Diffusion Tensor Tract Analysis of Patients with Traumatic Brain Injury: Stratification by Susceptibility Weighted Imaging
A H Bauer, S D Weiss, K Nael, H Fisk, B D Pressman, F G Moser

INTRODUCTION
Traumatic brain injury (TBI) is a prevalent public healthcare problem with 2.4 million emergency department visits, hospitalizations, or fatalities in 2010.1 TBI can damage white matter tracts resulting in memory impairment, attention deficit, and headaches.2, 3, 4 Traumatic axonal injury, axonal damage as a result of shear-strain forces,5-7 is believed to be the cause of these neurological and cognitive impairments.8

While fluid attenuated inversion recovery, diffusion weighted imaging, and gradient echo imaging have traditionally been utilized for the identification of traumatic axonal injury, susceptibility weighted imaging (SWI) has been shown to increase sensitivity, identifying tiny microhemorrhages otherwise undetectable with conventional MR imaging sequences.9,10,11,12 Likewise, diffusion tensor imaging (DTI) has been suggested to be sensitive in the detection of white matter injury with many studies investigating fractional anisotropy (FA) as a biomarker of TBI. Further, several studies have demonstrated correlation of lesions on DTI with cognitive performance.13-18

Recently, quantitative tractography, a method of performing diffusion tensor imaging analysis allowing calculation of FA and other diffusion tensor parameters averaged over the selected fiber tract, has shown utility in improving the diagnostic accuracy in patients with TBI and normal findings on routine MR images.19

The purpose of this study was to determine whether presence of microhemorrhage on SWI can be a determining factor in DTI tract analysis in patients with prior head trauma and to evaluate the diagnostic power of quantitative tractography in identifying SWI negative chronic brain trauma. Specifically, the aim was to determine whether there are changes in the diffusion characteristics and volume of the white matter
Diffusion Tensor Tract Analysis of Patients with Traumatic Brain Injury: Stratification by Susceptibility Weighted Imaging

tracts by performing a DTI tract analysis in SWI(+) and SWI(-) patients with prior TBI and in comparison with normal healthy controls without TBI.

METHODS

Participants.

This retrospective study was approved by the Institutional Review Board. From 2012 to 2014, 78 patients underwent 3.0 T MRI for the evaluation of TBI. Patients were included in this study if (a) they had a history of remote trauma (6-12 months prior); (b) they were between 20 and 60 years old (to limit the effect of changes in FA with age); (c) they had no history of other neurologic or vascular disease, chronic hypertension, or chronic alcoholism; (d) they had no findings of brain disease on conventional MRI including findings of trauma such as encephalomalacia or white matter disease (e) they had five or less microhemorrhages on SWI. The results were compared with 29 healthy control subjects (normative database) neither history of trauma as verified in the hospital electronic medical record nor any abnormalities on MRI of the brain.

Image acquisition.

All patients underwent MR imaging on a 3T Siemens Verio MR imaging system (Siemens, Erlangen, Germany) with a 12-channel phased array head coil. TBI protocol consisted of the following sequences: axial T1-weighted MPRAGE (TE = 2.96 ms, TR = 2100 ms, FA = 9°, [FOV] = 230 mm, matrix = 256, slice thickness = 1.2 mm, slice gap = 0.6 mm, image scan time ~ 5 min), axial FLAIR (TE = 89 ms, TR = 9000 ms, TI = 2500 ms, [FOV] = 230 mm, matrix = 320, slice thickness = 4 mm, slice gap = 1 mm, image scan time ~ 5 min), axial T2-weighted TSE (TE = 97 ms, TR = 6000 ms, [FOV] = 230 mm, matrix = 512, slice thickness = 4 mm, slice gap = 1 mm, image scan time ~ 5 min), axial diffusion weighted TSE EPI (TE = 100 ms, TR= 6500 ms, [FOV] = 230 mm, matrix = 128, slice thickness = 4 mm, slice gap = 1 mm, image scan time ~ 2 min), axial SWI (TE = 20 ms, TR = 27 ms, FA = 15°, [FOV] = 230 mm, matrix = 320, slice thickness = 2 mm, slice gap = 0.4 mm, image scan time ~ 4 min), and DTI (TR = 6500 ms, TE = 100 ms, FOV = 240 mm, matrix = 128, slice thickness = 3.0 mm, 20 directions; diffusion- weighted factor, b = 700 s/mm2). No MRI acquisitions were repeated.

Image analysis, post processing and tractography.

A single board-certified subspecialty certified neuroradiologist reviewed the conventional MRI to exclude subjects with findings of TBI and studies corrupted by motion, and assessed SWI for the presence and number of microhemorrhages. BrainSuite © software, version 14c, was then utilized for all image post-processing: automated co-registration, cortical extraction, multimodal region of interest (ROI) segmentation, geometric distortion correction, and quantitative diffusion tensor tractography. For more details, please see: http://brainsuite.org/.

Quantitative tractography parameters were as follows: track seeding = 0.5 seeds/voxel, stepsize = 0.25 mm, angle threshold = 20 degrees [0,90], FA threshold = 0.25 [0,1], and length threshold = 100 mm. Tractconnect MATLAB function (http://neuroimage.usc.edu/neuro/Resources/TractConnect) was then implemented to generate mean FA, mean mean diffusivity (MD), and voxel number (VN) for 6000 connection tracts between 330 ROIs per brain. Of the 6000 connection tracts calculated per brain, only those present in all subjects were included for statistical analysis.

Statistical analysis.

Statistical analysis was performed by using Matlab version 2015b Statistics and Machine Learning Toolbox™ and MedCalc for Windows, Version 14.12.0 (MedCalc Software, Mariakerke, Belgium). A two-way ANOVA was calculated with the independent variables of HISTORY OF TRAUMA and SWI POSITIVITY (presence or absence of microhemorrhages) and the dependent variable, FA, MD, or VN. Two-way ANOVA was performed for each connection tract to identify the tracts with the greatest statistical difference of each parameter between SWI(+), SWI(-), and controls. Bartlett test was performed to ensure homogeneity of variances (p > 0.05). Subsequent two-way ANCOVA was then performed on those tracts found to be statistically significant by two-way ANOVA to control for the covariate, AGE. Levene’s test was performed to ensure homogeneity of variances (p > 0.05). For interactions and main effects post-hoc paired comparisons testing (simple main effects analysis) took place. They were corrected using the Bonferroni method. Logistic regression analysis was performed to identify the contribution of each connection tract parameter to the model. Receiver operating characteristic (ROC) analysis was performed to ascertain the optimal connection tract parameters and threshold for determination of Trauma versus control, SWI(+) versus control, and SWI(-) versus control. Optimal thresholds were
calculated for each ROC curve to maximize both sensitivity and specificity employing the Youden statistic. Subsequently, an ROC curve for the combination of parameters was calculated, extrapolating from the maximum-likelihood estimation model of combining classifiers 20. Area under the curve (AUC) was calculated for each individual tract’s ROC curve as well as for the combined ROC curves. P < 0.05 was considered to indicate a statistically significant difference.

RESULTS

Of the 107 patients, 86 patients with a mean age of 36.4 were included: 27 patients with history of TBI and microhemorrhages (SWI(+)) (mean age ± SD: 34 years ± 11), 30 patients with history of TBI and without microhemorrhages (SWI(-)) (mean age ± SD: 34 years ± 9), and 29 patients from a normative database (Control) (mean age ± SD: 40 years ± 9). MRI images in 21 of the patients demonstrated findings of moderate or severe trauma or greater than 5 microhemorrhages on SWI and these patients were therefore excluded from the study.

Of the 6000 tracts calculated per brain, 613 were common to all subjects. Of the 27 patients demonstrating microhemorrhages, mean number of microhemorrhages was 3 ± 1. Locations of microhemorrhages included left and/or right superior, middle, inferior, orbitofrontal, and opercular frontal lobe, anterior, superior, middle and inferior temporal lobe, insula, parahippocampus, postcentral and angular parietal lobe, corona radiata, centrum semiovale, genu and splenium of the corpus callosum, and uncus.

SWI(+) vs. Control

No statistically significant difference was found in tract total average for any of the parameters including VN. Nine tracts demonstrated statistically significant differences in FA, 12 tracts in MD, and 14 tracts in VN. Classifiers with statistically significant differences within the ANCOVA model (P ≤ 0.02) and between SWI(+) subjects and controls (P ≤ 0.05) are tabulated in Table 1 with their corresponding means ± SD.

SWI(-) vs. SWI(+)

Two tracts demonstrated statistically significant differences in FA, 0 tracts in MD, and 9 tracts in VN. Classifiers with statistically significant differences within the ANCOVA model (P ≤ 0.02) and between SWI(+) subjects and SWI(-) subjects (P ≤ 0.05) are tabulated in Table 1 with their corresponding means ± SD.

Trauma (SWI(+) and SWI(-)) vs. Control

No statistically significant difference was found in tract total average for any of the parameters, including VN. Fifty-four tracts demonstrated statistically significant differences in FA, 53 tracts in MD, and 96 tracts in VN. Tracts with statistically significant differences between Trauma and Controls in greater than one classifier are provided in Table 2 with their corresponding means ± SD.

Logistic regression analysis utilizing the 22 tract classifiers with the most statistically significant differences between Trauma and Control (P ≤ 0.01) yielded significant contribution from four tract classifiers listed in Table 2: Left globus pallidus – Brainstem (P=0.0003, 95% CI, 1.4 – 3.0), Left putamen - Left posterior orbitofrontal gyrus (P = 0.0007, 95% CI, 0.48 – 0.82), Right pars opercularis - Right postcentral gyrus (P = 0.0024, 95% CI, 0.91 – 0.98), Left middle temporal gyrus - Left inferior temporal gyrus (P=0.013; 95% CI, 1.0-1.3). Optimal threshold values, area under the curve, and corresponding sensitivity and specificity for the combination of these four classifiers in the differentiation of Trauma versus Control are summarized in Table 3 with corresponding ROC curves provided in Figure 1.
In the current study, by using SWI imaging as a surrogate biomarker of TBI and automated tractography atlas-based spatial statistical software, we demonstrated that DTI tractography detects chronic white matter changes in patients with a history of TBI. We highlight several notable points:

The presented investigation adds clarification to the mounting evidence indicating DTI has the capability to detect chronic microstructural white matter alterations that result from TBI. As demonstrated in multiple prior studies of chronic TBI, there was decreased FA and/or increased MD in the superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus, cingulum bundle, corpus callosum, internal capsule and corticospinal tracts. With the exception of two studies that utilized SWI for exclusion criteria,
the majority of prior investigations looking at DTI measures in chronic TBI, used a T2*/GRE sequence to identify the presence of microhemorrhages in order to either include or exclude subjects or as a marker of traumatic axonal injury. Therefore, it is plausible that these studies may have underestimated the presence of microhemorrhages due to lower sensitivity of GRE compared to SWI in patients with TBI. Considering that microhemorrhages may lead to difficulties analyzing DTI parameters in white matter tracts because of susceptibility effects, one may assume that the reported reduced FA and increased MD of white matter tracts in TBI patients in studies utilizing GRE and not SWI may have been confounded by an underestimation of microhemorrhages. However, in our study, both SWI(+) and SWI(-) cohorts demonstrated similar shifts in FA and VN of select white matter tracts when compared to patients with no history of trauma. Further, some of these same tracts demonstrated a persistent significant difference between Trauma (SWI(+) and SWI(-) grouped together) and controls. This not only suggests that the results of the prior studies without SWI are less likely to be confounded, but also provides further support for the conclusion that DTI has the ability to detect white matter changes of TBI not detected with SWI, and therefore, the capacity to identify injury before thought to be either not present or undetectable.

While the majority of the prior studies report either decreased or no change in FA in chronic TBI, our investigation also identified tracts with increased FA, many oriented in the craniocaudal direction. Though a counterintuitive finding, a few studies have also found increased FA attributing this to diminished crossing fibers leading to increased axonal packing. However, many of the tracts with increased FA in the present study extended from the striatum to the brainstem, regions with relatively less crossing fibers (compared to regions like the corona radiata). Further, there were no significant decreases in FA of tracts that would be assumed to be crossing these regions. Another potential explanation for increased FA is increased myelination. Yet, increases in myelination would be contrary to the previous finding of decreased white matter volume of patients with chronic TBI, albeit in a different region. Still, alternative reasons for increased FA include microscopic deficits of axonal structures or decreases in axonal diameter, packing density, and branching. Aside from the theoretical causes of increased FA, what is clear is that the presented results suggest an alteration in the DTI streamlines in brains of patients with a history of TBI compared to those without history of TBI, perhaps in response to TBI, in regions implicated in chronic TBI according to the biomechanical model of concussion (nigrostriatal tract and pallidotegmental fasciculus coursing through the brainstem) as well as in locations established in prior studies (superior longitudinal fasciculus, uncinate fasciculus, inferior longitudinal fasciculus, cingulum bundle, corpus callosum, internal capsule and corticospinal tracts). Conceivably, in response to injury to neuronal fibers, the brain may strengthen certain pathways and weaken others to compensate long term. Similar findings have been shown in studies of psychiatric disorders possibly related to TBI. A curious finding was that VN showed significant increases with significant FA increases. VN is a measure of the volume of white matter corresponding to a distinct fiber bundle that exceeds the given FA threshold. VN and FA are inherently linked via the FA tracking threshold. Indeed, partial volume effects may also be an additional concern because effects are exaggerated for smaller tracts. However, studies suggest VN is not a direct cause or the result of observed FA and MD changes. Further, we found multiple tracts with significant differences in VN without significant differences in FA or MD and vice versa. Increased VN may be the consequence of two factors along the entire length of a tract: increased volume of parallel fibers or net decreased crossing fibers. It has been noted that tractographic FA values represent a mean of individual FA within voxels along a streamline. Therefore, in the case of loss from peripheral fiber contributions, where individual FA voxel values may be relatively lower, these mean FA values can reflect the core voxels with highest individual voxel FA values. This in turn can suggest that an increase in VN and concomitant increase in FA may represent an increase in length of a tract, increase in thickness of a tract, or decrease in crossing fibers. These results provide additional evidence that DTI may have the capacity to detect structural alterations in white matter tracts that are a response to TBI.

Utilizing DTI to detect the chronic white matter rewiring of TBI not visible by conventional MRI is becoming more feasible with a growing body of evidence. Drawing from the most significant atlas-based tractography parameters and performing combined ROC analysis, the best overall model we identified to distinguish chronic TBI from control yielded an area under the curve of 0.93, independent of the presence of microhemorrhages. While our study attempted to minimize potential confounding factors by restricting our

---

Diffusion Tensor Tract Analysis of Patients with Traumatic Brain Injury: Stratification by Susceptibility Weighted Imaging

---

5 of 9
Diffusion Tensor Tract Analysis of Patients with Traumatic Brain Injury: Stratification by Susceptibility Weighted Imaging

sample to chronic TBI in adults, controlling for age, utilizing automated atlas-based tractography software (removing error associated with manual ROIs), and assessing the influence of microhemorrhages, further study is warranted to determine the replicability.

Limitations of this study include the lack of clinical details of the study population sample. Many studies have shown psychiatric diseases can influence DTI parameters and therefore the lack of this confounding clinical information in our study limits the conclusions.48-50 Likewise, studies have demonstrated a sexual dimorphism in thalamic, corpus callosal and cingulum DTI parameters.51 Variability in the veracity and severity of reported trauma is a potential source of error, though this was heavily mitigated by the utilization of SWI. As with most publications involving DTI and chronic TBI, our MRI scanner and DTI technique was unable to resolve multiple fiber orientations within a single voxel, thereby restricting a detailed assessment of the influence of crossing fibers. Furthermore, trauma-induced loss of peripheral fibers may adversely influence tractographic statistics. Another limitation is the retrospective nature of the study, possibly introducing unknown bias. Lastly, the diagnostic accuracy of this MR imaging technique for the detection of TBI should be evaluated prospectively in a larger cohort across multiple centers with multiple MRI scanners.

CONCLUSION

Diffusion-tensor tractography is a promising technique in improving the detection of microstructural white matter abnormalities in patients with chronic TBI regardless of the presence of microhemorrhages. The results of this study should be confirmed in a larger cohort across multiple centers.

References

traumatic brain injury patients: DTI metrics are highly correlated with postural control. Hum. Brain Mapp. 31(7), 992–1002.


Author Information

Adam H. Bauer
Cedars-Sinai Medical Center
Los Angeles, CA

Sasha D. Weiss
Cedars-Sinai Medical Center
Los Angeles, CA

Kambiz Nael
Mount Sinai Hospital
New York, NY

H. Ron Fisk
Cedars-Sinai Medical Center
Los Angeles, CA

Barry D. Pressman
Cedars-Sinai Medical Center
Los Angeles, CA

Franklin G. Moser
Cedars-Sinai Medical Center
Los Angeles, CA