post-TBI (C) demonstrates clearance of edema and hematoma, and specific damage to the same region is demonstrated by HDFT (I). The standard clinical scans at 10 months show subtle changes that are difficult to interpret in the structural images (C) and DTI FA images (F). In contrast, the loss of left corona radiata fibers (I) clearly demonstrates substantial loss of innervation to the motor cortex, predicting the observed functional deficit.

points are presumed to be where axonal fiber bundles terminate (such as the cortex or nuclei), and these were identified along the length of the corona radiata in the posterior to anterior direction (Fig. 5 upper left). The right corona radiata fibers projecting to the central sulcus and precentral gyrus showed a 54% reduction in termination points compared with the left corona radiata. Also, the right corona radiata fibers projecting to the anterior areas, including premotor areas (that is, the supplementary motor area, presupplementary motor area, and cingulated motor area), showed a 97% reduction in termination points compared with the contralateral hemisphere. In

comparison, the corona radiata of an uninjured individual showed a relatively similar number of termination points in the left and right hemispheres (Fig. 5 upper right).

Since our goal was to determine if the etiology of the patient's motor deficits was damage to the motor pathways adjacent to the basal ganglia lesion, we focused on the subset of fibers that contribute to the corona radiata and directly project to spinal motor neurons: the corticospinal pathway. We tracked the corticospinal pathway fibers descending from the motor areas such as the precentral gyrus and central sulcus through the internal capsule and the midbrain (Fig. 6). In the standard clinical structural

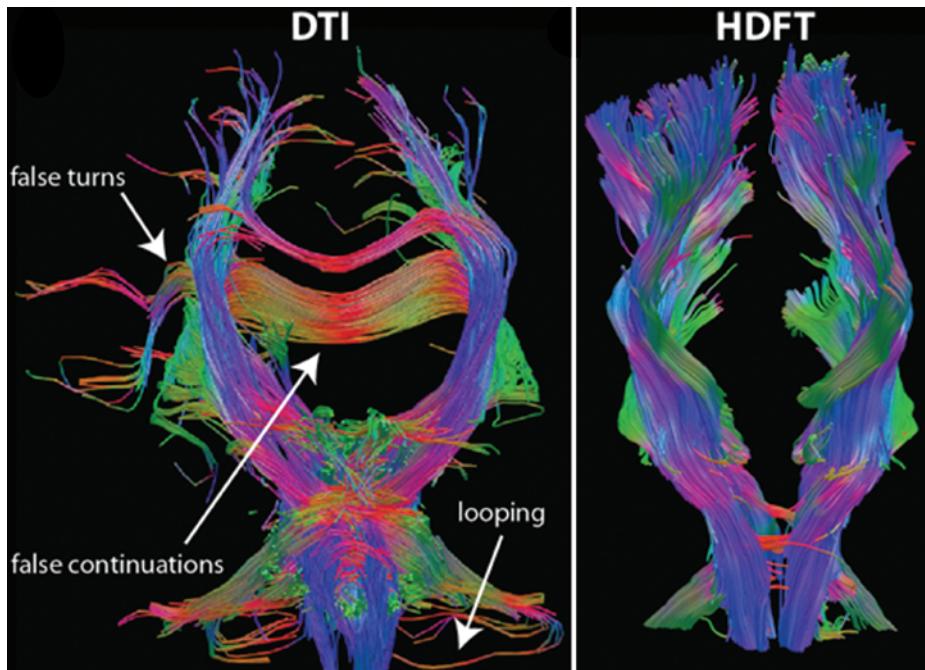


Fig. 3. **Left:** Corona radiata fibers in a healthy control mapped using DTI. Fibers are shown in the coronal plane as viewed from the front of the brain. This image contains fiber shapes and trajectories that are inconsistent with known anatomy, including false turns (fibers that deviate from the underlying pathway), false continuations (fibers that cross the midline), and “looping” (fibers that wander in arbitrary directions). **Right:** Fiber tracking of the corona radiata with HDFT does not show the same errors. These fibers match a priori anatomical expectations.

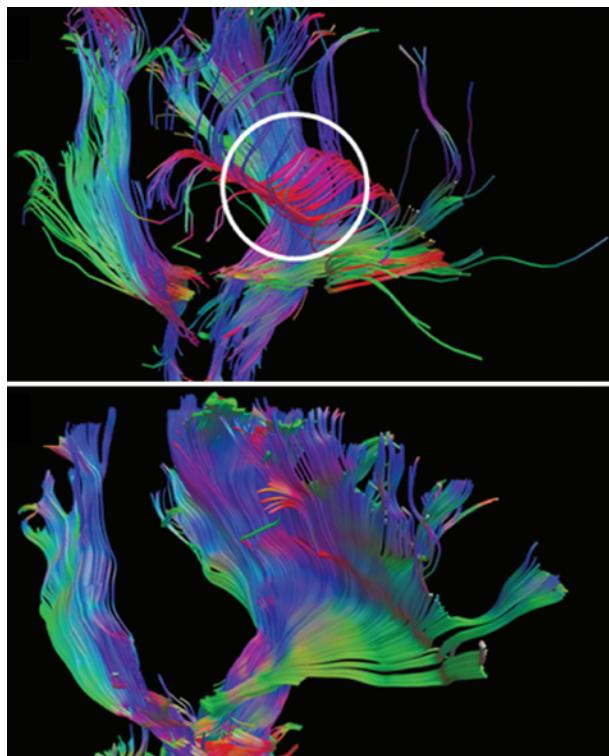


Fig. 4. Diffusion tensor imaging fiber tracking (**upper**) and HDFT (**lower**) in the TBI patient at 17 weeks postinjury. The DTI fiber tracking shows inaccurate fiber directions and termination points (**white circle**), whereas the HDFT scan shows accurate details of damaged areas of the right anterior corona radiata without false turns or false continuations.

scans (CT and T1- and T2-weighted MRI), most of the damage was visible in the basal ganglia, and no specific damage was apparent in the posterior limb of the internal capsule where the corticospinal pathway fibers traverse (Figs. 1 and 2B and C). Yet, large areas of fiber breaks were detected in the posterior limb of the internal capsule by HDFT (Fig. 6B). The corticospinal pathway fiber tracks of 6 healthy age- and sex-matched controls were analyzed and compared with corticospinal pathway fiber tracks of the TBI patient at 4 and 10 months postinjury (Fig. 6C). As expected, the TBI patient exhibited a decreased ratio of fibers at each level analyzed: precentral gyrus, internal capsule, and midbrain. In contrast, the ratios of right and left corticospinal pathway fiber tracks in the controls were close to 1 at these regions. At 4 months, the z scores of the patient’s left/right ratio for precentral gyrus, internal capsule, and midbrain were 2.65 ($p \leq 0.01$), 3.58 ($p \leq 0.001$), and 2.74 ($p \leq 0.01$), respectively, relative to the control values. At 10 months, the z scores of the patient’s left/right ratio for the precentral gyrus, internal capsule, and midbrain were 3.39 ($p \leq 0.01$), 3.60 ($p \leq 0.001$), and 3.55 ($p \leq 0.01$).

Physical examination correlated with the corticospinal pathway deficits. At follow-up 6 months postinjury, the patient had normal left lower-extremity strength but weakness of the left upper extremity. There was near paralysis of the left hand intrinsic muscles (1/5) and weakness of the biceps (2/5), triceps (2/5), and deltoid (2/5).

Discussion

We report the initial use of HDFT and quantification

TABLE 1: Percent volumetric fiber track difference of right side compared to left*

Structure	Left (cm ³)	Right (cm ³)	% Difference	z Score	p Value
corona radiata	94.9 ± 4.5	35.3 ± 0.2	62.8 ± 1.6	38.3	<0.0001
cingulum	47.9 ± 2.9	51.5 ± 3	6.9 ± 6.1	1.1	0.13
superior longitudinal fasciculus	68.1 ± 3.4	71.7 ± 1.4	6.3 ± 6.4	1	0.16

* Mean values ± SD are displayed for volume and percentage differences.

of left/right asymmetries to identify white matter damage following TBI. This novel approach successfully detected, visualized, and quantified damage when previous methods (CT, structural MRI, and DTI) did not provide these details. With HDFT, we identified a specific lesion of the corticospinal pathway in the corona radiata that was directly associated with the functional deficits in our TBI patient. The volumetric losses as well as the number of fibers projecting from the motor cortices were reduced in the injured side, correlating with the left upper-extremity weakness. The other methods focused on describing the basal ganglia hemorrhage, but the patient's hemiplegia (left-sided weakness) could not be solely explained by basal ganglia damage. With HDFT, we could specify lesions to the corticospinal pathway adjacent to the basal ganglia and quantify their extent beyond the capabilities of current neuroimaging modalities.

At 6 months' follow-up, only left upper-extremity weakness was present, and the lower-limb weakness had resolved. Basal ganglia hemorrhage was apparent on the standard clinical imaging methods (CT, structural MRI, and DTI), but the corticospinal pathway damage correlating with the patient's functional deficit (left-sided weakness) was not. Standard clinical structural imaging suggested damage in the posterior limb of the internal capsule but did not convey the spatial specificity and degree of damage to the descending motor pathways as HDFT did (Table 3). High-definition fiber tracking showed a reduction in the number of fibers descending from the motor areas of the cortex. Using HDFT, we were able to visualize the specific location and quantify the degree of white matter injury responsible for the patient's persistent motor deficits. The decrease in fiber detection was specific to the injured hemisphere and correlated with the left upper-extremity weakness.

After the identification of losses in the corticospinal section of the corona radiata, we performed a second analysis looking specifically at the entire corticospinal pathway projections. With this analysis, we were able to locate the specific area of damage as the fiber tracks descended from the cortex. These areas of fiber damage can be clearly visualized (Fig. 6A and B) and quantified (Fig. 6C). The major fiber breakage was localized to the region between the internal capsule and the midbrain, shown by the sudden decrease in the ratio of right and left corticospinal fibers. As depicted in Fig. 6, the surviving fibers of the right corticospinal pathway are from the dorsomedial area of the primary motor cortex, which is responsible for lower-extremity control. However, major fiber losses are seen in fibers projecting from the ventrolateral area, which contains neurons controlling the upper extrem-

ity. The locations of fiber breaks are consistent with the clinical symptoms showing normal left lower-extremity function and severe left upper-extremity weakness at 6 months' follow-up.

Throughout the analysis, the ratios of fiber tracks between the left and right sides were used for each individual (patient or healthy control). This method was used to reduce the variability due to interindividual white matter differences and scanning data quality differences. Although the right corticospinal pathway and corona radiata exhibited the most pronounced damage in our patient, it is possible that the corticospinal pathway on the left side also had some degree of damage due to contra coup injury. Thus, a limitation of our analysis is the fact that the degree of axonal damage may be even more severe than detected by our current methods.

Due to the concern that edema and hemorrhage in the basal ganglia following injury may artificially impact the fiber tracking (Fig. 2B), the data from a second MRI study performed at 10 months following injury were analyzed using HDFT. Edema and hemorrhage in the basal ganglia (Fig. 2C) had resolved at 10 months, but the corticospinal pathway damage was still apparent (Fig. 6C). In fact, the loss of fiber tracks was more pronounced at the 10-month time point compared with the 4-month time point, possibly due to chronic axonal Wallerian degeneration following injury. Similarly, the loss of fiber tracks in the left anterior corona radiata was found (Fig. 2I) at 10 months, possibly due to chronic degeneration. Although the anterior corona radiata has previously been described to have an important role in attentional control,¹⁴ we focus

TABLE 2: Repeat reliability test of corona radiata tractography*

Sample No.	Left Corona Radiata	Right Corona Radiata	Ratio (L/R) × 100%†
1	13,940	4,644	33.3%
2	14,093	4,597	32.6%
3	14,016	4,573	32.6%
4	14,013	4,536	32.4%
5	14,001	4,539	32.4%
6	13,941	4,546	32.6%
7	14,015	4,516	32.2%
8	13,933	4,600	33.0%
9	13,975	4,556	32.6%
10	14,069	4,543	32.3%

* All raw values are fiber track counts.

† Mean 32.6% ± 0.3%.

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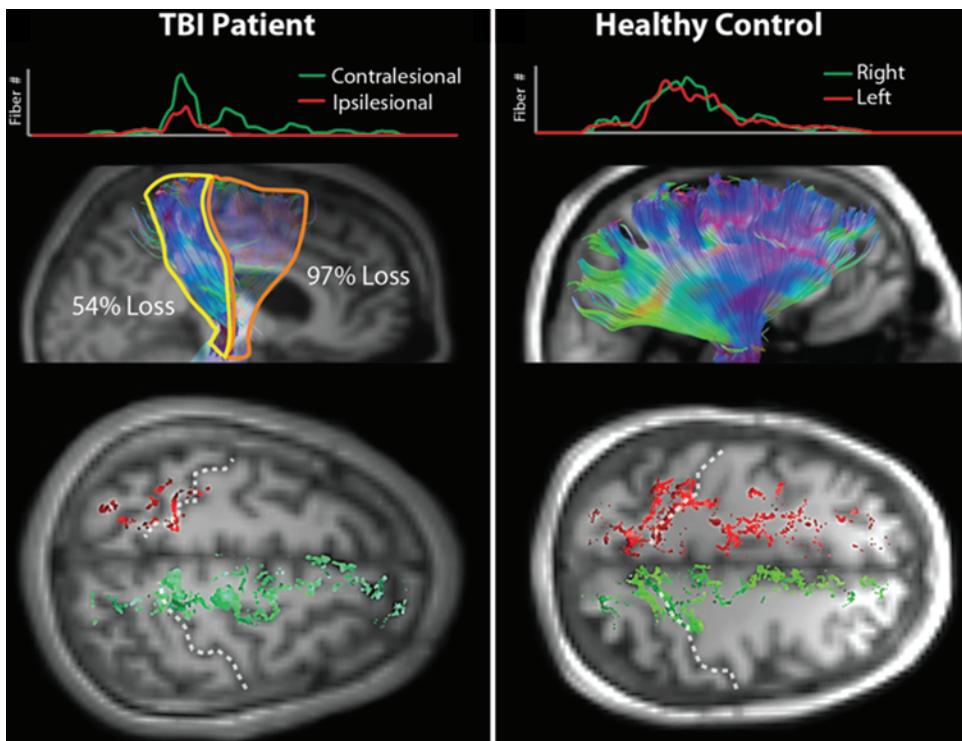


Fig. 5. Number of fiber termination points along the corona radiata in the TBI patient (**left**) and a healthy control (**right**). Major losses are noticeable for fibers terminating in the right central sulcus, precentral gyrus, and premotor areas of the injured patient. However, the healthy control does not have major differences between the corona radiata of left and right hemispheres. *Dashed white lines* show the central sulcus (border of the primary motor cortex) in the axial view images (*bottom row*).

on motor deficits for the scope of this case report. The replication of corticospinal pathway deficit at 10 months indicates that the damage visualized by HDFT is not an artifact of edema and hematoma.

Our results suggest that high-resolution white matter imaging and comparisons of left/right fiber tractography may provide valuable diagnostic information in characterizing the nature of motor pathologies. Previous studies using similar white matter imaging techniques, such as DTI, have been able to detect axonal damages induced by TBI.^{1,4,9–13,15} Due to its sensitivity in detection of white matter microstructure, DTI is reported by many authors as a sensitive technique to detect axonal damage in TBI. While DTI provides a sensitive detection of white matter pathology, HDFT can provide a complementary advantage in the detection of white matter injury. Whereas DTI has a limited ability to resolve crossing of fibers within a voxel,³ HDFT analysis utilizes diffusion spectrum imaging, which has a high angular resolution that allows tractography to navigate complex fiber crossings. Thus, HDFT provides high-resolution details of axonal pathways and projection fields that allow detection of specific location and degree of damage.

Traditional ways to quantify white matter integrity, such as DTI-based estimates of voxel FA (Fig. 2), have several limitations. These measures have a limited spatial resolution at the level of individual voxel, their values are difficult to interpret, and they cannot identify the specificity of the cortical origins of damaged fibers (for example, selective damage to upper-body fibers). In addition,

DTI FA measurement is compromised by interstitial fluid content.^{3,5,17,18} The DTI measurement becomes ambiguous in the presence of hemorrhage and edema (FA decreases when there is an increase in interstitial fluid or loss of axons). In contrast, our high angular resolution tracking technique, HDFT, has the ability to both localize and quantify axonal damage at the level of detail necessary for clinical purposes and is robust to changes in white matter pathway shape, interstitial fluid, and stochastic reseeding of the fiber tracks. This technique may have a valuable clinical diagnostic role that can augment current diagnostic imaging studies in the evaluation and management of TBI. The high spatial resolution of HDFT provides a better potential to link observed clinical symptoms with white matter damage. For example, we were able to show that the fibers affected by the midbrain lesion were primarily innervating upper-body areas of the motor cortex and this is in accordance with the contralateral, upper-extremity deficits reported in the clinical examination. Taking the limitations of current clinical imaging into account, tractography-based approaches in the clinical evaluation process may have significant potential for optimizing diagnosis.

The limitation of the current study is that we have only focused on motor deficits as a symptom of TBI. Given that there is damage to the corona radiata and possibly other pathways, various functional losses are expected. However, cognitive deficits such as memory, language function, and informational processing speed were not analyzed since such analysis was beyond the scope of

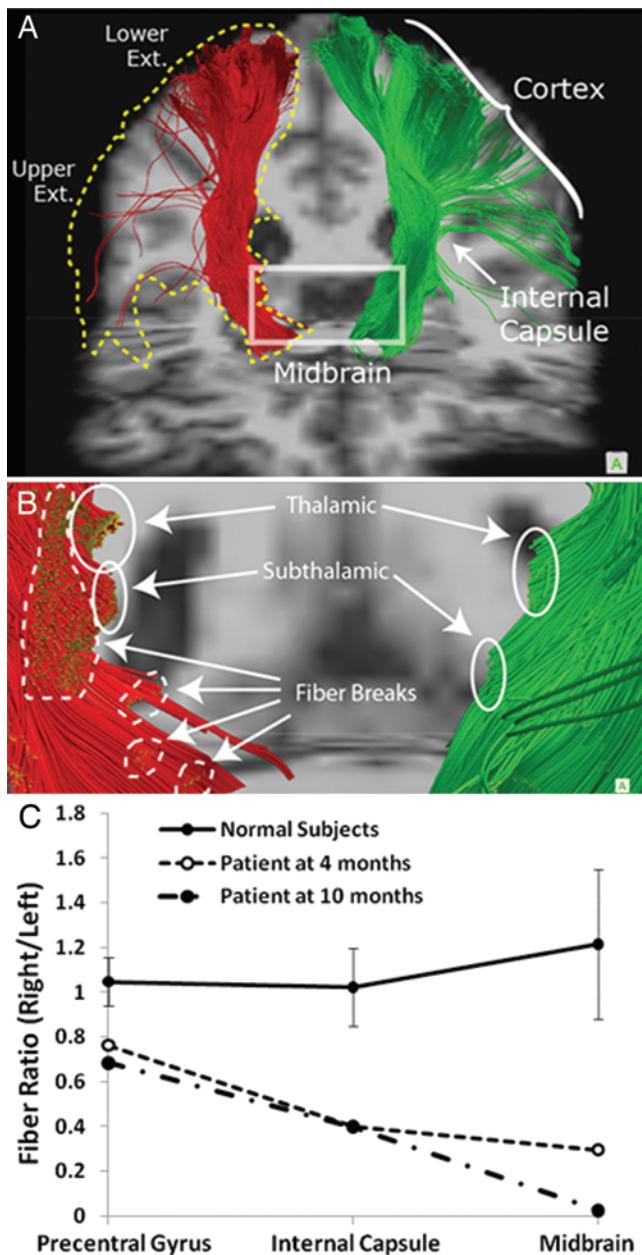


Fig. 6. Corticospinal fibers descending from the precentral gyrus imaged by HDFT. **A:** The right corticospinal pathway with significant damage is shown in red, and the left corticospinal pathway is shown in green. The yellow dotted outline shows the range of missing fibers detected at the cortical level in the right hemisphere. Ext. = extremity. **B:** A close-up view of the rectangular area in panel A shows fibers terminating in thalamic and subthalamic regions (solid lines), as well as regions of major fiber damage (dotted lines). **C:** Graph showing the ratios of left and right corticospinal fibers descending from the cortex for 6 healthy controls (mean \pm SD), the TBI patient at 4 months postinjury, and the TBI patient at 10 months postinjury. The ratios for the patient are decreased at all 3 levels at both time points. Positions of measurements are shown on the left hemisphere in panel A.

this paper. A future study analyzing white matter pathway damage in multiple patients with varying degrees of injury and areas of damage is needed to further demonstrate that HDFT findings also correlate with cognitive

TABLE 3: Summary of imaging findings by modality

Imaging Modality	Diagnostic Summary
CT	Large intraparenchymal hemorrhage in the right basal ganglia affecting the anterior limb of the internal capsule. Degree of damage in posterior limb of the right internal capsule is difficult to assess. (Day 5, 4 mos)
FLAIR	Mild compression of posterior limb of the internal capsule (Day 7). No compression of posterior limb of the internal capsule (4 mos).
T1-weighted MRI	Intraparenchymal hemorrhage in the right basal ganglia. Specific degree and location of damage in the right internal capsule is difficult to assess. (4 mos)
DTI (FA)	Significant loss of FA in the right basal ganglia. Slight signal loss of the anterior limb of the internal capsule extending into portions of the posterior limb, suggesting partial damage of motor tracts. (4 & 10 mos)
HDFT	Localized decrease in fibers of the motor areas of the corona radiata; substantial loss of axon volume in the motor (54%) and premotor areas (97%); 79% volume loss at the midbrain in the right corona radiata; focal fiber breaks in the corticospinal pathway in ventral aspects of right internal capsule that indicated reduced projection to left-hand M1, suggesting likely reduction of function; intact fiber projections from the lower-extremity areas of the motor cortex. (4 & 10 mos). The observations of 10 mos replicate the findings observed at 4 mos with a small increase in fiber loss at the level of the midbrain.

deficits. A prospective clinical trial in individuals with a high likelihood of TBI, such as athletes or soldiers, may provide additional support for the utility of HDFT if pre-injury and postinjury data can be compared. There is also a need to verify that the observed breaks in fiber streamlines that we visualized do in fact represent loss of axons. In a previous case report, we have shown that HDFT can identify the location of surgical cuts.² Future work will use presurgical and postsurgical scans in neurosurgery cases to segment and track microscopic fiber changes. In addition, animal studies can validate the use of fiber tractography in identifying axonal injury.

We present a case of severe TBI wherein a novel HDFT method provided clinically useful diagnostic information. The routine clinical imaging in this case, CT scanning, structural MRI, and diffusion imaging, revealed the presence of an intracerebral hematoma without any specificity to the effect on axonal tracks. High-definition fiber tracking allowed for the quantification of the axon volume loss and fiber loss far from the hematoma. In addition, this technique localized and visualized the fiber breaks and loss of projections to the premotor and motor cortices. The visualization and quantification of the losses of motor pathways correlated with the motor deficits observed in the patient. Although future studies

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are needed to confirm the utility of this technique, HDFT may potentially provide clinically useful characterization of axonal losses following TBI.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Boada, Okonkwo, Schneider. Acquisition of data: Shin, Pathak, Jarbo, Maserati. Analysis and interpretation of data: Shin, Verstynen, Pathak, Jarbo, Beers, Schneider. Drafting the article: Shin, Verstynen. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Okonkwo. Statistical analysis: Shin, Verstynen, Pathak, Jarbo. Administrative/technical/material support: Hricik, Maserati, Puccio. Study supervision: Beers, Puccio, Boada.

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Supplemental online information:

Video: http://mfile.akamai.com/21490/wmv/digitalwbc.download.akamai.com/21492/wm.digitalsource-na-regional/jns11-1282_video_new.aspx (Media Player).

http://mfile.akamai.com/21488/mov/digitalwbc.download.akamai.com/21492/qt.digitalsource-global/jns11-1282_video_new.mov (Quicktime).

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