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White Matter Microstructure in Chronic Moderate-To-Severe Traumatic Brain Injury: Impact of Acute-Phase Injury-Related Variables and Associations With Outcome Measures

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This study examines how injury mechanisms and early neuroimaging and clinical measures impact white matter (WM) fractional anisotropy (FA), mean diffusivity (MD), and tract volumes in the chronic phase of traumatic brain injury (TBI) and how WM integrity in the chronic phase is associated with different outcome measures obtained at the same time. Diffusion tensor imaging (DTI) at 3 T was acquired more than 1 year after TBI in 49 moderate-to-severe-TBI survivors and 50 matched controls. DTI data were analyzed with tract-based spatial statistics and automated tractography. Moderate-to-severe TBI led to widespread FA decreases, MD increases, and tract volume reductions. In severe TBI and in acceleration/deceleration injuries, a specific FA loss was detected. A particular loss of FA was also present in the thalamus and the brainstem in all grades of diffuse axonal injury. Acute-phase Glasgow Coma Scale scores, number of microhemorrhages on T2*, lesion volume on fluid-attenuated inversion recovery, and duration of posttraumatic amnesia were associated with more widespread FA loss and MD increases in chronic TBI. Episodes of cerebral perfusion pressure <70 mmHg were specifically associated with reduced MD. Neither episodes of intracranial pressure >20 mmHg nor acute-phase Rotterdam CT scores were associated with WM changes. Glasgow Outcome Scale Extended scores and performance-based cognitive control functioning were associated with FA and MD changes, but self-reported cognitive control functioning was not. In conclusion, FA loss specifically reflects the primary injury severity and mechanism, whereas FA and MD changes are associated with objective measures of

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general and cognitive control functioning.

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The axons of white matter (WM) are particularly vulnerable to stretch associated with acceleration–deceleration forces in traumatic brain injury (TBI; Strich, 1956; Peerless and Rewcastle, 1967). The ensuing WM pathology is a diffuse, predominantly secondary axotomy described as *diffuse axonal injury* (DAI; Povlishock, 1992; Smith et al., 2003). Oligodendrocytes and myelin sheaths are also affected in DAI, but these changes follow a protracted time course (Coleman and Freeman, 2010; Johnson et al., 2013b). DAI has been observed in all TBI severities (Bigler, 2013a,b).

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique for assessing WM microstructure in vivo (Basser and Pierpaoli, 1996; Pierpaoli et al., 1996; Beaulieu, 2002). This technique has been shown to reveal DAI in TBI survivors even when there is no sign of injury on conventional MRI (Kumar et al., 2009; Newcombe et al., 2011). From DTI, several measures can be derived, among which fractional anisotropy (FA) and mean diffusivity (MD) are commonly reported. FA is a measure considered to reflect primary and secondary axonal injury in TBI (Bigler, 2013a; Li et al., 2013), whereas MD, in general, is considered a measure of disorders of myelination as well as loss of axons (Song et al., 2002, 2005; Li et al., 2013). DTI data can be analyzed with different approaches, and it has been suggested that a combination of several methods should be used to explore the complexity of WM injury in TBI (Spitz et al., 2013; Leunissen et al., 2014). In the current study, tract-based spatial statistics (TBSS; Smith et al., 2006) and an automated tractography method (Visser et al., 2011) not previously used in TBI were implemented.

This study examines how injury mechanisms, neuroimaging, and clinical measures from the acute and early phases after injury impact WM FA, MD, and tract volumes in the chronic phase of TBI and how WM integrity in the chronic phase is associated with different outcome measures obtained at the same time. In particular, the current study seeks to verify whether FA, as opposed to MD, is the DTI measure that primarily reflects injury severity. This would be expected based on the specific increase in axonal loss in all WM regions with more severe injury (Gennarelli et al., 1982; Povlishock, 1992). In like manner, stronger acceleration/deceleration forces, reflected in increasing severity of DAI and considered to be associated with motor vehicle accidents (MVA) to a greater extent than falls (Adams et al., 1982, 1984; Meythaler et al., 2001; Davceva et al., 2012), should lead to greater axonal loss and hence more conspicuous FA decreases in TBI survivors.

Additionally, this study explores the relationship between WM FA and MD and common clinical and neuroimaging variables from the acute and early phases of TBI. The propagation of traumatic forces through WM has direct impact on the level of consciousness after TBI (Meythaler et al., 2001) and Glasgow Coma Scale (GCS) scores should therefore be associated with both FA and MD changes in the corpus callosum (CC), hemispheric WM, and mesencephalon (Ommaya and Gennarelli, 1974; Levin et al., 1988; Chatelin et al., 2011). DAI grading based on conventional MRI is used to assess DAI severity in the clinic (Gentry, 1994). The presence of microhemorrhages vs. no microhemorrhages has been shown to reduce FA and increase MD in several WM tracts, indicating a relationship between conventional MRI-based DAI grading and DTI measures (Kinnunen et al., 2011). The current study investigates whether DAI, as reflected in the number of microhemorrhages and the lesion volume load on fluid-attenuated inversion recovery (FLAIR) MRI in the early phase of TBI, is associated with chronic-phase FA and MD. The presence of significant relationships between conventional DAI measures from the acute/early phase of TBI and chronic-phase WM microstructure will support the clinical validity of conventional MRI in TBI patients. Acute-phase computer tomography (CT) of the head is standard procedure in moderate-to-severe TBI. From this, Rotterdam CT scores can be obtained (Maas et al., 2005). Rotterdam CT scores reflect mainly the presence of brain edema and mass lesions and, therefore, increased intracranial pressure (ICP). Increased ICP has not been shown to affect WM in the acute/early phase of TBI in adult rodents (Lafrenaye et al., 2012) or humans (Newcombe et al., 2011). To elucidate long-term influence of elevated ICP on WM microstructure, this study investigates the presence of an association between acute-phase Rotterdam CT scores and DTI measures from the chronic phase. Then, in a subgroup of severe-TBI patients admitted to the intensive care unit (ICU), the impact of the number of episodes with ICP >20 mmHg on chronic-phase WM microstructure is investigated. ICP and cerebral perfusion pressure (CPP) are linked, and decreased CPP is associated with risk of ischemic brain injury (Bullock and Povlishock, 2007). In other pathologies (premature birth, cerebrovascular disease) as well as in aging (Bendlin et al., 2010), reduced CPP leads primarily to demyelination (Fazekas et al., 1993; Back, 2006; Vernooij et al., 2008; Børch et al., 2010). Hence, CPP decreases in TBI may affect MD more than FA.

Finally, the current study investigates the relationship between WM microstructure and different types of outcomes in the chronic phase. The outcome measures included general outcome measured by Glasgow Outcome Scale Extended (GOSE), performance-based, and self-reported cognitive control functioning. Cognitive control or executive control functioning appears to be particularly important for independent living and mental health following TBI (Finnanger et al., 2013; Spitz et al., 2013). Despite a certain degree of overlap, information from performance-based and self-reported measures reflects different aspects of cognitive control (Isquith et al., 2013; Toplak et al., 2013) and may therefore be

supported by different neuronal correlates. The associations among FA, MD, and tract volumes and the different outcome variables were examined with the goal of establishing which of the WM measures were related to which outcome measures.

MATERIALS AND METHODS

The study protocol adhered to the Helsinki Declaration and was approved by the regional ethics committee. All participants received financial reimbursement of 1,000 Norwegian kroner. Written informed consent was obtained (also from parents if participants were under the age of 16 years).

TBI Group

In total, 73 survivors with chronic (more than 1 year after injury) moderate-to-severe TBI according to the Head Injury Severity Scale (HISS; Stein and Spettell, 1995) were recruited from the prospective and consecutive head injury database at St. Olav's Hospital, Trondheim University Hospital (Skandsen et al., 2010). All had been admitted from 2004 to 2008. Inclusion criteria in the current study were age between 14 and 66 years at time of DTI, fluency in the Norwegian language, ability to cooperate during neuropsychological testing as indicated by GOSE scores of $\geq$5 at 12 months after injury, absence of head injury before the injury leading to inclusion in the head injury database, absence of pre-existing neurologic or psychiatric conditions, and absence of standard MRI contraindications. Data from the acute and subacute phases related to injury mechanism, TBI severity, CT and MRI images, and clinical measures were obtained from the head injury database. For severe-TBI patients admitted to the ICU, ICP and CPP data were obtained from the ICU part of the head injury database (Schirmer-Mikalsen et al., 2013). All outcome data used in the current study were obtained at the time of the DTI investigation in the chronic phase of TBI.

Healthy Control Group

In total, 78 healthy age-, sex-, and education-matched controls were recruited (from friends and family of TBI patients as well as from different workplaces). The healthy controls underwent the same examinations as the TBI survivors at time of DTI scanning.

Acute-Phase Data

Injury mechanism was classified as MVA, fall, or other. Classification of the TBI as moderate or severe was based on HISS scores (Stein and Spettell, 1995), which in turn were based on GCS scores at admission (Teasdale and Jennett, 1974). GCS scores were assessed at time of arrival in the emergency room or before intubation in case of a prehospital intubation. All patients included in this study had a GCS score $\leq$13 that could not be explained by factors other than the head injury (Skandsen et al., 2010; Moen et al., 2012). A GCS score $\leq$8 is considered severe, and a GCS score between 9 and 13 is considered moderate TBI according to the HISS criteria (Stein and Spettell, 1995). The Rotterdam CT score (Maas et al., 2005) was from the worst CT scan obtained in the acute phase. The Rotterdam CT scoring was performed by one radiologist.

MRI at 1.5 T was acquired as soon as was feasible and the clinical condition allowed for it, between 2 and 41 (mean 12) days postinjury. Sagittal turbo spin-echo T2-weighted, sagittal, coronal, and transverse T2 FLAIR-weighted, transverse T2*-weighted gradient echo imaging and diffusion-weighted imaging with diffusion gradients in x, y, and z dimensions, and images at b = 0, 500, and 1,000 sec/mm^2 were used for DAI classification by two experienced senior neuroradiologists (Skandsen et al., 2010). DAI was classified as grade 1, traumatic lesions confined to lobar WM; grade 2, lesions also detected in CC; and grade 3, presence of brainstem lesions (Gentry, 1994). Total numbers of microhemorrhages were counted in the T2* scans, and total FLAIR lesion volume was obtained from manually drawn FLAIR lesion masks (Moen et al., 2012, 2014).

In the TBI patients, duration of posttraumatic amnesia (PTA) was assessed and recorded by experienced clinicians from notes made by nurses in the records, patients' recall of events, or, for patients referred to rehabilitation, the orientation log (Jackson et al., 1998). PTA duration was categorized into intervals of 0–1 week, 1–2 weeks, 2–3 weeks, 3–4 weeks, and >4 weeks (Russell and Smith, 1961).

In total, 21 severe-TBI survivors were treated in the ICU. There is no level 1 evidence for recommending thresholds for ICP or CPP (Bullock and Povlishock, 2007). The guideline suggests that ICP be kept below 20–25 mmHg, which has been shown to improve outcome (Vik et al., 2008; Karamanos et al., 2014). In this study, three or more episodes of ICP >20 mmHg during 1 day were registered as deviating from the treatment goal. For CPP, there is less consistent evidence for a certain threshold of CPP significantly impacting outcome, perhaps because of variable methods of deriving CPP (Rao et al., 2013) and/or the presence of varying degrees of autoregulation deficits in TBI patients (White and Venkatesh, 2008). The guidelines from 2007 recommend a CPP of <60 mmHg, but CPP <70 mmHg is advocated under certain circumstances to avoid risk of ischemia (Bullock and Povlishock, 2007). The earlier guidelines used a cutoff of CPP <70 mmHg (Maas et al., 1997). The patients in this study were admitted to the ICU before as well as after the guidelines for CPP treatment goals were changed. In the ICU database, three or more episodes per day with CPP <70 mmHg, 60–69 mmHg, and <60 mmHg are registered. Because there were few days with three or more episodes of CPP <60 mmHg, the number of days with three or more episodes <70 mmHg was used in this study. For details on ICU treatment after implementation of the 2007 guidelines see Schirmer-Mikalsen et al. (2013).

Chronic-Phase Data

Time since injury was calculated as the number of days between the time of injury and the day when the DTI scan was performed. Global outcome was measured with GOSE, assessing social reintegration and independent living after TBI (Jennett et al., 1981; Wilson et al., 1998). GOSE scores range from 1 (dead; minimum score) to 8 (upper level, good recovery; maximum score). GOSE was scored face-to-face via a structured interview by trained experimenters at the time of DTI. Number

of years of education completed was assessed based on both a self-report form and an interview at the time of scanning.

The Behavioral Rating Inventory of Executive Function Adult (BRIEF-A) was included as a self-report measure of cognitive control functioning (Roth et al., 2005). BRIEF-A consists of 75 items measuring behavioral, emotional, and cognitive aspects of cognitive control functioning. Each item is rated on a three-point frequency scale (0, never; 1, sometimes; 2, often). Five of the 75 items are designed to detect invalid response styles (inconsistencies or negativity), and the remaining 70 items make up three composite index scores: the global executive composite score, the behavioral regulation index, and the metacognitive index. The global executive composite score consists of items measuring inhibition, shift, and emotional control; the behavioral regulation index reflects self-monitoring items; and the metacognitive index includes items describing initiation, working memory, planning/organization, task monitoring, and organization of materials.

The Delis-Kaplan Executive Function System Trail Making Test (D-KEFS TMT; Delis, 2001) was included as a performance-based measure of cognitive control functioning. The D-KEFS TMT consists of five different subtests in which subtest 1 is visual scanning, subtest 2 is letter sequencing, subtest 3 is number sequencing, subtest 4 is letter–number sequencing, and subtest 5 is motor speed. Time used to complete each subtest was included in further analyses.

Statistical Comparisons of Demographics and Cognitive Control Measures Between TBI and Controls

Independent *t*-tests were applied to investigate the presence of group differences in age, years of completed education, and scores on the performance-based cognitive control measure D-KEFS TMT and the self-reported measure BRIEF-A. A χ^2 analysis was used to test differences in proportions between groups with regard to sex distribution. $P < 0.05$ (two-sided) was considered statistically significant.

Chronic-Phase MRI Acquisition

DTI scans were acquired in the chronic phase of TBI on a 3-T Siemens Trio with Quantum gradients (30 mT/m) with a 12-channel head matrix coil (Siemens AG, Erlangen, Germany). The DTI sequence was a single-shot balanced-echo EPI sequence acquired in 30 noncollinear directions with $b = 1{,}000$ sec/mm^2 that used the following parameters: TR 6,800 msec, TE 84 msec, FOV 240 × 240 mm, slice thickness 2.5 mm, acquisition matrix 96 × 96, giving isotropic voxels of 2.5 mm. Fifty-five transversal slices with no gaps were acquired, giving full brain coverage. For each slice, six images without diffusion weighting ($b = 0$) and 30 images with diffusion gradients were acquired. The DTI sequence was repeated twice for increased signal-to-noise ratio. To correct for image distortion, two additional $b = 0$ images were acquired with opposite-phase encoding polarity (Holland et al., 2010).

DTI Analyses

DTI data were analyzed with the tools of the FMRIB software library (FSL; Oxford Centre for Functional MRI of the Brain; www.fmrib.ox.ac.uk/fsl) and automated tractography as described by Visser et al. (2011). First, the two DTI acquisitions and extra $b = 0$ images were merged into a single 4D file, and image artifacts resulting from motion and eddy current distortions were minimized by registration of the DTI acquisitions to the $b = 0$ image by using affine registration. Image distortions caused by magnetic susceptibility artifacts were minimized with a nonlinear B0-unwarping method by using paired images with opposite-phase encoding polarities, resulting in opposite spatial distortion patterns, and by alignment of the resulting images with a fast nonlinear registration procedure (Holland et al., 2010). The brain was extracted by using the Brain Extraction Tool in FSL.

TBSS

FMRIB's Diffusion Toolbox was used to fit a diffusion tensor model to the raw diffusion data in each voxel. Voxelwise maps of the eigenvalues (λ_1, λ_2, λ_3), FA, and MD were calculated for the TBI and control groups. Voxelwise statistical analysis of the diffusion data was performed by TBSS (part of FSL; Smith et al., 2006, 2007). Briefly, all subjects' FA data were aligned with each other, thereby identifying the "most typical" subject in the study, which was used as the target image. This target image was aligned to the MNI152 standard space by using the nonlinear registration tool FNIRT that uses a b-spline representation of the registration warp field (part of FSL; Rueckert et al., 1999), and all of the FA images were transformed into 1 × 1 × 1 mm MNI152 space by combining the nonlinear transform to the target FA image with the affine transform from that target to MNI152 space. A mean FA image was created from all the aligned FA images and thinned to create a skeletonized mean FA representing the centers of all WM tracts common to all the subjects in the analysis. The mean FA skeleton was thresholded to $FA \geq 0.2$ to include the major WM pathways but to exclude peripheral tracts and gray matter. Each subject's aligned FA data were then projected onto the skeleton by searching perpendicular from the skeleton for maximum FA values in an individual subject's FA map. Statistical comparisons were restricted to voxels in the skeleton. Voxelwise statistics of the skeletonized FA, MD, and eigenvalue data were carried out in Randomise (part of FSL) to test for group differences (FA, MD, and eigenvalues) and to examine the relationships between FA and MD and the different independent variables. Randomise carries out permutation-based testing and inference by using threshold-free cluster enhancement (Nichols and Holmes, 2002) with a correction for multiple comparisons, and the statistical threshold for all the analyses was $P < 0.05$, corrected for sex and age at MRI. Two sample independent *t*-tests were performed to investigate the presence of significant group differences in FA and MD between the entire TBI group and the healthy control group and for dichotomized TBI groups moderate vs. severe TBI, injury mechanism MVA vs. fall, no DAI (grade 0) vs. all DAI grades 1 + 2 + 3, and DAI grade 1 vs. DAI grades 2 + 3. Randomise was also used to examine the relationships between FA and MD and the demographic (age at time of DTI), injury-related (GCS score and time since injury), clinical (duration of PTA, number of days with three or more episodes of ICP >20 mmHG or CPP <70 mmHg),

neuroimaging (number of microhemorrhages, volume of FLAIR lesions, and Rotterdam CT scores), global outcome (GOSE scores), self-reported (BRIEF subindices), and performance-based (D-KEFS TMT subtests 1–5) cognitive control function, performed as separate regression analyses. The anatomical locations of regions with significant group differences or associations with regard to FA and/or MD were identified in a WM atlas (Mori et al., 2005).

Automated Tractography Segmentation Method

Tractography. The Camino package was used for diffusion analysis and generation of streamlines (Cook, 2006). To parameterize voxel diffusion profiles, q-ball reconstruction was used because it is computationally efficient and provides adequate resolution of crossing fibers in many WM regions (Tuch, 2004). Spherical harmonics up to fourth order were used as basis functions. Up to three principal diffusion directions were determined for each voxel, and these were used as a basis for tractography. Streamlines were generated by using the interpolated deterministic streamlining method as implemented in Camino, with an FA threshold of 0.15. All voxels with an FA value >0.25 were used as seed voxels.

Nonlinear registration. The mean b = 0 volumes for all subjects were affinely registered with FLIRT (part of FSL) to the MNI152 template. A custom-made group template was created by averaging the registered volumes. The original b = 0 volumes were then nonlinearly registered with FNIRT to the group template. The streamlines were warped from subject space to the group template by using the deformation fields produced by FNIRT.

Clustering. To find consistent bundles of streamlines across subjects, a clustering approach previously described by Visser et al. (2011) was used, clustering the streamlines based on their pairwise distances. Before clustering, all streamlines were linearly resampled to 25 points, and the streamlines from all 99 subjects were concatenated. Clustering was performed on the merged data set consisting of streamlines from all subjects, allowing for the identification of clusters that were consistent across all subjects. To allow for the processing of the full set of data, the multisubject data set was randomly partitioned into subsets of 10,000 streamlines. In each of these subsets, 250 clusters were identified by using hierarchical clustering. The hierarchical clustering process was based on repeatedly finding clusters with the lowest mutual distance and merging them until 250 clusters were identified. The clustered subsets were then combined to obtain segmentations with the same number of clusters for the full data set by using a distance-based matching procedure to find corresponding labels across subsets. The clustering step was repeated 100 times with different random partitions to obtain a stable segmentation by selecting the cluster assignments that occurred most often for each streamline to find statistics indicating the consistency of these assignments between repetitions. Based on anatomical knowledge, WM tracts were identified in 10 randomly selected subjects from both groups by manually assigning the sets of labels (from the 250 labels) that corresponded to the following WM tracts: CC, superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (ILF/IFOF).

Only labels present in all individuals were included. The resulting WM tract labels could subsequently be applied to either the original or the resampled streamlines and were consistent in all individuals in the study. For each subject, the clusters were extracted with pruning (thresholding) and concatenated to form the corresponding fiber tracts, CC, SLF, and ILF/IFOF. Regions of interest (ROIs) were made for the extracted fiber tracts and converted into subject diffusion space to extract mean FA, MD, λ_1, λ_2, λ_3, and volume for each tract separately in the left and right hemispheres in each subject. Tract volume was calculated for each WM tract by adding the number of voxels containing at least one streamline and multiplying by voxel volume. It is important to note that this value reflects the number of voxels within the tract that exceeded the tracking FA threshold and might deviate from the actual volume.

For further analyses, values obtained from the tractography method were extracted and analyzed in SPSS (IBM, Armok, NY). Mann-Whitney U tests (two-tailed) with significance set to $P > 0.05$ were used to compare FA, MD, λ_1, λ_2, λ_3, and volume of CC, left and right SLF, and ILF/IFOF in the TBI and the healthy control groups resulting from lack of normal distributions. Separate partial correlation models adjusting for age and sex were applied for TBI survivors and healthy controls to investigate the relationship between the DTI measures obtained from tractography and the injury severity (GCS score), global outcome (GOSE score), and cognitive control measures (BRIEF-A and D-KEFS TMT subtests 1–5). For the TBI survivors, the relationships between the volumes of the tracts and DAI and time since injury were also investigated by partial correlation models adjusted for age and sex.

To compare more directly the FA values in CC from the TBSS and the automated tractography method, a ROI was manually drawn on the TBSS WM skeleton that included only voxels in CC. Mean FA was calculated from the CC TBSS ROI and compared with the mean FA in CC from the automated tractography method by using a Mann-Whitheny U test (two-tailed) with significance set to $P > 0.05$.

For images used in the figures, the FSL 1-mm mean FA template was used as the background image. The images are shown in radiological convention, i.e., the right side of the subject is on the left side of the image.

RESULTS

Among the 73 TBI subjects initially included, 14 were excluded because of vibration artifacts leading to signal voids in the DTI scans, two because of missing DTI scans, two because of missing correction scans, and six because of DTI acquisition in only 12 directions. This led to the inclusion of 49 TBI survivors (36 men, 73.5%) in the DTI analysis. Among the TBI survivors included, 53.1% had moderate TBI, 46.9% had severe TBI, 74.5% had any grade of DAI, and 46.8% had PTA duration of greater than 1 week (Table 1). The mean GOSE score at time of DTI was 6.7 (range 5–8); i.e., all TBI survivors in the current study recovered with moderate disability or better. The GOSE scores were not significantly different between the moderate (6.8 ± 1.1) and the severe (6.5 ± 1.1) TBI groups ($P = 0.36$).

TABLE 1. Demographics, Injury Characteristics, Global Outcome, and Cognitive Control Measures in the TBI and Healthy Control Groups*

	TBI group		Control group		
Variable	No.	Value	No.	Value	*P* value
Age in years (mean, SD)	49	29.2 (12.1)	50	32.7 (12.1)	n.s.
Male (%)	36	73.5	36	72	n.s.
Years of completed education (mean, SD)	49	11.9 (2.3)	50	12.16 (2.16)	n.s.
Moderate TBI (%)	26	53.1			
Severe TBI (%)	23	46.9			
Time since injury in years (mean, SD)	49	2.8 (1.1)			
Injury mechanism	49				
Motor vehicle accident (%)	23	46.9			
Fall (%)	22	44.9			
Other injury mechanism (%)	4	8.2			
GCS score (mean, SD)	49	8.8 (3.6)			
Rotterdam CT score (mean, SD)	38	2.7 (1.1)			
DAI grading	47	95.9			
No DAI (%)	12	25.5			
DAI 1 (%)	14	29.8			
DAI 2 (%)	16	34.0			
DAI 3 (%)	5	10.6			
Flair lesion volume (mean, SD)	38	1708.3 (2310.8)			
Number of microhemorrhages(mean, SD)	38	13.8 (12.2)			
ICP† (mean, SD)	16	2.8 (5.1)			
CPP‡ (mean, SD)	16	5.6 (5.1)			
PTA duration	47	95.9			
0–1 week (%)	24	49.0			
1–2 weeks (%)	9	18.4			
2–3 weeks (%)	5	10.2			
3–4 weeks (%)	3	6.1			
>4 weeks (%)	5	10.2			
GOSE score (mean, SD)	49	6.7 (1.4)			
BRIEF-A					
GEC (mean, SD)	48	105.4 (25.4)	49	94.7 (14.5)	<0.05
BRI (mean, SD)	48	44.6 (10.9)	49	38.7 (6.8)	<0.01
MI (mean, SD)	48	60.8 (15.9)	49	56.0 (9.2)	n.s.
D-KEFS TMT					
Subtest 1 (mean, SD)	48	22.1 (6.8)	50	21.0 (5.5)	n.s.
Subtest 2 (mean, SD)	48	28.5 (11.5)	50	25.0 (8.1)	n.s.
Subtest 3 (mean, SD)	47	28.3 (11.2)	50	27.3 (14.9)	n.s.
Subtest 4 (mean, SD)	47	79.8 (29.1)	50	76.6 (33.3)	n.s.
Subtest 5 (mean, SD)	48	22.9 (7.3)	50	20.7 (5.2)	n.s.

*Between group differences for age, years of completed education, and cognitive control measures were investigated with independent *t*-tests. A χ^2 test was applied in order to test differences between groups with regard to sex distribution. $P < 0.05$ (two-sided) was considered statistically significant. TBI, traumatic brain injury; MRI, magnetic resonance imaging; DAI, traumatic axonal injury; GCS, Glasgow Coma Scale; CT, computer tomography; ICP, intracranial pressure; CPP, cerebral perfusion pressure; BRI, Behavioral Regulation Index; MI, Metacognitive Index; GEC, Global Executive Composite; TMT, Trail Making Test; SD, standard deviation; PTA, Posttraumatic Amnesia; GOSE, Glasgow Outcome Scale Extended.
†Number of days with three or more episodes of ICP >20 mmHg measured in only a subgroup of severe TBI.
‡Number of days with three or more episodes of CPP <70 mmHg measured in only a subgroup of severe TBI.

Fifty healthy controls matching the 49 TBI survivors were included in the current study. They were chosen from among the controls with high-quality DTI scans. A summary of the group characteristics for the TBI and control subjects included in the study is given in Table 1. There were no statistically significant differences with regard to age, sex distribution, length of completed education, or the different scores on the performance-based test of cognitive control and D-KEFS TMT between the TBI and the control groups (Table 1). The TBI group scored significantly higher than the healthy controls on the BRIEF-A global executive composite score and the behavior regulation index, but there was no group difference for the metacognitive index (Table 1).

TBSS Analyses of Group Differences Between TBI and Control Groups

Significantly decreased FA and increased MD were present in all major WM tracts and in the brainstem in

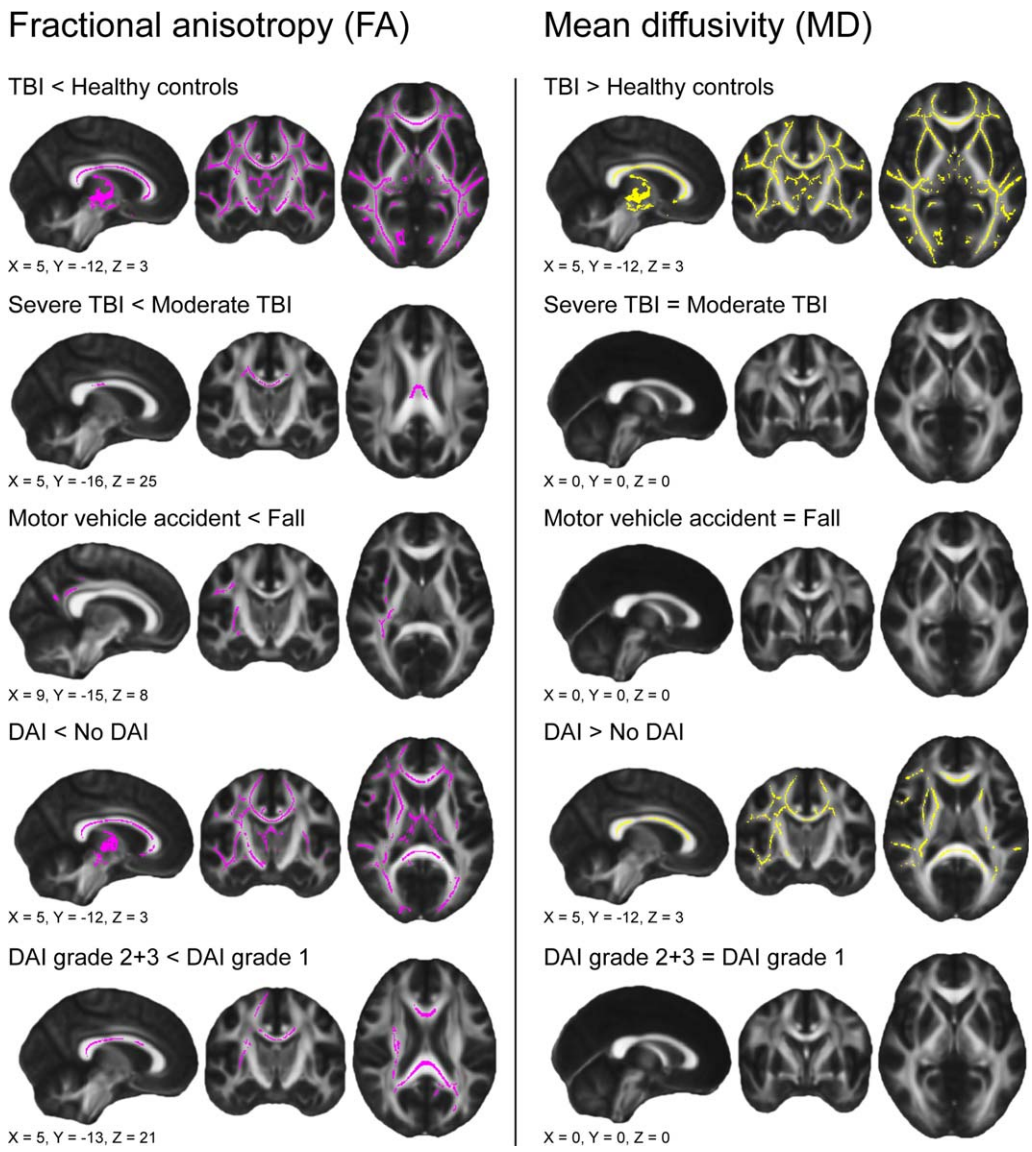

Fig. 1. Between-group TBSS results for FA and MD. The statistical threshold for significant group differences was $P < 0.05$, corrected for gender, age at MRI, and multiple comparisons as implemented in Randomise. The FSL 1-mm mean FA template was used as the background image. The images are shown in radiological convention; i.e., the right side of the subject is on the left side of the image. The x, y, and z refer to MNI template coordinates. ns, non-significant.

the TBI group compared with the control group (Fig. 1). The reduced FA was caused mainly by an increase in the radial eigenvalues (data not shown). In the control group, a strong negative association was found between FA and age at time of scanning in all major WM tracts, except for very limited involvement of the internal capsule (Fig. 2). A positive association between MD and age was more circumscribed and included the anterior CC, fornix, external capsule, and optic radiation in the healthy controls (Fig. 2). No associations between FA or MD and age were present in the TBI group.

Impact of Acute-Phase Injury-Related, Neuroimaging, and Clinical Variables on Chronic-Phase FA and MD in the TBI Group

Injury severity and mechanism had a significant impact on FA in particular. The severe-TBI group had significantly lower FA in the truncal part of the CC compared with the moderate-TBI group, but there was no difference in MD (Fig. 1). The MVA group had significantly lower FA in the right hemisphere SLF, posterior corona radiata, ILF/IFOF, and external capsule compared with the fall group (Fig. 1). No differences in MD were

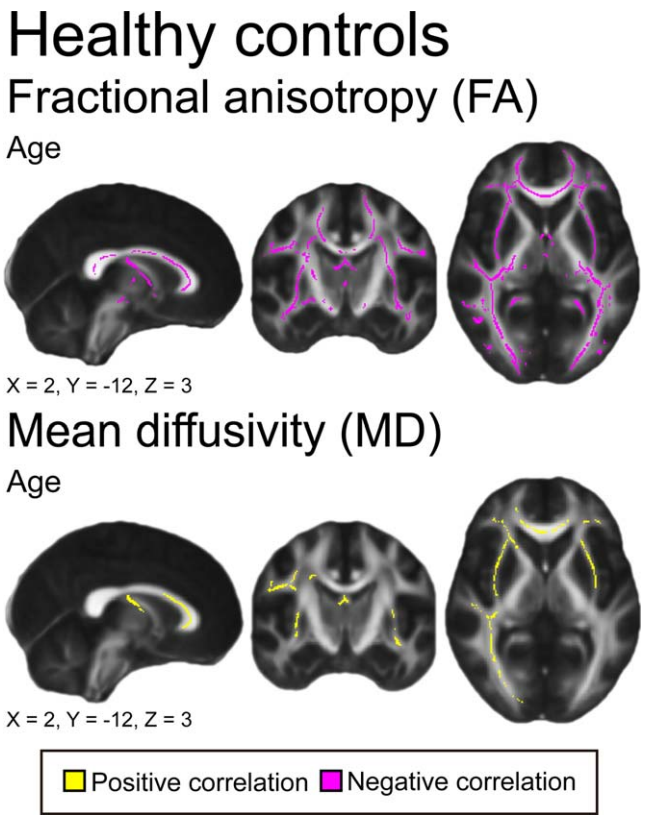

Fig. 2. Association between age and FA and MD as obtained with TBSS in the control group. No effect of age on FA or MD was found in the TBI group. The statistical threshold was set to $P < 0.05$, corrected multiple comparisons as implemented in Randomise. The FSL 1-mm mean FA template was used as the background image. The images are shown in radiological convention, i.e., the right side of the subject is on the left side of the image. The x, y, and z refer to MNI template coordinates.

observed between the MVA and the fall groups. The group with DAI had significantly lower FA in the entire CC, anterior and posterior limbs of the internal capsule, peripheral parts of intra- and interhemispheric tracts, thalamus, and brainstem compared with the no-DAI group (Fig. 1). MD was not decreased in the deeper midline structures (i.e., thalamus and brainstem) but was decreased in the long intrahemispheric tracts and CC in the DAI group compared with the non-DAI group (Fig. 1). In the DAI grade 2 + 3 group, FA was significantly lower in the CC and the right anterior corona radiate plus external capsule compared with the DAI grade 1 group, but there were no MD differences (Fig. 1).

Time since injury was not associated with FA or MD values. GCS scores were positively associated with FA, most notably in the CC and the thalamus but also in the external capsule, SLF, ILF/IFOF, and more peripheral hemispheric tracts (Fig. 3). The MD increases associated with lower GCS scores were more or less the inverse of the FA decreases (Fig. 3). PTA duration was negatively associated with FA values in all WM tracts, including the peripheral hemispheric tracts and temporal lobe tracts as well as the thalamus but excluding the posterior limb of the internal capsule (Fig. 3). MD was similarly but inversely related to PTA duration (Fig. 3). The number of microhemorrhages and the FLAIR lesion volume were significantly associated with reduced FA in all major WM tracts, including the peripheral parts of the hemispheric WM and the thalamus (Fig. 3). The association between the number of microhemorrhages and FLAIR volumes with MD was the inverse of that of FA (Fig. 3). Rotterdam CT scores were not associated with FA or MD values. The number of days with three or more episodes of ICP >20 mmHg was not associated with FA or MD changes. The number of days with three or more episodes of CPP <70 mmHg was associated with increased MD in the anterior CC and corona radiate (Fig. 3) but not FA changes.

Associations Among Different Outcome Measures in the Chronic Phase and FA and MD From the TBSS Analysis in TBI and Control Groups

In the TBI group, GOSE scores were positively associated with FA in the CC, external capsule, SLF, and ILF/IFOF, including some of the more peripheral parts, plus the brain stem (Fig. 3). For MD, a significant negative association was also present in the thalamus (Fig. 3). In the TBI group, the scores for D-KEFS TMT subtests 1–4 were negatively correlated with FA and positively correlated with MD in all central and peripheral WM tracts. The correlations were most striking between FA and subtests 1, 3, and 4, whereas the significant correlations between FA and subtest 2 were limited predominantly to the right hemisphere (Fig. 4). For subtests 1–4, FA and MD changes were the inverse of each other (Fig. 4). There were no associations between FA or MD and subtest 5, i.e., the motor speed test. In the control group, FA correlated with subtest 3, similar to that in the TBI group, although the more superior brain regions and the thalamus were not involved in the controls (Fig. 4). There were no statistically significant correlations between FA and the other D-KEFS TMT subtests in the controls. There were no associations between the BRIEF-A subindices and FA or MD in the TBI or control groups.

Automated Tractography in TBI and Control Groups

Representative tractographies of the CC, SLF, and ILF/IFOF in one TBI survivor and one control subject are shown in Figure 5. TBI survivors had significantly lower tract volumes for all tracts studied except for left SLF (Table 2). Moreover, the median FA value was significantly lower in all tracts in the TBI compared with the control group. Median MD, λ_1, λ_2, and λ_3 values were significantly higher in the TBI group than in the controls (Table 2). The direct comparison between FA in the CC obtained from TBSS and automated tractography showed that FA was significantly higher ($P < 0.001$) in the TBSS

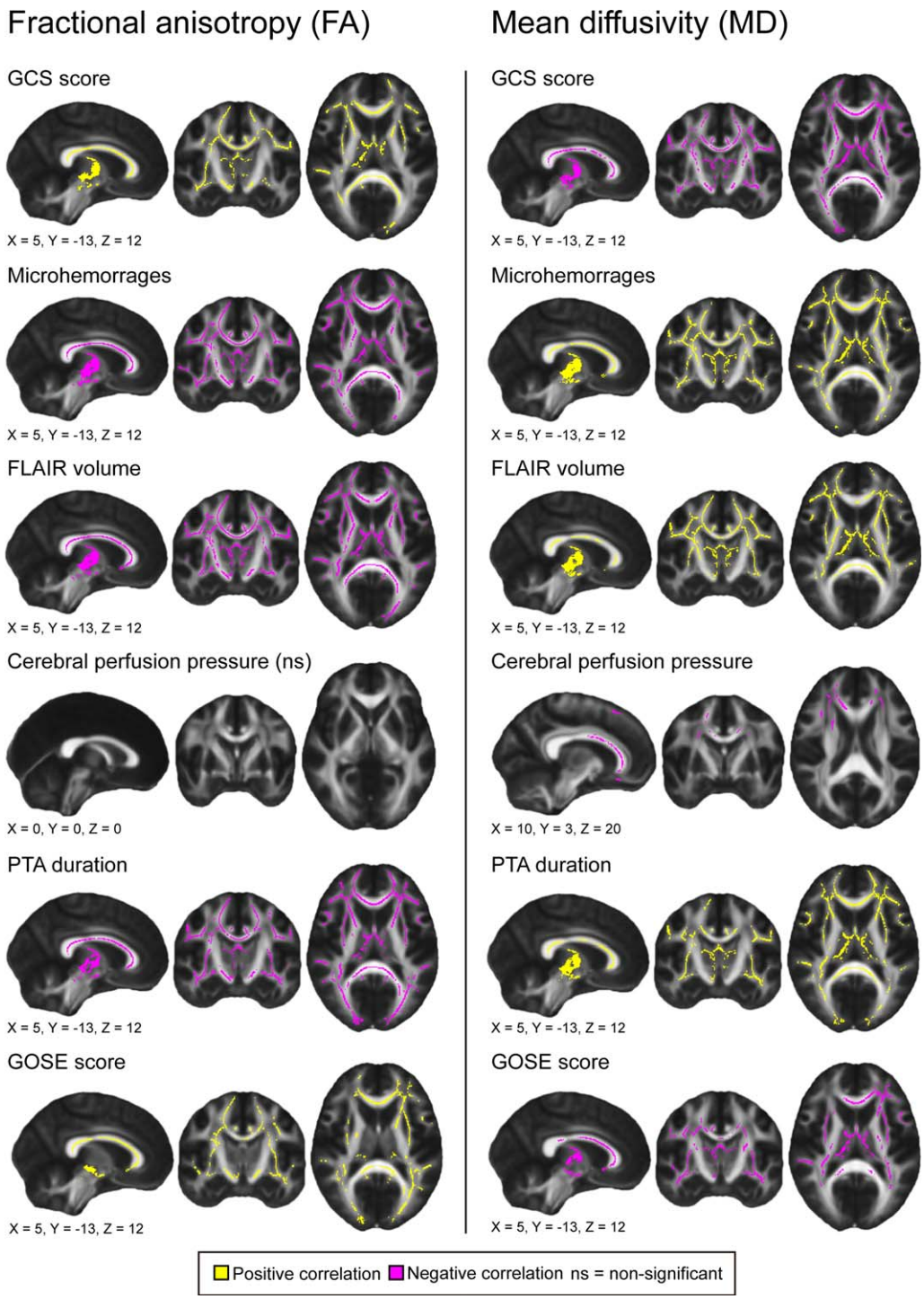

Fig. 3. Associations between acute-phase injury-related variables and neuroradiological findings as well as chronic-phase global outcome, FA, and MD as obtained with TBSS. The statistical threshold was set to $P < 0.05$, corrected for gender, age at MRI, and multiple comparisons as implemented in Randomise. The FSL 1-mm mean FA template was used as the background image. The images are shown in radiological convention; i.e., the right side of the subject is on the left side of the image. The x, y, and z refer to MNI template coordinates.

analysis in both the TBI and the control groups (TBI, mean FA = 0.65 ± 0.06 [median = 0.66]; controls, mean FA = 0.72 ± 0.04 [median = 0.72]) compared with FA from automated tractography (TBI, FA = 0.41 ± 0.02 [median = 0.42]; controls, FA = 0.44 ± 0.02 [median = 0.43]).

Fig. 4. Associations between performance-based cognitive control function (D-KEFS TMT) and FA and MD as obtained with TBSS in the TBI and control groups. The statistical threshold was set to $P < 0.05$, corrected for gender, age at MRI, and multiple comparisons as implemented in Randomise. The FSL 1-mm mean FA template was used as the background image. The images are shown in radiological convention; i.e., the right side of the subject is on the left side of the image. The x, y, and z refer to MNI template coordinates; ns, nonsignificant.

In the TBI group, GCS scores were associated with volume loss in the CC and the right ILF/IFOF (Table 3). Furthermore, the volume of ILF/IFOF (left, $r = -0.346$, $P = 0.02$; right, $r = -0.470$, $P = 0.001$) was negatively correlated with DAI grade; no similar correlations were present for the other tracts' volumes. Time since injury correlated positively with CC volume ($r = 0.304$, $P = 0.043$) but not with the other tracts' volumes. Mean MD was the parameter from tractography that most consistently correlated with GOSE scores (Table 3). For the tract volumes, only the ILF/IFOF volumes were correlated with GOSE scores. No other consistent findings were present (Table 3). No significant relationships between BRIEF-A subindices' scores and the automated tractography parameters were demonstrated in the TBI or the healthy control groups (Table 4). D-KEFS TMT subtest 1–5 scores were somewhat inconsistently associated with FA and MD values obtained from the automated tractography analysis (Table 4). The associations with tract volumes and performance on D-KEFS TMT were even more variable (Table 4). In the controls, D-KEFS TMT subtests 1 and 3 were significantly correlated with volume of the CC and FA plus volume of the right ILF/IFOF. No other correlations were found between the automated tractography measures and D-KEFS TMT scores in the controls.

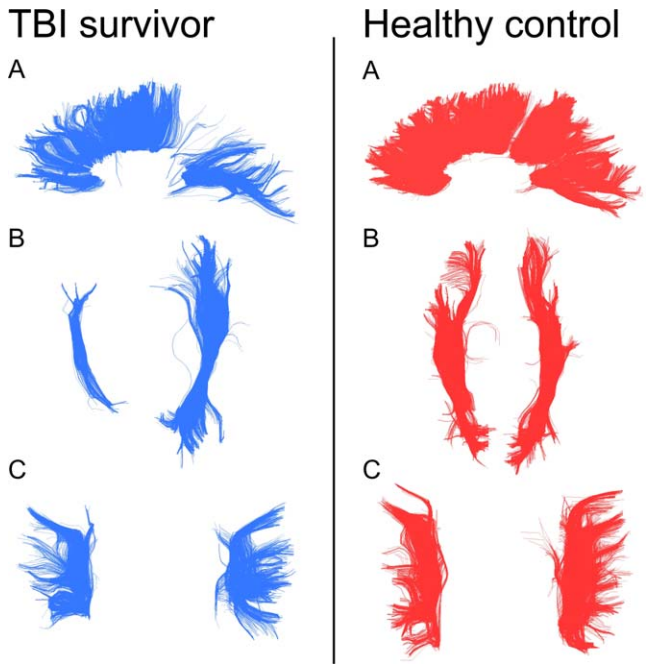

Fig. 5. Representative tractography images of corpus callosum (**A**), superior longitudinal fasciculus (**B**), and inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (**C**) in one TBI survivor (male with severe TBI, age 21 years at time of DTI) and one healthy control (female, age 20 years).

DISCUSSION

The current study reveals extensive changes in WM FA, MD, and tract volumes in chronic moderate-to-severe-TBI survivors with relatively good overall outcome and highly similar performance-based cognitive control functioning compared with a well-matched healthy control group. There are six main findings in this study are as follows. 1) FA was the primary denominator of injury severity and mechanism (acceleration/deceleration injuries); 2) DAI of any grade led to lower FA in the thalamus and brainstem; 3) in severe TBI, days with CPP <70 mmHg had minor effects specifically on MD; 4) elevated ICP derived from episodes with ICP >20 mmHg as well as acute-phase Rotterdam CT scores did not significantly affect chronic-phase FA or MD; 5) the relationship between chronic-phase outcome and DTI measures varied between DTI analysis methods as well as between types of outcomes but appeared, in general, to be associated with both FA and MD and to a very limited extent with tract volumes; and 6) decreased general outcome (GOSE scores) and performance-based cognitive control function in the chronic phase of TBI were associated with widespread FA and MD changes, whereas self-reported cognitive control functioning was not.

Impact of Acute-Phase Injury, Clinical, and Neuroimaging Variables on FA, MD, and Volumes in Chronic, Moderate, and Severe TBI

The reduced FA in TBI resulted from increased diffusivity perpendicular to the tract axis, which implies loss of axons and myelin (Beaulieu, 2002; Song et al., 2003). FA was shown to be a particularly sensitive marker of injury severity, which was demonstrated by the group comparisons between severe vs. moderate TBI, MVA vs. fall injuries, and DAI grade 2 + 3 vs. DAI grade 1, as was predicted. These findings extend previous claims that FA is a representative measure of TBI (Kinnunen et al., 2011; Bigler, 2013a,b) and show that FA loss directly reflects the severity and mechanism of the acute injury in TBI.

Because DAI and GCS scores are connected (Ommaya and Gennarelli, 1974; Gennarelli et al., 1982; Skandsen et al., 2010), it was not surprising that GCS scores were associated with FA as well as with MD values in the CC, long intrahemispheric tracts, thalamus, and brainstem. The locations of the WM changes agree both with the known propagation of the traumatic forces through WM from biomechanical modeling and with earlier reports on correlations between GCS scores and DTI parameters that used a variety of approaches (Adams et al., 1989; Chatelin et al., 2011; Bayly et al., 2012; McAllister et al., 2012; Sorg et al., 2013). The duration of PTA was significantly associated with FA and MD in both central and peripheral WM tracts and the thalamus. Furthermore, tracts connecting the temporal lobe with both posterior and anterior brain regions were affected. This suggests that PTA duration is a result of widespread disconnection of WM, including the temporal lobes and thalamus, which corresponds well with the overall disorientation and reduction in several cognitive domains often

TABLE 2. Median (in Italics) and Mean FA, MD, λ1, λ2, λ3, and Tract Volumes With Standard Deviations (in Parenthesis) Obtained Via Automated Tractography in TBI and Healthy Control Groups*

WM tract		TBI group		Control group		*P* value
Corpus callosum (CC)	FA	*0.416*	(0.414 ± 0.018)	*0.434*	(0.436 ± 0.018)	<0.001
	MD	*0.82*	(0.83 ± 0.04)	*0.78*	(0.78 ± 0.03)	<0.001
	λ1	*1.23*	(1.23 ± 0.05)	*1.19*	(1.19 ± 0.03)	<0.001
	λ2	*0.72*	(0.73 ± 0.04)	*0.68*	(0.67 ± 0.03)	<0.001
	λ3	*0.53*	(0.54 ± 0.04)	*0.48*	(0.49 ± 0.03)	<0.001
	vol (ml)	*117.30*	(117.71 ± 28.21)	*135.09*	(137.07 ± 17.01)	<0.001
Left inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (L ILF/IFOF)	FA	*0.375*	(0.377 ± 0.02)	*0.398*	(0.397 ± 0.012)	<0.001
	MD	*0.81*	(0.83 ± 0.07)	*0.77*	(0.78 ± 0.03)	<0.001
	λ1	*1.16*	(1.18 ± 0.08)	*1.13*	(1.13 ± 0.04)	<0.001
	λ2	*0.74*	(0.75 ± 0.07)	*0.70*	(0.70 ± 0.03)	<0.001
	λ3	*0.54*	(0.55 ± 0.06)	*0.51*	(0.50 ± 0.03)	<0.001
	vol (ml)	*39.36*	(38.53 ± 10.78)	*45.60*	(44.74 ± 9.01)	<0.001
Right inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (R ILF/IFOF)	FA	*0.373*	(0.374 ± 0.021)	*0.397*	(0.396 ± 0.022)	<0.001
	MD	*0.81*	(0.82 ± 0.04)	*0.77*	(0.77 ± 0.03)	<0.001
	λ 1	*1.17*	(1.17 ± 0.05)	*1.12*	(1.12 ± 0.04)	<0.001
	λ 2	*0.74*	(0.75 ± 0.04)	*0.70*	(0.70 ± 0.03)	<0.001
	λ 3	*0.54*	(0.55 ± 0.04)	*0.50*	(0.50 ± 0.03)	<0.001
	vol (ml)	*39.17*	(37.38 ± 9.32)	*43.45*	(43.61 ± 7.95)	<0.001
Left superior longitudinal fasciculus (L SLF)	FA	*0.378*	(0.376 ± 0.018)	*0.390*	(0.388 ± 0.016)	<0.001
	MD	*0.77*	(0.77 ± 0.03)	*0.73*	(0.73 ± 0.03)	<0.001
	λ 1	*1.08*	(1.09 ± 0.04)	*1.05*	(1.05 ± 0.03)	<0.001
	λ 2	*0.71*	(0.71 ± 0.03)	*0.67*	(0.67 ± 0.03)	<0.001
	λ 3	*0.50*	(0.5 ± 0.03)	*0.47*	(0.47 ± 0.02)	<0.001
	vol (ml)	*19.20*	(19.83 ± 4.47)	*21.16*	(21.05 ± 5.3)	<0.001
Right superior longitudinal fasciculus (R SLF)	FA	*0.348*	(0.347 ± 0.015)	*0.361*	(0.362 ± 0.016)	<0.001
	MD	*0.77*	(0.78 ± 0.03)	*0.73*	(0.73 ± 0.03)	<0.001
	λ 1	*1.07*	(1.07 ± 0.04)	*1.03*	(1.03 ± 0.03)	<0.001
	λ 2	*0.72*	(0.72 ± 0.03)	*0.68*	(0.68 ± 0.03)	<0.001
	λ 3	*0.53*	(0.53 ± 0.03)	*0.49*	(0.49 ± 0.03)	<0.001
	vol (ml)	*35.73*	(36.26 ± 6.08)	*41.11*	(39.6 ± 5.69)	<0.001

λ, Lambda (eigenvalue); SD, standard deviation; MD, λ1, λ2, and λ3 are given in 10^{-3} mm^2/sec. Between-group differences were investigated with a Mann-Whitney U test. $P < 0.05$ (two-sided) was considered statistically significant, not corrected for multiple comparisons.

observed during PTA (Marshman et al., 2013). To date, only the relationship between PTA and FA in mild TBI has been studied with a whole-brain WM ROI approach (Benson et al., 2007).

The lack of normal age-related FA and MD changes in the TBI group further emphasized the impact of TBI on WM, demonstrating that moderate-to-severe TBI leads to WM pathology, superseding normal physiological processes. There was no effect of time since injury on FA or MD in the TBSS analysis. This may be related to the fact that all TBI survivors were in the chronic phase, well past the first year after injury. One longitudinal study of FA changes in severe TBI showed no further decline in FA between 2 and 5 years after injury (Dinkel et al., 2013), whereas two other longitudinal studies during the first 6 months to 1 year after TBI reported changes within the study period (Sidaros et al., 2008; Bendlin et al.,2008; Kumar et al., 2009; Ljungqvist et al., 2011). Another study showed that, after age was taken into account, FA and MD did not change over time in TBI survivors (Kinnunen et al., 2011). Taken together, FA and MD appear to stabilize 1 year after TBI, although histopathological changes in WM are reported to continue (Vargas and Barres, 2007; Johnson et al., 2013a). It was surprising that a positive correlation between time since injury and CC volume was demonstrated in the current study. It is difficult to reconcile this finding with the previous finding of total WM loss of ~2% of the intracranial volume during the first year after TBI (Brezova et al., 2014). One might speculate that reorganization is more prominent in the CC because of its sheer size and/or that gliosis formation is more marked because the CC suffers the greatest strain (Ommaya and Gennarelli, 1974; Levin et al., 1988; Chatelin et al., 2011), leading to volume increase with time since injury.

The presence and severity of DAI, described from the early-phase MRI scans (FLAIR lesion volumes, number of microhemorrhages, and DAI grade), were demonstrated to be closely linked to both FA and MD changes in chronic TBI. Hence, early-phase conventional MRI-based DAI grading is a valuable tool for describing lasting WM injury in TBI. As was expected from the distribution

of DAI lesions in the different DAI grades (Gentry, 1994), reduced FA and increased MD were observed in the CC in the DAI grade 2 + 3 group vs. the DAI grade 1 group. However, there was no significant difference in brainstem FA or MD between the DAI grades. This may be due to DAI of any grade impacting the brainstem. This interpretation is supported by the comparison between the no-DAI vs. the DAI group, which revealed significant FA changes in both the brainstem and the thalamus in the DAI group. Indeed, the brainstem appears to be particularly sensitive to DAI, inasmuch as significantly smaller brainstem volumes are observed in all grades of DAI vs. no DAI already in the early phase of TBI (Brezova et al., 2014). An alternative explanation is that brainstem FA and MD changes in the chronic phase of TBI developed over time as a result of axotomoy of efferent and afferent axons in the hemispheric WM present in all grades of DAI. Furthermore, the current results demonstrate that the thalamus is particularly sensitive to DAI. The thalamic FA changes in the chronic phase may reflect secondary changes resulting from disconnection of the thalamus and cortex resulting from DAI in corona radiate/hemispheric WM and/or represent primary thalamic injury, given that DAI lesions in the thalamus are present in the early phase after TBI (Little et al., 2010; Moen et al., 2012, 2014). Only the volume of ILF/IFOF was correlated with DAI grade. This finding may point to deeper intrahemispheric tracts being more affected with increasing DAI grade.

As was predicted, number of days with three or more episodes of CPP <70 mmHg was associated with increased MD but not FA changes in the severe TBI group admitted to the ICU. This suggests that oligodendrocytes are particularly vulnerable to CPP decreases in TBI, similar to observations in other cerebral pathologies and in normal aging (Fazekas et al., 1993; Back, 2006; Vernooij et al., 2008; Børch et al., 2010). The cutoff of CPP <70 mmHg is high according to today's guidelines (Bullock and Povlishock, 2007) and may include normal physiological CPP fluctuations. However, because the number of events was based on the number of days with at least three episodes of CPP <70 mmHg, it seems likely that CPP dysregulation was present in the severe TBI patients included in the analysis. The MD changes associated with the CPP measures were located in the arterial territory shared by the middle and anterior cerebral arteries, pointing to an ischemic origin of the MD changes and demonstrating increased vulnerability of watershed areas to CPP drops. It should be noted that a possible effect of decreased CPP on MD is unlikely to affect general outcome (e.g., GOSE scores), which is the most common end point used to evaluate ICU treatment protocols. Still, the MD increases in anterior CC and corona radiata may influence cognitive outcome, given that MD in these regions was associated with performance on D-KEFS TMT subtests. There was no measurable influence of days with three or more episodes of ICP >20 mmHg on WM FA or MD in the severe-TBI group admitted to the ICU. This is in line with acute data from rodents (Lafrenaye et al., 2012) and results from the early phase of TBI in human adults (Newcombe et al., 2011). In a study of the long-term effect (~5 years) of raised ICP in the acute phase after TBI on CC microstructure in children, the patient group with ICP >20 mmHg and/or ICP-lowering treatment for more than 3 days was shown to have reduced FA and increased MD in the CC compared with the group without ICP elevation (Tasker et al., 2010). It may be that children are more sensitive to ICP >20 mmHg because their normal ICP is lower than that in adults (Rangel-Castilla et al., 2008). Taken together, the lack of associations between FA or MD and episodes of ICP >20 mmHg as well as acute-phase Rotterdam CT scores indicated that elevated ICP per se did not lead to additional WM injury in adults surviving TBI.

White Matter in Chronic Moderate and Severe TBI as Revealed by Automated Tractography

The automatic tractography method demonstrated that the volumes of the WM tracts were significantly reduced in the chronic phase of TBI, concurring with the WM atrophy taking place during the first year after TBI (Brezova et al., 2014). The results demonstrate that CC had the greatest volume loss (~16% of controls), followed by ILF/IFOF (~10%) and SLF (0–7%). In the current study, automated tractography gave quite consistent FA, MD, eigenvalues, and volumes for right and left SLF and ILF/IFOF in both the TBI and the control groups. Previous studies have used other tractography methods, more mixed TBI groups, and shorter follow-up since time of injury, which might have led to their somewhat inconsistent findings (Brandstack et al., 2013; Kurki et al., 2013).

In the TBI group, GCS scores were associated with greater volume loss in CC but not consistently with the volume of the other tracts. CC is considered to be the tract experiencing the largest force in TBI (Ommaya and Gennarelli, 1974; Levin et al., 1988; Chatelin et al., 2011). It is therefore not surprising that the largest and most consistent effect on volume was found in this structure. However, as described above, CC volume was also found to be positively associated with time since injury. Together these findings suggest that both the initial traumatic forces and the inherent pathophysiological responses in CC following TBI lead to the macro- and microstructural CC changes observed.

Even though the tractography results appeared to be consistent with regard to tract FA, MD, and volumes in the TBI and control groups, the associations between these measures and the CGS scores and different outcome measures were highly inconsistent compared with the same analysis performed with TBSS. The most consistent finding for GCS scores was increased MD in CC, right and left SLF, and right ILFO/IFO. Mean FA value of an entire tract did not appear to reflect injury severity to the same extent as MD of the entire tract. These results are in agreement with a previous study showing that FA values obtained with tractography are significantly affected by the methodology used and often deviate considerably

TABLE 3. Partial Correlations (Adjusted for Age and Sex) Among Mean FA and MD, and Tract Volumes Obtained With Automated Tractography and GCS and GOSE Scores in the TBI Group*

	Value	Score	Partial correlation (r)	*P* value
Corpus callosum (CC)	Mean FA	GCS	0.242	0.101
		GOSE	0.232	0.116
	Mean MD	GCS	−0.391	0.007
		GOSE	−0.300	0.040
	volume	GCS	0.326	0.025
		GOSE	0.279	0.057
Left inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (L ILF/IFOF)	Mean FA	GCS	0.247	0.094
		GOSE	0.260	0.078
	Mean MD	GCS	−0.281	0.056
		GOSE	−0.447	0.002
	Volume	GCS	0.242	0.101
		GOSE	0.481	0.001
Right inferior longitudinal fasciculus/inferior fronto-occipital fasciculus (R ILF/IFOF)	Mean FA	GCS	0.345	0.018
		GOSE	0.117	0.435
	Mean MD	GCS	−0.360	0.013
		GOSE	−0.318	0.029
	Volume	GCS	0.417	0.004
		GOSE	0.379	0.009
Left superior longitudinal fasciculus (L SLF)	Mean FA	GCS	0.163	0.273
		GOSE	0.446	0.002
	Mean MD	GCS	−0.377	0.009
		GOSE	−0.399	0.005
	Volume	GCS	−0.122	0.416
		GOSE	0.082	0.582
Right superior longitudinal fasciculus (R SLF)	Mean FA	GCS	0.251	0.089
		GOSE	0.222	0.134
	Mean MD	GCS	−0.316	0.030
		GOSE	−0.346	0.017
	volume	GCS	0.063	0.676
		GOSE	0.154	0.303

*Partial correlations (*r*) among white matter integrity (tract FA, MD, volume), Glasgow Coma Scale (GCS), and Glasgow Outcome Scale Extended (GOSE) scores. Results are adjusted for age and sex. Statistically significant was set at $P < 0.05$ (two-sided), uncorrected for multiple comparisons.

from the values for the central parts of a tract (Kurki et al., 2013). The impact of analysis method on FA is clearly illustrated in the current study. The direct comparison between FA in CC from tractography and from the CC ROI using TBSS showed significantly lower FA with tractograhy. This result is to be expected because automated tractography encompasses larger parts of the CC and therefore includes more peripheral parts with lower FA values. By including WM with lower FA, it seems that the effect of injury severity on WM FA is not as striking. These results point to TBSS as the method of choice for depicting injury mechanism and severity.

Chronic-Phase Outcome Measures and Associations With WM FA, MD, and Tract Volumes

In the TBSS analysis, widespread FA decreases and MD increases in the same regions were demonstrated to be associated with poorer general outcome (GOSE scores) and performance-based cognitive control functioning, D-KEFS TMT subtests 1–4. The tractography analysis, on the other hand, showed that mean MD in all tracts was associated with GOSE scores, whereas FA was not. Furthermore, FA, MD, and tract volumes from automated tractography were found to be associated with D-KEFS TMT subtests 1–5, but these findings were highly inconsistent with regard to subtests and tracts involved. In summary, these results demonstrate that chronic-phase FA and MD changes are significantly related to outcome but that different approaches to DTI analysis as well as the type of outcome measured give somewhat varying results. Tract volumes were to a very limited extent and very inconsistently associated with outcome and will not be discussed further.

In the TBI group, widespread regions of reduced FA and increased MD were associated with poorer performance on D-KEFS TMT subtests 1–4 but not subtest 5 measuring motor speed. This result illustrates how subtests 1–4 rely more on integration and communication within a distributed cognitive control brain network (Dosenbach et al., 2007; Power and Petersen, 2013)

TABLE 4. Partial Within-Group Correlations (Adjusted for Age and Sex) Among Mean FA, MD, Mean Tract Volumes, and Self-Reported (BRIEF-A) and Performance-Based (D-KEFS TMT) Cognitive Control Function in the TBI and Healthy Control Groups†

	Self-reported (BRIEF-A)			Perfomance-based (D-KEFS TMT)				
	BRI	MI	GEC	Subtest 1	Subtest 2	Subtest 3	Subtest 4	Subtest 5
TBI group (n = 46)								
FA								
Corpus callosum	−0.093	0.027	−0.025	−0.291	−0.233	−0.333★	−0.325★	−0.172
Right ILF/IFOF	−0.062	−0.061	−0.012	−0.297★	−0.361★	−0.093	−0.281	−0.130
Left ILF/IFOF	−0.034	−0.131	−0.099	−0.263	−0.135	−0.341★	−0.236	−0.173
Right SLF	−0.044	−0.062	−0.059	−0.423†	−0.348★	−0.288	−0.344★	−0.278
Left SLF	−0.013	−0.100	−0.071	−0.504‡	−0.368★	−0.482‡	−0.397†	−0.392†
MD								
Corpus callosum	−0.007	−0.064	−0.040	0.450†	0.304★	0.401†	0.374★	0.216
Right ILF/IFOF	−0.073	−0.118	−0.103	0.546‡	0.414†	0.320★	0.375★	0.282
Left ILF/IFOF	0.161	0.221	0.210	0.183	0.055	0.209	0.047	0.088
Right SLF	0.021	0.050	0.043	0.485‡	0.369★	0.337★	0.295	0.327★
Left SLF	0.018	−0.085	−0.043	0.405†	0.305★	0.422†	0.402†	0.242
Volume								
Corpus callosum	−0.059	−0.061	−0.066	−0.400†	−0.130	−0.340★	−0.217	−0.267
Right ILF/IFOF	−0.206	−0.100	−0.154	−0.364★	−0.295	−0.126	−0.302★	−0.204
Left ILF/IFOF	−0.251	−0.288	−0.292	−0.085	0.084	−0.043	0.037	−0.031
Right SLF	−0.206	−0.229	−0.234	−0.271	−0.103	−0.046	−0.200	−0.100
Left SLF	−0.121	−0.116	−0.127	−0.096	0.750	−0.229	−0.053	0.039
Control group (n = 49)								
FA								
Corpus callosum	−0.041	0.116	0.050	−0.139	0.014	−0.244	−0.027	−0.016
Right ILF/IFOF	0.148	0.150	0.161	−0.251	−0.216	−0.370★	−0.125	−0.063
Left ILF/IFOF	0.055	0.056	0.060	−0.138	−0.129	−0.249	−0.112	−0.121
Right SLF	−0.041	0.088	0.033	−0.189	−0.018	−0.193	−0.039	0.036
Left SLF	0.109	0.209	0.177	−0.008	−0.120	−0.109	0.047	0.014
MD								
Corpus callosum	−0.053	−0.038	−0.048	0.033	−0.091	0.125	0.054	−0.072
Right ILF/IFOF	−0.073	−0.164	−0.134	−0.025	−0.167	0.072	0.045	−0.069
Left ILF/IFOF	−0.167	−0.226	−0.215	−0.165	−0.014	0.189	0.015	−0.170
Right SLF	−0.109	−0.129	−0.130	0.014	−0.032	0.229	−0.003	−0.111
Left SLF	−0.011	−0.059	−0.041	0.021	−0.168	0.118	−0.081	−0.149
Volume								
Corpus callosum	0.197	0.125	0.169	−0.061	−0.180	−0.290★	−0.173	−0.234
Right ILF/IFOF	0.028	0.047	0.041	−0.312	−0.265	−0.344★	−0.180	−0.162
Left ILF/IFOF	0.490	0.096	0.081	0.128	−0.081	−0.245	0.096	−0.001
Right SLF	−0.122	0.006	−0.055	−0.255	−0.166	−0.264	−0.089	−0.088
Left SLF	0.116	0.171	0.158	0.091	−0.235	−0.249	−0.020	0.144

Partial correlations (r) between white matter integrity (tract FA, MD, volume), performance-based (D-KEFS Trails) and self-report (BRIEF-A) measures of cognitive control function. Results are adjusted for age and sex. BRI, Behavioral Regulation Index; MI, Metacognitive Index; GEC, Global Executive Composite; ILF/IFOF, inferior longitudinal fasciculus/inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus. Corrections for multiple comparisons were not applied.

★$P < 0.05$ (two-tailed).

†$P < 0.01$ (two-tailed).

‡$P < 0.001$ (two-tailed).

compared with pure motor speed. Previous studies have demonstrated associations between reduced FA and increased MD in several of the same WM tracts and poorer cognitive control functioning after TBI (Niogi et al., 2008; Kinnunen et al., 2011; Leunissen et al., 2013; Spitz et al., 2013). Moreover, the current data support an important role of microstructural integrity of the thalamus for cognitive control functioning, in particular, but not for overall outcome, which is indicated by the lack of significant association between GOSE scores and FA and MD in the thalamus in the TBSS analysis. In the healthy zcontrol group, FA was positively associated with D-KEFS TMT subtest 3. In general, significant associations between FA or MD and performance-based scores on neuropsychological tests are infrequent in healthy controls but are a common finding in groups with different cerebral pathologies (Eikenes et al., 2011, 2012; Deng et al., 2013; Nir et al., 2013), in agreement with the current results.

The significant self-reported deficits in cognitive control functioning measured with BRIEF-A in the TBI group were not correlated with FA, MD, or tract volumes from the TBSS and automated tractography analyses. The

lack of a relationship between self-reported changes in cognitive control function and changes in FA and MD combined with the presence of such associations for performance-based measures of cognitive control supports the suggested distinction between cognitive control functioning measured by self-report as opposed to performance-based measurement (Isquith et al., 2013; Toplak et al., 2013). In a recent study, we demonstrated that increased BOLD activation in prefrontal and parietal cortex after moderate-to-severe TBI was associated with fewer self-reported cognitive control problems, possibly representing compensatory mechanisms (Olsen et al., 2014). Overall, WM integrity appears to determine the objective effectiveness (i.e., performance-based measure) of cognitive control functioning, whereas gray matter changes, such as those detected with functional MRI, seem to underlie the individual's experience of effort with regard to cognitive control (i.e., self-report) following TBI.

Limitations

The strength of the current study is the prospective design with clinical and neuroimaging data plus the well-matched healthy control group. Still, some clinical data were available only for subgroups of TBI survivors, as is shown in Table 1. Moreover, when the TBI group was divided into clinical subgroups, the number of individuals in some of the subgroups was small, e.g., DAI-3 group, which made it impossible to study all the different DAI grades separately. Furthermore, many statistical tests were performed, but only the TBSS analyses were corrected for multiple comparisons. This increases the risk of type I errors. Also, not all data had a normal distribution, and parametric correlation analyses were used, e.g., GCS scores and number of days with CPP and ICP deviations, which might have caused type II errors. Finally, the selection of only D-KEFS TMT and BRIEF-A, though representing key measurement tools of self-reported and performance-based cognitive control functioning, leaves some uncertainty about whether other assessment tools could have provided different results.

The associations between the automated tractography measures and the different acute-phase and outcome measures were rather inconsistent compared with those obtained with TBSS. The use of tractography requires further refinement and investigations to verify its role in TBI studies.

CONCLUSIONS

Loss of FA and tract volumes and increases in MD following moderate-to-severe TBI were widespread and reflected the propagation of traumatic forces through the brain. Chronic-phase FA was related particularly to injury severity and mechanism, whereas both FA and MD were important for outcome. Tract volumes, on the other hand, were not consistently found to be related to outcome. DAI of all grades specifically affected thalamus and brainstem microstructure in the chronic phase. Performance-based but not self-reported cognitive control functioning was associated with WM FA and MD changes, suggesting that the brain correlates differ between self-reported and performance-based cognitive control measures. From previous and current findings, performance impairments appear to be more closely related to WM microstructure, whereas self-reported problems are associated with changes in cortical activations.

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