Inter-Subject Variability of Axonal Injury in Diffuse Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a leading cause of cognitive morbidity worldwide for which reliable biomarkers are needed. Diffusion tensor imaging (DTI) is a promising biomarker of traumatic axonal injury (TAI); however, existing studies have been limited by a primary reliance on group-level analytic methods not well suited to account for inter-subject variability. In this study, 42 adults with TBI of at least moderate severity were examined 3 months following injury and compared with 35 healthy controls. DTI data were used for both traditional group-level comparison and subject-specific analysis using the distribution-corrected Z-score (DisCo-Z) approach. Inter-subject variation in TAI was assessed in a threshold-invariant manner using a threshold-weighted overlap map derived from subject-specific analysis. Receiver operator curve analysis was used to examine the ability of subject-specific DTI analysis to identify TBI subjects with significantly impaired processing speed in comparison with region of interest–based fractional anisotropy (FA) measurements and clinical characteristics. Traditional group-wise analysis demonstrated widespread reductions of white matter FA within the TBI group (voxel-wise $p < 0.05$, corrected), despite relatively low consistency of subject-level effects secondary to widespread variation in the spatial distribution of TAI. Subject-specific mapping of TAI with the DisCo-Z approach was the best predictor of impaired processing speed, achieving high classification accuracy (area under the curve [AUC]=0.94). In moderate-to-severe TBI, there is substantial inter-subject variation in TAI, with extent strongly correlated to post-traumatic deficits in processing speed. Significant group-level effects do not necessarily represent consistent effects at the individual level. Better accounting for inter-subject variability in neurobiological manifestations of TBI may substantially improve the ability to detect and classify patterns of injury.

Keywords: cognitive function; diffusion tensor imaging; traumatic axonal injury; traumatic brain injury

Introduction

TRAUMATIC BRAIN INJURY (TBI) is a leading cause of morbidity, disability, and economic loss in the United States and worldwide.^{1,2} Functional outcomes of patients with TBI have improved little in recent decades, and a substantial portion of those surviving moderate-to-severe injury ultimately experience unfavorable neurocognitive outcome.² Difficulties in developing more tailored and effective rehabilitation strategies stem in part from the heterogeneity of pathology, which impedes mechanistic understanding of TBI-related effects, as well as from limitations in the ability to assess the full extent of neurobiological manifestations within individual patients in clinical settings. Reliable biomarkers of injury applicable to assessment of individual patients with TBI are needed both to facilitate mechanistic understanding of the diverse effects of TBI and to guide clinical management through improved prognostication.

Recent advances in neuroimaging techniques have led to several important insights into the pathophysiology of TBI. In particular, diffusion tensor imaging (DTI) has become a well-established means of detecting and characterizing associated white matter injuries. By employing a series of motion-probing magnetic resonance gradients, DTI measurements of the directional dependence of water diffusion can be used to make inferences about the local microstructure.³ Although the manifestations of TBI on DTI are at least partially dependent on timing of assessment and severity of injury, TBI is most commonly characterized by a reduction of white matter fractional anisotropy (FA),⁴ believed to indicate TAI based on radiology–pathology correlation in animal models.^{5–7} Importantly, TAI as revealed by DTI often extends beyond the spatial extent of focal traumatic lesions and may be present in the setting of a “normal” clinical magnetic resonance imaging (MRI).⁸ Mounting pathologic and radiologic evidence supports that the extent of white matter injury is directly related to acute

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measures of injury severity, such as Glasgow Coma Scale score and duration of post-traumatic amnesia,^{9–11} as well as to long-term cognitive impairment and disability across a spectrum of injury severity.^{11–14} White matter DTI abnormalities also are related to alterations in connectivity of functional brain networks, suggesting that microstructural injuries are the substrate of impaired connectivity within brain networks subserving cognition.¹⁵

To date, most DTI investigations in TBI have relied on analytic approaches that assess differences in average effects between groups,⁴ typically comparing people with TBI with healthy controls. Given substantial variation in the clinical manifestations of TBI,¹⁶ however, the ability to characterize neurobiological manifestations at the single-subject level holds great but as yet largely untapped potential to complement group-level analysis by allowing inter-subject variability in brain–behavior relationships to be evaluated. As the cognitive and behavioral sequelae of TBI primarily may be due to disruption of white matter connectivity, individualized measures of the distribution of white matter injury may be particularly valuable.

In recognition of the need to develop subject-level DTI analysis, several voxel-wise analytic approaches have been proposed.^{17–19} These methods involve quantitative comparison of a single subject's DTI data with that of a normative control population, employing Z-transformation of scalar metrics based on the voxel-wise mean and standard deviation (SD) of the controls. Abnormalities are typically defined as contiguous voxels that survive corrections based on both Z score and minimum cluster size thresholds. Particularly promising are the distribution-corrected Z-score (DisCo-Z)¹⁹ and Enhanced Z-score Microstructural Assessment of Pathology (EZ-Map)¹⁸ methods which improve upon previous approaches by better accounting for the statistical properties of Z-transformation of DTI scalars, thus allowing for unbiased identification of DTI abnormalities within an individual. Both methods have been shown to produce a statistically robust evaluation of a single subject's DTI data, compared with a group of controls at the voxel-wise level,¹⁹ and importantly may be used to provide subject-level quantification of white matter injury while preserving information regarding its spatial distribution.^{20,21} Additionally, the DisCo-Z method, by rendering the probability of voxel-wise extrema equivalent between the study and control populations, provides a means of estimating the null distribution of DTI “lesions.”

While individual-level analytic approaches have mostly been used to detect white matter DTI alterations in mild TBI, such approaches also may be valuable for examining white matter effects in more severe brain injuries, given that the true extent of damage is likely to extend well beyond what is evident on conventional neuroimaging. Individual-level analysis can address an important limitation of group-wise analysis, specifically that group effects are not necessarily reflective of effects occurring in individual subjects. For instance, group effects may be driven by a minority of subjects with extreme characteristics. Alternatively, effects that are not significant at the group level may reflect heterogeneity in the population or differential effects in certain subgroups. Thus, an important but unresolved question concerns the degree to which well-established group differences in DTI measures are representative of effects in individuals with moderate-to-severe diffuse TBI.

Determination of the spatial distribution of white matter injury in TBI also is affected by the analytic strategy. Although TBI is generally assumed to be associated with heterogeneous patterns of white matter injury, such inferences have typically been based on inconsistencies in spatial distribution of injury patterns across different studies employing group methods of analysis,⁴ as well

as observed heterogeneity in spatial distribution of focal macrostructural lesions.²² Conversely, other investigations have detected widespread DTI alterations throughout the white matter at the group level, suggesting that white matter damage may occur diffusely.¹¹ Conclusions, however, have been limited by differences across studies in data acquisition, analytic methodology, study populations, and timing of assessment, which may account for some of the observed differences in spatial patterns. By drawing statistical inference at the level of individual subjects, the degree of injury pattern overlap and mismatch between subjects can be more directly investigated while controlling for other potential sources of variation. Such an approach allows for more explicit investigation and ultimately identification of regions that are both consistently and variably affected. While regions affected consistently may reflect vulnerability to TAI, those affected variably may be of particular interest in understanding the variable range of clinical outcomes in TBI. Ultimately, the ability to characterize neurobiological injuries at the level of the individual subject holds tremendous potential to better understand the relationship of brain trauma to post-traumatic cognitive deficits and is a requisite for use of advanced imaging in the clinical realm to benefit the care of individual patients with TBI.

In the present study, we evaluate the extent of spatial heterogeneity of white matter damage within a cohort selected for predominantly diffuse moderate-to-severe TBI. First, we use the DisCo-Z method to generate individual-level injury maps. Next, we compute the spatial overlap of injury patterns between TBI subjects in a threshold-insensitive fashion to quantitatively assess the degree of spatial consistency of injury patterns across patients in relation to group-level differences. Lastly, we evaluate the potential clinical relevance of this fully automated subject-specific approach by examining the relationship between extent of injury and cognitive processing speed. To evaluate the ability of subject-specific whole-brain analysis to predict the presence of post-traumatic cognitive deficits, we also compare the classification accuracy of a whole-brain injury summary statistic (derived from DisCo-Z analysis) with that of single region of interest (ROI) FA measurements in identifying those subjects with impaired processing speed.

Methods

Study population

This study was approved by the Institutional Review Board of the home institution and written informed consent was obtained from the participants or their legally authorized representatives. A total of 42 adults with TBI were examined approximately 3 months following injury (mean $104 \pm \text{SD } 18$ days), as part of a planned longitudinal study. Recruitment spanned a 40-month period between August 2012 and December 2015. Commonly used clinical indices of TBI severity were abstracted from the medical record or measured prospectively during hospitalization. These included the initial Glasgow Coma Scale (GCS) from the emergency department; time to follow commands (TFC), defined as the number of days between the TBI and consistent following of simple motor commands over a 24-h period; and duration of post-traumatic amnesia (PTA), defined as the number of days between the TBI and the date of the first of two scores ≥ 25 on the Orientation Log²³ administered ≤ 72 h apart. For patients who were discharged from rehabilitation care while still in PTA, their PTA duration was estimated conservatively at days between TBI and rehabilitation discharge +1.

Subjects were included based on age between 18–64 years and a history of non-penetrating TBI of at least moderate severity defined

by at least one of the following: 1) GCS <13 in the emergency department (not due to sedation, paralysis, or intoxication); 2) documented loss of consciousness for ≥ 12 h; and 3) PTA ≥ 24 h. Participants were excluded for: 1) history of prior TBI, central nervous system disease, seizure disorder, schizophrenia, or bipolar disorder; 2) history of abuse of alcohol or stimulants (e.g., cocaine) likely to have resulted in neurologic sequelae; 3) pregnancy; 4) inability to complete MRI scanning due to ferromagnetic implants, claustrophobia, or restlessness; 5) non-fluency in English; and 6) level of disability too great to allow for completion of testing and scanning 3 months post-TBI. To maximize the likelihood of TAI in the absence of large focal brain lesions, participants also were excluded if the total estimated volume of focal intraparenchymal lesions was greater than 5 cm³ for subcortical lesions and 50 cm³ for cortical lesions. In addition, 35 healthy volunteers matched to TBI subjects by age, gender, and years of education were recruited. Exclusion criteria for controls were the same as above, with an additional exclusion for any history of TBI resulting in loss or alteration of consciousness.

DTI acquisition and processing

Brain MRI examinations were performed on a 3 tesla MRI scanner (Siemens Trio, Siemens, Erlangen, Germany), which included two 30-direction DTI acquisitions with two b-values ($b=0$ sec/mm² and $b=1000$ sec/mm²). Seven b0 images were spaced out throughout the acquisition. DTI was acquired at 2.2 mm isotropic resolution using an echo time of 84 msec, repetition time of 6500 msec, and flip angle of 90°. In addition, a high-resolution T1 magnetization-prepared rapid gradient echo sequence was acquired at 1 mm isotropic resolution using an echo time of 3.08 msec, repetition time of 1620 msec, and a flip angle of 15°. T1-weighted images were utilized for manual segmentation of focal lesions by a trained observer under supervision of a neurologist with extensive experience in lesion assessment. Also, accuracy of lesion segmentation was also verified by a neuroradiology fellow (J.B.W.). Each subject's T1-weighted image was then registered to Montreal Neurological Institute (MNI) space using a diffeomorphic registration procedure.²⁴ The resultant transformations were then used to map each subject's focal lesion masks into standard space, where the volume of encephalomalacia was subsequently quantified.

DTI volumes were first visually inspected for artifacts. Subsequently, the two DTI acquisitions were concatenated to improve signal-to-noise ratio. The image processing tools available in FMRIB Software Library (FSL) were then used to correct DTI volumes for eddy current distortions and remove non-brain tissue.^{25,26} Using a

tensor-based registration procedure, which combines affine and diffeomorphic registration steps (DTI-TK),^{27,28} each subject's DTI data was first registered to an unbiased population-specific DTI template²⁹ before ultimately being co-registered to a standard-space DTI template (IIT-256).³⁰ This procedure was motivated by previous studies demonstrating that voxel-wise analyses of DTI data are particularly sensitive to accuracy of co-registration, which can be improved by utilizing information encoded by the entire diffusion tensor.^{31,32} In a recent head-to-head comparison, DTI-TK outperformed other commonly used methods of DTI co-registration,³³ important for minimizing potential shape and volumetric confounds of voxel-wise DTI data analysis in clinical populations.²⁸

Co-registered DTI data were then resampled into the standard MNI coordinate system and subject-specific voxel-wise maps of FA were derived. Finally, to restrict analysis to white matter, each subject's FA map was masked using a custom white matter mask derived from FSL's fast segmentation³⁴ applied to the 1-mm MNI 152 template brain, combined with white matter ROIs from the ICBM-152 Johns Hopkins White Matter Atlas³⁵ to better represent deep white matter structures.

DTI analysis

To compare group-wise differences in FA with inter-individual consistency in the TBI group, DTI data was analyzed in both a group-wise and a subject-specific fashion. Following pre-processing, group level voxel-wise comparison of FA between TBI subjects and controls was performed using the nonparametric permutation tool "randomize,"³⁶ part of FSL, while utilizing the threshold-free cluster enhancement (TFCE) method of multiple comparison correction.³⁷ Individual DTI analysis was performed using the DisCo-Z method, which has previously been described in detail.¹⁹ Briefly, subject-specific FA maps in both the control and subject groups are initially Z-transformed using the voxel-wise mean and standard deviation of the control population. Z-thresholds for the control and subject populations are then corrected to maintain identical alpha between groups, thereby eliminating bias resulting from differing degrees of freedom and non-independence of control subject responses with respect to the reference mean and standard deviation.^{19,38} The magnitude of threshold adjustment, which depends only on the size of the control population, renders the probability of obtaining voxel-wise extrema from DTI scalar maps equivalent in two otherwise identical groups.¹⁹ To focus specifically on TAI, we only considered the lower portion of this distribution (clusters of abnormally low FA).

TABLE 1. REGIONS OF INTEREST USED TO INVESTIGATE RELATIVE FREQUENCY OF REGIONAL INJURY ACROSS TBI SUBJECTS, AS WELL AS THE FREQUENCY DISTRIBUTION OF INJURED TRACTS WITHIN INDIVIDUAL TBI SUBJECTS

Label	Region of interest	Label	Region of interest
1	Anterior corona radiata (left)	15	Lower cingulum (left)
2	Anterior corona radiata (right)	16	Lower cingulum (right)
3	Anterior limb Internal capsule (left)	17	Middle cerebellar peduncle
4	Anterior limb internal capsule (right)	18	Posterior corona radiata (left)
5	Body of corpus callosum	19	Posterior corona radiata (right)
6	Cingulum bundle (left)	20	Posterior limb internal capsule (left)
7	Cingulum bundle (right)	21	Posterior limb internal capsule (right)
8	Cerebral peduncle (left)	22	Superior cerebellar peduncle (left)
9	Cerebral peduncle (right)	23	Superior cerebellar peduncle (right)
10	External capsule (left)	24	Superior corona radiata (left)
11	External capsule (right)	25	Superior corona radiata (right)
12	Genu of corpus callosum	26	Superior longitudinal fasciculus (left)
13	Inferior cerebellar peduncle (left)	27	Superior longitudinal fasciculus (right)
14	Inferior cerebellar peduncle (right)	28	Splenium of corpus callosum

Regions are derived in an automated fashion from the ICBM-152 Johns Hopkins White Matter Atlas.³² TBI, traumatic brain injury.

FIG. 1. Map of regions of interest used to investigate relative frequency of regional injury across traumatic brain injury (TBI) subjects, as well as the frequency distribution of injured tracts within individual TBI subjects. Regions are derived in an automated fashion from the ICBM-152 Johns Hopkins White Matter Atlas.³⁵ Color image is available online at www.liebertpub.com/neu

Spatial consistency of injury patterns was then assessed across a range of DisCo-Z thresholds ($0 < |\text{DisCo-Z}| < 4$) by computing effect overlap maps in a manner analogous to that proposed by Seghier and Price.³⁹ Subject-specific DisCo-Z maps are computed at each threshold value, then combined across subjects to form an overlap map in which the value of each voxel represents the proportion of subjects with effects present at that voxel for a given threshold. A weighting function is then applied to penalize lower thresholds, and final threshold-weighted overlap map (OM) is derived by taking the area under the curve of the cumulative histogram at each voxel across subjects. We utilized the following linear weighting function proposed by Seghier and Price,³⁹ which ensures OM values range from 0–1, with 1 indicating an effect in a particular voxel is present in each subject at each threshold:

$$W_{DZ} = 2 \times \frac{DZ}{DZ_{\max} - DZ_{\min}}$$

Additionally, to examine whether more severely impaired processing speed is associated with a specific, consistent pattern of injury, we computed overlap maps separately among the TBI subjects with and without impaired processing speed.

To illustrate the relative frequency of regional injury across TBI subjects, each subject's DisCo-Z map was calculated at a single threshold, $|\text{DisCo-Z}| > 2$. Additional spatial thresholding was applied using Monte Carlo simulation to determine the necessary cluster size correction to maintain a family-wise error rate at $p < 0.05$ based on the average smoothness of the FA data (3.8 mm). This additional correction takes advantage of the notion that voxel-wise extrema resulting from TAI are more likely to be spatially

contiguous than extrema resulting from chance. Next, the ICBM-152 Johns Hopkins White Matter Atlas³⁵ was used to define 28 ROIs in an automated fashion (Table 1; Fig. 1). For each region, the frequency of injury across the population was calculated. A region was considered to be injured in a particular subject if it contained any abnormal voxels in the subject's final DisCo-Z injury map. The number of regions containing injury across the population also was calculated.

Finally, to evaluate the relevance of subject-specific DTI assessment to post-traumatic cognitive functioning, we examined the relationship between extent of injury and processing speed. The Processing Speed Index (PSI) from the Wechsler Adult Intelligence Scale-IV was selected as a measure likely to be sensitive to the spatial extent of TAI in TBI.⁴⁰ First, a regression analysis was performed between the PSI standard score and voxel-wise FA within the TBI population using permutation testing with TFCE for

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE TBI AND CONTROL GROUPS

Measures	TBI	Controls	p
N	42	35	-
Age, years (SD)	35 (14.9)	35 (10.3)	1
Number male (%)	29 (69)	26 (74.3)	0.6
Education, years (SD)	13.3 (2.4)	13.2 (2.2)	0.8
PSI (SD)	83 (19.2)	96.6 (16.8)	0.001

TBI, traumatic brain injury; SD, standard deviation; PSI, Processing Speed Index.

TABLE 3. INJURY CHARACTERISTICS FOR THE TBI GROUP

Variable	Distribution in sample (N=42)
Mechanism, n (%) [*]	
Vehicular	30 (71)
Fall	9 (21)
Intentional injury	2 (5)
Initial GCS in ED (M/SD) ^{**}	9.8 (4.2)
TFC, days (M/SD)	8.5 (27.6)
PTA, days (M/SD)	27.6 (21.6)

^{*}Mechanism of injury was unknown for one participant.

^{**}GCS was available for only 27 cases due to intubation or sedation in the ED for 15 cases.

TBI, traumatic brain injury; GCS, Glasgow Coma Scale; ED, emergency department; M, mean; SD, standard deviation; TFC, time to follow commands; PTA, post-traumatic amnesia.

multiple comparison correction. Correlations were deemed significant if the corrected p was <0.05 . Then, to examine the utility of individual DisCo-Z maps in predicting post-traumatic deficits, we performed a receiver operating characteristic (ROC) curve analysis for identification of TBI patients with impaired processing speed, defined as <1.5 SD below the control group mean, a commonly used cutoff for determining impairment on neuropsychological tests. For this analysis the total number of abnormal voxels in each subject's DisCo-Z map is extracted and square root transformed to improve normality.²⁰ Classification accuracy of the DisCo-Z measure was compared with that of FA measurements in ROIs commonly used to index severity of TBI by assessing the area under the ROC curve. Comparison ROIs including sub-regions of the corpus callosum, sub-regions of the corona radiata, superior longitudinal fasciculi, and posterior limbs of the internal capsules. Lastly, we assessed classification accuracy of subject-specific DTI analysis while controlling for age and focal lesion volume by repeating the ROC analysis after regressing the effects of these covariates from the DisCo-Z measure.

Results

Demographic and clinical characteristics of the TBI and control groups are listed in Table 2. There were no significant demographic differences between groups. Processing speed at 3 months following injury was significantly reduced in the TBI group, compared with controls ($p < 0.001$). Injury characteristics for the TBI group are displayed in Table 3, which shows that the majority were due to vehicular incidents. The severity indices shown in Table 3 confirm that the sample, overall, had sustained severe TBI. The mean value of the GCS score is likely a significant underestimate of overall severity, as 15 values were missing due to acute intubation and/or sedation. Three participants with TBI required acute surgical intervention (craniotomy or craniectomy).

Group-wise differences in FA and the TBI-subject overlap map are displayed in Figure 2. Voxel-wise comparison of FA at the group level demonstrated widespread reductions in FA among the TBI group ($p < 0.05$, TFCE-corrected; Fig. 2, top row). The corresponding T-map for the group-wise contrast of control FA $>$ TBI FA depicts strong group-level effects throughout the majority of white matter (Fig. 2, middle row). The threshold-weighted overlap map for the TBI group demonstrated generally low inter-individual consistency of effects (Fig. 2, bottom row), with a majority of voxel-wise OM values in the TBI group falling within the null distribution (Fig. 3). Visual comparison of the TBI group overlap map with the group-level T-map indicated regions of strong and statistically-significant effects at the group level which corresponded to low consistency on overlap map, particularly in more peripheral aspects of white matter (Fig. 2). In contrast, a relatively higher level of inter-individual consistency was observed among TBI subjects in certain regions such as the corpus callosum and orbitofrontal white matter (Fig. 2, bottom row). Overlap maps computed separately in TBI subjects with impaired processing speed revealed strikingly higher consistency of injury in the corpus callosum and orbitofrontal white matter (Fig. 4). In

FIG. 2. Result of voxel-wise whole-brain white matter fractional anisotropy (FA) comparison between the traumatic brain injury (TBI) and control groups (top row), depicting widespread regions of significantly lower FA in the TBI group ($p < 0.05$, threshold-free cluster enhancement-corrected). The t -map corresponding to group-level comparison ($t > 0$ for the contrast of control $>$ TBI) depicts strong group-wise effects throughout a large extent of white matter (middle row). The threshold-weighted overlap map, computed in the TBI sample, however, depicts a more spatially specific pattern of individual-level effects (bottom row). Display thresholds for both the t -map and the overlap map are from 0 to 75% of the maximum voxel-wise value. Color image is available online at www.liebertpub.com/neu

FIG. 3. Overlapping histograms of voxel-wise overlap map (OM) values in both the traumatic brain injury (TBI) and control samples, depicting that the majority of OM values in the TBI group fall within the null distribution. Color image is available online at www.liebertpub.com/neu

contrast, TBI subjects without impaired processing speed demonstrated a much more inconsistent injury pattern (Fig. 4).

Imposing the single threshold ($|\text{DisCo-Z}| > 2$) on the individual DisCo-Z maps provided a visual representation of variation in spatial distribution and extent of injury patterns among individual subjects within the TBI group. Representative individual subject maps are depicted by Figure 5. Foci of reduced FA in individual subjects were observed both in white matter directly underlying regions of cortical encephalomalacia, as well as in regions distant from areas of focal lesions.

Using individual DisCo-Z maps to evaluate region-by-region frequency of damage across the TBI group demonstrated a similar pattern to the TBI overlap maps, with wide variation in the frequency with which a particular region contained damage in TBI subjects (Fig. 6; Table 4). Specific regions varied from 10–79% in the frequency with which they were injured across TBI subjects at this threshold. The most consistently damaged region in the TBI population was the genu of the corpus callosum. Considering the corpus callosum as a whole, however, revealed evidence of damage

in 90% (38/42) of TBI subjects. Similarly, evaluation of individual subjects revealed wide heterogeneity in the number of regions injured, ranging from 0 to 82% (23/28).

Voxel-wise regression of FA data with processing speed across the TBI group demonstrated widespread direct correlation between FA and PSI over a large spatial distribution (Fig. 7). In total, 12 of 42 (29%) TBI patients were classified as having impaired processing speed. In ROC curve analysis, classification accuracy for impaired processing speed was highest for the DisCo-Z summary statistic with an area under the ROC curve (AUC) of 0.94, suggesting high classification accuracy (Fig. 8). After controlling for the effects of focal lesion volume and age, we found that the DisCo-Z summary statistic remained an accurate classifier (AUC = 0.88).

Discussion

In this study, we used a subject-specific DTI analytic approach to investigate the degree of inter-individual variation in patterns of TAI associated with moderate-to-severe TBI in the absence of large focal lesions. Consistent with our hypothesis, there was a substantial degree of variability in both the spatial distribution and extent of injury across the TBI population. While it has typically been assumed that TBI is associated with a heterogeneous pattern of white matter injury, surprisingly few studies have directly evaluated this question, and those have been focused on mild TBI.¹⁴ Our findings in a more severely injured sample, selected for predominantly diffuse injury and assessed at a consistent time-point, provide new and strong evidence in support of the notion that, at least in relative terms, the distribution of TAI is widely variable. Further, by assessing consistency over a range of thresholds, our findings carry the additional strength of being robust to the issue of using an arbitrary threshold to define abnormality. These results underscore the importance of addressing inter-subject variation in neurobiological manifestations of TBI not only in studies applying DTI but any neuroimaging investigation in TBI. Understanding the sources and consequences of inter-subject variation may lead to improved statistical power for identifying and characterizing brain injury-behavior relationships.

We observed widespread statistically significant group differences in FA between the TBI and control groups, consistent with a wealth of previous investigations.^{11,41} Interestingly, however, such widespread group differences were present despite relatively low levels of inter-individual consistency of injury patterns. These findings suggest that group differences may be detected when spatially-coherent injuries are present in only a few subjects within the TBI sample and further, that spatially specific effects are sparse at the individual subject level. Accordingly, our results also underscore that group-level effects are not necessarily reflective of effects in each subject with TBI, particularly with regard to a specific spatial pattern of injury. Thus, focusing on any specific region or subset of regions within the brain risks underestimating the number of individuals with damage.

Employing the overlap mapping approach to assess the aggregate effects of TBI on white matter revealed that, despite the degree of spatial heterogeneity, there were certain regions with substantially more consistent damage across the sample, notably the corpus callosum and orbitofrontal white matter. The corpus callosum in

FIG. 4. Threshold-weighted overlap map computed selectively among traumatic brain injury patients with impaired processing speed (top row), demonstrating much higher inter-individual consistency of injury patterns, compared with traumatic brain injury patients without impaired processing speed (bottom row). Particularly high consistency values are present in the corpus callosum and orbito-frontal white matter in the impaired group. Color image is available online at www.liebertpub.com/neu

FIG. 5. Individual-subject distribution-corrected Z-score (DisCo-Z) maps within five representative traumatic brain injury subjects, with areas of white matter injury displayed via a color overlay map superimposed on each subject's T1-weighted structural image. Individual subject maps demonstrated wide inter-individual variability in injury patterns. While some regions of traumatic axonal injury (TAI) were detected directly underlying regions of focal encephalomalacia (white arrow), most TAI lesions did not correspond to focal lesions evident on conventional structural imaging. Color image is available online at www.liebertpub.com/neu

FIG. 6. Twenty-eight regions of interest derived from the Johns Hopkins White Matter Atlas overlaid on a template brain in standard space and color-coded according to the frequency with which the region was injured across the traumatic brain injury group. The most frequently injured regions were the sub-regions of the corpus callosum and the anterior corona radiata. Color image is available online at www.liebertpub.com/neu

particular is thought to be particularly vulnerable to rotational shearing forces given its close interface with dura matter,⁴² and has been strongly implicated in numerous imaging and pathological studies of head trauma.^{4,43,44} An alternative explanation for this predilection could be a detection bias introduced by reliance upon the tensor model of diffusion, which most accurately reflects white matter structure in large, unidirectional bundles of white matter.⁴⁵ The lack of consistent findings in other large white matter tracks in our data such as the left internal capsule, however—in addition to the identification of higher consistency values within the orbitofrontal white matter, a region with lower normal FA values due to higher complexity of white matter architecture—⁴⁶ argue for anatomical vulnerability rather than detection bias as the primary basis

for these findings. Vulnerability of the orbitofrontal white matter in particular may be explained by a combination of shearing forces, implicated in the pathobiology of axonal injuries at the gray–white junction,⁴⁷ and a strong predilection for direct impacts to the overlying orbitofrontal cortex.⁴⁸

With regard to the relation of white matter injury to cognitive processing speed, our approach contrasts with prior reports that have typically used ROI-based or tract-based DTI measures within specific regions such as the corpus callosum or superior longitudinal fasciculus¹¹ to index individual severity of TBI. Instead, we mapped the spatial extent of injury in individual subjects without an *a priori* spatial hypothesis. ROC curve analysis indicated that certain regions with relatively higher consistency of injury across

TABLE 4. FREQUENCY OF INJURY OF EACH ROI ACROSS THE TBI SAMPLE DEPICTING SUBSTANTIAL VARIATION ACROSS ROIS, WITH THE MOST FREQUENTLY INJURED REGIONS BEING THE SUB-REGIONS OF THE CORPUS CALLOSUM

Region of interest	Frequency	Region of interest	Frequency
Genu of corpus callosum	0.79	Superior corona radiata (left)	0.55
Body of corpus callosum	0.76	Superior longitudinal fasciculus (left)	0.55
Splenium of corpus callosum	0.76	Anterior limb Internal capsule (left)	0.52
Anterior corona radiata (left)	0.74	Cingulum bundle (left)	0.45
Anterior corona radiata (right)	0.74	External capsule (left)	0.45
External capsule (right)	0.67	Middle cerebellar peduncle	0.40
Superior corona radiata (right)	0.64	Posterior limb internal capsule (left)	0.38
Superior longitudinal fasciculus (right)	0.64	Cerebral peduncle (left)	0.33
Posterior limb internal capsule (right)	0.62	Superior cerebellar peduncle (right)	0.21
Superior corona radiata (left)	0.62	Superior cerebellar peduncle (left)	0.19
Posterior corona radiata (right)	0.60	Lower cingulum (right)	0.14
Anterior limb internal capsule (right)	0.55	Inferior cerebellar peduncle (left)	0.12
Cingulum bundle (right)	0.55	Inferior cerebellar peduncle (right)	0.12
Cerebral peduncle (right)	0.55	Lower cingulum (left)	0.10

ROI, region of interest; TBI, traumatic brain injury.

FIG. 7. Result of voxel-wise linear regression of fractional anisotropy (FA) with Processing Speed Index within the traumatic brain injury sample, depicting widespread regions of significant direct correlation (regions where lower FA is correlated with lower Processing Speed Index score, indicating slower processing speed); $p < 0.05$, threshold-free cluster enhancement–corrected. Color image is available online at www.liebertpub.com/neu

the TBI group were relatively more accurate in classification of those subjects with impaired processing speed. Importantly, however, the individual-level mapping approach conferred a classification advantage over single ROI measures, and was highly accurate even after controlling for the effects of age and focal lesion volume. The broad spatial dependence of processing speed in the TBI group evidenced by voxel-wise regression analysis suggests the basis of this classification advantage is the ability of the DisCo-Z method to account for spatially heterogeneous injury patterns.

Further, the injury overlap map computed separately among TBI subjects with impaired processing speed demonstrated higher consistency values distributed throughout a large extent of white matter relative to TBI subjects without impaired processing speed, supporting this notion. The strikingly high consistency values of the corpus callosum and orbitofrontal white matter among the impaired processing speed group, however, may suggest that these regions have relatively greater importance. These findings are in accordance with existing literature, which suggests that cognitive processing speed depends on a wide range of white matter architecture.⁴⁹ The corpus callosum, however, has been consistently implicated in the pathophysiology of impaired processing speed in

TBI and other disorders,^{4,50,51} potentially owing to high degree of connectivity and central role in interhemispheric communication.⁵²

Taken together, these results suggest that the DisCo-Z analytic approach provides clinically relevant information about the spatial extent of injury within individual subjects, and can provide novel, complementary information to traditional group-level analytic approaches. Personalized injury maps provide intuitive data visualization, and can be readily interpreted for understanding the extent and distribution of injury in the context of an individual patient. Employing this approach in future studies of TBI will be important for explaining clinically heterogeneous patterns of cognitive sequelae following TBI. Further, this approach provides a route by which DTI and other neuroimaging biomarkers could be adapted to better stratify injury severity and inform prognostic assessment in clinical practice. Provided the assembly of a normative database under identical scanning conditions, as well as oversight to ensure data quality and fidelity of processing, such an automated approach, is potentially suitable for implementation in clinical settings.

Limitations of the current study should be borne in mind when interpreting these results. In particular, findings may not generalize to TBI with both TAI and large focal lesions, since patients with the

FIG. 8. Result of receiver operating characteristic curve analysis for classification of traumatic brain injury subjects with significantly impaired processing speed. The most accurate classifier was the distribution-corrected Z-score (DisCo-Z) cluster volume measure, which achieved high classification accuracy (area under the curve = 0.94). Color image is available online at www.liebertpub.com/neu

latter were excluded. In addition, for practical reasons, we excluded patients who were too agitated, restless, or claustrophobic to tolerate MRI scanning at 3 months post-TBI, or who were incapable of behavioral testing at that interval. Thus, generalization to more severely injured or slow-to-recover patients is uncertain. For this investigation, we chose to focus solely on FA as it is by far the most commonly used surrogate imaging measure of TAI.⁴ Nonetheless, it is possible that similar analysis on alternative DTI metrics would yield additional important insights into microstructural effects of TBI. The degree to which alternative DTI measures offer complementary or redundant information in TBI is an important area for future research.

Conclusion

We demonstrated that even in moderate-to-severe TBI, there is a substantial degree of inter-subject variation in both the extent and spatial distribution of TAI, which is strongly correlated with post-traumatic deficits in processing speed. Our results suggest that individual-level DTI analysis can complement traditional group-wise approaches to DTI analysis by better taking into account inter-subject variability. Employing such an approach in future neuroimaging studies of TBI not limited to DTI may substantially improve the ability to detect and classify patterns of injury, thereby allowing for a more thorough understanding of brain injury-clinical variability following TBI.

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Author Disclosure Statement

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