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ORIGINAL RESEARCH

Fractal dimension brain morphometry: a novel approach to quantify white matter in traumatic brain injury

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Abstract

Traumatic brain injury (TBI) is the main cause of disability in people younger than 35 in the United States. The mechanisms of TBI are complex resulting in both focal and diffuse brain damage. Fractal dimension (FD) is a measure that can characterize morphometric complexity and variability of brain structure especially white matter (WM) structure and may provide novel insights into the injuries evident following TBI. FD-based brain morphometry may provide information on WM structural changes after TBI that is more sensitive to subtle structural changes post injury compared to conventional MRI measurements. Anatomical and diffusion tensor imaging (DTI) data were obtained using a 3 T MRI scanner in subjects with moderate to severe TBI and in healthy controls (HC). Whole brain WM volume, grey matter volume, cortical thickness, cortical area, FD and DTI metrics were evaluated globally and for the left and right hemispheres separately. A neuropsychological test battery sensitive to cognitive impairment associated with traumatic brain injury was performed. TBI group showed lower structural complexity (FD) bilaterally ($p < 0.05$). No significant difference in either grey matter volume, cortical thickness or cortical area was observed in any of the brain regions between TBI and healthy controls. No significant differences in whole brain WM volume or DTI metrics between TBI and HC groups were observed. Behavioral data analysis revealed that WM FD accounted for a significant amount of variance in executive functioning and processing speed beyond demographic and DTI variables. FD therefore, may serve as a sensitive marker of injury and may play a role in outcome prediction in TBI.

Keywords Fractal dimension · DTI · TBI · Cognitive domain scores

Abbreviations

BET	Brain Extraction Tool
DTI	Diffusion Tensor Imaging
FAST	FMRIB's Automated Segmentation Tool
FD	Fractal Dimension
FLIRT	FMRIB's Linear Image Registration Tool
FMRIB	Functional Magnetic Resonance Imaging of Brain
FNIRT	FMRIB's Nonlinear Image Registration Tool
FSL	Functional MRI of the brain Software Libraries
FWER	Family-Wise Error Rate
FWHM	Full-Width Half-Maximum

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GLM	general linear model
GM	grey matter
MPRAGE	magnetization prepared rapid gradient echo
MRI	magnetic resonance imaging
SPM	statistical parametric mapping
TBI	Traumatic Brain Injury
VBM	voxel based morphometry
WM	white matter

Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide with immense negative impact on society, economy and healthcare systems. The Centers for Disease Control and Prevention estimates that every year 1.7 million people in USA sustain TBI, and TBI contributes to 30% of all injury related deaths in the USA (Faul et al. 2010). An estimated 5.3 million people (close to 2% of the population) are currently living with TBI-related disabilities in the USA with an estimated cost of more than $60 billion per year due to injury-related work loss and disability (Faul et al. 2010; Finkelstein et al. 2006). However, the overall impact may be much higher as studies suggest that published statistics underestimate the TBI burden (Powell et al. 2008; Bazarian et al. 2006).

Despite societal impact of TBI, approaches to characterize TBI severity and outcome have shown little progress in more than three decades (Maas et al. 2010). Currently, the severity grades of mild, moderate, and severe TBI are defined by using clinical and radiographic indices. Glasgow Coma Scale (GCS), length of loss of consciousness, and post-traumatic amnesia form some of the clinical criteria; evidence of intra-cranial lesions on computed tomography (CT) scans or magnetic resonance imaging (MRI) are the basis of the radiographic criteria and outcome is measured using the Glasgow Outcome Scale Extended (GOS-E) (Teasdale and Jennett 1976; Wilson et al. 1998). However, TBI is highly heterogeneous in cause, severity, pathology and clinical course and these measures often fail to capture this complexity (Yue et al. 2013).

For example, current neuroimaging techniques have limited sensitivity to detect physiological alterations caused by TBI. The focal lesions detected by CT or MRI in TBI, such as contusions and axonal shearing injuries, are often not predictive of long-term functional disability after TBI, especially in mild cases. Overall, approximately 70% of patients with TBI do not show any visible lesions using conventional MRI or CT techniques (Huang et al. 2009). In addition, the absence of abnormality on conventional neuroimaging techniques in the majority of mild TBI patients, even with post-concussive symptoms and cognitive and/or behavioral deficits, illustrates the limited prognostic value of conventional neuroimaging techniques (Johnston et al. 2001; Kirkwood et al. 2006). The heterogeneity of TBI, combined with the lack of accurate radiological indices for TBI, is thus hindering development of targeted treatment and neuroprotective strategy (Maas et al. 2010). A novel neuroimaging based biomarker, which can address this neurobiological heterogeneity, may help in early diagnosis and follow up rehabilitation care plans of patients with TBI.

Neuroimaging and neuropathology in TBI: The unsolved issues

A classic finding in moderate and severe TBI is axonal injury (Gennarelli et al. 1982). White matter (WM) fibers are injured due to rotational forces on the brain within the cranial cavity, a condition often referred to as diffuse axonal injury (DAI) (Adams et al. 1989). DAI has been linked to cognitive status (Rabinowitz et al. 2018; Scheid et al. 2006) and has been linked to poor outcome in TBI (Maas et al. 2008). However, current evaluation of DAI with MRI is often problematic as it depends on the sensitivity of the MR imaging sequences, selection of patients, and time between injury and scan (Skandsen et al. 2010). Due to these reasons the results of studies correlating MRI evaluation of DAI and functional outcome are often conflicting (Chelly et al. 2011).

Fractal dimension analysis: A novel way to measure WM changes

Novel imaging approaches that aim to characterize DAI have focused on axonal integrity which can be detected by focusing on the structure's shape (morphology) complexity (Kinnunen et al. 2011; Kraus et al. 2007). The change in brain shape is a common underlying outcome in TBI (Cloots et al. 2008; Feng et al. 2010) and can capture both the focal (contusions, lacerations, hematomas and tentorial/tonsilar herniation) and diffuse (diffuse axonal injury, cerebral swelling) nature of tissue injury. While volumetrics have a longstanding application to TBI (Bigler 2015) shape morphometry has only recently been applied to the study of TBI and largely in mild TBI (Tate et al. 2016; Bolzenius et al. 2018). Fractal dimension (FD) is a novel and quantitative technique to estimate WM shape through brain morphometry (Zhang et al. 2008; Zhang et al. 2007). "Fractal" is a term coined by Mandelbrot (Mandelbrot 1982) to describe the irregular but self-similar shapes of natural objects. Another aspect of a fractal is it gives a measure of the complexity of any rough and irregular object. The cortical fractal structure, therefore, can be characterized by a single numerical value (the fractal dimension, FD) that summarizes the irregularity of the cortical sulci and gyri and the boundary between subcortical grey and white matter (Bullmore et al. 1994). FD measures have been successfully applied to reveal gender and age structural differences in the cerebral cortex in the absence of disease and to investigate various psychiatric and neurological disorders. (Esteban et al. 2007; Mustafa et al. 2012; Zhang et al. 2008; Zhang et al. 2007). In all these studies WM complexity (WMc) was reduced in brain pathology. However, to the best of our knowledge, FD is yet to be evaluated in the TBI population. There are several reasons why fractal analysis may be a useful approach for analyzing brain WM shape in TBI: (1) FD can capture very complicated morphology of structures in a simple and quantitative description and can characterize the WM shape within the brain. (2) Given that in general the higher spatial resolution of T1-weighted 3D anatomic images upon which the FD analysis is made, the WMc index could capture WM changes which may be in many cases beyond the resolution capability of conventional clinical MR scans such as T2-weighted (T2-W) or PD-weighted. In this study, therefore, we examined whether white matter FD characteristics were different in chronic TBI patients, as compared to healthy controls, and whether these FD measures correlate with cognitive outcome.

Comparing FD with diffusion tensor imaging (DTI) and other volumetric markers

As FD offers additional benefits over other structural measurements of WM (e.g., White matter voxel based morphometry), we also examined how FD compares with these measures in predicting cognitive function parameters in TBI. The comparison with DTI was of special interest. DTI provides quantitative information about integrity of WM microstructures by evaluating isotropic and anisotropic water diffusion within neuronal fiber tracts. DTI based measures are quite promising in evaluating DAI and has received widespread application in TBI research (Kinnunen et al. 2011; Kraus et al. 2007; Douglas et al. 2015). However, as noted above FD is a measure of a distinct phenomenon i.e. structural complexity (shape) of brain tissue hence, this may provide additional information that may complement DTI. As FD evaluates the WM complexity of the whole brain, it is important to know how this correlates with volumetric change of WM. In addition to WM, we also compared FD with GM volume and thickness changes using popular openware FreeSurfer, which can generate maps of whole brain GM atrophy. Generalized cerebral atrophy is a well-established consequence of moderate-to-severe TBI and the degree of atrophy is related to injury severity (Ghosh et al. 2009). It is therefore imperative to evaluate how WM structural complexity changes may relate to overlying GM alterations.

Hence, given the potential importance of white matter pathology to outcome in TBI, and FD is a promising new technique in determining the integrity of white matter beyond currently available techniques, studies of FD are warranted in TBI population. In this study, a group of chronic TBI subjects of moderate-to-severe severity and a group of demographically matched healthy controls underwent MRI (anatomical and diffusion tensor imaging) and neuropsychological testing. The primary objective of the current investigation was to test the hypothesis that WMc is reduced in chronic TBI subjects. The secondary objective was to examine the relationship between WMc and cognition assessed with standard neuropsychological testing. Additionally, we compared the FD-assessed WMc vs DTI/volumetric measures in predicting cognitive outcome.

Methods

Study subjects included 17 individuals with moderate to severe TBI assessed using the Glasgow coma scale (GCS, range 3 to 8) and healthy controls (HC) ($n = 13$) matched for age, gender and education (Table 1). The study was approved by both the Kessler Foundation IRB as well as the IRB of the University of Medicine and Dentistry of New Jersey where the imaging data were collected. All participants signed informed consent, and were reimbursed $100 for their time.

All the TBI subjects in our study were of right handed and had moderate to severe TBI per GCS. T1-weighted imaging was normal in 2 patients (11.7%) and T2-W normal in 3 patients (17.6%). Definite and possible intraparenchymal microbleeds indicative of diffuse axonal injury were found in 35% of the patients (Microbleed group: 6 patients, 5 males, mean age 28.2 ± 6.9 years, average time since injury 26 months; non-microbleed group:11 patients (65%), 8 males, mean age 30.2 ± 14.5 years, average time since injury 25 months). There was no group difference for age, gender, and duration of TBI. Microbleeds were mainly found in frontal and temporal white matter bilaterally.

Neuropsychological assessment

On the day of MRI, all participants completed a standardized neuropsychological test battery sensitive to cognitive impairment associated with traumatic brain injury. The following cognitive functions of specific interest were evaluated: (i) verbal short-term learning and memory performance via the Hopkins Verbal Learning Test – Revised (HVLT-R); (ii) the executive functions of set-shifting, inhibitory control and cognitive flexibility were measured using the Delis–Kaplan Executive Function System (Delis et al. 2001). We used the alternating-switch cost index (time to complete alternating letter and number Trails B time to complete numbers-only Trail A) from the Trail Making subtest and the inhibition/switching minus baseline score from the Color–Word subtest (high scores indicating poor performance); (iii) information processing speed via the Symbol Digit Modalities Test (SDMT); and (iv) attention - via the Visual Search and Attention Test (VSAT).

Table 1 Demographics of Healthy Controls and TBI Patients

Subjects	Age	Gender	Education (in years)
Healthy Controls ($n = 13$)	26.9 ± 10.4	8 Male, 3 female	14.7 ± 2.4
TBI patients ($n = 17$)	27.7 ± 10	12 male, 5 female	13.7 ± 2.6

Gender and age information not available for two healthy controls

Z-scores were calculated for all subjects, with the mean and standard deviation (SD) of data from healthy subjects used to define z-scores for all subject groups. Negative scores indicate performance below the mean of healthy subjects. Domain scores for measures of executive function, attention, processing speed and memory were generated by averaging the standardized data from tests assessing these cognitive domains.

Imaging protocol

High resolution 3D T1-weighted (T1-W) axial magnetic resonance images (MRI) of the whole brain were obtained using a magnetization prepared rapid gradient echo (MPRAGE) sequence on a 3 T Siemens Allegra (Erlangen, Germany) scanner. TBI patients were scanned three months after resolution of post traumatic amnesia, or the acute confusional state, which frequently follows coma emergence. Imaging parameters were: TR (repetition time) = 2000 ms, TE (echo time) = 4.9 ms, flip angle = 8°, inversion time (TI) = 900 ms, slice thickness = 0.96 mm, in-plane resolution = 0.96 × 0.96 mm^2, and number of slices = 172. DTI data were also acquired using a single shot echo planar imaging (SS-EPI) sequence along 12 diffusion weighted (b = 1000 s/mm^2) directions and one b = 0 s/mm^2. Imaging parameters were: 26 slices, thickness = 4 mm with 2.0 × 2.0 mm in-plane resolution; pulse sequence parameters were: repetition time TR = 7300 ms, echo time TE = 88 ms, number of averages = 8.

Data analysis

A comprehensive quantitative analysis was performed on brain grey and white matter structures of TBI and control subjects. The techniques used to quantitatively assess WM damage were; a) FD analysis, b) DTI evaluation, and c) whole brain intracranial WM volume measurement. Grey matter changes were quantitatively assessed using cortical thickness analysis. The purpose of this comprehensive analysis was to evaluate the sensitivity of FD measure (in detecting structural change of the WM system in TBI patients) over currently available techniques such as VBM, DTI. More details on each of these methods are given below.

White matter (WM) analysis

Fractal dimension (FD) analysis FD analysis was carried out using our customized in-house routines (details described elsewhere (L. Zhang et al. 2006). Briefly the image processing included: skull stripping of T1-W images using FMRIB Software Library (FSL version 5.0) Brain Extraction Tool (BET) (Smith et al. 2004) (http://www.fmrib.ox.ac.uk/fsl/ Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford, UK). Brain extraction was followed by segmentation into WM, grey matter (GM) and cerebrospinal fluid (CSF) probability maps using FSL's FAST tool (Y. Zhang et al. 2001). WM probability maps were then binarized using a threshold value of 0.5 (this value was chosen after validation by considering two other threshold values such as 0.6 and 0.7). A 3D thinning method was then applied to the WM binary image to obtain the 3D WM skeleton. The 3D thinning algorithm removed as many boundary voxels as possible without changing the general shape of the WM, until a center line of one voxel width (skeleton) remained. Masks for left and right hemispheres were created using FSL. Hemispheric masks were then applied to WM skeleton and WM general structure images to get the WM skeleton and WM general structure of left and right hemispheres. FD values were estimated using a 3D box-counting method (L. Zhang et al. 2006) using the WM skeleton and WM general structural image masks. The box-counting method was preferred since it can be applied to structures without self-similarity, such as the human brain. (The box-counting method works by repeatedly applying different-sized meshes (r) to the fractal image and counting the number of boxes (N) needed to completely cover the fractal). Finally, a linear regression fit after log transformation was used to estimate FD values using Eq. 1 given below

$$\ln N = \text{FD} \ln(1/r) + \ln k, \quad (1)$$

where k is a nuisance parameter, in self-similar scale (linear portion in the logarithmic function).

In this study we estimated FD values of the three WM features (shape representations): skeleton, surface and general structure. Skeleton FD was calculated by counting the boxes needed to cover the WM skeleton; surface FD was evaluated by counting the boxes needed to cover the boundary of WM/GM interface; general structure FD was estimated by counting the boxes needed to cover all the WM voxels (which included skeleton and surface). The skeleton (consists of central line of each WM tract/bundle), also known as WM interior structure preserves the topological and geometric information of the WM. The skeleton configuration represents the interior structure complexity of the brain WM. The surface structure consists of voxels at the boundary i.e. GM/WM interface, reflecting the shape of the gyral and sulcal convolutions in the GM/WM interface. General structure comprises of all WM voxels representing the volume changes. Because the WM skeleton, general structure and surface represent three different aspects of brain WM structure, it was expected that they may serve as more comprehensive and distinct shape complexity measures to evaluate the WM structure shape/structure changes brought out by pathophysiological mechanisms of TBI.

DTI analysis DTI images were processed using FSL openware (http://fsl.fmrib.ox.ac.uk/fsl). The processing steps included correction for eddy current distortion effects. The b-matrix was rotated after eddy current distortion effects in order to preserve correct orientation information. Then, diffusion tensor model was fitted to these corrected images using "*dtifit*" routine and maps of diffusion tensor metrics namely fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were obtained. Whole brain, right and left hemisphere WM masks obtained by segmenting T1-W images were then multiplied (after registering with the b0 image) with FA, MD, AD and RD maps. Mode values of whole brain, right and left hemisphere FA, MD, AD and RD were measured from the histogram plots of each subject. Statistical analysis was performed using either T-test or Mann-Whitney U test depending on data meeting the assumptions of normality.

White matter intracranial volume analysis Whole brain (intracranial) white matter, grey matter and cerebrospinal fluid volumes were obtained for both control and TBI patients using SPM software. A T-test was performed to compare the differences in whole brain WM and cerebrospinal fluid (CSF) intracranial volumes between TBI patients and controls.

Freesurfer based automated Grey matter analysis

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis version 4.0.4 (http://surfer.nmr.mgh.harvard.edu.libproxy2.umdnj.edu/) (Fischl et al. 2004; Jovicich et al. 2009). Briefly, this processing included the removal of non-brain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical WM and deep GM volumetric structures (Fischl et al. 2002; Fischl et al. 2004), intensity normalization (Sled et al. 1998) tessellation of the GM–WM boundary, automated topology correction (Fischl et al. 2001; Segonne et al. 2007), and surface deformation following intensity gradients to optimally place the GM/WM and GM/CSF borders (Dale et al. 1999; Fischl and Dale 2000). The resulting cortical models were registered to a spherical atlas. The cerebral cortex was parcellated into regions based on gyral and sulcal structures (Desikan et al. 2006). Results for each subject were visually inspected to ensure accuracy of registration, skull stripping, segmentation, and cortical surface reconstruction. A p value of <0.05 corrected for multiple comparisons using a false discovery rate (FDR) was considered for the level of significance for measures of cortical thickness, cortical area and cortical volume.

Statistical analysis between imaging and clinical measures

IBM SPSS for Windows version 21 (Armonk, New York) was used for database and statistical analysis. A two-tailed unpaired Student's t-test or Fisher's exact test was used to compare demographic, neuropsychological and FD findings between healthy controls and patients with TBI. To investigate the correlation between FD and cognitive variables, univariate correlations between continuous variables were assessed using the Pearson correlation coefficient and those between discrete variables were assessed with the Spearman rank correlation coefficient. A stepwise linear regression analysis was performed to assess the relative contributions of the main demographic (age, education and sex) and WM parameters (FD, DTI parameters) in predicting the cognitive domain index scores. Forward and backward stepwise analyses were conducted using the Wald statistic as a criterion, with $p = 0.05$ for entry and $p = 0.10$ for removal.

Results

Neuropsychological testing

Patients with TBI differed from healthy controls (HC) (with poorer scores compared to HC) on all cognitive domains - memory/learning ($p = 0.02$), executive function ($p = 0.001$), attention ($p = 0.001$) and processing speed ($p = 0.002$).

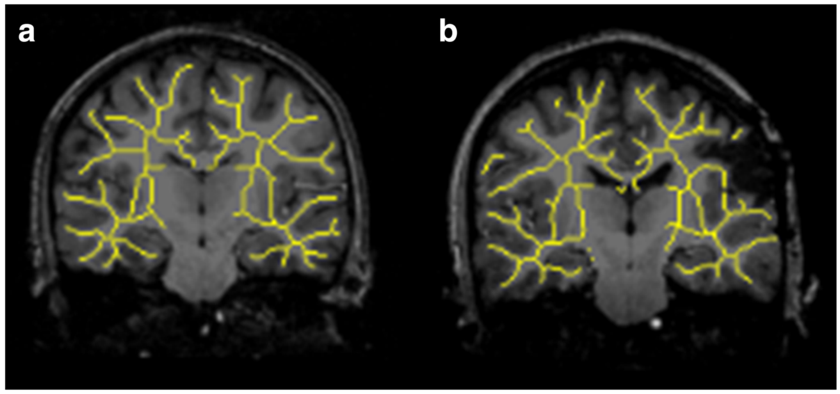
Fractal dimension changes in TBI

Skeleton FD values of right (TBI 2.24 ± 0.06; HC 2.30 ± 0.06 (Mean ± SD)) ($p = 0.04$) and left (TBI 2.25 ± 0.04; HC 2.30 ± 0.05 (Mean ± SD) ($p = 0.01$) hemispheres was significantly reduced in TBI (Fig. 1). Figure 2 shows an example of segmented WM skeletons overlaid on T1-weighted anatomical image for a healthy control (Fig. 2a) and TBI patient (Fig. 2b) with visible injury in the right hemisphere. There were no significant differences in surface or general structure FD values between TBI and HC.

Relation between Intraparenchymal microbleed and fractal dimension

Significant ($p < 0.05$) reductions were observed in the skeleton FD values of right (non-microbleed - 2.28 ± 0.05; Microbleed - 2.19 ± 0.04 (Mean ± SD)) and left (non-microbleed - 2.27 ± 0.03; Microbleed - 2.21 ± 0.05 (Mean ±

Fig. 1 Significant reductions in skeleton FD values of whole brain (left), left (middle) and right (right) hemisphere WM structure complexity in TBI (Grey bars) compared with healthy controls (white bars), $^*p \leq 0.05$



SD)) hemispheres with patients with microbleeds showing lower structural complexity compared to those without microbleeds. However, we failed to observe any significant difference in surface or general structure FD values between microbleed and nonmicrobleed group.

DTI

No significant differences in FA (Fig. 3), MD (Fig. 4) or RD values were observed between TBI and HC either in the whole brain or on the right or left hemisphere WM tissue. The only significant difference was observed in AD values in left hemisphere ($p = 0.03$) and right hemisphere ($p < 0.05$).

White matter intracranial volume changes

Whole brain WM volume (in units of ml) was slightly reduced in TBI patients (mean = 512.36 ml) when compared to HC (mean = 514.43 ml) but did not reach statistical significance. On the other hand, CSF volume was found to be significantly ($p < 0.001$) increased in TBI (mean = 271.43 ml) when compared to HC (mean = 218.57 ml). Since the ventricles change volume, it is expected that white matter structural morphometry may change. To verify whether the CSF volume change was driving the WM shape change, we performed correlation between the FD metric and CSF volume metric. No significant correlation was observed between the two metrics ($r = -0.306$, $p = 0.423$), suggesting that pathophysiology of TBI may deferentially affect WM structure and the ventricles. The data also suggest that the FD measure of the WM structural morphometry is not significantly influenced by the volumetric changes.

Grey matter volume and cortical thickness changes

No significant difference in either grey matter volume or cortical thickness or cortical area was observed in any of the brain regions between TBI and HC. Among the deep grey matter structures, however, right thalamus ($p = 0.01$) atrophied significantly in the TBI group vs. HC.

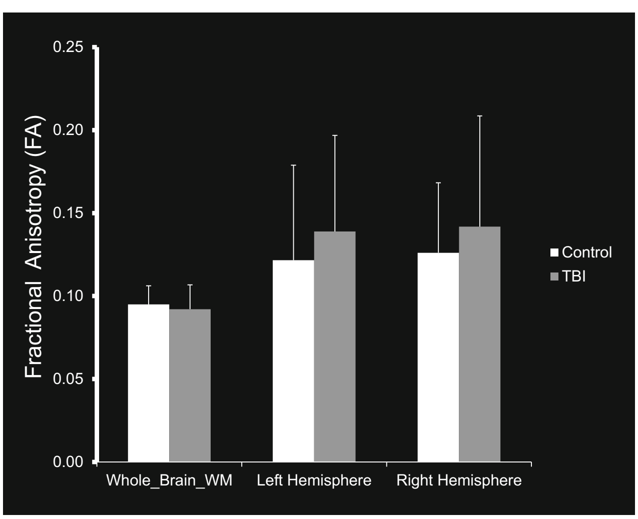


Fig. 2 A white matter skeleton image overlaid on a T1-weighted anatomical image in a healthy control (**a**) and patient with traumatic brain injury (**b**). A visible injury appears on the right side in b

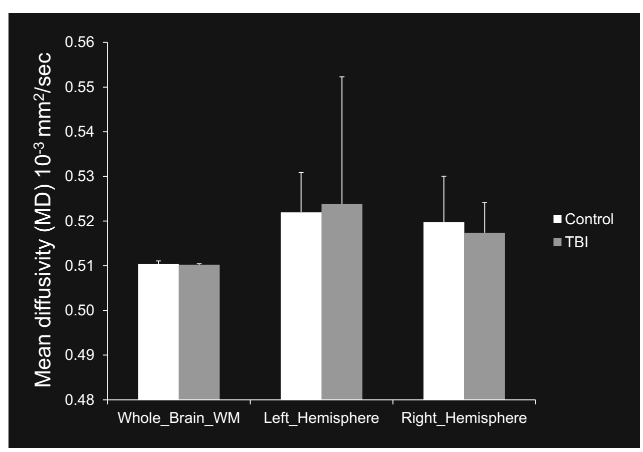


Fig. 3 No Significant reductions in brain WM DTI measure (FA values) in TBI (Grey bars) compared with healthy controls (white bars) in the whole brain (left), and left (middle) and right (right) hemispheres

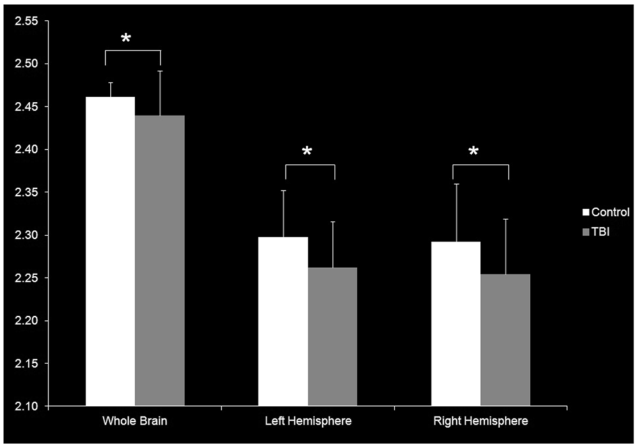


Fig. 4 No Significant reductions in brain WM DTI measure (MD values) in TBI (Grey bars) compared with healthy controls (white bars) in the whole brain (left), and left (middle) and right (right) hemispheres

Relationship between WM shape change and neuropsychological function

To examine the contribution of WM shape change (skeleton FD values) to neuropsychological outcome in TBI, hierarchical linear regressions were performed, separately for each of four cognitive domains: executive function, memory, attention and processing speed. The education was not included in the first step as it was highly correlated with FD-skeleton. For executive function domain, the model explained 63% of variance ($F_{6,18} = 5.12$, $p = 0.003$). The FD-skeleton accounted for additional 19.5% of variance beyond demographic and DTI variables ($p = 0.02$). For processing speed, the model explained 47% of variance ($F_{5,19} = 3.32$, $p = 0.02$). The FD-skeleton accounted for additional 22% of variance beyond demographic and DTI variables ($p = 0.03$). For memory domain, the model explained 57% of variance ($F_{6,18} = 3.99$, $p = 0.01$). The FD-skeleton accounted for additional 13.1% of variance beyond demographic and DTI variables ($p < 0.1$), which was borderline significant. For attention, the model explained 43% of variance ($F_{6,18} = 2.33$, $p = 0.07$). The FD-skeleton accounted for additional 12.1% of variance beyond demographic and DTI variables ($p < 0.1$), which was borderline significant. For this domain the DTI contributed significantly ($\Delta R^2 = 0.24$, $p = 0.04$).

Discussion

The present study demonstrates the ability of FD based white matter complexity analysis to discriminate between persons with traumatic brain injury and healthy volunteers. This measure was also shown to be predictive of cognitive outcome after TBI. The work builds on previous studies, demonstrating that FD based brain morphometry is a sensitive technique for imaging white matter changes in different neurological conditions (Esteban et al. 2007; Rajagopalan et al. 2013; L. Zhang et al. 2008; L. Zhang et al. 2007). Here, for the first time, we used FD based brain morphometry to explore the relationship between white matter structure and cognitive function following traumatic brain injury. This is particularly important, as the cognitive deficits commonly observed after traumatic brain injury, such as executive function impairment, are thought to be caused by the disruption of distributed brain networks by diffuse axonal injury. In this study our primary focus was to determine if FD can provide additional information about the consequences of TBI by focusing on shape as opposed to other metrics, e.g., structure, water diffusion, spectroscopy that could potentially help clinicians more objectively diagnose/classify TBI. Since many TBIs do not have a focal but diffused injury, the injury is likely better characterized by a global index rather than local or WM tract degeneration measurements.

FD-characterized complexity provides information about WM pathology in TBI

FD analysis of skeletonized WM (yellow lines in Fig. 2 and in supplementary figs. S1 and S2) measures the internal shape complexity of WM architecture of the brain. The WM fiber network is a complicated multilayered structure formed by arborization of axons within the brain, fiber-bundle crossings and bundle bifurcations. FD values represent the different complexity levels seen at different parts of the brain. Decreased FD of the WM skeletons was observed in the TBI group in the current study. One factor that may lead to reduced WM FD values may be due to the decrease in number of WM fiber bundles. WM fiber destruction is very well known in TBI, even with mild TBI (Bigler 2004). Another related factor may be the increased amorphousness of the WM skeleton. We hypothesize that due to shearing and stretching of the WM (i.e., DAI), it may lose some of its shape and become more amorphous despite the presence of WM fibers. This will also lead to reduced WM FD values. In our study, the evidence of association between WM pathology and reduced FD value comes from the correlation between microbleed and reduced FD values. Neuropathologic evidence suggests that diffuse axonal injury is typically accompanied by microbleeds, or so-called tissue tear hemorrhages (Graham DI 2000; Scolding 1999). In our study, the FD value inversely correlated with numbers of microbleeds, which may be an indicator of DAI.

FD-characterized brain WM complexity was associated with cognitive outcome

The TBI group differed from the controls on almost all measures of cognitive function: memory/learning, executive function, attention and processing speed. For executive function and processing speed the WM FD contributed significantly to the cognitive domain scores above and beyond demographic variables and DTI variables. For memory function and attention the contribution was borderline significant. As executive functioning and processing speed are the most common cognitive domains affected in TBI, these results further show that FD, as a marker of WM pathology, may be a marker of cognitive outcome. This suggests that a global measure such as FD is a useful index, as it appears to relate more clearly to declines in cognitive functions which rely on widespread cortical and subcortical networks. However, the mechanistic implication of this association is not entirely clear at this moment and requires further validation.

FD-characterized complexity provides WM morphological information beyond other neuroimaging parameters

The FD values were different between TBI and controls and it was also associated with cognitive outcome in executive function and processing speed, the two most commonly affected cognitive domains in TBI. This raises the possibility that FD may provide structural information that is not available through other MR imaging parameters. Compared with other MR WM structural measures, FD of WM skeletons provides unique information about WM morphology. FD relies on the large-scale (macro) shape of the WM, it may be potentially less susceptible to differences in signal to noise ratio (SNR) and therefore may represent a more robust measure of WM health (however, this speculation needs to be verified by further studies). In fact, when characterizing the relative SNR of the patient and control groups, control subjects had significantly ($p = 0.021$) higher SNR compared to TBI patients. However, the relationship between FD and SNR evaluated using Spearman's r analysis was nor significant between general structure FD and SNR ($r = -0.039$, $p = 0.842$), and skeleton FD and SNR ($r = -0.093$, $p = 0.631$)). These findings indicate that although the image SNR was different between the two groups, it is unlikely that the difference played a significant role in determining FD as the SNR is not related to the measure.

Of these metrics, voxel-based intensity analysis is most commonly used to quantify regional WM pathology, such as distribution and extent of WM hyperintensities associated with lesions on T2-weighted images (Wen and Sachdev 2004), and location and degree of FA reductions, which indicate loss of axonal fibers and/or myelin on DTI images (Medina et al. 2006). On the other hand, ROI-based methods on DTI images examine the WM integrity locally by measuring mean values of directional water molecule distributions in WM bundles in terms of FA or mean diffusivity generated from manually selected ROIs. Although DTI provides unique information about the morphology of intra-WM structures, no DTI shape quantification studies have been found, owing to methodological challenges. Compared with the fiber orientation map of DTI, FD-based WM measurement provides information on fiber-branching patterns that is not measurable using current quantitative DTI measures. Among the DTI measures only the AD values were different between TBI patients and controls. Compared to previous studies (Kinnunen et al. 2011; Kraus et al. 2007), we focused on global DTI parameters rather than voxel-based DTI parameters and this may account for this discrepancy. The GM and WM volumes were also not different between the groups.

Limitations

Our TBI population consisted of patients with moderate to severe TBI. While it is not surprising that moderate and severe injuries tend to show evidence of white matter changes and cognitive impairment, acquiring data on all severities in one study would allow for the milder injuries to be assessed in the context of a spectrum of injury. We could not achieve this goal in our study due to the inability to recruit patients with mild TBI. However, one must remember that in terms of white matter changes, there is some overlap between amount of pathology and the different clinical classifications of TBI severity. Certain injuries classified acutely as mild based on acute TBI variables such as loss of consciousness may be closer to moderate in the degree of pathology. Conversely, certain individuals with moderate or severe TBI may show more intact white matter than expected based on accepted means of clinical classification of injury severity. Hence none of the classifications are foolproof. There is an underlying assumption that any injury-related deviation in these metrics must be diffuse and/or great enough in magnitude to reach a level of significance that overwhelms the variance that standard anatomy will introduce when averaged across a full hemisphere. While more standard tract based statistics or averages across regions of interest in well-known white matter atlases do not offer the simplicity of yielding a single, hemispheric specific metric, comparison with more standard methods (such as TBSS) in future studies may provide better insight into WM pathophysiological mechanisms of TBI. Finally, although our correlation analysis showed no relationship between SNR and FD measure, a significant lower SNR in patient group compared to healthy controls may have affected other measurements. Our future TBI studies will avoid this phenomenon (inconsistent SNR across groups and conditions) by improving raw data quality and using various filtering methods to increase SNR.

Conclusions

The present findings demonstrate that TBI results in chronic changes to the white matter microstructure, in form of shape change and loss of complexity, a new way to look into neuropathology of TBI. Moreover, the data presented here demonstrate that FD analysis of WM complexity allows for a more sensitive delineation of severity of white matter pathology, and may help explain apparent discrepancies between clinically diagnosed injury severity and cognitive outcomes in individuals with TBI.

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Compliance with ethical standards

Conflict of interest The authors do not have any conflict of interest.

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