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TITLE: High Resolution Diffusion Tensor Imaging of Cortical-Subcortical White Matter Tracts in TBI

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14. ABSTRACT
Patients with TBI present with variable degrees of chronic neurobehavioral deficits, defined as disturbances of cognition, mood, and behavior, which interfere with a return to their previous level of function and quality of life. Current clinical assessments of TBI rely on various cognitive tests and especially on patient self-report. However, self-report of injury variables such as loss of consciousness and post-traumatic amnesia tend to be inaccurate and are unreliable. In addition, while standard neuropsychological testing of cognitive function can reliably assess moderate to severe TBI, it lacks the sensitivity for milder TBI. Given that even mild TBI can result in sustained neurobehavioral deficits years after the injury it is crucial to develop objective and quantifiable methods of assessing the neuropathology in TBI in order to better diagnose, treat, and assess the long term outcomes of TBI of all severities. Diffusion tensor imaging (DTI) has recently shown promise for the evaluation of neuropathology in patients with mild to moderate TBI. While still inadequate in evaluating individual patients, further refining of DTI techniques could provide the needed sensitivity and specificity to facilitate clinically accurate diagnosis.

15. SUBJECT TERMS- Traumatic brain injury, magnetic resonance imaging, human subjects, diagnostic assessment

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1. **INTRODUCTION:**

Disruption of function secondary to traumatic brain injury (TBI) is believed to be due in large part to shear and strain forces that often occur with TBI (Graham, Gennarelli et al. 2002). These injuries result in neuropathology identified as diffuse or traumatic axonal injury. Such injury can disrupt critical cortical-subcortical pathways and lead to widespread cognitive dysfunction (Gennarelli, Thibault et al. 1982; Povlishok 1992). The purpose of the research was to test the overall hypothesis that TBI does result in damage to the subcortical networks and that damage to these networks is responsible in part for sustained cognitive impairment. To test this overall hypothesis we applied high resolution diffusion tensor magnetic resonance imaging (DTI) to characterize the integrity of white matter tracts in the human brain in adults between the ages of 18 and 60 with and without a history of single, closed head TBI of either mild or moderate to severe injury. The primary findings from the funded research included establishing a strong relationship between damage to thalamic fiber projects and cognitive function, establishment of a relationship between verbal learning (the primary complaint of our research participants) and white matter integrity in the tracts connecting frontal and temporal regions of the brain, and findings of atrophy even in those patients who reported being fully recovered. The research is important both in terms of the relationship between damage to white matter tracts and function but also for implications of traumatic brain injury on long term health.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Traumatic brain injury, concussion, diffusion tensor imaging, atrophy, white matter integrity, thalamus

3. **OVERALL PROJECT SUMMARY:** Summarize the progress during appropriate reporting period (single annual or comprehensive final). This section of the report shall be in direct alignment with respect to each task outlined in the approved SOW in a summary of Current Objectives, and a summary of Results, Progress and Accomplishments with Discussion. Key methodology used during the reporting period, including a description of any changes to originally proposed methods, shall be summarized. Data supporting research conclusions, in the form of figures and/or tables, shall be embedded in the text, appended, or referenced to appended manuscripts. Actual or anticipated problems or delays and actions or plans to resolve them shall be included. Additionally, any changes in approach and reasons for these changes shall be reported. **Any change that is substantially different from the original approved SOW (e.g., new or modified tasks, objectives, experiments, etc.) requires review by the Grants Officer's Representative and final approval by USAMRAA Grants Officer through an award modification prior to initiating any changes.**

The project summary, as requested, includes a reporting of work accomplished with reference to the statement of work. Where appropriate when the statement of work is related to scientific findings, methods, results, and discussion of those findings are included. This section is organized with respect to the original statement of work. This statement was not revised during the project period. Study hypotheses and aims are

included below and underlined so that the specific technical work product can be reviewed within the context of the research aims. The grant was carried out over 3 years.
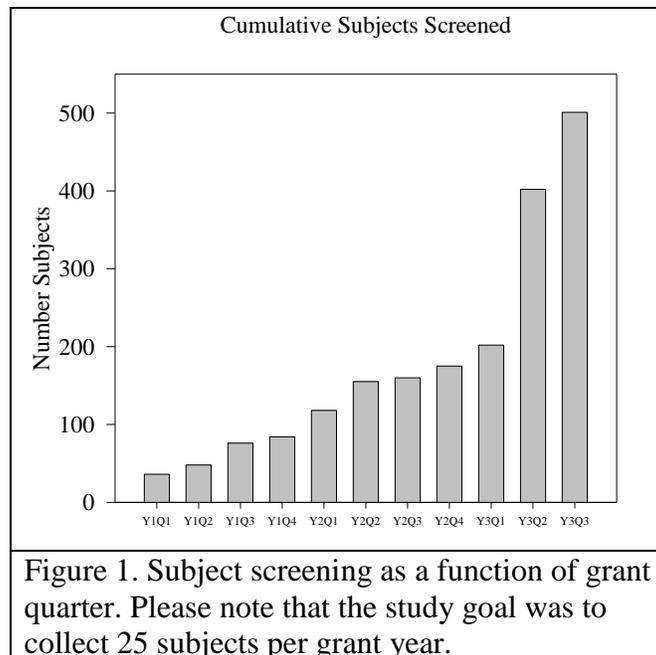
Year 1, Items 1-2
1. **Complete all required administrative approvals and university approvals for the initiation of new research.**
2. **Obtain human subjects approval through the DOD.**

Human subjects approvals at both the institutional and HRPO levels of review were in place within the first quarter of the project. These remained in place until the grant was completed. The IRBs were closed to recruitment in August of 2011.

Year 1, Item 3; Years 2-3, Item 2. Begin (Year 1) and continue (Years 2-3) subject recruitment including talks by the PIs to local brain injury groups, patient advocacy groups and other physicians.

All subject recruitment goals were met and the final numbers of subjects recruited, consented, and who participated in all parts of the research met the overall goals of the SOW. We did have a period of slow recruitment during Year 2 and took corrective action by increasing our recruitment processes from community talks by the PI, advertisements on Craig's List and through the University email system to also include placing advertisements on the public transportation systems (both bus and subway) within the greater Chicago area. These efforts resulted in a dramatic increase in the number of subjects screened (at study end more than 400 subjects were screened). These large numbers were required due to study inclusion and exclusion criteria. The exclusion criterion that resulted in the largest numbers of subjects excluded with items related to past medical history, past psychiatric history, past and current drug use, and history of litigation.

Figure 1. Subject screening as a function of grant quarter. Please note that the study goal was to collect 25 subjects per grant year.

Year 1, Item 4. Hire a research assistant.
This was completed in the first quarter of year 1 and this position remained filled until all data collection had been completed.

Year 1, Item 5. Finalize the imaging protocol and complete quality assurance testing prior to the first subject.
The imaging protocol was optimized and established within the first quarter of Year 1. The final imaging protocol included a calibration scan (ASSET) collected in the axial plane with a repetition time of 150ms, a echo time of 2.1ms, a 30cm field of view and a imaging matrix of 32 x 32. A total of 40 slices were collected each having a width of 6mm. No gap was included between slices. This calibration allowed for parallel imaging. Following the calibration scan, a fluid attenuated inversion recovered imaging (FLAIR) sequence was collected to allow characterization of white matter lesions. The FLAIR sequence was collected in the axial plane with a repetition time of 10s, a echo time of 160ms, a $22cm^2$ field of view and a imaging matrix of 352 x 192. A total of 27 slices were collected each having a width of 4mm. To allow full brain coverage and to reduce artifacts, a 1mm gap was introduced between each slice. Following the FLAIR, a T1 weighted fast inversion recovered spoiled gradient scan was collected. This T1 SPGR was collected to allow 3D reconstruction and visualization of brain structures and was collected in all three planes (axial, coronal, sagittal). Each was collected with a repetition time of 13.8ms, a echo time of 4.3ms, a 25° flip angle, a $22cm^2$ field of view with ¾ phase encoding and a imaging matrix of 512 x 192. An inversion preparation time of 300 ms was also used for all three SPGRs. These sequences were collected to support study Aim 1 (to characterize and quantify neuropathology in frontal, temporal, and basal ganglia regions in chronic TBI using both diffusion tensor imaging and structural magnetic resonance imaging). These data were also needed to support Aims 1-3 by allowing reconstruction of the diffusion tensor imaging data. A total of 120 slices were collected each having a width of 1.5mm and no gap between slices. Three diffusion tensor imaging sequences were collected to support the primary aims of the grant (to characterize white matter integrity). These three sequences were identical in repetition time (4500ms) and echo time (80ms) and a 20cm field of fiew. To assess subcortical structures, the diffusion tensor sequence utilized a narrow slice thickness (3mm) with a 1mm gap and high resolution (matrix = 256x192). A whole brain dataset (slice thickness = 5mm; matrix= 128 x 128) was collected to examine u fibers and cortico-cortico fibers in support of Aims 1 (to characterize and quantify neuropathology in frontal, temporal, and basal ganglia regions in chronic TBI using both diffusion tensor imaging and structural magnetic resonance imaging), 2 (to characterize white matter integrity of the cortical-subcortical fibers connecting basal ganglia and frontal regions using fiber tractography), and 3(to characterize the role of short-range (cortical u-fibers), as compared to long-range WM fiber tract integrity in TBI). Finally, and consistent with the research plan, a T2 weighted fast spin echo sequence (repetition time = 5000ms, a echo time of 102ms, a $22cm^2$ field of view, using a slice thickness = 4mm and a imaging matrix of 512 x 288) and a gradient recalled echo sequence (repetition time = 475ms, a

echo time of 15ms, a 22cm^2 field of view, using a slice thickness = 3mm and a imaging matrix of 512 x 192) were collected to visualize pathology and any residual blood product.
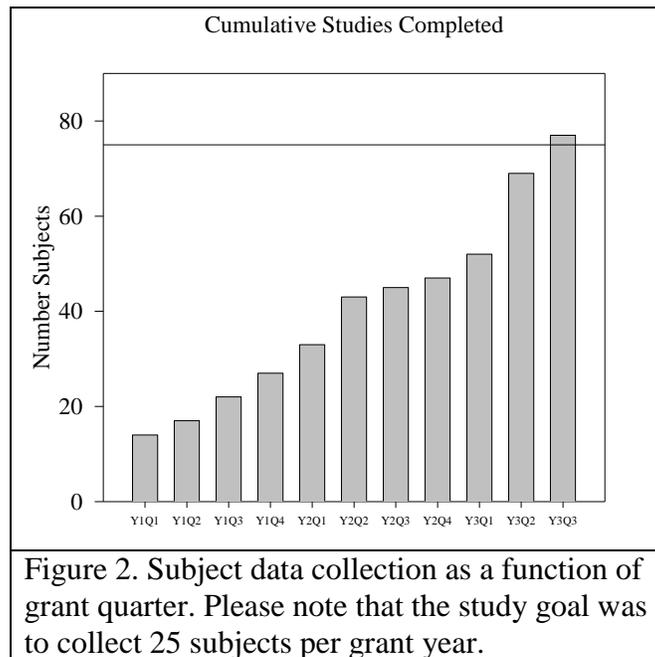
The quality assurance protocol was also established in the first grant quarter and included collection of phantom data with imaging parameters for the high resolution diffusion sequence including repetition time (4500ms) and echo time (80ms) and a 20cm field of fiew with a narrow slice thickness (3mm) and 1mm gap at high resolution (matrix = 256x192).

Year 1, Item 6. Recruit and test 25 subjects.
Year 2, Item 3. Recruit and test 25 subjects.
Year 3, Item 3. Recruit and test 25 subjects.

In year 1 and year 3, all data collection goals were met. In year 2, we only collected data on 23 of the 25 proposed subjects. Our increased recruitment efforts detailed above however in Year 3 allowed us to meet the overall aim of 75 subjects by the 3rd quarter of the final year. The horizontal line included in Figure 2 represents the overall study goal of 75 subjects. Please note that a total of 78 subjects were actually collected as two sets of data were excluded due to excessive head motion.

Figure 2. Subject data collection as a function of grant quarter. Please note that the study goal was to collect 25 subjects per grant year.

In the final sample, a total of 25 healthy controls (this met the stated study goal), 25 mild severity TBI (this met the stated study goal), and 26 moderate to severe TBI (the stated goal was for a sample size of 25) were collected. A breakdown of key demographic and injury data is presented in Table 1.

Table 1. Demographic and Injury Data for Final Sample			
	Control	Mild TBI	Moderate TBI
Gender (%M)	76	60	46%
Marital status (% single; % married; % divorced)	88,12,0	84,16,0	61,30,8
Endorsement of cognitive complaints (% yes)	0	28.0	30.8
Endorsement of behavioral complaints (% yes)	0	8	15.4
Return to Work/School (% Yes)	NA	96	100
Work/School at Evaluation (% Yes)	NA	56	96
Work/School at TBI (%Yes)		100	100
Age at Evaluation Mean(SD)	23.72 (3.14)	24.88 (5.42)	34.9231 (12.40)
No. Years Education Mean(SD)	16.48 (2.21)	15.56 (1.87)	16.7692 (2.14)
Age at Injury Mean(SD)			18.04 (7.15)
Chronicity of Injury (months) Mean(SD)			87.72 (72.31)
Beck Depression Inventory (total) Mean(SD)	4.16 (5.28)	7.36 (6.53)	8.23 (6.43)
Mini Mental State Exam (total) Mean(SD)	29.68 (0.63)	29.52 (0.71)	29.54 (0.81)

For the mild TBI the top three causes of injury were 8% were injured due to motor vehicle accident, 12% as a pedestrian injury secondary to motor vehicle accident, and 56% via athletic injury. The moderate severe TBI also reported the primary causes of injury as due to motor vehicle accident (39%) and sports related injury (31%).

Year 1, Item 7. Begin work on analysis protocols using these first 25 subjects as models. This will include a review of the literature to assess any new work that might highlight additional anatomical targets which have come to light since the grant application

The analytic methods required were designed to support the study Aims and allow testing of the study Hypotheses. The funded Aims and Hypotheses are included below.

The **specific aims** of the research were:
1. To characterize and quantify neuropathology in frontal, temporal, and basal ganglia regions in chronic TBI using both diffusion tensor imaging and structural magnetic resonance imaging;
2. To characterize white matter integrity of the cortical-subcortical fibers connecting basal ganglia and frontal regions using fiber tractography;
3. To characterize the role of short-range (cortical u-fibers), as compared to long-range WM fiber tract integrity in TBI;
4. To characterize cognitive function in chronic TBI using a neuropsychological test battery focused on executive function and attention.

These aims will allow us to test our **specific hypotheses** that:
1. TBI results in permanent changes to the cortical white matter microstructure when compared to healthy controls when assessed with fractional anisotropy;
2. Cortical u-fibers are resistant to milder brain injuries but show reduced integrity in more moderate injuries;
3. TBI patients with disrupted cortical-subcortical connections will demonstrate greater cognitive impairment than TBI patients with reduced cortical white matter integrity but without disrupted cortical-subcortical connections;
4. White matter integrity as assessed with the proposed high-resolution sequence is more sensitive to changes in cognition than standard diffusion tensor sequences and standard structural imaging.

In order to support Aim 1, whole brain diffusion tensor imaging data required reconstruction, conversion to a 4D data set (x, y, z, diffusion directions), coregistration with the T1 weighted image, normalization, creation of white matter masks for each tract, and extraction of the DTI values (fractional anisotropy was the primary dependent variable). These methods were not altered from the original grant and are described in detail in a publication from my laboratory (Kraus, Susmaras et al. 2007). This publication is included as Appendix 1. A brief description follows.

The 28 diffusion directions, along with the B0 image, were used to calculate the fractional anisotropy (FA). The images were reconstructed and data calculated using DTI Studio (Wakana, Jiang et al. 2004). For quality assurance, each set of data was examined for image quality and head movement. Head movement was required to be within one voxel across the image acquisition. For this study, and because of the lower signal to noise ratio that comes with increased spatial resolution, a background noise level was evaluated and determined based upon these first 25 subjects and was set as 100 arbitrary MRI units. The data were then read into Statistical Parametric Mapping software for analysis (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) allowing for co-registration with their correspondingT1 weighted anatomic image and normalization to the Montreal Neurological Institute (MNI) template. For this study, we calculated FA for all major white matter tracts including the anterior and posterior corona radiata (respectively, ACR and PCR), cortico-spinal tracts (CST) which included parts of the cortico-pontine tract and parts of the superior thalamic radiation, cingulum fibers (CG), forceps minor (fMin), forceps major (fMaj), the body, genu, and splenium of the corpus callosum (bCC, gCC, and sCC), the inferior fronto-

occipital fasciculus (IFO), the superior longitudinal fasciculus (SLF), external capsule (ExCap) and the sagittal stratum including the optic radiations (SS). A representative subject's FA map with superimposed ROIs is presented in Figure 3.
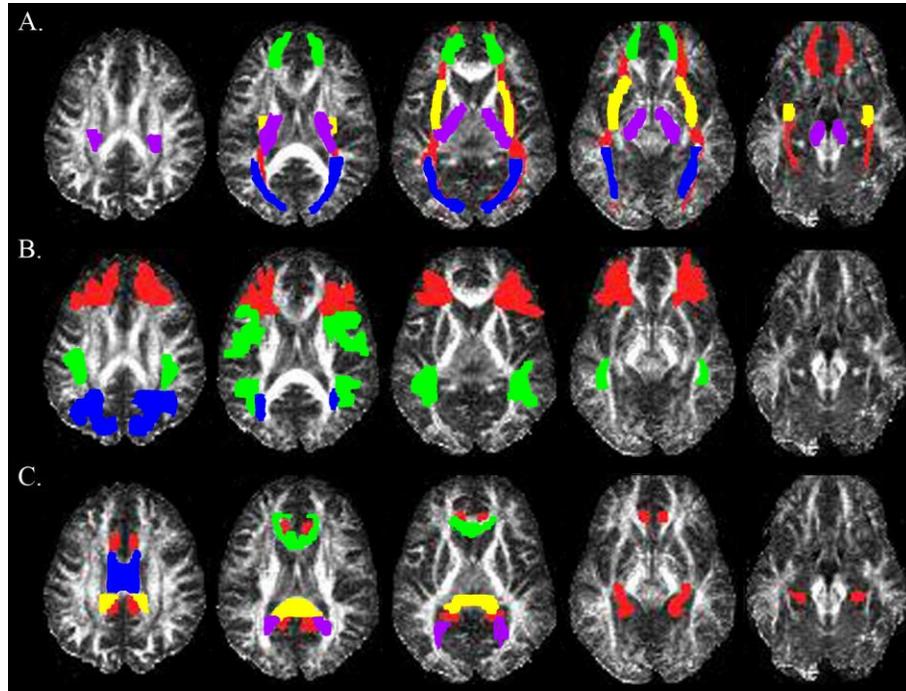

Figure 3. Example region of interest masks for a single representative subject: (A) forceps minor (green), cortico-spinal tract (purple), inferior frontal-occipital fasciculus (red), external capsule (yellow), sagittal stratum (blue); (B) anterior corona radiata (green), superior longitudinal fasciculus (red), posterior corona radiata (blue); (C) cingulum (red), corpus callosum body (blue), splenium (yellow), and genu (green), and forceps major (purple).

This data was used, in combination with data from other grants, to support multiple publications directly related to the topic of this grant (Geary, Kraus et al. 2010; Little, Kraus et al. 2010; Geary, Kraus et al. 2011) and those for which healthy control data was used as a comparison into other neurodegenerative populations such as Parkinson's disease (Schulze, Geary et al. 2011; Planetta, Schulze et al. 2013). These TBI publications directly address and support the following specific study hypotheses:

Study hypothesis 1. TBI results in permanent changes to the cortical white matter microstructure when compared to healthy controls when assessed with fractional anisotropy;

In order to examine long term effects of brain injury on white matter we examined fractional anisotropy in the the cortical-spinal tract (CST), anterior corona radiata (ACR), posterior corona radiata (PCR), forceps minor (fMin) and forceps major (fMaj), sagittal stratum (SS),

internal capsule (IC), inferior frontal occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), and in the genu (gCC), body (bCC), and splenium (sCC) of the corpus callosum(Little, Kraus et al. 2010). Separate ROIs were placed in the left and right hemisphere where appropriate.   These ROIs were drawn with reference to the color-coded FA and T2 image for each subject and with reference to a DTI atlas. (Mori, Wakana et al. 2005) Each ROI, with the exception of the external capsule, had an area of 15mm^3. Because of the width of the external capsule, the IC ROI had an area of 10mm^3. The bCC ROI was placed on the slice in which the body of the left and right superior branches of the corpus callosum met in the mid-sagittal slice. On this same axial slice, the ACR, SLF, PCR, and CST were drawn. The CST was placed in the posterior limb 20mm posterior to the edge of the bCC ROI. The ACR was placed 15mm anterior to the intersection of the corpus callosum with the CST. The PCR was placed 15mm posterior to the posterior intersection of the CST and CC. The SFL was placed lateral and anterior to the bCC ROI. The gCC and sCC were placed on the axial slice which clearly showed both the internal and external capsules. These were placed at midline. The IC, EC, and SS were placed on the same axial slice as used for the gCC and sCC in all subjects. The EC was placed in the middle of the posterior aspect of the EC whereas the IC was placed midway (anterior to posterior) between the intersection of the IC and EC at the location where the EC was most lateral to the edge of the brain. Finally, the fMin, fMaj, and IFOF were drawn on the slice through which the anterior commissure was visible on the T2. The fMin was placed anterior and lateral to the boundary of the corpus callosum. The fMaj was placed posterior and lateral to the posterior boundary of the corpus callosum. The IFOF was located lateral and anterior to the fMaj.

Figure 4 shows the results of this analysis. Those with a history of moderate to severe TBI showed reductions in integrity of white matter in the ACR, PCT, fMaj and body of the corpus callosum. Mild TBI did not differ from controls.
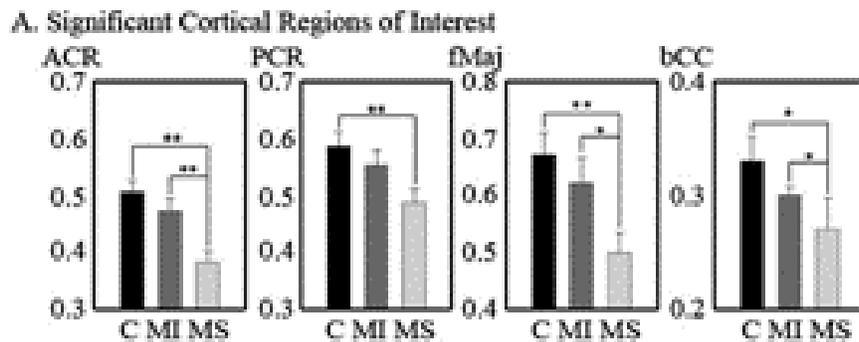

Figure 4. Average cortical and subcortical FA. Significant post-hoc comparisons between groups are indicated (* p<0.05; ** p<0.01).

To further examine the relationship between damage in cortical white matter tracts and cognition we identified the neuropsychological measure most sensitive to the complaints of our patients with mild TBI. More than 80% report a primary complaint of "things being harder to learn". As such, we set out to examine the relationship between chronic damage to white matter and function on the California Verbal Learning Test. In our first publication (Geary, Kraus et al. 2010), we showed that mild TBI patients demonstrated statistically significant differences from age and education matched control participants in performance

on the first trial of a verbal learning task. Performance on this trial was associated with reduced fractional anisotropy in the uncinate fasciculus and the superior longitudinal fasciculus providing an anatomical correlate for the cognitive findings. This is shown in Table 2 below and supported by Appendix 3..

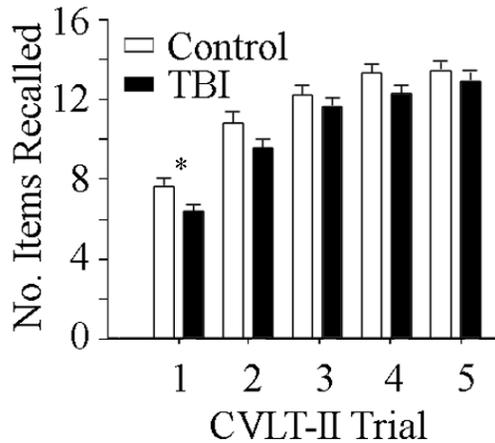|		ACR		PCR		fMin	fMaj	EC	UF		CG	SS	CST	gCC
	Hemisphere	L	R	L	R	L	R	R	L	R	R	L	R	
CVLT	Trial 1					.452**			.336*		.316*			
	Trial 2	.376*	.346*			.419**	.327*							
	Trial 3	.321*												
	Trial 4	.319*				.321*								
	Trial 5													
	List B	.324*	.353*			.446**								.386*
	BDI Raw Score												.323*	
	FrSBe Apathy							.419**		.325*				
	PCSC Total			.416*	.505**			-.355*				.373*		

**p= 0.01 level
*p= 0.05 level

Table 2. Significant Bivariate Correlation in Regions of Interest with Cognitive and Behavioral Variables
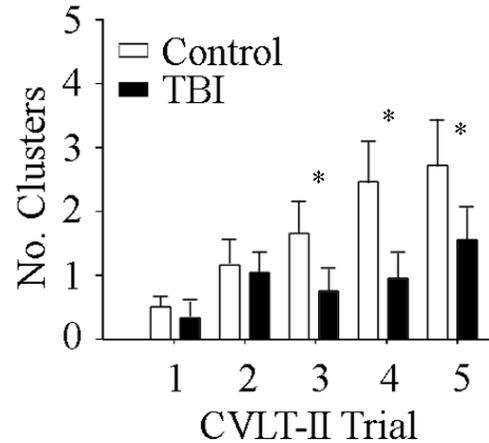
Mild TBI patients were not impaired relative to control participants on total learning or memory composite variables. Performance on the first learning trial was not related to any psychological variables including mood. We concluded that patients with mild TBI demonstrate diminished verbal learning that is not often interpreted in standard neuropsychological assessment.

Given the relevance of this finding to the hypothesis, we further examined the mechanisms that might underlie this cognitive effect. As such, we examined strategy use on the California Verbal Learning Test-Second Edition. Our findings (shown in Figure 5) support the primary hypothesis that mTBI participants under-utilize semantic clustering strategies during list-learning relative to control participants. Despite achieving comparable total learning scores, we posit that the persisting learning and memory difficulties reported by some mTBI patients may be related to reduced utilization of efficient internally-driven strategies that facilitate learning. Given that strategy training has demonstrated improvements in learning and memory in educational and occupational settings, we offer that these findings have translational value in offering an additional approach in remediation of learning and memory complaints reported by some following mTBI.
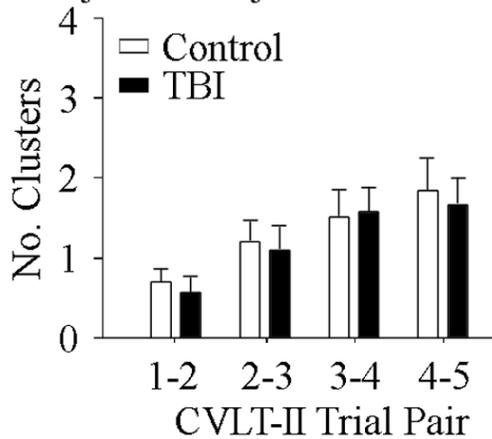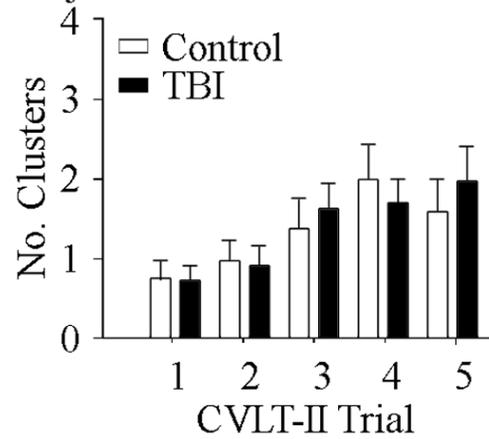
Figure 5. A. CVLT-II raw recall findings across trials one through five for controls and patients with mTBI. Statistically significant difference between groups was only observed on the first learning trial. **B.** Chance adjusted semantic clusters across trials one through five for control and **mTBI** participants. Statistically significant differences between groups were observed on trials three through five. **C.** Chance adjusted subjective clusters scores across trials for control and **mTBI** participants. No statistically significant differences between groups were observed across trials. **D.** Chance adjusted serial clusters across trials one through five for control and **mTBI** participants. No statistically significant differences between groups were observed across trials.

These findings, when taken together, support the hypothesis TBI results in permanent changes to the cortical white matter microstructure when compared to healthy controls when assessed with fractional anisotropy. They further support the hypothesis that such changes in white matter integrity underlie cognitive dysfunction following TBI.

Study hypothesis 2. Cortical u-fibers are resistant to milder brain injuries but show reduced integrity in more moderate injuries;

This hypothesis was not supported. In support of the grant application we examined DTI data was collected from 6 subjects with a history of closed head type TBI; 3 miTBI (Mean Age=31.4, Mean Education = 17.2, Mean Premorbid IQ = 114.3), 3 moTBI (Mean Age=29.7, Mean Education = 15.2, Mean Premorbid IQ = 111.3) who were all at least 2 years from injury and 3 healthy controls (Mean Age=32.1, Mean Education = 16.2 Mean Premorbid IQ = 114.2).
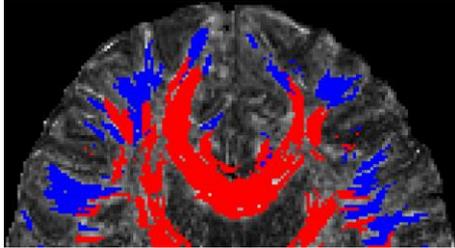

Figure 6.Tractography used to differentiate short and long-range white matter fiber tracts.

We examined FA measurements of short and long range white matter fiber tracts in and around the frontal lobe were carried out on each subject. Briefly, because of the higher resolution and smaller voxel sizes in the higher resolution sequence, tractography was utilized to characterize the branching of the longer-range fibers. To do this, we used seed voxels in the larger fibers and excluded any branch associated with these fibers. Similarly, we used seed voxels in the more lateral regions and around the convexities to identify short-range fibers. We further limited this identification to require that the short-range fibers could not exceed a length of 30mm. Long-range fibers were required to exceed a length of 50mm. Although this analysis did not eliminate the potential of having a branch of a long-range fiber classified as short or of having a short-range fiber classified as long, the majority of short-range fibers are correctly classified as the shorter range U-fibers and the majority of long-range fibers will be a major fiber tract. This conservative approach will allow for calculation of FA in each class of fibers although not all short range fibers will be identified. One sample of this classification is provided in Figure 6.

Results. As can be seen in Figure 6, our seed voxels in larger fibers characterized large white matter fiber tracts (blue) and also the shorter range fibers (red) which are commonly observed more laterally in and around gyri and sulci. We then used this classification as a mask and extracted FA values from these regions. The results

Figure 7. Sample short-range fibers in frontal (A) and parietal (B) lobes and FA for each subject (small symbols) in the long-range and both regions of short-range fibers. The group means are shown by the large symbols. Controls are presented in black, miTBI in red, and moTBI in green.

of these classifications for our final sample of 75 subjects is presented in figure 7. In contrast to our preliminary data, there were no differences in white matter integrity between short and long fibers. We are at present attempting to investigate the mechanism behind this finding.
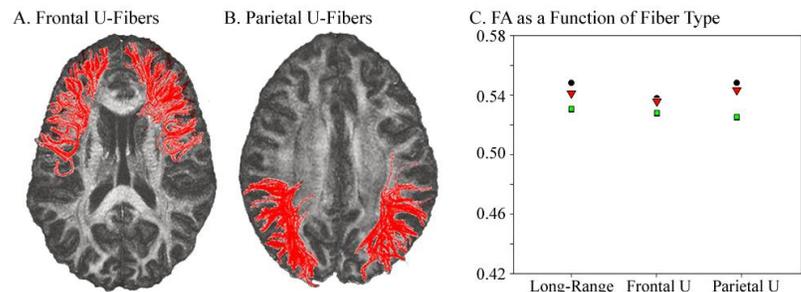
Study hypothesis 3. TBI patients with disrupted cortical-subcortical connections will demonstrate greater cognitive impairment than TBI patients with reduced cortical white matter integrity but without disrupted cortical-subcortical connections (Little, Kraus et al. 2010).

It is important to note that a publication from our group is dedicated to reporting the results of this hypothesis. The objective of the study was to characterize the relationship between of damage to thalamic projection fibers and cognitive impairment in patients with traumatic brain injury (TBI). The motivation for the grant and study was based upon the finding that impairments of executive function are common in many neurologic and psychiatric populations (brain injury, certain frontal lobe function) and that traumatic brain injury (TBI) is commonly associated with impairments in cognition and behavior, which are known to depend upon frontal lobe structure and function. However, there is often an absence of observable structural changes in the frontal lobe that could account for the magnitude or extent of or presence of observed cognitive and behavioral changes. This dissociation led us to test the hypothesis that executive dysfunction in TBI is due in large part to damage to thalamic projection fibers involved in frontal-subcortical networks. This hypothesis was tested using diffusion tensor imaging in 24 TBI patients and 12 age- and education- matched controls.

Details in the methods that were validated during this portion of the scope of work can be found in Appendix 2.

For the results, TBI was found to be associated with integrity of white matter tract thalamic fibers and projection fibers from the anterior and ventral anterior nuclei.

Figure 8. Average subcortical FA. Mean FA extracted from the thalamus and from fibers identified from seed regions in the AN and VA Significant post-hoc comparisons between groups are indicated (* $p<0.05$; ** $p<0.01$).

Importantly, fractional anisotropy in fibers from the anterior and ventral lateral thalamic nuclei but not from cortical regions (including those in the frontal lobes) was associated with deficits in executive function suggesting that thalamic integrity should be further investigated as a mechanism underlying impairment. This is shown in Figure 9.

a. Scatterplots between Executive Domain Scores and Thalamic Nuclei

Executive and AN   Executive and VA   Executive and VL

Domain Score

b. Scatterplots between Attention Domain Scores and Thalamic Nuclei

Attention and AN   Attention and VA   Attention and VL

Domain Score

c. Scatterplots between Memory Domain Scores and Thalamic Nuclei

Memory and VPL

Domain Score

Figure 9. Relationship between thalamic FA and cognition. Scatterplots of FA from thalamic seed voxels relative to executive (A), attention (B), and memory (C) domain scores for TBI patients. Best-fit lines are indicated in gray. Unfilled circles represent mild TBI while filled circles represent moderate to severe TBI.

Year 1, Item 8. Carry out quality assurance testing on all image data that is acquired.
It is important to note that although continuous quality assurance analysis was carried out throughout the grant on a frequency of no less than once per month this continued analysis was not specifically listed in the SOW. As such, we report those findings within this specific task.

The quality assurance protocol proved valuable three times in the first year when changes in signal intensity and nyquist ghost were identified leading to service calls. These data for the course of the grant are presented in Figure 3. As can be seen we collected data as proposed one time per month. In months where problems were noted a second or third QA protocol was run to ensure the scanner had indeed been fixed. As can be seen the overall mean signal and ghost are quite stable with these exceptions noted. As such, there are no concerns with the data.
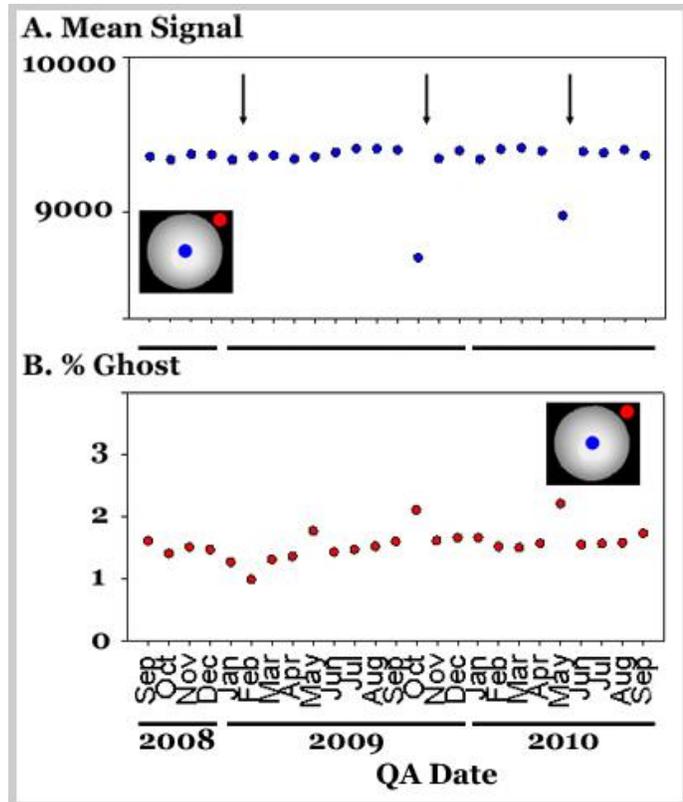

Figure 3. Quality assurance data on the scanner and coil including mean signal and percent nyquist ghost.

Year 2-Year 3, Task 1. Complete and obtain all continuing approvals for human subjects research.

This was maintained throughout the grant and documentation provided to HRPO.

3. **KEY RESEARCH ACCOMPLISHMENTS:** Bulleted list of key research accomplishments emanating from this research. Project milestones, such as simply completing proposed experiments, are not acceptable as key research accomplishments. Key research accomplishments are those that have contributed to the major goals and objectives and that have potential impact on the research field.

- Demonstration of a chronic alteration in white matter integrity even in chronic mild, single injury TBI(Geary, Kraus et al. 2010; Little, Kraus et al. 2010; Geary, Kraus et al. 2011).
- Demonstration of a predominate damage load of closed head injury on thalamic fibers with a strong relationship to executive function (Little, Kraus et al. 2010).
- Demonstration of a potential underlying mechanism between verbal learning impairments and injury burden (Geary, Kraus et al. 2010) and the offering of a potential mechanism that might allow mediation (Geary, Kraus et al. 2011).
- Although not part of the scope of work, and in combination with data collected to support other research, the in press publication related to single mild and multiple TBI as they

relate to long term chronic atrophy. All but 6 subjects from this grant were included. (Little, Geary et al. in press)

4. **CONCLUSION:** Summarize the importance and/or implications with respect to medical and /or military significance of the completed research including distinctive contributions, innovations, or changes in practice or behavior that has come about as a result of the project. A brief description of future plans to accomplish the goals and objectives shall also be included.

The results of the work accomplished are significant. First, we have provided data to suggest that there is a central mechanism of cognitive impairment in TBI. If validated by other laboratories this has the potential to change treatment approaches and assessment of treatment validity. Beyond the publication of the work in the thalamus we have also published work that challenges current approaches to neuropsychological testing. Finally, we have recently contributed data to the important question of TBI as a risk factor for neurodegeneration. Our data shows clear atrophy even in those with a history of a single TBI. We have moved into the development of DTI methods and analysis as a diagnostic tool including the development of a turnkey analysis pipeline which is supported by TATRC.

5. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

a. List all manuscripts submitted for publication during the period covered by this report resulting from this project. Include those in the categories of lay press, peer-reviewed scientific journals, invited articles, and abstracts. Each entry shall include the author(s), article title, journal name, book title, editors(s), publisher, volume number, page number(s), date, DOI, PMID, and/or ISBN.

(1) Lay Press:
Dissemination of information on brain injury and imaging on PBS Nova Science Now (2008)
Transcript: http://www.pbs.org/wgbh/nova/transcripts/0306_sciencen.html
Interview: http://www.pbs.org/wgbh/nova/body/brain-trauma.html

Video Series on Pediatric Brain Injury for Educators (2011)
"In Harm's Way: Traumatic Brain Injury in Young Children" Brain Injury Awareness for Head Start Providers; Produced by the New Mexico Aging and Long-Term Services Department (2009)

Video Series on Pediatric Brain Injury for Educators (2011)
"In Harm's Way: Traumatic Brain Injury in Young Children" Brain Injury Awareness for Head Start Providers; Produced by the New Mexico Aging and Long-Term Services Department (2009)

Video Series on Traumatic Brain Injury in Native Americans
"The Critical Link: CHRs & Brain Awareness for Community Health Representatives" Brain Injury Awareness for Community Health Providers;

Produced by the New Mexico Aging and Long-Term Services Department (2009)

Interviews and appearance on WGBH PBS www.teachersdomain.com (2009)
http://www.teachersdomain.org/resource/oer09.sci.life.stru.braintrauma/

Interviews and appearance on Brainline (2010)
http://www.brainline.org/content/2011/02/dr-deborah-little.html
Interviews on pediatric brain injury and magnetic resonance imaging

Dissemination of information on brain injury and imaging on Brainline (2011)
http://www.brainline.org/content/2011/04/neuroimages.html

(2) Peer-Reviewed Scientific Journals:

Planetta M, Schulze ET, Little DM, Vaillancourt DE. Thalamic projection fiber integrity in de novo Parkinson's disease. *American Journal of Neuroradiology*. 2013 Jan; 34(1); 74-79. (PMID: 22766668).

Schulze ET, Geary EK, Susmaras TM, Paliga JT, Maki PM, Little DM. Anatomical correlates of age-related working memory declines. *Journal of Aging Research. 2011;*2011:606871 (PMID: 22175019).

Geary EK, Kraus MF, Pliskin NH, Rubin L, Little DM. Passive learning strategies in chronic mild traumatic brain injury. *Journal of the International Neuropsychological Society*, 2011; 17: 709-719.

Kraus MF, Little DM, Wojtowicz SM, Sweeney JA. Procedural learning impairments identified via predictive saccades in chronic traumatic brain injury. *Cognitive and Behavioral Neurology* 2010; 23(4): 210-217 (PMID: 21150346).

Geary EK, Kraus MF, Pliskin NH, Little DM. Impairments in verbal learning in chronic mild traumatic brain injury. *Journal of the International Neuropsychological Society* 2010; 16(3):506-516.

Little DM, Kraus MF, Joseph J, Geary EK, Susmaras T, Zhou XJ, Pliskin N, Gorelick PB. Thalamic integrity underlies executive dysfunction: Evidence from Traumatic Brain Injury. *Neurology* 2010; 74: 558-564 (PMID: 20089945). [Note Supplemental Data on-line.]

Little DM, Kraus MF, Jiam C, Moynihan M, Siroko M, Schulze E, Geary EK. Neuroimaging of hypoxic-ischemic brain injury. *NeuroRehabilitation* 2010; 26: 15-25.

(3) Invited Articles:

Marion DW, Curley KC, Schwab J, Hicks RR, and the mTBI Diagnostics Workshop. Proceedings of the Military mTBI Diagnostics Workshop held in St. Pete Beach, August 2010. *Journal of Neurotrauma*, 2011, 28:517-526 (PMID: 21265587).
Little DM, Geary EK, Moynihan M, Alexander A, Pennington ML, Glang P, Schulze ET, Dretsch M, Pacifico A, Davis ML, Stevens A, Huang JH. Imaging Chronic Traumatic Brain Injury as a Risk Factor for Neurodegneration. *Alzheimer's and Dementia*. In Press.

Pacifico A and members of the Comparative Effectiveness Working Group. Comparative Effectiveness of Neuroimaging Modalities for the Detection of Traumatic Brain Injury. In press. *Neurology.* Please note that this publication is a response to a Congressional request for information.

Weiner MW, Friedl KE, Pacifico A, Chapman J, Jaffee MS, Little DM, Manley GT, McKee A, Petersen RC, Pitman RK, Yaffe K, Zetterberg H, Obana R, Bain LJ, Carrillo M. Military risk factors for Alzheimer's Disease. *Alzheimer's and Dementia*. 2013 Jul;9(4):445-51. doi: 10.1016/j.jalz.2013.03.005.

b. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.

Nothing to report.

6. **INVENTIONS, PATENTS AND LICENSES:** List all inventions made and patents and licenses applied for and/or issued. Each entry shall include the inventor(s), invention title, patent application number, filing date, patent number if issued, patent issued date, national, or international.

Nothing to report.

7. **REPORTABLE OUTCOMES:** Provide a list of reportable outcomes that have resulted from this research. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. This list may include development of prototypes, computer programs and/or software (such as databases and animal models, etc.) or similar products that may be commercialized.

Nothing to report.

8. **OTHER ACHIEVEMENTS:** This list may include degrees obtained that are supported by this award, development of cell lines, tissue or serum repositories, funding applied

for based on work supported by this award, and employment or research opportunities applied for and/or received based on experience/training supported by this award.

Nothing to report

9. **REFERENCES:** List all references pertinent to the report using a standard journal format (i.e., format used in *Science*, *Military Medicine*, etc.).

Geary, E. K., M. F. Kraus, et al. (2010). "Verbal learning differences in chronic mild traumatic brain injury." J Int Neuropsychol Soc 16(3): 506-516.

Geary, E. K., M. F. Kraus, et al. (2011). "Verbal learning strategy following mild traumatic brain injury." J Int Neuropsychol Soc 17(4): 709-719.

Gennarelli, T. A., L. E. Thibault, et al. (1982). "Diffuse axonal injury and traumatic coma in the primate." Annals of Neurology 12(6): 564-574.

Graham, D., T. Gennarelli, et al. (2002). Trauma. Greenfield's Neurpathology. D. Graham and P. Lantos. London, Arnold, Hodder Headline Group. 2.

Kraus, M. F., T. Susmaras, et al. (2007). "White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study." Brain 130(Pt 10): 2508-2519.

Little, D. M., E. Geary, et al. (in press). "Imaging chronic trauamtic brain injury as a risk factor for neurodegeneration." Alzheimer's & Dementia.

Little, D. M., M. F. Kraus, et al. (2010). "Thalamic integrity underlies executive dysfunction in traumatic brain injury." Neurology 74(7): 558-564.

Mori, S., S. Wakana, et al. (2005). MRI Atlas of Human White Matter Amsterdam, The Nethelands Elsevier

Planetta, P. J., E. T. Schulze, et al. (2013). "Thalamic projection fiber integrity in de novo Parkinson disease." Ajnr: American Journal of Neuroradiology 34(1): 74-79.

Povlishok, J. T. (1992). "Traumatically induced axonal injury: pathogenesis and pathobiological implications." Brain Pathology 2(1): 1-12.

Schulze, E. T., E. K. Geary, et al. (2011). "Anatomical correlates of age-related working memory declines." J Aging Res 2011: 606871.

Wakana, S., H. Jiang, et al. (2004). "Fiber tract-based atlas of human white matter anatomy." Radiology 230: 77-87.

10. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study

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Traumatic brain injury (TBI) is a serious public health problem. Even injuries classified as mild, the most common, can result in persistent neurobehavioural impairment. Diffuse axonal injury is a common finding after TBI, and is presumed to contribute to outcomes, but may not always be apparent using standard neuroimaging. Diffusion tensor imaging (DTI) is a more recent method of assessing axonal integrity *in vivo*. The primary objective of the current investigation was to characterize white matter integrity utilizing DTI across the spectrum of chronic TBI of all severities. A secondary objective was to examine the relationship between white matter integrity and cognition. Twenty mild, 17 moderate to severe TBI and 18 controls underwent DTI and neuropsychological testing. Fractional anisotropy, axial diffusivity and radial diffusivity were calculated from the DTI data. Fractional anisotropy was the primary measure of white matter integrity. Region of interest analysis included anterior and posterior corona radiata, cortico-spinal tracts, cingulum fibre bundles, external capsule, forceps minor and major, genu, body and splenium of the corpus callosum, inferior fronto-occipital fasciculus, superior longitudinal fasciculus and sagittal stratum. Cognitive domain scores were calculated from executive, attention and memory testing. Decreased fractional anisotropy was found in all 13 regions of interest for the moderate to severe TBI group, but only in the cortico-spinal tract, sagittal stratum and superior longitudinal fasciculus for the mild TBI group. White Matter Load (a measure of the total number of regions with reduced FA) was negatively correlated with all cognitive domains. Analysis of radial and axial diffusivity values suggested that all severities of TBI can result in a degree of axonal damage, while irreversible myelin damage was only apparent for moderate to severe TBI. The present data emphasize that white matter changes exist on a spectrum, including mild TBI. An index of global white matter neuropathology (White Matter Load) was related to cognitive function, such that greater white matter pathology predicted greater cognitive deficits. Mechanistically, mild TBI white matter changes may be primarily due to axonal damage as opposed to myelin damage. The more severe injuries impact both. DTI provides an objective means for determining the relationship of cognitive deficits to TBI, even in cases where the injury was sustained years prior to the evaluation.

Introduction

Traumatic brain injury (TBI) of all severities is a significant public health problem with an incidence between 180 and 500 per 100 000 population per year (Bruns and Hauser, 2001, 2003; Bazarian *et al.*, 2005). Recently the numbers of soldiers returning from military conflicts with TBI has created a clinical crisis for the United States Veterans Administration Hospitals (Taber *et al.*, 2006). In addition, greater public attention is finally being paid to the problems of athletes with persistent problems secondary to TBI (Guskiewicz *et al.*, 2000; Pellman *et al.*, 2004). Taken together, the burden on healthcare systems for both civilian and military TBI is large.

TBI is clinically rated as mild, moderate or severe based on acute TBI variables that include duration of loss of consciousness (LOC), Glasgow Coma Score (GCS) and post-traumatic amnesia (PTA) (Levin *et al.*, 1979). Mild TBI (MTBI) is the most common severity, with a recent WHO task force reporting that 70–90% of all treated TBI fell into this category (Holm *et al.*, 2005).

Neurobehavioural deficits, especially in cognition, are often the cause of significant disability after TBI (CDC, 2003). Observed cognitive changes that follow TBI can include decreased mental flexibility, trouble shifting sets, impaired attention, poor planning, lack of organization, problems with sequencing, impaired judgment, deficits in verbal fluency, problems with working memory, as well as increased impulsivity (Levin and Kraus, 1994; Miller, 2000; Godefroy, 2003). Determining the extent of clinically relevant neuropathology (defined as neuropathology associated with persistent neurobehavioural deficits) associated with TBI, particularly in the milder spectrum, is problematic. As such, there is a need for objective and quantifiable measures of neuropathology that can be applied to all severities of TBI for the purpose of determining the relationship between trauma and persistent disability. This methodology would provide the foundation for more accurate injury severity grading, prognosis and treatment planning without having to rely on often incomplete or inaccurate historical data that has been used as predictors of outcomes including LOC, PTA and GCS.

Pathophysiology of TBI

There are several significant pathophysiologic sequelae of TBI that are likely important to neurobehavioural outcome, including the location and severity of the injury, diffuse effects and secondary mechanisms of injury. Primary neurologic injury due to TBI can be direct and/or indirect. Contusions are common following TBI, and can directly disrupt function in both cortical and sub-cortical regions. Certain brain regions may be more vulnerable to contusion following trauma, such as the frontal and anterior temporal cortices, due to their position within the skull (Adams *et al.*, 1980; Levin *et al.*, 1992). Disruption of function can also result from more diffuse damage to white matter tracts

that are particularly susceptible to the shearing forces that often occur with TBI (Graham *et al.*, 2002). Such diffuse axonal injury (DAI) can disrupt critical cortical-subcortical pathways and lead to widespread cognitive dysfunction (Gennarelli *et al.*, 1982; Povlishok, 1992). DAI can result directly from the trauma, or secondary due to ischaemia. Brain oedema and shift can compromise blood supply and lead to secondary infarction in the corpus callosum and deep grey matter, and elevated intracranial pressure (ICP) can cause damage to the brainstem in TBI (Graham *et al.*, 1987). And although the diagnosis of DAI can only be clearly confirmed by microscopic examination, it may be inferred from specific neuroimaging findings such as haemorrhages in the corpus callosum or areas of rostral brainstem (Geddes, 1997; Geddes *et al.*, 1997).

DAI may be the only significant pathology found in certain cases of TBI, and has been identified via direct pathological studies as well as neuroimaging in mild TBI (Povlishock *et al.*, 1983; Graham *et al.*, 1989; Blumbergs *et al.*, 1994; Goodman, 1994; Mittl *et al.*, 1994; Aihara *et al.*, 1995; Blumbergs *et al.*, 1995; Gennarelli, 1996; Inglese *et al.*, 2005b). Changes in white matter, observed as hyperintense T2 signal, have been observed in mild TBI (Inglese *et al.*, 2005a, b). These lesions have been reported primarily in the corpus callosum, internal capsule, and centrum semiovale (Inglese *et al.*, 2005b). Another issue is the specificity of lesion type and the clinical relevance of these lesions found in mild TBI. Kurca and colleagues reported that mild TBI subjects with defined traumatic lesions (including both gray and white matter) showed significantly greater impairment on neuropsychological evaluations and subjective reports of symptoms consistent with postconcussion syndrome (Kurca *et al.*, 2006).

As would be expected, as injury severity increases, the pathophysiology identified on MRI also increases. For example, chronic moderate to severe TBI has been related to atrophy in the corpus callosum. The degree of atrophy in the corpus callosum did appear to be related to behavioural measures of reaction time (although not significantly) (Mathias *et al.*, 2004). In chronic (at least 3 months post injury) severe TBI, increased atrophy was reported in the corpus callosum, fornix, anterior limb of the internal capsule, superior frontal gyrus, para-hippocampal gyrus, optic radiations and optic chiasma (Tomaiulo *et al.*, 2005). There were only modest correlations between atrophy of the corpus callosum and memory function (Tomaiulo *et al.*, 2005).

Although there is some evidence to suggest that standard T1- or T2-weighted anatomic MR imaging shows promise for quantifying pathophysiology in TBI, it may not be as sensitive to the neuropathology of milder injuries (Hughes *et al.*, 2004). The limitation of standard imaging is highlighted by modest relationships between cognitive function and standard anatomic imaging findings. Diffusion tensor imaging is a very promising methodology in this regard.

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a relatively recent tool developed using MRI technology. DTI allows for the specific examination of the integrity of white matter tracts, tracts which are especially vulnerable to the mechanical trauma of TBI. DTI is a modification of diffusion-weighted imaging. Standard MRI structural imaging itself is not sensitive enough in identifying impairment in mild injury (Hughes et al., 2004). Because DTI is more sensitive to changes in the microstructure of white matter, it shows considerable promise in the assessment of TBI.

DTI is based upon the diffusivity of water molecules, which is variably restricted in different tissues. In white matter, it is more limited in the directions of diffusion. In healthy tracts, the anisotropy (limited directionality of diffusion) is higher than in less-organized gray matter. This difference allows for the calculation of fractional anisotropy (FA) values for tissue, and the generation of white matter fibre maps. The values for FA range from 0 to 1 where 0 represents isotropic diffusion, or lack of directional organization, and 1 represents anisotropic diffusion, or organized tissues such as in white matter tracts [see Le Bihan et al. (2001)]. Recently, there has been an increase in applications of DTI, with previous research demonstrating its potential utility in qualifying and quantifying neuropathology in TBI, in which diffuse axonal injury is common (Huismana et al., 2004). Although the specifics are still not well understood, FA is believed to reflect many factors including the degree of myelination and axonal density and/or integrity (Arfanakis et al., 2002; Song et al., 2002b, 2003; Harsan et al., 2006). More discrete analysis of the axial ($\lambda_{\parallel}$) and radial diffusivity ($\lambda_{\perp}$) also provide potential measures of the mechanisms that underlie changes in white matter following injury (Pierpaoli et al., 2001; Song et al., 2002a). $\lambda_{\parallel}$ reflects diffusivity parallel to axonal fibres. Increases in $\lambda_{\parallel}$ are thought to reflect pathology of the axon itself, such as from trauma. $\lambda_{\perp}$ reflects diffusivity perpendicular to axonal fibres and appears to be more strongly correlated with myelin abnormalities, either dysmyelination or demyelination. Although there is some preliminary evidence that these measures might be useful in vivo in trauma (Rugg-Gunn et al., 2001) it is not yet entirely clear whether $\lambda_{\parallel}$ and $\lambda_{\perp}$ are differentially affected by trauma, and this may be a function of severity as well as acuity.

The literature involving the application of DTI in chronic TBI is limited but shows promise. In chronic moderate to severe TBI, reduced FA has been reported (Nakayama et al., 2006; Tisserand et al., 2006; Xu et al., 2007), even in the absence of observable lesions in standard structural MRI (Nakayama et al., 2006). Despite general acceptance of this finding of abnormal FA, the relationship of white matter integrity to cognitive function in TBI is not yet clear, and the few studies to assess this in TBI have varied in outcomes. For example, in a group of chronic severe TBI subjects with cognitive impairment there was no relationship between reduced FA in the corpus callosum and neuropsychological measures of memory or executive function, though there was a relationship with performance on the Mini-Mental State Exam (Nakayama et al., 2006). However, Salmond and colleagues reported a relationship between reduced FA and measures of learning and memory (Salmond et al., 2006) in moderate and severe TBI. One problem is that the existing studies differ in methodology, including placement of regions of interest, variability in patient populations (such as severity and acuity/chronicity of TBI subjects), and in the specific neuropsychological testing used to assess cognition.

Hence, given the potential importance of white matter pathology to outcome in TBI, and the sensitivity of DTI in determining the integrity of white matter, further studies are warranted. A more standardized methodology is needed that can be used to assess the spectrum of white matter abnormalities in TBI, at any point after injury, that would also allow for correlation with clinically relevant issues such as cognitive function. The current investigation was designed with these issues in mind.

In this study, a group of chronic TBI subjects of all severities and a group of demographically matched healthy controls underwent MRI (anatomical and diffusion tensor imaging), neuropsychological testing and a neurobehavioural examination.

The primary objective of the current investigation was to test the hypothesis that white matter integrity is reduced across the spectrum of TBI severity in chronic subjects. The secondary objective was to examine the relationship between white matter integrity and cognition assessed with standard neuropsychological testing across the domains of executive, attention and memory function.

Methods
Subjects

A total of 39 subjects with a history of TBI, closed head type, participated in this study (Table 1). Twenty-two subjects (13 females, 9 males) had a history of MTBI and 17 (9 females, 8 males) had a history of moderate to severe TBI (M/STBI). Of these, two subjects with a history of MTBI were excluded for excessive head motion. The final sample included 20 MTBI subjects (12 females, 8 males) and 17 (9 females, 8 males) had a history of M/STBI. All were at least 6 months out from injury; with the average time out from injury being 107 months for all TBI subjects. Subjects were recruited from the University of Illinois Medical Center and via advertisements. Eighteen healthy controls (11 females, 7 males) were recruited from the community. Experimental procedures complied with the code of ethics of the World Medical Association and the standards of the University of Illinois Institutional Review Board. All subjects provided written informed consent consistent with the Declaration of Helsinki.

Subjects were excluded if they had a history of psychiatric disorder before the TBI, substance abuse, current pending

Table I Demographic information for traumatic brain injury and control subjects

	Control		MTBI		M/STBI		All groups	Control vs. MTBI	Control vs. M/STBI	MTBI vs. M/STBI
	M	SEM	M	SEM	M	SEM				
Age	32.83	2.51	35.85	2.10	34.88	2.82	0.673	0.360	0.590	0.781
Number of years of education	16.76	0.44	16.55	0.53	15.47	0.77	0.276	0.763	0.154	0.244
WTAR Pre-morbid IQ estimate	113.24	1.80	112.65	2.43	106.59	2.60	0.100	0.852	0.043*	0.098
Time from injury (in months)			92.55	18.61	124.35	23.12	0.286			0.286
Age at time of injury (years)			29.00	2.37	24.50	2.51	0.199			0.199
Length of LOC (h)			0.11	0.05	237.00	111.50	0.042*			0.042*

P-values are listed under each contrast and asterisks indicate significant differences between groups (*$P < 0.05$). SEM = standard error of the mean; WTAR = Wechsler test of adult reading; MTBI = mild traumatic brain injury; M/STBI = moderate to severe traumatic brain injury; LOC = loss of consciousness.

litigation or any other neurological or medical condition that could result in cognitive changes (e.g. severe hypertension, diabetes). Subjects were not receiving any treatments for cognitive deficits at the time of the study, pharmacological or otherwise. The criteria used for defining MTBI, set forth by the American Congress of Rehabilitation Medicine (Medicine, 1993), are as follows: MTBI is diagnosed when at least one of the following criteria is met (1) any period of loss of consciousness; (2) any loss of memory for events immediately before or after the accident; (3) any alteration in mental state at the time of the accident (e.g. feeling dazed, disoriented or confused) and (4) focal neurological deficit(s) that may or may not be transient (Medicine, 1993; Cassidy et al., 2004). For this study, subjects were categorized as moderate or greater severity TBI if the LOC was greater than 30 min and/or the GCS was less than 13 (Levin et al., 1992; Medicine, 1993; Cassidy et al., 2004; Tagliaferri et al., 2006). These criteria allowed the separation of MTBI from moderate to severe TBI for the purposes of the present study. For the MTBI group, the average reported LOC was 0.1 h (range = 0–0.50 h), for the M/STBI group average LOC was 213.5 h (range = 0.25–1440 h). Data on acute TBI variables such as LOC were collected by medical record when available and by subject and family report. For the MTBI cases, all except one (who met criteria for mild TBI by history with positive LOC but did not seek immediate attention) were seen and diagnosed acutely at an ER or outpatient setting.

In terms of clinical details concerning the index traumatic event, for many of the cases the TBI was the primary diagnosis at the time of their injury. Five MTBI and five M/STBI cases had associated injuries (traumatic injuries other than the TBI). Of these, most were fractures of the clavicle or an extremity. The most common mechanisms of injury were motor vehicle accidents (17 subjects). The remainder included bicycle accidents, blunt head trauma and falls. On the neurological exam (exclusive of cognitive testing) done at the time of evaluation, only eight TBI subjects (two MTBI, six M/STBI) showed abnormalities, which were primarily soft signs such as mildy unsteady tandem gait. Of the MTBI group, all but two were employed or in school at the time of evaluation; all but three of the M/STBI group were either employed or in school at the time of evaluation.

Healthy controls were excluded if they had any history of psychiatric illness or TBI, substance abuse/dependency or a history of significant medical or neurological illness that would be associated with significant changes in the brain, such as diabetes, seizures or stroke. The healthy control group was not significantly different from the TBI groups in age or years of education (Table 1). The controls and MTBI groups were not significantly different in estimates of premorbid IQ (Table 1). The M/STBI did differ from the controls in terms of premorbid IQ estimates. The M/STBI group did not differ from MTBI in age at the time of injury.

DTI data acquisition
Studies were acquired on a 3.0-Tesla whole body scanner (Signa VHi, General Electric Medical Systems, Waukesha, WI) using a customized DTI pulse sequence with a quadrature head coil. The sequence is based on a single-shot EPI pulse sequence with the capability of compensating eddy currents induced by the diffusion gradients via dynamically modifying the imaging gradient waveforms. The diffusion-weighting orientations are designed based on the electrostatic repulsion model proposed by Jones et al. (1999) (TR = 5200 ms, TE = minimum (81 ms), b-values = 0, 750 s/mm^2, diffusion gradient directions = 27, FOV = 22 cm, Matrix = 132 × 132 (reconstructed to 256 × 256, slice thickness = 5 mm, gap = 1.5 mm, ramp-sampling = on, NEX = 2, total acquisition time = 5:46).

An additional 3D high-resolution anatomical scan was also acquired to allow coregistration with the DTI data and normalization to the Montreal Neurological Institute template (MNI) (3D inversion recovery fast spoiled gradient recalled (3D IRfSPGR), plane = axial, TR = 9 ms, TE = 2.0 ms, flip angle = 25°, NEX = 1, bandwidth = 15.6 kHz, acquisition matrix = 256 × 256, FOV = 22 × 16.5 cm^2, slice thickness/gap = 1.5/0 mm/mm, slices = 124).

Neuropsychological assessment
Subjects completed a test battery that was assembled to assess executive function, attention and memory. Since TBI commonly affects frontal lobe function, the battery was weighed more heavily on executive measures to heighten sensitivity to deficits in this area of cognition. Tests included the Tower of London (Shallice, 1982; Culbertson and Zilmer, 2001), Stroop Colour–Word Test (Stroop, 1935; Jensen and Rohwer, 1966; Golden and Freshwater, 2002), Paced Auditory Serial Addition Test (PASAT) (Gronwall and Sampson, 1974; Gronwall, 1977), Trail Making Test

Table 2 Neuropsychological test results and domain scores for all groups

	Control		MTBI		M/STBI		All groups	Control vs.	Control vs.	MTBI vs.
	M	SEM	M	SEM	M	SEM		MTBI	M/STBI	M/STBI
Executive measures executive domain	0.00	0.15	−0.37	0.14	−0.87	0.14	<0.001**	0.075	<0.001**	0.016**
Tower of London (total moves)	101.89	4.03	98.20	3.49	99.65	3.24	0.764	0.491	0.670	0.766
Stroop color-word [age-corrected (s)]	52.22	2.74	45.30	2.28	38.12	2.98	0.002**	0.059	0.001**	0.060
PASAT total	133.00	11.87	125.40	7.42	109.31	10.67	0.263	0.583	0.151	0.212
Trails B (s)	50.17	3.88	58.10	6.27	77.53	7.52	0.009**	0.302	0.002**	0.053
CPT number of errors of commission	8.06	1.43	14.15	1.46	13.76	1.95	0.016*	0.005**	0.023*	0.873
COWAT total	44.44	2.49	40.35	2.23	36.24	2.90	0.090	0.227	0.038*	0.261
RUFF unique designs	48.88	2.99	46.49	1.56	37.21	1.38	<.001**	0.470	0.001**	<0.001**
Digit span backward scaled score	8.00	0.54	7.85	0.63	6.71	0.47	0.228	0.859	0.079	0.168
Spatial Span Backward scaled score	8.83	0.36	8.50	0.53	7.18	0.46	0.039*	0.613	0.007**	0.070
Attention measures attention domain	0.00	0.15	−0.93	0.46	−1.83	0.60	0.022*	0.075	0.005**	0.237
Digit span forward scaled score	10.61	0.61	11.60	0.44	11.00	0.68	0.461	0.190	0.673	0.450
Spatial span forward scaled score	9.89	0.46	9.10	0.45	8.59	0.41	0.134	0.229	0.043*	0.415
Trails A (s)	21.33	1.96	23.75	1.64	33.06	3.88	0.007**	0.347	0.010**	0.026*
CPT number of errors of omission	0.67	0.16	3.00	1.11	4.35	1.31	0.042*	0.056	0.007**	0.434
Memory measures memory domain	0.00	0.21	−0.15	0.17	−1.04	0.31	0.006**	0.586	0.008**	0.013*
CVLT total trials 1–5	58.50	1.96	55.95	2.27	46.76	2.75	0.003**	0.406	0.001**	0.014*
CVLT long-free recall	12.56	0.58	12.60	0.57	10.06	1.09	0.037*	0.957	0.049*	0.039*
BVMT trials 1–3	27.22	1.41	25.65	0.99	21.47	1.82	0.019*	0.360	0.017*	0.043*
BVMT delay recall	10.06	0.45	10.00	0.42	8.59	0.68	0.090	0.928	0.076	0.075
Other measures										
CPT Hit reaction Time (ms)	405.83	16.77	368.99	10.90	400.77	22.00	0.230	0.068	0.855	0.184
Grooved pegboard [dominant hand (s)]	62.17	2.57	64.75	1.93	76.71	3.93	0.002**	0.421	0.004**	0.007**

P-values are listed under each contrast and asterisks indicate significant differences between groups after correction for multiple comparisons (*$P < 0.05$; **$P < 0.01$). PASAT = paced auditory serial addition test; Trails = trail making test; CPT = Conners' continuous performance test; COWAT = controlled oral word association test; RUFF = Ruff figural fluency test; CVLT = California verbal learning test; BVMT = brief visual spatial memory test.

(Reitan, 1958), Conners' Continuous Performance Test (Conners and Staff, 2000), Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976; Benton and Hamsher, 1989), Ruff Figural Fluency Test (Ruff, 1988), Wechsler Test of Adult Reading (WTAR) (Psychological, 2001), California Verbal Learning Test – Second Edition (CVLT-II) (Delis *et al.*, 2000), Brief Visual Spatial Memory Test – Revised (BVMT-R) (Benedict, 1997), Digit Span and Spatial Span from the Wechsler Memory Scales – Third Edition (Wechsler, 1997) and the Grooved Pegboard (Klove, 1964; Matthews and Klove, 1964). In addition, subjects had to pass tests for malingering and effort, including the Test of Memory Malingering (TOMM) and Dot Counting to ensure that only subjects who performed testing effortfully were included (Rey, 1941; Tombaugh, 1996, 1997).

Z-scores were calculated for all subjects, with the mean and SD of data from healthy subjects used to define z-scores for all subject groups. Negative scores indicate performance below the mean of healthy subjects. Domain scores for measures of executive function, attention and memory were generated by averaging the standardized data from tests assessing these cognitive domains as presented in Table 2.

DTI data analysis

The 28 diffusion directions, along with the B0 image, were used to calculate FA as the primary indicator of white matter integrity. The images were reconstructed and FA, λ_1, λ_2 and λ_3 were calculated using the program from Johns Hopkins, DTI Studio (Wakana *et al.*, 2004). The 28 diffusion-weighted image sets were examined for image quality and head movement. Head movement was required to be within one voxel across the image acquisition. Because noise can introduce bias in estimates of the eigenvalues and because noise decreases the signal-to-noise ratio we applied a background noise level to all subjects prior to calculation of pixel-wise FA and the eigenvalues (λ_1, λ_2, λ_3) (background noise = 125). It is important to note that the application of this criterion and the noise itself can influence calculation of anisotropy. However, because the analyses focus on differences between groups the bias introduced by this noise floor should not influence group differences. The FA, λ_1, λ_2 and λ_3 were then converted to ANALYSE format and read into Statistical Parametric Mapping software for analysis (SPM2, Wellcome Department of Imaging Neuroscience, London, UK). DTI data from each subject was co-registered with their corresponding T1-weighted anatomic image set (after skull stripping) using a normalized mutual information cost function and trilinear interpolation. Normalization parameters were determined based upon the high-resolution T1 image relative to the Montreal Neurological Institute (MNI) template. These normalization parameters were then applied to the FA and eigenvalue images. Each image was visually checked for accuracy after both the co-registration and normalization steps. From these eigenvalue maps, axial ($\lambda_\parallel = \lambda_1$) and radial [$\lambda_\perp = (\lambda_2 + \lambda_3)/2$] diffusivity were calculated. Although no additional smoothing was applied to
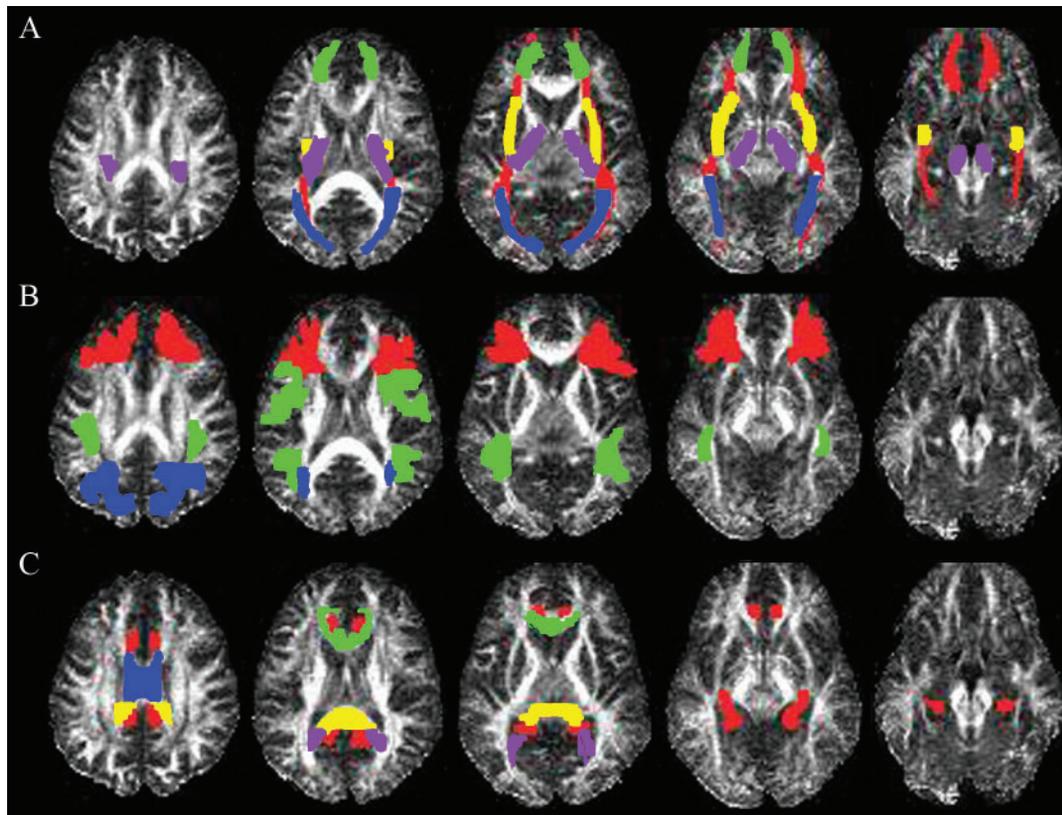
Fig. I Example region of interest masks for a single representative subject: (**A**) forceps minor (green), cortico-spinal tract (purple), inferior frontal-occipital fasciculus (red), external capsule (yellow), sagittal stratum (blue); (**B**) anterior corona radiata (green), superior longitudinal fasciculus (red), posterior corona radiata (blue); (**C**) cingulum (red), corpus callosum body (blue), splenium (yellow), and genu (green) and forceps major (purple).

the data the magnitude of spatial filtering which occurs during normalization to standardized space can potentially affect the DTI data (see Jones *et al.*, 2005; Smith *et al.*, 2006). In some cases, large smoothing kernels can potentially reduce group differences (Jones *et al.*, 2005).

Region-of-interest analysis

All ROI analyses were carried out on data from each individual subject and hand-drawn in standardized space. ROIs were drawn individually on the FA maps with respect to the T2 FSE and colour-coded FA maps.

The specific ROIs included: anterior and posterior corona radiata (respectively, ACR and PCR), cortico-spinal tracts (CST) which included parts of the cortico-pontine tract and parts of the superior thalamic radiation, cingulum (CG) fibres, forceps minor (fMin), forceps major (fMaj), the body, genu and splenium of the corpus callosum (bCC, gCC and sCC), the inferior fronto-occipital (IFO) fasciculus, the superior longitudinal fasciculus (SLF), external capsule (ExCap) and the sagittal stratum including the optic radiations (SS). A description of the identification of these ROIs follows. A representative subject's FA map with superimposed ROIs is presented in Fig. 1.

The cingulum was defined firstly as the long association fibre that is located internal to the cingulate gyrus and running along its entire length continuing into the parahippocampal gyrus. It was defined dorsally by the corpus callosum continuing into the temporal lobe along the ventral/medial wall of the hippocampal

gyri. Some of the cingulum fibres intersect with fibres of the superior longitudinal fasciculus, inferior longitudinal fasciculus, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus and uncinate fasciculus. The anterior and posterior corona radiata are the fibres which run throughout the internal capsule. The anterior corona radiata was defined as those fibres which run through limb of the internal capsule and contain nerve tracts running to and from the anterior areas of the cortex. The posterior corona radiata was defined by the posterior limb of the internal capsule. However, the cortico-spinal tract is a large part of the corona radiata. However, because we wanted to examine the cortico-spinal tract individually we have excluded these fibres from our definitions of anterior and posterior corona radiata. The external capsule contains cortico–cortico association fibres. The superior longitudinal fasciculus (fibres running from frontal to parietal to occipital and vice versa), inferior fronto-occipital fasciculus and the uncinate fasciculus (fibres running from ventral frontal lobe to pole of temporal lobe) run through the external capsule. The external capsule was defined as the white matter tracts located lateral to the lentiform nucleus, most specifically the putamen of the basal ganglia, and lateral to the extreme capsule is the claustrum. The external capsule, claustrum and extreme capsule are very closely associated. We are unable to discriminate between these tracts. In order to examine the external capsule separately from the SLF and IFO we excluded any fibre defined as external capsule from the SLF or IFO. The IFO runs from the frontal lobe to the occipital and temporal lobes ipsilaterally.

It is deep within the cerebral hemisphere and runs laterally to the caudate nucleus. The SLF connects the anterior part of the frontal lobe to the occipital and temporal lobes. This tract has extensive branching in the frontal, parietal and temporal lobes. We excluded fibres associated with the IFO from these masks. Although the corpus callosum contains fibres which run anterior to posterior we wanted to investigate differential loss of the genu, splenium, and body of the corpus callosum as well as in forceps major and minor. The corpus callosum was first defined as a whole and then subdivided. The forceps minor were characterized as those fibres located inferior to the IFO and medially to the anterior portion of the corona radiata. Forceps major was defined as those fibres posterior to the posterior corona radiata and medial to the sagittal stratum. The corticospinal tract was identified by following the fibre bundle from the brainstem into the cortex. We refer herein to the corticospinal tract but also include the cortico-bulbar and cortico-pontine tract in this ROI. Although we define these regions there is considerable overlap between many of these tracts. Because of this we inspected each ROI relative to every other ROI to ensure that the same voxel was not included in more than one ROI. To ensure that FA was only calculated from white matter tissue, a threshold of 0.20 was applied prior to extraction of individual subjects' FA maps.

White matter load

This was used as an index of global white matter integrity. It was defined as the number of ROIs that showed significantly decreased FA values compared to controls. This measure was used as it may be more sensitive to white matter abnormalities by looking at the actual number of affected areas across the brain independent of individual variability in the specific location of these white matter abnormalities. To measure the White Matter Load, z-scores were calculated for the FA within each ROI. The control group mean and SD were treated as zero. We then calculated the number of ROIs which showed decreased FA for each subject. We used a conservative criterion of 1 SD below the control mean to define decreased integrity. White Matter Load was then calculated as the total number of regions which showed impaired white matter relative to values from controls. The value for White Matter Load can range from 0 to 13 (13 ROIs).

Statistical analyses

Neuropsychological test scores were analysed using a one-way ANOVA with group membership (controls, MTBI, M/STBI) and were corrected for multiple comparisons using the least significant difference post-hoc tests. The primary measures of interest were three scores which were each a composite of those individual test results which loaded preferentially on executive, memory and attention domains, respectively. Because these three domain scores are more stable than individual tests scores they were also used to assess relationships between measures of white matter integrity and cognition using bivariate Pearson correlations.

The primary analyses carried out on the dependent measures extracted from the DTI data was a two-way mixed design ANOVA with cerebral hemisphere (right, left) as the within subjects comparison and group membership (controls, MTBI and M/STBI) as the between subjects comparison. For those regions where areas in both hemispheres were assessed together (corpus callosum and cerebral peduncles) the analysis was a one-way between subjects ANOVA with group membership (controls, MTBI and M/STBI) as the between-subjects comparison. The primary dependent measure
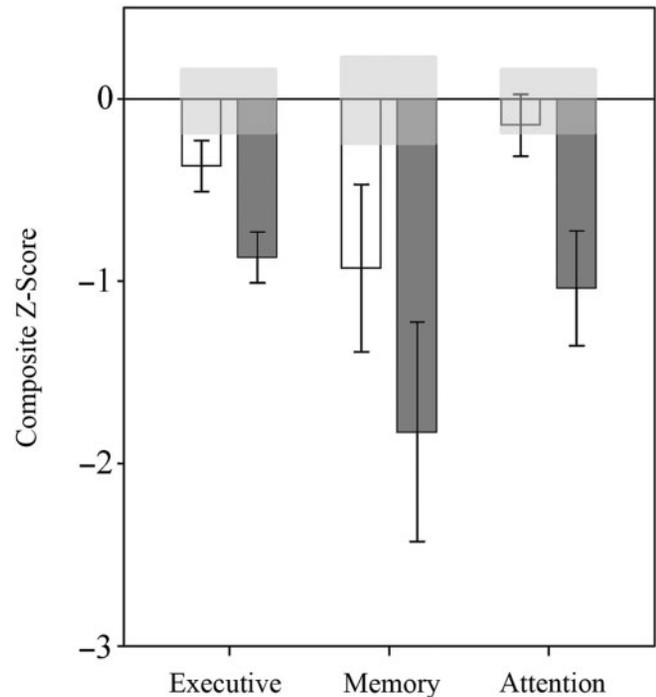

Fig. 2 Mean domain scores (normalized z-scores) for the MTBI (white) and M/STBI (dark gray). Note that the light gray box around zero indicates 1 SEM around the control mean.

was FA. Data were confirmed to have a normal distribution using the Kolmogorov–Smirnov test.

Results

Neuropsychological testing

Group means are presented for the each neuropsychological test in Table 2. Of note, the only individual measure which differed significantly between the controls and MTBI was the number of commissions on the CPT [$F(1,37) = 8.86$, $P = 0.005$], which is a measure associated strongly with prefrontal function (Miranda et al., in press). Mean cognitive domain scores are also presented in Fig. 2. M/STBI differed from the controls on almost all measures. The trend in means for the individual tests indicate that the controls have the highest performance, followed by MTBI, with M/STI showing the most severe and global impairment. The MTBI group did not differ significantly from controls in any domain scores when compared to the controls ($P > 0.050$). The M/STBI group performed significantly worse than both the controls and MTBI in the executive [M/STBI versus Controls: $F(1,34) = 18.08$, $P < 0.001$; versus MTBI: $F(1,35) = 6.39$, $P = 0.016$] and memory domains [M/STBI versus Controls: $F(1,34) = 7.83$, $P = 0.008$; versus MTBI: $F(1,35) = 6.79$, $P = 0.013$]. M/STBI performed considerably worse than the controls on the attention domain [$F(1,34) = 9.14$, $P = 0.005$] but did not differ from MTBI [$F(1,34) = 3.194$, $P = 0.083$].

Fractional anisotropy: symmetry

Although there was a main effect of symmetry across the CST ($P = 0.038$) and ACR ($P = 0.043$) with FA in the right hemisphere being higher than the left there were no differential symmetry effects across the three groups. As such, the remaining analyses are presented collapsed across hemispheres.

Fractional anisotropy

Overall, there was a main effect of group membership on whole brain FA [$F(2,54) = 4.52$, $P = 0.015$] relative to controls. Post-hoc testing demonstrated that the M/STBI had reduced FA relative to both controls [$F(1,34) = 6.47$, $P = 0.016$] and MTBI [$F(1,36) = 5.36$, $P = 0.027$]. In the ROI analyses, with the exception of fMin [$F(2,54) = 2.71$, $P = 0.076$] and ExCap [$F(2,54) = 3.06$, $P = 0.055$], significant main effects of group membership were observed for all other ROIs. As the primary contrast of interest was comparison between controls and both TBI subject groups, z-scores were calculated with the controls set to zero. As can be seen in Fig. 3, MTBI showed reduced FA along the CST [$F(1,37) = 4.99$, $P = 0.032$], SLF [$F(1,37) = 9.08$, $P = 0.005$] and SS [$F(1,37) = 6.84$, $P = 0.013$]. FA values for all ROIs in the M/STBI group were decreased compared to controls ($P < 0.05$; see Table 3).

Comparisons between MTBI and M/STBI showed that the M/STBI had reduced FA in the corpus callosum [gCC: $F(1,36) = 8.42$, $P = 0.006$; bCC: $F(1,36) = 15.63$, $P < 0.001$; sCC: $F(1,36) = 18.76$, $P < 0.001$], Cing [$F(1,36) = 12.84$, $P < 0.001$], fMaj [$F(1,36) = 18.34$, $P < 0.001$], CST [$F(1,36) = 5.27$, $P = 0.028$], IFO [$F(1,36) = 4.48$, $P = 0.042$], PCR [$F(1,36) = 4.80$, $P = 0.035$] and in the SS [$F(1,36) = 5.23$, $P = 0.028$].

Axial and radial diffusivity

To investigate potential mechanisms for changes in white matter integrity in chronic TBI, both axial and radial diffusivity were extracted from a whole brain white matter mask as well as from the ROIs which showed sensitivity to all severities of head injury (SS, SLF, CST). As with the earlier FA analysis, these values were transformed to z-scores based upon the control group mean. There was an overall main effect of group for both axial ($\lambda_\parallel$) and radial ($\lambda_\perp$) diffusivity in the whole brain ($P < 0.004$ for all comparisons). However, these results were primarily driven by increased diffusivity in M/STBI. As can be seen in Fig. 4, M/STBI, relative to controls, showed increased $\lambda_\parallel$ and $\lambda_\perp$ in all regions [whole brain $\lambda_\parallel$: $F(1,34) = 10.40$, $P = 0.003$; whole brain $\lambda_\perp$: $F(1,34) = 14.30$, $P = 0.001$; SS $\lambda_\parallel$: $F(1,34) = 40.96$, $P < 0.001$; SS $\lambda_\perp$: $F(1,34) = 14.12$, $P \leqslant 0.001$; SLF $\lambda_\parallel$: $F(1,34) = 43.56$, $P < 0.001$; SLF $\lambda_\perp$: $F(1,34) = 14.29$, $P = 0.001$; CST $\lambda_\parallel$: $F(1,34) = 8.83$, $P = 0.005$; CST $\lambda_\perp$: $F(1,34) = 7.79$, $P = 0.009$). The MTBI showed increased $\lambda_\parallel$ relative to controls in the SS
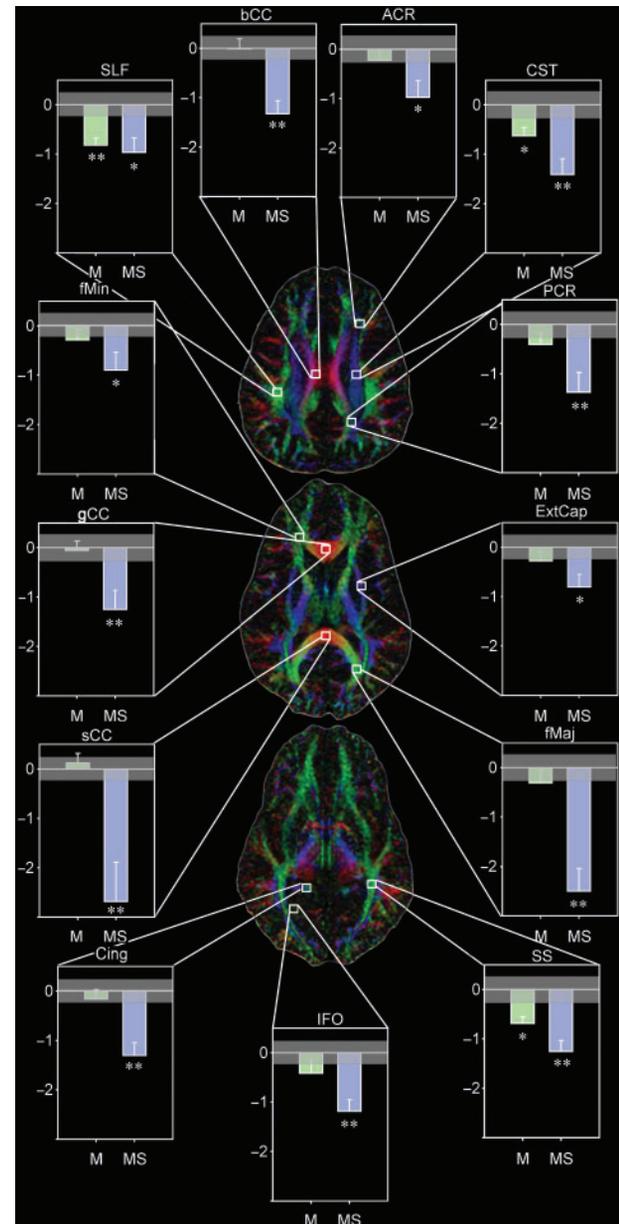

Fig. 3 Mean normalized FA for each ROI for the MTBI (green) and M/STBI (blue). Single asterisks indicate $P < 0.05$, double asterisks indicate $P < 0.001$ for the control group compared to either MTBI (M) or M/STBI (MS). Note that the light gray box around zero indicates ISEM around the control mean. Abbreviations: ACR, PCR: anterior and posterior corona radiata, CST: corticospinal tracts, Cing: cingulum, fMin, fMaj: forceps minor and major, bCC, sCC, gCC: body, genu and splenium of the corpus callosum, IFO: inferior fronto-occipital fasciculus, SLF: superior longitudinal fasciculus, SS: sagittal stratum, ExtCap: external capsule. Note that white boxes on the colour-coded direction map indicate the target fibres but do not indicate the entire region of interest.

[$F(1,34) = 4.78$, $P = 0.008$] and SLF [$F(1,34) = 4.78$, $P = 0.035$] but not in the whole brain or CST. The MTBI showed no significant increases in radial diffusivity in any region.

Table 3 Mean FA for all three groups for each ROI.

Region of interest (ROI)	Control		MTBI		M/STBI		All groups	Control vs. MTBI	Control vs. M/STBI	MTBI vs. M/STBI
	M	SEM	M	SEM	M	SEM				
Whole brain	0.35	0.002	0.35	0.001	0.34	0.003	0.015*	0.375	0.016*	0.027*
Cingulum (Cing)	0.38	0.005	0.38	0.004	0.35	0.005	<0.001**	0.599	0.001**	0.001**
External capsule (ExCap)	0.36	0.003	0.36	0.003	0.35	0.004	0.055	0.370	0.027*	0.106
Cortico-spinal tract (CST)	0.48	0.004	0.46	0.003	0.45	0.006	0.001**	0.032*	0.001**	0.028*
Inf. frontal-occipital (IFO)	0.40	0.005	0.39	0.006	0.37	0.005	0.007**	0.256	0.001**	0.042*
Anterior corona radiata (ACR)	0.35	0.004	0.34	0.003	0.33	0.006	0.033*	0.475	0.023*	0.060
Posterior corona radiata (PCR)	0.40	0.003	0.39	0.003	0.38	0.006	0.006**	0.222	0.005**	0.035*
Forceps major (fMaj)	0.39	0.006	0.38	0.005	0.37	0.009	0.076	0.367	0.044*	0.145
Forceps minor (fMin)	0.50	0.007	0.49	0.008	0.42	0.014	<0.001**	0.393	<0.001**	<0.001**
Sagittal stratum (SS)	0.47	0.008	0.45	0.004	0.43	0.007	<0.001**	0.013*	<0.001**	0.028*
Sup. longitudinal (SLF)	0.41	0.005	0.39	0.003	0.39	0.006	0.009**	0.005**	0.015*	0.655
Corpus callosum										
Body (bCC)	0.42	0.012	0.42	0.010	0.36	0.013	<0.001**	0.967	0.001**	<0.001**
Genu (gCC)	0.50	0.009	0.50	0.007	0.45	0.015	0.003	0.854	0.009**	0.006**
Splenium (sCC)	0.56	0.006	0.57	0.005	0.49	0.020	<0.001**	0.054	0.002**	<0.001**

Standard errors of the mean (SEM) are presented in parentheses. *P*-values are listed under each contrast and asterisks indicate significant differences between groups (*$P < 0.05$; **$P < 0.01$). Inf = Inferior, Sup = Superior.
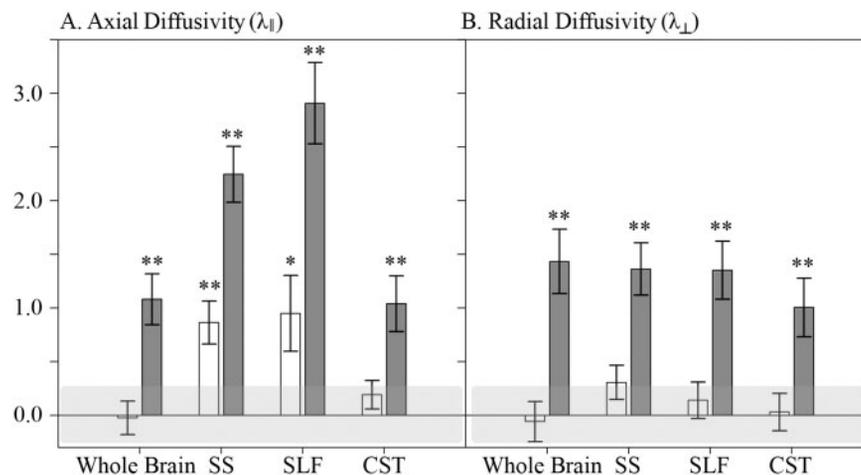

Fig. 4 Mean normalized axial ($\lambda_{\parallel}$) and radial ($\lambda_{\perp}$) diffusivity for the MTBI (white bars) and M/STBI (dark gray bars). Single asterisks indicate $P < 0.05$, double asterisks indicate $P < 0.01$ either the MTBI or M/STBI was compared to controls. Note that the light gray box around zero indicates 1 SEM around the control mean. Abbreviations: SS: sagittal stratum, SLF: superior longitudinal fasciculus, CST: corticospinal tract.

White matter load

The White Matter Load was the total number of regions with FA 1SD below the control mean (please see the 'Methods' section for a complete description).

Each control, on average, had reduced FA in 3.6 out of 13 ROIs ($M = 3.61$, SEM = 0.55). The load (or number of regions with reduced FA) increased as the severity of head injury increased. The MTBI had an average load of about six ROIs classified as reduced ($M = 5.9$, SEM = 0.72), whereas the M/STBI showed reduced FA in 8 out of 14 ROIs ($M = 9.06$, SEM = 0.89). The controls had significantly lower load than the MTBI [$F(1,37) = 6.16$, $P = 0.018$] and M/STBI [$F(1,34) = 27.69$, $P < 0.001$]. Finally, the M/STBI did have a larger load than the MTBI [$F(1,36) = 7.74$, $P = 0.009$].

Relationship between white matter integrity and neuropsychological function

To examine the relationship between both white matter integrity and white matter load with neuropsychological function we conducted a series of correlations for the entire group of TBI subjects. As is depicted in Fig. 5, there was a significant correlation between the executive and memory domains with the composite white matter load [executive: $r(54) = -0.41$, $P = 0.002$; attention: $r(54) = -0.26$, $P = 0.058$; and memory: $r(54) = -0.40$, $P = 0.000$]. Also depicted in
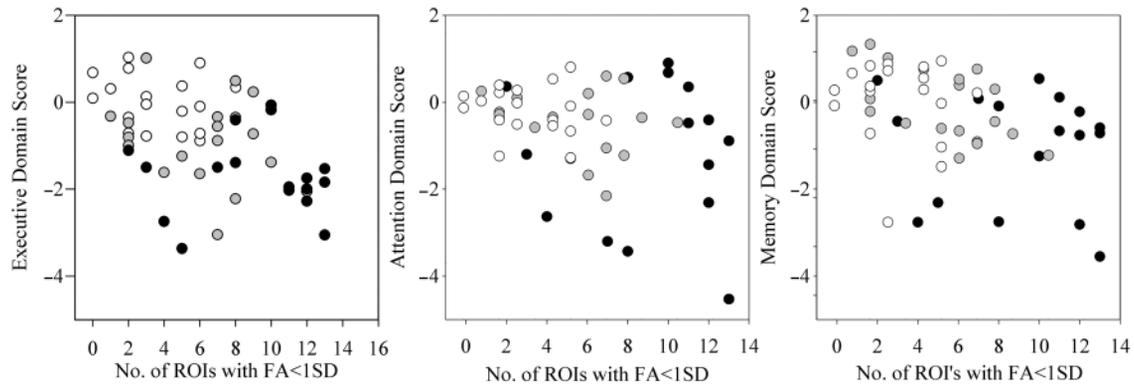
Fig. 5 Plots indicating the relationship between each normalized domain score (left: executive, middle: attention, right: memory) as a function of the number of ROIs with FA <1 SD from the control mean. Controls are indicated by white dots, MTBI (gray dots), and M/STBI (black dots).

Fig. 5 is the overlapping distribution of load and neuropsychological function amongst all the three groups.

In terms of correlations between FA in specific ROIs with these domain scores there were significant correlations between executive function and bCC ($r=-0.368$, $P=0.006$), sCC ($r=-0.348$, $P=0.009$), CST ($r=-0.390$, $P=0.003$), ExCap ($r=-0.265$, $P=0.050$), fMaj ($r=0.563$, $P<0.001$), fMin ($r=.281$, $P=0.038$), IFO ($r=-0.346$, $P=0.009$), ACR ($r=-0.383$, $P=0.004$), PCR ($r=-0.407$, $P=0.002$), SLF ($r=-0.305$, $P=0.023$), SS ($r=-0.495$, $P<0.001$) and Cing ($r=-0.277$, $P=0.041$). Only the fMaj ($r=-0.310$, $P=0.022$) and PCR x($r=0.271$, $P=0.046$) correlated with the attention domain. The bCC ($r=-0.030$, $P=0.026$), sCC ($r=-0.328$, $P=0.015$), fMaj ($r=-0.432$, $P=0.001$), fMin ($r=-0.269$, $P=0.047$), IFO ($r=-0.314$, $P=0.019$), PCR ($r=-0.330$, $P=0.014$), SS ($r=-0.316$, $P=0.019$) and Cing ($r=-0.311$, $P=0.021$) all corrected with the memory domain. Although we do not have the statistical power to examine these correlations within each subject group the trend is such that these patterns appear consistent within both the MTBI and M/STBI.

Conclusions

In this study, the moderate to severe TBI subjects demonstrated reduced white matter integrity, relative to controls, in all 13 regions of interest. The MTBI showed reduced white matter integrity in the superior longitudinal fasciculus, sagittal stratum and corticospinal tract (Fig. 3). The total number of regions with reduced white matter integrity (White Matter Load) was greatest in the moderate to severe group, and least in the controls (Fig. 5). The MTBI subjects fell between these two groups, being significantly different than controls (Fig. 5).

In M/STBI increased radial and axial diffusivity is observed both in the whole brain and in specific regions of interest (Fig. 4). This finding likely reflects damage to

both myelin and to axons. In MTBI, relatively normal radial diffusivity and increased axial diffusivity suggests that irreversible damage to myelin is less common in MTBI as compared to M/STBI but that axonal damage is present even 6 months following injury. It could be that the injury in the MTBI group had less of an effect on myelin due to trauma acutely or that the less severe injury allowed some degree of myelin damage that was reversible. Only three ROIs were assessed in this analysis, and further research is warranted.

M/STBI differed from the controls on almost all measures of cognitive function, being more impaired in each domain than controls or the MTBI group. Although there was a trend in executive and attention function to be more impaired, the MTBI group did not differ significantly from controls in any domain scores.

The moderate to severe TBI subjects showed reduced function across all domains. There was a modest negative correlation between FA in individual regions of interest with cognitive function. However, the relationship between overall white matter load was more strongly related to the domains of executive and memory function than FA in individual ROIs. This suggests that a global measure such as white matter load is a useful index, as it appears to relate more clearly to declines in cognitive functions which rely on widespread cortical and subcortical networks.

While it is not surprising that moderate and severe injuries tend to show evidence of white matter changes and cognitive impairment, acquiring data on all severities in one study allows for the milder injuries to be assessed in the context of a spectrum of injury, from the healthy controls to the more severe injuries. Importantly, the controls were fairly well matched to the TBI groups in terms of age and years of education. None of the subjects were actively involved in litigation. These findings are consistent with TBI existing on a spectrum of neuropathologic severity and resulting disability, placing subjects with a history of mild TBI between controls and more severe injuries. In addition

to demonstrating that TBI, regardless of severity, results in chronic changes to the white matter microstructure, the present findings suggest that injury severity may differentially impact axons and myelin. This finding begins to address the issue of mechanism in the differential effects of mild versus more severe TBI on white matter.

In terms of white matter changes, there is some overlap between amount of pathology and the different clinical classifications of TBI severity. This is important in understanding variation in recovery. Certain injuries classified acutely as mild based on acute TBI variables such as loss of consciousness may actually be closer to moderate in the degree of pathology. Conversely, certain individuals with moderate or severe TBI may show more intact white matter than expected based on accepted means of clinical classification of injury severity. The data presented here demonstrate that DTI allows for a more sensitive delineation of severity and mechanism of white matter pathology, and may help to explain apparent discrepancies between clinically diagnosed injury severity and cognitive outcomes across the spectrum of TBI.

Acknowledgements

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Thalamic integrity underlies executive dysfunction in traumatic brain injury

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ABSTRACT

Objective: To quantify the effects of traumatic brain injury on integrity of thalamocortical projection fibers and to evaluate whether damage to these fibers accounts for impairments in executive function in chronic traumatic brain injury.

Methods: High-resolution (voxel size: 0.78 mm × 0.78 mm × 3 mm^3) diffusion tensor MRI of the thalamus was conducted on 24 patients with a history of single, closed-head traumatic brain injury (TBI) (12 each of mild TBI and moderate to severe TBI) and 12 age- and education-matched controls. Detailed neuropsychological testing with an emphasis on executive function was also conducted. Fractional anisotropy was extracted from 12 regions of interest in cortical and corpus callosum structures and 7 subcortical regions of interest (anterior, ventral anterior, ventral lateral, dorsomedial, ventral posterior lateral, ventral posterior medial, and pulvinar thalamic nuclei).

Results: Relative to controls, patients with a history of brain injury showed reductions in fractional anisotropy in both the anterior and posterior corona radiata, forceps major, the body of the corpus callosum, and fibers identified from seed voxels in the anterior and ventral anterior thalamic nuclei. Fractional anisotropy from cortico-cortico and corpus callosum regions of interest did not account for significant variance in neuropsychological function. However, fractional anisotropy from the thalamic seed voxels did account for variance in executive function, attention, and memory.

Conclusions: The data provide preliminary evidence that traumatic brain injury and resulting diffuse axonal injury results in damage to the thalamic projection fibers and is of clinical relevance to cognition. *Neurology*® **2010;74:558–564**

GLOSSARY

ACR = anterior corona radiata; **AN** = anterior thalamic nucleus; **bCC** = body of the corpus callosum; **CST** = cortical-spinal tract; **DAI** = diffuse axonal injury; **DM** = dorsomedial nucleus; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **fMaj** = forceps major; **fMin** = forceps minor; **FOV** = field of view; **FSE** = fast spin echo; **gCC** = genu of the corpus callosum; **IC** = internal capsule; **IFOF** = inferior frontal occipital fasciculus; **LOC** = loss of consciousness; **miTBI** = mild TBI; **msTBI** = moderate to severe TBI; **NEX** = number of excitations; **PCR** = posterior corona radiata; **PTA** = posttraumatic amnesia; **PU** = pulvinar; **ROI** = region of interest; **sCC** = splenium of the corpus callosum; **SLF** = superior longitudinal fasciculus; **SS** = sagittal stratum; **TBI** = traumatic brain injury; **TE** = echo time; **TR** = repetition time; **VA** = ventral anterior thalamic nucleus; **VL** = ventral lateral thalamic nucleus; **VPL** = ventral posterior lateral nucleus; **VPM** = ventral posterior medial nucleus.

Traumatic brain injury (TBI) is a serious public health problem with a high incidence[1-3] which can result in structural damage to the cerebrum including contusions, edema, and diffuse axonal injury (DAI).[4] DAI has been demonstrated in all stages and severities[5-7] and is often the only significant pathology in milder injury.[6,8-15] The variable nature of injury mechanism, severity, lesion presence, and location makes the identification and definition of the key cere-

bral mechanisms which underlie behavioral impairments challenging. Behaviorally, patients with a history of TBI commonly have deficits in cognition, behavior, and mood that load heavily on the executive or frontal lobe functions.[16-20] However, the relationship between measures of frontal lobe structure and shearing within frontal lobe white matter tracts and cognition are generally weak.[7,19,21] This weak relationship between frontal structure and function, coupled with the finding that DAI not only affects local function but can also disrupt critical cortical-subcortical pathways,[22,23] led us to the general hypothesis that damage to cortical-subcortical fibers projecting to and from the thalamus contribute to chronic impairment in cognition and behavior. This hypothesis is supported by the report that thalamic volume is related to 2-year outcome.[24] We tested the hypothesis that damage to thalamic projection fibers underlies executive function impairments using high-resolution diffusion tensor imaging of the thalamus (DTI) in a group of healthy controls and in 2 groups of patients who had sustained a closed-head brain injury.

METHODS **Standard protocol approvals, registrations, and patient consents.** The research was conducted in compliance with both institutional (University of Illinois at Chicago) and federal (Department of the Army) human subjects guidelines using standards consistent with the declaration of Helsinki. All subjects provided prospective, written, informed consent.

Participant characteristics. A total of 24 patients with a history of a single, closed-head type TBI were recruited via advertisements in local newspapers (no patients were recruited from an active clinical practice) and were screened and consented in the order they responded to advertisements. Inclusion criteria for patients and controls included age at study (18–50 years of age included), education (at least 1 year of high school), negative history (prior to TBI) for psychiatric illness, and English as a native language. For patients with TBI, age at injury was required to be after age 16 and at least 12 months prior to study. Patients were classified as having had a mild TBI (miTBI) if they reported either no loss of consciousness (LOC) or a LOC less than 30 minutes and posttraumatic amnesia (PTA) for less than 24 hours. Patients were classified as moderate to severe TBI (msTBI) if they experienced LOC greater than 30 minutes, PTA greater than 24 hours, or a positive MRI or CT study for contusion, edema, or ischemia at the time of injury. Detailed clinical assessments were carried out (M.F.K.) to establish injury severity and extract specific injury variables including mechanism of injury, presence and duration of LOC, neurologic examination, presence of posttraumatic headache, and associated injuries at the time of TBI. See table e-1 on the *Neurology*® Web site at www.neurology.org for details. Estimates of PTA and LOC are

presented as the nature and time from injury makes accurate estimates difficult. Subjects were excluded if they were taking any medications used to enhance cognitive function, had significant depressive symptoms, had current or past litigation related to the injury, or had failure on tests of effort and symptom validity. All but 2 of the patients with TBI had returned to work or school following the injury. Of the 2, 1 was unable to return to work and the other dropped out of college. The gross majority of subjects reported a level of function less than prior to the injury (20 of 24) even though more than 14 returned to the same job or matriculated to the next stage of schooling. Of the 24 patients with TBI, all but 3 reported some degree of sustained problems with cognition or sustained alteration in cognitive function at the time of testing. In terms of alterations in behavior, 12 of the 24 reported sustained alterations in behavior following the TBI.
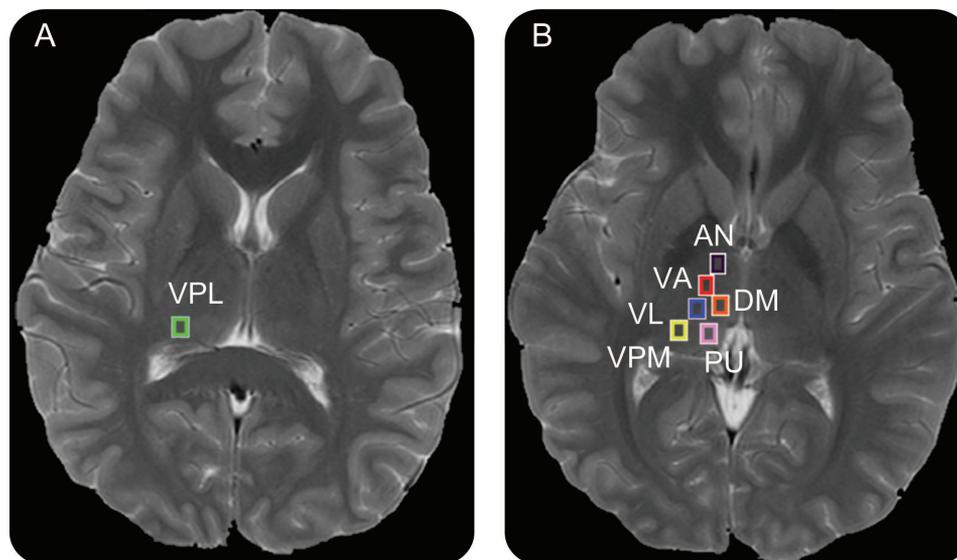
The groups were matched on age and education, with controls reporting 15 years of formal education (mean = 15.4, SEM = 0.6) and age at study of 31 years (mean = 30.8, SEM = 3.04); miTBI reporting 16 years of formal education (mean = 16.4, SEM = 0.36) and age at study of 31 years (mean = 31.2, SEM = 2.71); and msTBI reporting 16 years of formal education (mean = 16.1, SEM = 0.60) and age at study of 33 years (mean = 33.3, SEM = 3.20). The miTBI and msTBI were roughly matched for age at injury (miTBI: mean = 27.2 years of age, SEM = 2.4; msTBI: mean = 25.3 years of age, SEM = 2.9). All 3 groups were matched on estimates of premorbid IQ (controls: mean = 112.4, SEM = 3.55; miTBI: mean = 111.2, SEM = 2.78; msTBI: mean = 111.7, SEM = 1.6).

Statistical analyses. Neuropsychological test scores were analyzed using a one-way analysis of variance with group membership (controls, miTBI, msTBI) as the between-subjects factor and were corrected for multiple comparisons using the least significant difference post hoc tests. The primary measures of interest were 3 scores which were each a composite of those individual test results which loaded preferentially on executive, memory, and attention domains. Group differences on individual neuropsychological tests were corrected for multiple comparisons using the Bonferroni correction. The primary analyses carried out on the dependent measures extracted from the DTI data were a one-way mixed design analysis of variance with group membership (controls, miTBI, and msTBI) as the between-subjects factor. The primary dependent measure was fractional anisotropy (FA). Data were confirmed to have a normal distribution using the Kolmogorov-Smirnov test. To examine the relative contributions of thalamic and cortical (to include cortico-cortico and corpus callosum white matter) regions of interest, both bivariate correlations and stepwise linear regressions were used.

Neuropsychological testing. Subjects completed a neuropsychological battery comprised of tests known to be sensitive to the cognitive deficits associated with TBI, with a focus on tests of executive function, attention, memory, and processing speed. Additional measures were included to assist in the estimation of premorbid function and to assess effort. Tests and selected scores from the tests are included in table e-2. These test scores were converted to standardized *z* scores (based upon control means) and combined to create 3 cognitive domains (executive, attention, memory).

Image acquisition. In order to reliably perform the FA analysis and fiber tracking in the thalamus, we used a customized high-resolution DTI protocol which relied on a single-shot EPI acquisition[25] together with parallel imaging using an 8-channel phased-array head coil on a GE 3.0 T Signal HDx scanner (Gen-

Seed regions for the ventral posterior lateral nucleus (VPL) (green), anterior thalamic nucleus (AN) (purple), ventral anterior thalamic nucleus (VA) (red), dorsomedial nucleus (DM) (orange), ventral lateral thalamic nucleus (VL) (blue), ventral posterior medial nucleus (VPM) (yellow), and pulvinar (PU) (pink) overlaid on the T2-weighted images.

eral Electric Healthcare, Milwaukee, WI). The imaging parameters included repetition time (TR)/echo time (TE) = 5,000/64 msec, b = 0,1000 s/mm^2, diffusion directions = 27, field of view (FOV) = 20 × 20 cm^2, matrix = 256 × 256, slice thickness/gap = 3/0 mm, slices = 7, number of excitations (NEX) = 8, and acceleration factor = 2. In order to visualize the thalamus and differentiate the thalamus from surrounding structures, a set of 2D T2-weighted images were acquired (fast spin echo [FSE], axial, TR/TE = 4,000/80 msec, ETL = 8, matrix = 512 × 256, FOV = 20 × 20 cm^2, slices = 7, slice thickness/gap = 3/0 mm). To visualize the dorsomedial nucleus, 3-dimensional inversion recovery spoiled gradient recalled echo (3DIRpSPGR) images were acquired (TR/inversion time/TE = 13.8/600/2.7 msec, flip angle = 25°, matrix = 512 × 192, FOV = 22 × 16 cm^2, slices = 120, slice thickness = 1.5 mm, NEX = 1, bandwidth = ±15.6 kHz).

Diffusion tensor imaging and analysis. DTI is a type of diffusion-weighted imaging that allows the assessment and visualization of large white matter fibers on a millimeter-level multidimensional scale. DTI takes advantage of the diffusivity of water and the restrictions imposed on the diffusion of water by white matter fiber tracts. When fiber tracts are dense the restriction imposed by their density leads to directionally dependent or anisotropic diffusion with the shape of water diffusion occurring preferentially along those tracts. When there is less organization or a lack of aligned and organized fiber structures (i.e., gray matter, CSF, axonal loss, or demyelination) the shape of water diffusion will be more isotropic. Commonly, the degree of alignment and anisotropy is calculated as the FA. FA values range from 0 to 1, where 0 represents isotropic diffusion and 1 represents anisotropic diffusion.

In the present study, the diffusion images were reconstructed and FA calculated using DTI Studio.[26] For each slice, the set of 28 DTI images were examined for image quality. Head movement was required to be within 1 voxel across the image acquisition. Because noise can introduce bias in estimates of the eigenvalues and decrease the signal-to-noise ratio, a background noise level of 125 (MR units) was applied prior to calculation of

pixel-wise FA, eigenvectors, and eigenvalues. All region of interest (ROI) analyses were carried out on each individual in original image space.
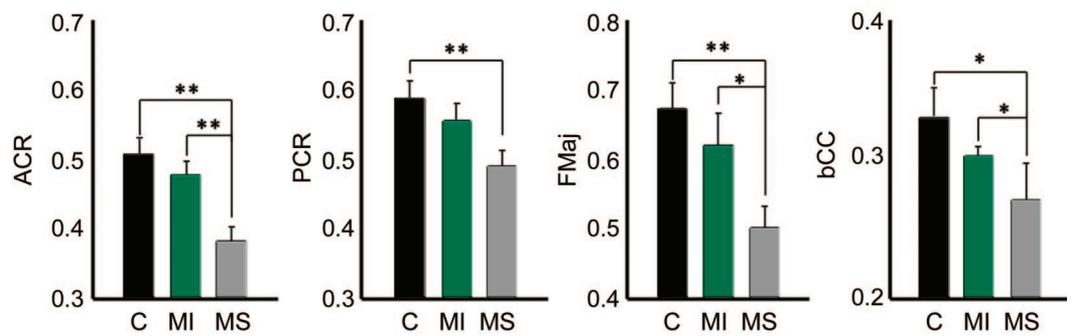
Effects of trauma on cerebral white matter. To assess the effects of trauma on DTI, 3 analyses were applied. Gross measures of whole brain FA and thalamic FA were extracted. For the whole brain mask, each voxel with a FA greater than 0.2 was included (ensuring only white matter in the calculations). Second, specific ROI were drawn on corpus callosum and cortico-cortico white matter tracts, which have been previously implicated in head injury.[7] These "cortical" ROIs were placed on the cortical-spinal tract (CST), anterior corona radiata (ACR), posterior corona radiata (PCR), forceps minor (fMin) and forceps major (fMaj), sagittal stratum (SS), internal capsule (IC), inferior frontal occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), and in the genu (gCC), body (bCC), and splenium (sCC) of the corpus callosum. Separate ROIs were placed in the left and right hemisphere where appropriate. Details on placement can be found in figure e-1.

Finally, fiber tracking was used to assess damage to the fibers projecting from the thalamus. Seed voxels (small ROIs) were placed in 7 thalamic regions (shown in figure 1) including the anterior thalamic nucleus (AN), ventral anterior thalamic nucleus (VA), ventral lateral thalamic nucleus (VL), dorsomedial nucleus (DM), ventral posterior lateral nucleus (VPL), ventral posterior medial nucleus (VPM), and pulvinar (PU). The purpose of these seed voxels is to identify all fiber tracts which run through this region. FA can then be extracted from these fibers identified by the seed voxels and fiber tracking from these seeds. Interrater reliability was greater than 0.94 for placement of AN, VA, DM, VL, and PU seed voxels. Interrater reliability was 0.85 for VPL and VPM. Specific details and rules for placement are included in appendix e-1 and figure e-2.
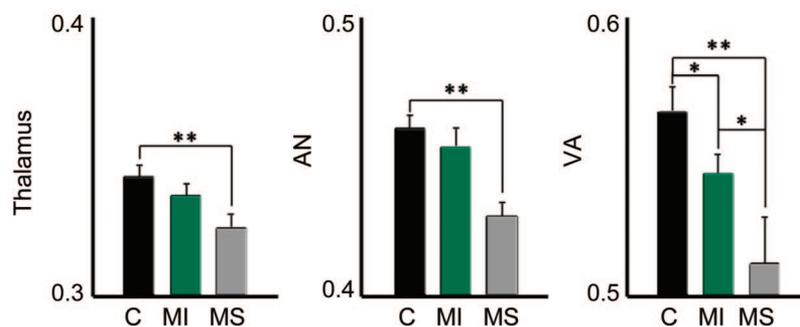
RESULTS Behaviorally, patients with a history of TBI performed worse on measures of executive func-

Figure 2   Average cortical and subcortical fractional anisotropy (FA)

A   Significant cortical regions of interest

B   Significant subcortical regions of interest

Mean FA extracted from the anterior corona radiata (ACR), posterior corona radiata (PCR), forceps major (fMaj), and body of the corpus callosum (body of the corpus callosum) as well as from the thalamus and from fibers identified from seed regions in the anterior thalamic nucleus (AN) and ventral anterior thalamic nucleus (VA). Significant post hoc comparisons between groups are indicated (*$p < 0.05$; **$p < 0.01$). Cortical in this figure refers to regions of interest that include cortico-cortico tracts and regions in the corpus callosum.

tion relative to controls [$F(2,36) = 5.15$, $p = 0.011$, $\eta^2 = 0.26$]. Although there were trends for reduced attention and memory performance in TBI, neither of these comparisons reached significance. These findings are consistent with previous work from our group and the literature in general.[7,27-29] A detailed list of performance for each subject group on each test can be found in table e-2.

There was an overall effect of subject group (controls, miTBI, msTBI) on FA in the ACR [$F(2,36) = 9.71$, $p < 0.001$, $\eta^2 = 0.0.37$], PCR [$F(2,36) = 3.91$, $p = 0.030$, $\eta^2 = 0.19$], fMaj [$F(2,36) = 5.07$, $p = 0.012$, $\eta^2 = 0.23$], and bCC [$F(2,36) = 4.002$, $p = 0.028$, $\eta^2 = 0.20$], with the greatest differences between controls and those with more severe injury (msTBI; see figure 2A). The patients did not differ from controls in the remaining cortical ROIs (see table e-3 for additional details). Nor did they differ in whole brain FA. There was an overall effect of subject group on thalamic FA [$F(2,36) = 5.40$, $p = 0.009$, $\eta^2 = 0.25$] with controls having higher FA in the thalamus than msTBI. Although there was a trend for the miTBI to show reduced FA relative to

controls in thalamic FA, the comparison did not reach significance (see table e-3 for additional details).

Comparisons between groups on FA extracted from the seed regions in the thalamic nuclei are presented in figure 2B. There was an effect of subject group only in fibers extracted from the AN [$F(2,36) = 5.82$, $p = 0.007$, $\eta^2 = 0.26$] and VA [$F(2,36) = 4.82$, $p = 0.015$, $\eta^2 = 0.23$] seed voxels. Post hoc comparisons among controls, miTBI, and msTBI are also indicated on figure 2B.

To examine the relationship between cognition and fiber tract integrity, a series of bivariate correlations were conducted. All of the ROIs were included and examined relative to the neuropsychological domain scores for executive function, memory function, and attention. Correlations were conducted for the control and TBI separately so as not to bias the correlation simply because patients show lower FA than controls.

For controls, there was a statistical relationship between the executive domain score and FA of the gCC ($r = 0.685$, $p = 0.014$) as well as FA of fibers identified with the VL seed voxel ($r = 0.586$, $p = $

A Scatterplots between executive domain scores and thalamic nuclei

B Scatterplots between attention domain scores and thalamic nuclei

C Scatterplot between memory domain scores and thalamic nuclei

● Mild TBI
● Moderate to severe TBI

Scatterplots of FA from thalamic seed voxels relative to executive (A), attention (B), and memory (C) domain scores for traumatic brain injury (TBI) patients. Best-fit lines are indicated in black.

0.045). The attention domain scores were also correlated with FA from the VL ($r = 0.668$, $p = 0.018$) and VPL ($r = 0.639$, $p = 0.025$). Memory function in controls was associated with FA in the genu of the gCC ($r = 0.667$, $p = 0.018$) and inferior frontal occipital fasciculus ($r = 0.605$, $p = 0.037$).

Scatterplots of the significant correlations between neuropsychological function and FA for the TBI are presented in figure 3. In the TBI groups, there were no correlations between any cortical or corpus callosum ROIs with executive function, attention, or memory performance. There was a relationship between the attention domain and FA in the gCC ($r = 0.506$, $p = 0.012$). For thalamic seed voxels, executive function was related to FA extracted from seed voxels in the AN ($r = 0.497$, $p = 0.014$), VA ($r = 0.741$, $p < 0.001$), and VL ($r = 0.540$, $p =$

0.006). Similar relationships were also found between the attention domain score and integrity of fibers from the AN ($r = 0.489$, $p = 0.015$), VA ($r = 0.786$, $p < 0.001$), and VL ($r = 0.523$, $p = 0.009$). In contrast, memory function was associated with integrity of VPL fibers ($r = 0.540$, $p = 0.006$). Integrity of DM was not associated with memory function. Correlations between individual neuropsychological tests and ROIs can be found in table e-4.

We also examined the injury variable duration of loss of consciousness relative to FA measures and relative to domain scores. Accurate ranges of LOC were collected for 19 of 24 subjects. The remaining subjects reported LOC but did not have a witness present. Duration of LOC was negatively correlated with the executive domain ($r = -0.460$, $p = 0.048$) and memory domain ($r = -0.500$, $p = 0.029$).

LOC also correlated with FA from the bCC ($r = -0.661$, $p = 0.002$).

Because of a significant amount of shared variance between nuclei, a series of linear regressions were applied to the TBI data with the executive function domain score as the dependent variable. In the first stepwise linear regression, the frontal lobe ROIs including the ACR, fMin, and gCC were entered. This model did not account for the executive domain variance ($r^2 = 0.19$, $p = 0.236$). Because the white matter tracts are not contained within the frontal lobe, we expanded this regression to include any ROIs which have fiber projections to or from the frontal lobes. This model was expanded to include not only the ACR, fMin, and gCC but also the CST, SS, and IFOF. Although this model accounted for more variance than the first model, it still did not reach significance ($r^2 = 0.322$, $p = 0.291$). This same strategy was applied to the fiber projections from the thalamic nuclei. The projections from the AN, VA, VL, and DM were entered into a linear regression with executive function as the dependent measure. This model did account for variance in the executive domain ($r^2 = 0.674$, $p < 0.001$). Within this model, the only unique predictor was FA from the VA seed voxels ($p = 0.001$) with VA accounting for 26% of the unique variance. Duration of LOC was also added into the regression models. Although it accounted for additional variance in the subcortical model ($r^2 = 0.701$, $p < 0.001$), LOC on its own was not a significant unique predictor.

DISCUSSION The present study presents preliminary support for a thalamic hypothesis as a central mechanism of injury and resultant cognitive impairment in TBI. The thalamus, although not located near the skull and therefore less susceptible to direct contusion, is likely differentially sensitive to shear and strain injury because of the corticospinal fibers which extend from the spine to the cortex. Within the thalamus, incoming sensory, motor, and cognitive processing pathways are organized and integrated within distinct nuclei. Following this integration, various thalamic nuclei send diffuse and specific efferent projections to cortical, cerebellar, and subcortical regions. The thalamus is also known to gate and mediate many cognitive, sensory, motor, and behavioral functions and damage to these projection fibers can result in widespread functional impairments.[30,31] Overall, thalamic lesions are associated with a decrease in executive function with larger lesions associated with greater deficits.[32,33] In the case of frontal lobe functions, impairments in executive function could be accounted for by damage to the fiber projections to and from the dorsomedial nucleus or anterior thalamic or ventral anterior thalamic nuclei rather than the frontal lobes per se.

However, because the thalamus is a relay center for the majority of cortical fiber projections, characterization of thalamic damage must include assessments of the integrity not only of thalamus proper but also for fibers entering or exiting the thalamic nuclei. The fiber tracking methods employed here with the spatial resolution provided by the sequences used allow this concern to be addressed. These projection fibers may in fact be even more susceptible to TBI than the thalamus itself because of the sharp turning angles of the cortical-subcortical fibers both as they leave the thalamus and again as they enter the cortex.[22,23]

The present data reaffirm the presence of executive dysfunction in TBI and suggest that executive dysfunction is correlated with cortical-subcortical damage rather than simply due to damage to the cortical frontal lobe structures, cortico-cortico tracts, or corpus callosum alone. This conclusion is supported both by the presence of correlations between executive function and FA in thalamic nuclei and also by the absence of correlations with FA in the measured cortical regions. The data do not, however, identify the location of damage within these fiber tracts. The primary damage to these fibers could occur at the boundary of the thalamus as the fibers exit the thalamus or it could occur at the junction of gray and white matter as the fibers enter the cortex.

Although these conclusions are based upon a relatively small sample (n = 24), the data suggest that thalamic integrity may be a central mechanism in TBI and provide initial evidence that damage to thalamic projection fibers, especially those involved in frontal-thalamic circuitry, is of great importance in understanding executive dysfunction following TBI. Furthermore, the findings support the need for further investigation into the applicability of these measures in other populations which demonstrate executive dysfunction.

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Verbal Learning Strategy Following Mild Traumatic Brain Injury

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Abstract

That learning and memory deficits persist many years following mild traumatic brain injury (mTBI) is controversial due to inconsistent objective evidence supporting subjective complaints. Our prior work demonstrated significant reductions in performance on the initial trial of a verbal learning task and overall slower rate of learning in well-motivated mTBI participants relative to demographically matched controls. In our previous work, we speculated that differences in strategy use could explain the differences in rate of learning. The current study serves to test this hypothesis by examining strategy use on the California Verbal Learning Test-Second Edition. Our present findings support the primary hypothesis that mTBI participants under-utilize semantic clustering strategies during list-learning relative to control participants. Despite achieving comparable total learning scores, we posit that the persisting learning and memory difficulties reported by some mTBI patients may be related to reduced usage of efficient internally driven strategies that facilitate learning. Given that strategy training has demonstrated improvements in learning and memory in educational and occupational settings, we offer that these findings have translational value in offering an additional approach in remediation of learning and memory complaints reported by some following mTBI. (*JINS*, 2011, *17*, 709–719)

Keywords: Post-concussive syndrome, Concussion, Semantic, Cognition, Executive functions, Brain/behavior relationships

INTRODUCTION

That learning and memory difficulties are an acute consequence of mild traumatic brain injury (mTBI) is well supported. That deficits persist years following injury, however, is a controversial issue. While the majority of individuals do not appear to experience persisting cognitive difficulties after mTBI, a subset of patients do demonstrate such difficulties (Benedictus, Spikman, & van der Naalt, 2010; Ponsford et al., 2000). For a myriad of complex reasons (e.g., psychological, motivational), this subset proves a challenge for clinicians. Prior work conducted in our laboratory using a non-clinical, non-litigating sample of mTBI patients attempted to address issues related to memory complaints often raised by clinical

patients and their families (Geary, Kraus, Pliskin, & Little, 2010). Our previous work focused on trial-by-trial performance on a measure of verbal learning in a sample of community-recruited mTBI participants. We reported that mTBI participants demonstrated diminished acquisition on the initial learning trial and evidenced an overall slower rate of learning across trials in the context of equivalent performance relative to controls on the total learning and memory indices (Geary et al., 2010). Furthermore, performance on the verbal learning task was related to imaging measures showing a relationship between the effects of injury on cerebral white matter integrity and behavioral performance. One limitation of our previous work was that we were unable to comment on the specific mechanism that may underlie our behavioral findings. In this previous work, we proposed the hypothesis that meta-cognitive strategy use might underlie the verbal learning deficiency in mTBI.

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Examining higher-order "meta-cognitive" learning and memory strategies has particular relevance in patient populations including mTBI where evidence of chronic primary temporal lobe/diencephalic memory dysfunction is not generally supported (Binder, Rohling, & Larrabee, 1997; Cicerone & Kalmar, 1995; Dikmen et al., 2009; Ettenhofer & Abeles, 2009; Iverson, 2005; Schretlen & Shapiro, 2003; West, Curtis, Greve, & Bianchini, 2010). Others have argued that memory deficiencies following mTBI could be influenced by dysfunction in frontal-subcortical networks which may support meta-cognitive functions (Alexander, Stuss, & Gillingham, 2009; Bruce & Echemendia, 2003; Little et al., 2010). In learning and memory, meta-cognitive functions such as restructuring information via the identification of shared relationships between items and/or other internally driven mnemonic devices increase one's ability to learn and recall information (Becker & Lim, 2003; Schefft, Dulay, & Fargo, 2008). Studies in TBI and other neurologic populations provide evidence that successful recall of items on list-learning tasks is influenced by how well one consistently uses an efficient (i.e., semantic, subjective) recall strategy (Bruce & Echemendia, 2003; Chan et al., 2000; Gongvatana et al., 2007; Gsottschneider et al., 2010; Luek, 1976; Ribeiro, Guerreiro, & De Mendonça, 2007).

When conceptualizing meta-cognitive strategies hierarchically in terms of degree of cognitive engagement, semantic clustering arguably constitutes a sophisticated strategy. Semantic clustering encompasses mentally grouping items from the same taxonomic category at greater than chance levels and is most often associated with improved learning and recall (Delis, Freeland, Kramer, & Kaplan, 1988). In order for semantic clustering strategies to be used, an individual must first identify that semantic relationships exist, use the strategy by compartmentalizing words during list encoding, and then use the semantic groups during both initial and subsequent recall. In list-learning tasks such as the California Verbal Learning Test (CVLT-II), this process involves recognizing that the pseudo-random presentation of 16 target words consists of items from four semantic categories, regrouping words according to these categories, and organizing these words by category during recall.

In contrast to semantic clustering, subjective clustering may involve restructuring the list based on phonemic features of items or another personally derived mnemonic strategy. Because subjective clustering is internally derived, it is suspected when one recalls two or more words together from one trial to the next independent of semantic or serial clustering strategies.

Finally, serial clustering, or recalling words in the order of presentation, may partially reflect the tendency to recall the first words and last words presented (primacy/recency effects). Of all three strategies, serial clustering requires the least amount of cognitive engagement as the structure is externally facilitated by presentation order. If used at the exclusion of the other two strategies, serial clustering tends to be the least efficient as it often results in poorer performance (Delis et al., 1988). Serial clustering is often most readily applied across trials in memory impaired populations

(Gsottschneider et al., 2010; Jefferies, Hoffman, Jones, & Ralph, 2008; Ranjith, Mathuranath, Sharma, & Alexander, 2010).

In our prior work, while there were no significant group differences on the traditional executive function measures in our analyses (Geary et al., 2010; Kraus et al., 2007), we speculated that differences in the rate of learning between groups could be related to less often analyzed executive functions including strategy use on the CVLT-II. Like others, we reasoned that these individualized measures of performance may be more sensitive to subtle diffuse effects following mTBI (Cicerone, Levin, Malec, Stuss, & Whyte, 2006; Schweizer, Alexander, Gillingham, Cusimano, & Stuss, 2010). The purpose of the present investigation is to test the hypothesis that semantic clustering will predict learning rate for control participants but not for our mTBI participants.

METHODS

Participants

From a larger sample of participants described previously (Geary et al., 2010), CVLT-II response data were available and analyzed for a total of 35 mTBI participants (19 females) and 28 healthy controls (15 females). Participants were recruited via advertisements in the community seeking individuals who had ever sustained a closed head injury, concussion, or traumatic brain injury. No participants were recruited from active clinical practices for treatment of TBI. All participants provided written informed consent and experimental procedures complied with the code of ethics of the World Medical Association, Declaration of Helsinki, and Institutional Review Board. Participants were excluded if they had a history of psychiatric disorder before the TBI, substance abuse/dependency, current or past litigation, failure on a formal measure of effort, or any other neurologic or medical condition that could result in cognitive changes (e.g., hypertension, severe chronic pain). For this study, participants were also excluded if there was positive radiologic finding of contusion or bleed, or, upon review of both T2- and T1-weighted magnetic resonance imaging, evidence of skull fracture suggesting significant trauma to the head. No mTBI participants had evidence of focal neurological symptom at the time of evaluation. Additionally, participants were not receiving any psychiatric medication or medications used for cognitive enhancement at the time of the study. The criteria used for defining mTBI follow the guidelines set forth by the American Congress of Rehabilitation Medicine (ACRM, 1993), including endorsement of at least one of the following: any period of loss of consciousness (LOC); any loss of memory for events immediately before or after the accident (PTA); any alteration in mental state at the time of the accident; focal neurological deficit (ACRM, 1993; Cassidy et al., 2004). These criteria help ensure that our sample were, in fact, mild severity (LOC less than 30 min; PTA less than 24 hr, and/or the Glasgow Coma Scale greater than or equal to 13) (ACRM, 1993; Cassidy et al., 2004; Levin, 1992; Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006).

Table 1. Demographics and brain injury variables

	Control (*n* = 28)		mTBI (*n* = 35)		*t* value	*p* value
	Mean	*SD*	Mean	*SD*		
Demographic variables						
Age	31.64	9.02	33.91	10.09	−0.93	0.356
Years of education	15.79	1.73	16.37	2.09	−1.193	0.238
Years of employment	12.05	9.86	16.24	10.25	−1.618	0.111
Hollingshead highest level of employment	6.47	1.61	6.43	1.52	0.088	0.930
WTAR Full-Scale IQ estimate	110.21	11.40	110.54	9.67	−0.124	0.902
TOMM Trial 2	50.00	0.00	49.90	0.32	1.547	0.129
Dot Counting	8.60	2.50	9.07	2.49	−0.647	0.521
Employed/student at evaluation (% sample)	92.90%		94.30%			
Gender (M/F)	13	15	16	19		
TBI variables						
Age at TBI (years)	—	—	28.54	10.81		
Time since injury (years)	—	—	5.63	6.57		
Length of loss of consciousness (*N* = 17) (minutes)	—	—	5.71	9.21		
Length of post-traumatic amnesia (*N* = 10) (minutes)	—	—	33.50	26.98		
Returned to work/school following injury (% sample)	—	—	94.30%			

For individuals who had witness-confirmed information on duration of LOC and/or PTA the average reported LOC was 5.7 minutes (N=17; range = 0–30 min) and average reported PTA was 33.5 min (N = 10; range = 0–60 min). For patients without specific information regarding LOC (N = 18) or PTA (N = 25), we relied upon estimates of self-report and witness report of duration of LOC or PTA. These criteria reduce the risk of Type I error as the reliance on self-report and inclusion of no minimum LOC raises the possibility that participants classified as mTBI may not have sustained a brain injury. We adopted this more conservative approach to ensure that we did not bias data in favor of the study hypothesis by including complicated mild or moderate TBI.

The mechanism of injury for the mTBI participants included motor vehicle accidents (MVA; N = 9), pedestrian *versus* MVA (N = 2), assault (N = 3), sports-related (N = 10), and falls or blows to the head (N = 11). Twelve patients reported experiencing more than one mTBI (range, 2–7 mTBI). Given that the purpose of this study was to elaborate on findings from the originally published work, and the original findings were supported regardless of the inclusion of multiple TBI patients, we did not exclude on the basis of history of multiple mTBI. Demographic data and injury related variables are presented in Table 1.

MATERIALS AND PROCEDURE

Neuropsychological Assessment

As detailed previously, participants completed an extensive neuropsychological test battery that was assembled to assess executive function, attention, and memory (Kraus et al., 2007). Performance on individual measures from this battery for both groups are presented in Table 2. The CVLT-II was used to assess list-learning and memory. In addition to capturing the amount of verbal information an individual can learn and recall, the CVLT-II measures many individualized elements of precisely how information is learned (Delis, Kramer, Kaplan, & Obers, 2000a). We examined the following CVLT-II strategies.

Calculation of Clustering Scores

Chance adjusted (CA) semantic category clustering individual trials

Semantic clustering involves recalling two or more words by virtue of shared semantic category. Recent theories of semantic clustering argue that organization processes occur during list-learning, presumably as semantic categories are identified. Semantic cluster scores were calculated based on the list-based measure of observed minus expected clustering offered by Stricker, Brown, Wixted, Baldo, and Delis (2002), which was recently demonstrated to show improved classification rates when used with clinical samples (Delis et al., 2010). For scoring *observed* semantic clusters, one point is given for each correct semantic cluster (i.e., each pair of words from the same semantic category), for a maximum of 12 points for each trial. For example, successive recall of the words *cat/dog/fish* would yield an observed semantic cluster score of two. The CA semantic clustering score used in analyses is the observed semantic clustering score minus the expected semantic clustering score. To calculate expected semantic clustering score, we adopted the method illustrated in Equation 1 (Delis, Kramer, Kaplan, & Obers, 2000b).

$$\text{Eq. 1.} \quad \text{Expected Sem Cl} i = \frac{[(r-1)(m-1)]}{N_L - 1}$$

where, "i" represents a given trial, "r" the number of correct words recalled on trial i, "m" represents the number of members

Table 2. Neuropsychological test performance

	Control (n = 28)		mTBI(n = 35)		t value	p value	η²
	Mean	SD	Mean	SD			
Executive							
COWAT Total	42.79	11.39	40.51	11.09	0.798	0.425	0.010
CPT Errors of Commission	11.21	6.27	14.09	6.55	−1.753	0.085	0.049
Digit Span Backward	8.61	2.42	7.60	2.66	1.553	0.126	0.038
Trails B (s)	51.18	12.87	48.00	11.49	1.034	0.305	0.017
Stroop Color-Word (s)	52.54	10.67	49.86	9.68	1.043	0.301	0.018
Spatial Span Backward (s)	10.93	2.57	11.37	2.60	−0.675	0.502	0.007
RUFF Unique Designs (s)	45.99	13.43	43.94	9.03	0.723	0.472	0.009
Attention							
Digit Span Forward (s)	11.11	2.63	11.43	2.19	−0.530	0.598	0.005
Spatial Span Forward (s)	11.43	3.10	10.09	3.45	1.606	0.113	0.041
Trails A (s)	51.61	15.21	48.34	11.12	0.983	0.329	0.016
CPT Number of Omissions Raw	3.25	6.73	1.71	2.37	1.250	0.216	0.025
Other Memory							
BVMT Trials 1–3 Total	27.39	5.00	25.17	5.23	1.709	0.093	0.046
BVMT Delay Recall	9.96	1.53	9.49	1.79	1.125	0.265	0.020

Note. (s) = standard score; CPT = Conners Continuous Performance Test; COWAT = Controlled Oral Word Association Test; RUFF = Ruff Figural Fluency Test; BVMT = Brief Visual Spatial Memory Test.

of each semantic category on the original list, and "N_L" the total number of words on the original list. As such, the CA scores can range from a high of 9.0 (perfect semantic clustering with a total recall score of 16) to a low of −3.0 (no observed semantic clustering with a total recall score of 16) (Delis et al., 2000b).

Chance adjusted (CA) subjective clustering individual trials

Subjective clustering involves word pairs recalled together from one trial to the next, which do not adhere to semantic or serial clustering strategies. For example, subjective clusters may consist of seemingly unrelated words, which have been grouped using some mnemonic by the individual (e.g., *car* full of *lettuce*) or words that share phonemic qualities (e.g., *sofa/soup*). The observed directional subjective clustering score includes any target words recalled together (either in forward order or backward order) across two consecutive trials. The expected subjective clustering score is calculated using the method illustrated in Equation 2.

$$\text{Eq. 2.} \quad \text{Expected Subj Cl}ii = \frac{[(2c)(c-1)]}{hk}$$

The expected value consists of "ii" which represents the subjective clustering score between two given trials, "c," which is the number of common items recalled in Trials t and t + 1 (regardless if grouped together), "h," which is the number of recalled items in Trial t, and "k," which is the number of items recalled in Trial t + 1 (Sternberg & Tulving, 1977). The CA subjective clustering score used in analyses is the observed subjective clustering score minus the expected subjective clustering score. An example is if the word pair

car/lettuce (subjective observed score of 1) is recalled together on trial one and trial two with 8 total words correctly recalled on trial one (t = 8) and 9 total words correctly recalled on the trial two (t + 1 = 9). If there were 4 words in common across both trials (but only one subjective cluster), the subjective clustering expected score would be calculated using: c = 4 (4 words recalled on both trial 1 & trial 2), h = 8 as trial 1 had 8 total correct words recalled, k = 9 as trial 2 had 9 total correct words recalled: 2(4)*(4−1)/(8*9) = 0.333. This result is then inserted into the CA subjective clustering formula of observed subjective clustering (*car/lettuce*, subjective observed score of 1) minus expected subjective clustering or [1–0.333] = 0.667, yielding a subjective clustering score of 0.667 for trial 1 to trial 2. A higher number demonstrates greater frequency of subjective clustering.

Chance adjusted (CA) serial clustering individual trials

Serial clustering encompasses recalling items in the order in which they were presented. The serial position effect (Young, Hakes, & Hicks, 1965) is demonstrated by a tendency to recall more items from the first (i.e., primacy) and last (i.e., recency) portions of a word list. On the CVLT-II, a serial recall *strategy* is an extension of the serial position effect as it involves grouping items in the order in which they were presented. For serial cluster scoring, one point was given each time two correct items from the list are recalled in the same order in which they were presented. For example, successive recall of the second and third words would yield a serial forward order score of one. We also scored serial clusters backward with one point given every time a correct target word immediately followed another correct target word in reverse order.

The bidirectional serial clustering observed score encompasses a summation of observed forward (F) serial clustering and observed backward (B) serial clustering. The CA serial clustering score is illustrated in Equation 3:

$$\text{Eq. 3.} \quad (\text{Observed F} + \text{B Serial Cl}i) - \text{Expected F}$$
$$+ \text{B Serial Cl}i = \frac{[(c-1)]}{15}$$

where "i" is represents a given trial and "c" is the number of correctly recalled items for the trial. The CA serial score thereby reflects observed bidirectional serial clustering minus expected bidirectional serial clustering.

Statistical Analysis

Consistent with previous work (Geary et al., 2010), data from each individual were fitted to a power function (Eq. 4). The power function, which is commonly applied in the behavioral learning literature (Anderson, 1982; Logan, 1998), was done by applying a two-parameter power function and calculating the best-fit line. The primary dependent measure for this analysis was total number of correctly recalled items per trial. This function was applied to data from each participant. We extracted the y-intercept (represented by y in Eq. 4), which equates to the location at which the best-fit line crosses the y-axis, and slope (represented by b in Eq. 4) which reflects how quickly learning is accomplished and/or the position at which the line becomes asymptotic. Unlike the CVLT-II learning trials 1–5 slope which reflects a least squares linear regression, the power function allows for characterization of the rate of change (exponential growth).

$$\text{Eq. 4.} \quad y = ax^b$$

Correlations and regression analyses were used to evaluate the extent to which each of the clustering strategies predicted the rate of learning, the primary outcome measure, in patients and controls separately. First, Pearson's correlations were conducted to evaluate the unadjusted relationship between the three CA clustering strategies and overall rate of learning. Next, stepwise regression analyses were conducted to assess the extent to which each strategy contributed unique variance to overall learning rate.

RESULTS

Consistent with our prior reported observations (Geary et al., 2010), groups differed on performance on the initial learning trial of the CVLT-II ($p < .05$). This relationship is shown in Figure 1a. Table 3 details performance on CVLT-II variables. Groups did not differ significantly on total learning or delayed memory scores or ListB recall (all p's $> .05$). Groups did differ on average CA semantic clustering across five trials ($p < .05$).

Pearson's correlations were conducted to evaluate the unadjusted relationship between the three CA clustering
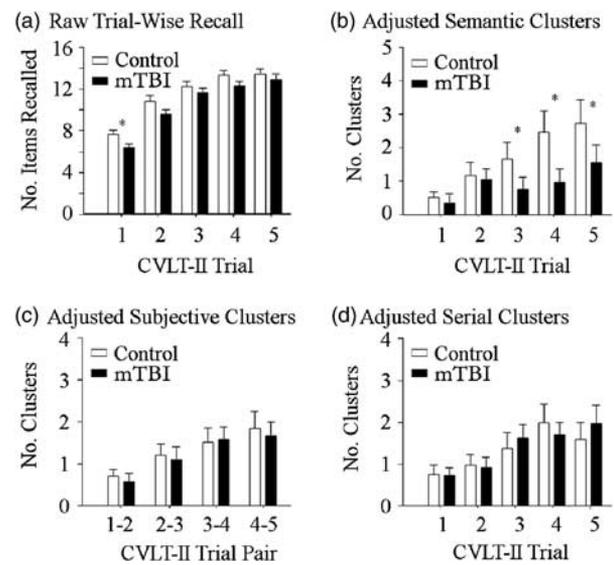

Fig. 1. a: CVLT-II raw recall findings across trials one through five for controls and patients with mTBI. Statistically significant difference between groups was only observed on the first learning trial. b: Chance adjusted semantic clusters across trials one through five for control and mTBI participants. Statistically significant differences between groups were observed on trials three through five. c: Chance adjusted subjective clusters scores across trials for control and mTBI participants. No statistically significant differences between groups were observed across trials. d: Chance adjusted serial clusters across trials one through five for control and mTBI participants. No statistically significant differences between groups were observed across trials.

strategies and overall rate of learning. For control participants, average CA semantic ($r = 0.566$; $p < .01$) and average CA subjective ($r = 0.565$; $p < .01$) clustering was related to overall learning rate. For mTBI, only CA serial clustering was related to overall learning rate ($r = 0.432$; $p < .01$).

To test our primary hypothesis that clustering strategy could explain learning rate on the CVLT-II, a stepwise linear regression analysis was undertaken by group entering the average five-trial CA semantic clustering score, average five-trial bidirectional CA serial clustering score, and average four CA subjective clustering scores, as predictors of rate of overall learning. These analyses revealed that for the control participants, average CA semantic clustering score ($\beta = 1.17$; $t(25) = 6.45$; $p < .001$) and average CA serial clustering score ($\beta = 0.82$; $t(25) = 4.53$; $p < .001$) were significant predictors of overall rate of learning ($R^2 = 0.63$; $F(2,25) = 20.980$; $p < .001$) accounting for 32% and 31%, respectively, of the variance in overall learning rate. For mTBI participants, only the average CA serial clustering score ($\beta = 0.43$; $t(33) = 2.75$; $p < .01$) was a significant predictor of learning rate ($F(1,33) = 7.58$; $p < .01$) accounting for 19% of the variance.

To better understand differences in strategy use on the CVLT-II, we conducted three separate *post hoc* mixed factor analyses of variance (i.e., one per clustering strategy).

Table 3. Raw scores of CVLT-II performance

	Control (N = 28)		mTBI (N = 35)		t value	p value	η²
	Mean	SD	Mean	SD			
Trial 1 Raw	7.64	2.04	6.40	1.79	2.576	0.012	0.098
Trial 2 Raw	10.79	2.62	9.57	2.67	1.810	0.075	0.051
Trial 3 Raw	12.21	2.47	11.66	2.46	0.892	0.376	0.013
Trial 4 Raw	13.29	2.32	12.26	2.60	1.633	0.108	0.042
Trial 5 Raw	13.46	2.01	12.94	2.48	0.900	0.372	0.013
Total Trials 1–5 Raw	57.39	9.61	52.83	10.26	1.804	0.076	0.051
List B Raw	6.93	2.72	6.34	2.26	0.933	0.354	0.014
Short-Free Recall Raw	12.04	3.43	11.29	2.81	0.954	0.344	0.015
Short-Cued Recall Raw	12.46	2.55	11.80	2.87	0.960	0.341	0.015
Long-Free Recall Raw	12.43	3.27	11.46	2.89	1.249	0.216	0.025
Long-Cued Recall Raw	13.18	2.34	12.11	2.91	1.571	0.121	0.039
Recognition Hits Raw	15.14	1.04	14.40	1.82	1.921	0.059	0.057
False Positive Hits Raw	2.11	3.99	2.20	2.63	−0.111	0.912	0.000
Discrimination Raw	3.32	0.75	2.99	0.66	1.873	0.066	0.054
Forced Choice Raw	16.00	0.00	15.97	0.18	0.878	0.384	0.014
Total Intrusions	1.86	2.24	2.11	1.95	0.237	0.628	0.004
Average Chance Adjusted Semantic Clustering	1.70	2.09	0.73	1.14	2.331	0.023	0.087
Average Chance Adjusted Serial Clustering	1.36	1.32	1.42	1.29	−0.186	0.853	0.001
Average Chance Adjusted Subjective Clustering	1.30	1.06	1.23	1.30	0.245	0.807	0.001

We used the strategy score for each trial as the within-subject factor (e.g., (1)CA semantic clustering score on five trials, (2)CA serial clustering score on five trials; (3)four CA subjective clustering scores: trial 1 to trial 2; trial 2 to trial 3; trial 3 to trial 4; trial 4 to trial 5) and Group (control, mTBI) as the between-subject factor. As shown in Figure 1b–d, there was no significant group by trial interaction effect for any clustering strategy or significant trial by trial differences between groups on CA subjective (Figure 1c) or CA serial clustering (Figure 1d) variables. However, these analyses revealed a significant between group effect with control participants using more CA semantic clusters compared to mTBI participants $F(1,61) = 5.994$; $p < .001$; $\eta^2 = 0.091$. Table 4 details CA semantic clustering by group for each learning trial.

Although we did not include ListB in our primary learning analyses as it is difficult to reliably analyze strategy use in only one presentation and ListB shares semantic categories with ListA (i.e., proactive interference effects), we did examine transfer of strategy effects by comparison of Trial 1 of ListA and ListB. Consistent with our previous work, our groups did not differ on total raw recall on ListB (Geary et al., 2010) and there were no between group differences or interaction effects. However, to examine potential transfer of strategy (DeRosa, Doane, & Russell, 1970), we conducted post hoc stepwise regression analyses that demonstrated semantic clustering predicted 24% of the variance of ListB recall for controls only ($\beta = 0.49$; $t(27) = 3.75$; $p < .001$). For mTBI, only serial clustering was a significant predictor of ListB recall ($\beta = 0.36$; $t(33) = 2.22$; $p < .05$).

Recalling that our prior finding (Geary et al., 2010) was of a relationship of diminished recall on the first recall trial, we also conducted a post hoc examination of recall consistency across trials. This analysis revealed less consistency in recall in mTBI relative to controls from trial 1 to trial 2, $t(61) = 2.130$, $p = 0.037$, but not on the remaining trials. Table 5 details these analyses.

Table 4. CVLT-II semantic clustering chance adjusted

	Control (N = 28)		mTBI (N = 35)		
	Mean	SD	Mean	SD	
Trial 1	0.47	1.01	0.29	1.54	
Trial 2	1.12	2.13	1.02	1.86	
Trial 3	1.64	2.69	0.75	1.96	*
Trial 4	2.45	3.37	1.03	2.35	*
Trial 5	2.94	3.48	1.35	2.64	*

Note. *p < 0.05.

Table 5. Recall consistency of Recall Across Trials

	Control (N = 28)		mTBI (N = 35)		
	Mean	SD	Mean	SD	
Words Recalled T1-T2	6.32	2.37	5.14	2.02	*
Words Recalled T2-T3	9.14	2.97	7.77	3.01	
Words Recalled T3-T4	11.00	3.14	9.83	2.88	
Words Recalled T4-T5	11.68	3.02	10.69	3.11	

Note. *p < 0.05

DISCUSSION

The current study serves to characterize the mechanisms that underlie reductions in rate of verbal learning in mTBI (Geary et al., 2010). To our knowledge, this is the first study to examine verbal learning strategy use within and across trials in a mTBI sample who achieved comparable total learning and memory scores relative to control participants. This approach is consistent with recent interest examining qualitative aspects of learning and memory performance, such as strategy use (Baldo, Delis, Kramer, & Shimamura, 2002; Millis & Ricker, 1994; Nolin, 2006; Schefft et al., 2008). Semantic and subjective strategy formation and implementation are considered qualitative aspects of learning and memory performance. Such behaviors fall under the category of executive functions (Alexander & Stuss, 2006; Matsui et al., 2008) reflective of active engagement of self-generated or internally driven reasoning skill. Semantic clustering arguably represents the most efficient and highest-order organization strategy to facilitate learning (Becker & Lim, 2003). Given the evidence of frontal lobe dysfunction and reduced strategy use in TBI of greater severity (Levine et al., 1998; Millis & Ricker, 1994; Schefft et al., 2008; Strangman et al., 2008), we questioned if diminished internally derived meta-cognitive strategy use could explain decreased rate of learning across trials in a mTBI sample. Our present findings are supportive of the hypothesis that mTBI participants are under-utilizing semantic clustering relative to control participants. In the context of comparable total immediate recall and delayed memory scores, control participants use semantic clustering whereas the mTBI do not to a similar degree.

The frontal lobe's involvement in executive functions such as strategic processes of learning and memory is well supported (Alexander, Stuss, & Fansabedian, 2003; Alexander et al., 2009; Baldo et al., 2002; Cabeza & Nyberg, 2000; Turner, Cipolotti, Yousry, & Shallice, 2007; Turriziani, Smirni, Oliveri, Semenza, & Cipolott, 2010). We have previously reported no significant group differences between control and mTBI participants on administered measures of executive functioning (Geary et al., 2010; Kraus et al., 2007). In retrospect, these previous reports may not have been sufficient to conclude that subtle executive deficits do not persist following mTBI. We undertook the current analysis with the speculation that perhaps our executive function measures were not sensitive to detect subtle but diffuse deficits that may be experienced following mTBI (Cicerone et al., 2006).

Traditionally, varied and overlapping skills believed dependent on prefrontal cortex are grouped under the executive function rubric (Stuss & Levine, 2002). Executive functions can be conceptualized as a hierarchy of cognitive processes with meta-cognitive processes such as those related to internally derived strategy use at the apex. In our larger battery, our executive function measures (set-shifting, response-inhibition, sustained attention) (Kraus et al., 2007) share a common feature of an externally facilitated structure through the form of verbal instruction, visual stimulus, or visual feedback. In this way, these measures provide overt passive "structure" to the tasks. It may be that examining individualized aspects of performance in mTBI may increase the sensitivity of assessment (Cicerone et al., 2006; Stuss & Levine, 2002) and capture internally derived executive functions that may be more diffusely represented such as strategy use (Cicerone et al., 2006).

Meta-cognitive functions also includes the awareness that strategy use facilitates learning/recall on a word-list and then using that strategy in another word-list (Ellis, 1965). In the CVLT-II, transfer of learning strategy is likely evident when semantic clustering is used both during ListA learning trials and on the single presentation of ListB (DeRosa et al., 1970). Our groups did not differ on total raw recall on ListB and there were no between group difference or interaction effect evident on repeated ANOVA comparing ListA trial 1 to ListB raw recall performance (Geary et al., 2010). ListB consists of 16 items from four semantic categories, two categories overlap with categories on ListA. Despite proactive interference effects which are greatest among words from shared semantic categories (Delis et al., 2000b), *post hoc* stepwise regression found that semantic clustering predicted ListB recall for controls, but not for mTBI. This finding offers additional support that the mTBI participants exhibit deficient semantic strategy use as they under-use the semantic clustering strategy with a novel word list.

Unlike semantic clustering, serial clustering does not involve actively restructuring information as it is presented. Rather, serial clustering is externally facilitated as it embodies recalling items in the order in which they are presented. An over-reliance on serial clustering, at the expense of semantic clustering, in other neurological populations has been demonstrated to negatively correlate with overall recall (Delis et al., 1988; Gsottschneider et al., 2010; Jefferies et al., 2008; Ranjith et al., 2010). Our present findings are consistent with our hypothesis that mTBI participants use a less efficient serial strategy relative to controls. For mTBI participants, averaged CA serial clustering was the only significant predictor of learning rate.

As diffuse or traumatic axonal injury is the most frequent neuropathologic observation following mTBI of all etiologies, it has been speculated that disrupted connection between frontal-subcortical networks could explain deficiencies in cognitive performance (Becker & Lim, 2003; Ghajar, Ivry, & The Cognitive Neurobiological Consortium, 2008; Hartikainen et al., 2010; Zappalá & Trexler, 1992). This hypothesis was recently examined using functional magnetic resonance imaging in TBI participants (mild-severe) during performance of a list-learning paradigm (Strangman et al., 2008). Participants were imaged under three list-learning conditions, two of which involved semantically related word-lists. On the final "directed" condition, participants were instructed on the use of a semantic clustering strategy. Findings revealed that during the directed semantic clustering condition, both TBI and control groups displayed improvements in recall, but that controls demonstrated

increased coupling with activation observed in dorsolateral prefrontal cortex (DLPFC) and angular gyrus (AG), while the TBI participants did not. These findings were interpreted as indications of variable disruptions along the superior longitudinal fasciculus (SLF) connecting angular gyrus and DLPFC. The authors speculated that while the TBI participants did not engage the more efficient DLPFC-AG network, they still experienced improvements in learning by a separate processing network. These findings have particular relevance given prior report of a relationship between integrity of the SLF assessed via diffusion tensor imaging and behavior (Bendlin et al., 2008; Geary et al., 2010; Kinnunen et al., 2011; Mayer et al., 2009; Sidaros et al., 2009). From these works, the possibility is raised that dysfunction of the SLF in mTBI may underlie deficient meta-cognitive strategy use and explain over-reliance on more externally derived strategy use.

The use of more externally driven strategies or application of variable strategies may result in inconsistent patterns of recall. Indeed, list recall in moderate-severe TBI has been suggestive of a disorganized haphazard learning style coupled with an increased reliance on serial clustering (Deluca, Schultheis, Madigan, Christodoulou, & Averill, 2000; Millis & Ricker, 1994). Recalling that our prior work focused on early learning inefficiency (Geary et al., 2010), our finding of less consistent recall from trial 1 to trial 2 may suggest that the mTBI participants are responding to the second trial as if it were a novel list *versus* a repeated presentation (Delis et al., 2000a) or possibly reflective of diminished attention (DeJong & Donders, 2010). This has also been offered as a theory to explain behavior in patients with frontal lobe dysexecutive syndrome (Roofeh et al., 2006; Stuss & Alexander, 2007). We also considered that our mTBI participants might commit more intrusion errors reflective of reduced self-monitoring as has been offered by others (Busch, McBride, Curtiss, & Vanderploeg, 2005), but this was not the case ($p > .05$), suggesting no source memory problems.

Study Limitations

In any TBI study, a primary concern is the inclusion of participants with a history of mTBI without witness confirmation of LOC or PTA. While our inclusion criteria was biased against inclusion of those with potentially greater severity of injury, given the reliance on retrospective self-report, it is possible that some of these individuals (N = 14 without witness-confirmed LOC *or* PTA) either did not sustain a TBI or sustained a TBI of greater than mild severity. Additionally, there is always concern with lifetime history and inclusion of participants with multiple TBIs. In fact, 12 of the TBI participants in this study reported a history of multiple mTBI. Primary CVLT-II trials 1–5, total learning, ListB and delayed memory analyses conducted with and without these participants demonstrated no change in the previously published findings (Geary et al., 2010). However, while comparisons of single *versus* multiple mTBI participants detected no significant differences between the TBI groups on variables of interest, the inclusion of individuals

with multiple injuries raises the possibility that findings could be driven, in part, by changes attributable to multiple mild injuries as has been suggested by others (Weber, 2007). As such, future studies should be undertaken examining strategy use in a large group of patients with multiple mTBI so that number of TBIs can be examined directly. Furthermore, future studies would benefit by the collection of objective data on the duration of LOC and objective measurements of PTA for each injury. A prospective, longitudinal investigation of acute TBI course and recovery would achieve such aims.

We did not collect any data regarding the functional significance of the initial learning deficiency or ask any questions particularly relevant to meta-cognitive strategy use (e.g., "do you find it harder to organize information during your day-to-day?"). Future studies comparing strategy use and learning performance to more specific outcome variables would prove especially informative.

Despite these limitations, the clinical significance of reduced meta-cognitive strategy use in mTBI participants warrants further exploration. Notably, our groups did not differ on standard measures of executive function, which some suggest may not be sensitive to detect the subtle diffuse deficits following mTBI (Cicerone et al., 2006; Stuss & Levine, 2002). Given the continued debate regarding persisting cognitive deficits following mTBI and the issues regarding the ecological validity and sensitivity of neuropsychological assessment to detect persisting cognitive changes in patients with a history of mTBI (Alexander, 1995; Iverson, 2010; Satz et al., 1999; Silver, 2000), this study endeavored to elaborate on the individualized learning strategies of mTBI participants. Specifically, while chronic memory dysfunction is not supported in the mTBI literature, the issue may be one of what constitutes "memory" as standardly interpreted in neuropsychological evaluations. Perhaps the persisting learning and memory difficulties reported by some mTBI patients are related to reduced usage of internally driven strategies that facilitate learning and enhance recall. That mTBI participants use less semantic clusters relative to controls and use serial strategies is compelling especially given the comparable total learning (trials 1–5) score. Adopting a serial recall strategy *versus* a semantic strategy could require TBI participants to use other cognitive processes (Strangman et al., 2008) to achieve comparable total learning scores. Given that strategy training has demonstrated improvements in learning and memory (Basso, Lowery, Ghormley, Combs, & Johnson, 2006; Fiszdon et al., 2006; O'Brien, Chiaravalloti, Arango-Lasprilla, Lengenfelder, & DeLuca, 2007; Schefft et al., 2008), these findings have translation value in offering that mTBI patients be given recommendations such as consideration of strategy use when learning information to potentially remediate learning inefficiencies.

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Verbal learning differences in chronic mild traumatic brain injury

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Abstract

Following mild traumatic brain injury (TBI), a percentage of individuals report chronic memory and attention
difficulties. Traditional neuropsychological assessments often fail to find evidence for such complaints. We hypothesized
that mild TBI patients may, in fact, experience subtle cognitive deficits that reflect diminished initial acquisition
that can be explained by changes in cerebral white matter microstructure. In the data presented here, a sample of
nonlitigating and gainfully employed mild TBI patients demonstrated statistically significant differences from age
and education matched control participants in performance on the first trial of a verbal learning task. Performance
on this trial was associated with reduced fractional anisotropy in the uncinate fasciculus and the superior longitu-
dinal fasciculus providing an anatomical correlate for the cognitive findings. Mild TBI patients were not impaired
relative to control participants on total learning or memory composite variables. Performance on the first learning
trial was not related to any psychological variables including mood. We concluded that patients with mild TBI
demonstrate diminished verbal learning that is not often interpreted in standard neuropsychological assessment.
(*JINS*, 2010, 1–11.)

Keywords: Concussion, Diffusion tensor imaging, Single trial learning

INTRODUCTION

There is a significant disparity between recent neuroimag-
ing work that detects measurable changes in brain structure
and white matter integrity many years following mild
traumatic brain injury (TBI) (Kraus, Susmaras, Caughlin,
Walker, Sweeney, & Little, 2007; Lo, Shifteh, Gold, Bello, &
Lipton, 2009; Niogi et al., 2008; Rutgers, Toulgoat, Cazejust,
Fillard, Lasjaunias, & Ducreux, 2008; Wozniak et al., 2007)
and documentation of persisting memory deficits that may
exist in well motivated, nonlitigating, nondepressed, osten-
sibly "recovered" individuals (Belanger & Vanderploeg,
2005; Gentilini et al., 1985; Iverson, Lovell, & Smith, 2000;
Ponsford et al., 2000). This discrepancy has led some to
question the ecological validity and sensitivity of neuropsy-
chological assessment to detect persisting cognitive changes

in patients with a history of mild TBI (Satz et al., 1999;
Silver, 2000). We set out to address this disparity by com-
paring neuroimaging measures with verbal memory perfor-
mance in a sample of nonlitigating, nondepressed, chronic,
mild TBI patients. Rather than rely upon composite measures
of learning and memory, we focused on trial-by-trial perfor-
mance on a measure of verbal memory.

Acute mild TBI is commonly associated with symptoms
including visual disturbance, sensitivity to noise/light, nau-
sea/vomiting, and headache (Ropper & Brown, 2005) as
well as alterations in cognition and behavior with specific
impairments in memory (Belanger & Vanderploeg, 2005),
attention (Kwok, Lee, Leung, & Poon, 2008; Rao et al.,
1997), working memory (McAllister, Flashman, McDonald, &
Saykin, 2006), processing speed (Willmott, Ponsford,
Hocking, & Schönberger, 2009), executive functioning
(Wozniak et al., 2007), and mood (Jorge, Acion, Starkstein, &
Magnotta, 2007). Neuropsychological studies in acute mild
TBI have demonstrated that the majority of individuals

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recover and that cognitive and behavioral difficulties remit over a period of weeks to months (Macciocchi, Barth, Alves, Rimel, & Jane, 1996; Maddocks & Saling, 1996; Teasdale & Engberg, 1997). While postconcussive memory complaints are frequently reported in chronic mild TBI (Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009), several studies in chronic mild TBI patients have included participants with psychiatric disturbance or those involved in litigation which raises questions about effort and motivation.

Memory studies in acute mild TBI have traditionally assessed memory using measures of total immediate learning and delayed recall (Chamelian & Feinstein, 2006; Ettenhofer & Abeles, 2009; Mooney, Speed, & Sheppard, 2005). These studies, having found no objective evidence of memory complaints, attributed chronic complaints to psychological or motivational factors rather than the pathophysiology of the injury itself (Ettenhofer & Abeles, 2009; Larrabee, 1997; Mooney & Speed, 2001; Mooney et al., 2005). Others have argued such methods may miss more subtle functional deficits in learning and memory experienced in chronic mild TBI (Bigler, 2008; Gioia & Isquith, 2004; Yeates & Taylor, 2005).

As a cognitive domain, memory is a highly integrated series of functions dependent on a distributed neural network. In formal neuropsychological assessments, learning and memory are characterized by juxtaposing total recall across multiple presentations with total recall following a delay. In an information-processing framework, encoding encompasses the end result of fundamental steps of both attending to and acquiring the information at first trial to the final trial. New information is deemed encoded once it is able to be recalled following both immediate presentation and following a delay (Bauer, Grande, & Valenstein, 2003). Within this specific framework, there are three crucial steps for memory formation including acquisition, encoding, and retrieval. In this model, acquisition refers to ability to recall information following a single presentation whereas encoding encompasses all information retrieved across all presentations. In the case where materials are presented only once, both acquisition and encoding reflect the same process.

Characterizing the specific nature of the memory complaint (e.g., acquisition, encoding, retrieval) is often left to a neuropsychologist. It is not uncommon to hear reports of memory deficits offered by mild TBI patients and their collaterals. Further inquiry often elicits statements such as, "he can remember if I tell him two times" coupled with the admission that under such circumstances, the patient then demonstrates an intact ability to learn and recall information. Traditional neuropsychological assessments designed to evaluate memory (i.e., mesial temporal lobe/dienchephalic dependent functions) use repeated presentation of material to then make comparisons of the gross ability to encode information *versus* what information was later recalled. Given the nature of the memory complaint described by many mild TBI patients, the traditional method of neuropsychological interpretation may miss subtle, but functionally significant deficiencies in acquisition of material presented a single time. Indeed, when confronted with well-motivated, nonlitigating, nonsomatizing, nondepressed and ostensibly recovered clinical patients, the subjective day-to-day memory complaint of some with mild TBI proves perplexing.

In the current study, we explore the possibility that chronic mild TBI patients may demonstrate a subtle initial learning deficit that can be explained by changes in white matter integrity using diffusion tensor imaging (DTI). Diffuse axonal injury is the primary injury in mild TBI regardless of etiology and as such, can be used to quantify pathology providing a neuroanatomic basis for alterations in memory performance (Kraus et al., 2007). The overarching hypothesis is that patients with mild TBI exhibit decreased initial learning ability relative to healthy controls. The secondary hypothesis is that this deficit resolves with repeated presentations of material. Furthermore, in light of the speculation that cognitive complaints are at least in part attributable to psychological factors such as somatization in patients with chronic mild TBI (Chamelian & Feinstein, 2006; Suhr & Gunstad, 2002), we examined the relationship between the cognitive variables of interest, injury variables, and various mood measures.

METHODS

Participants

Forty participants with a history of mild closed head TBI (23 females, 17 males) at least 6 months from injury were recruited from the University of Illinois Medical Center *via* advertisements in the community seeking individuals who had ever sustained a closed head injury, concussion, brain injury, or traumatic brain injury. None were recruited from active clinical practice. Thirty-five healthy controls (19 females, 16 males) were also recruited from the community to match the TBI on age, years of education, years of employment, and estimated premorbid intelligence (see Table 1). Highest level of occupational achievement was determined using the Hollingshead Four Factor Index of Socioeconomic Status Occupational Scale with values ranging from 1 (e.g., menial labor) to 9 (e.g., executive) (Hollingshead, 1975). All participants provided written informed consent and experimental procedures complied with the code of ethics of the World Medical Association, the University of Illinois Institutional Review Board, and Declaration of Helsinki.

Participants (control and TBI) were excluded if they had a history of psychiatric disorder before the TBI, substance abuse/dependency, current or past litigation, failure on a formal measure of effort, or any other neurologic or medical condition that could result in cognitive changes (e.g., hypertension, severe chronic pain). Participants were not receiving any psychiatric medication or medications used for cognitive enhancement at the time of the study. The criteria used for defining mild TBI follow the guidelines set forth by the American Congress of Rehabilitation Medicine (1993)

Table 1. Participant demographics, mood and behavioral data, and frequency of reported post-concussive symptoms complaints

	Control (*n* = 35)		TBI (*n* = 40)			
	Mean	*SD*	Mean	*SD*	T value	*p* value
Demographic variables						
Age	32.54	10.77	34.53	10.22	−0.817	.416
Years of Education	16.00	1.83	16.38	2.12	−0.814	.418
Years of Employment	12.73	11.37	15.74	9.96	−1.205	.232
Hollingshead Highest Level of Employment	6.50	1.59	6.43	1.56	0.172	.864
WTAR Full Scale IQ Estimate	111.31	10.53	111.68	9.56	−0.156	.877
TOMM Trial 2	50.00	0.00	49.90	0.31	1.667	.102
Dot Counting	8.42	2.30	9.00	2.42	−0.899	.373
Employed/Student at Evaluation (% sample)	94.3%		92.5%			
Gender (M/F)	16	19	17	23		
TBI variables						
Age at TBI (years)	—	—	29.58	1.73		
Time Since Injury (years)	—	—	5.29	1.01		
Length Loss of Consciousness (N = 20) (minutes)	—	—	5.10	1.93		
Length of Post Traumatic Amnesia (N = 13) (minutes)	—	—	30.38	7.75		
Current Cognitive Complaints (% sample)	0.0%		82.5%			
Current Behavioral Complaints (% sample)	2.9%		47.5%			
Returned to Work/School Following Injury (% sample)	—		92.5%			
Mood variables						
BDI Total	3.77	5.04	11.65	10.07	−4.190	<.001
FrSBe Apathy Before (T-score)	—	—	47.58	12.92	—	—
FrSBe Apathy After (T-score)	43.74	9.83	55.98	20.37	−3.854	<.001
PCS Symptom Endorsement (often to all the time)						
Memory Problems	2.9%		47.5%			
Difficulty Concentrating	8.6%		45.5%			
Irritability	5.7%		27.5%			
Headache	0.0%		30.0%			
Fatigue	14.3%		30.0%			
Anxiety	5.7%		22.5%			
Aggravated by Noise	8.6%		20.0%			
Judgment Problems	2.9%		10.0%			
Dizziness	0.0%		12.5%			
Visual Disturbance	0.0%		10.0%			

including endorsement of at least one of the following: any period of loss of consciousness; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and focal neurological deficit (American Congress of Rehabilitation Medicine, 1993; Cassidy et al., 2004). For this study, participants were categorized as moderate and subsequently excluded if the duration of loss of consciousness (LOC) was greater than 30 min, post-traumatic amnesia (PTA) was greater than 24 h, there was positive radiologic finding of contusion or bleed, or evidence of skull fracture suggesting significant trauma to the head. Beyond self-report, witness reports, discharge notes from the emergency department, and previous medical records were used to confirm severity. These criteria help en-sure that the only patients remaining were, in fact, mild severity (LOC less than 30 min; PTA less than 24 h, and/or the Glasgow Coma Scale greater than 13) (American Congress on Rehabilitation Medicine, 1993; Cassidy et al., 2004; Levin, 1992; Tagliaferri, Compagnone, Korsic, Servadei, Kraus, 2006). For the individuals who had information on duration of loss of consciousness and/or posttraumatic amnesia confirmed by witness reports, the average reported LOC was 5.1 min (*n* = 20; range, 0–30 min) and average reported PTA was 27.9 min (*n* = 13; range, 0–60 min). For patients without specific information regarding LOC (*n* = 20) or PTA (*n* = 27), we relied upon estimates of self-reported and witness reported of duration of LOC or PTA and discharge note diagnosis from emergency departments when available for the purpose of study inclusion only.

The mechanism of injury varied and included motor vehicle accidents ($n = 10$), pedestrian MVA ($n = 3$), assault ($n = 3$), sports related ($n = 11$), and falls or blows to the head ($n = 13$). No TBI patient evidenced any frank structural lesion suggestive of focal injury on neuroimaging. Fourteen patients reported experiencing more than one TBI (range, 2–7). Analyses were conducted without these 14 participants with no effect on statistical significance on learning and memory or DTI analyses. As such, all participants were included in subsequent analyses. Demographic data and injury related variables are presented in Table 1.

MATERIALS AND PROCEDURE

Neuropsychological Assessment

As detailed in prior work, participants completed an extensive neuropsychological test battery that was assembled to assess executive function, attention, and memory (Kraus et al., 2007). The California Verbal Learning Test-Second Edition (CVLT-II) was used to assess memory. Our motivation for using this tool, rather than a customized learning task, is that the CVLT-II is a widely available clinical tool. The CVLT-II consists of two different lists of words (List A and List B). Each list is comprised of sixteen words from four related categories presented in a pseudo-random manner. List A is administered five times followed immediately by the sole presentation of List B. Participants receive a point for each accurately recalled item.

Participants were also administered the Beck Depression Inventory-Second Edition (BDI-II) to assess for mood disturbance. While our TBI participants endorsed a significantly higher number of depressive symptoms than controls (see Table 1), the TBI group mean of 11.08 ($SD = 10.07$) is within the "minimal" depression criterion category. Concentration difficulties, sleep disturbance, and fatigue are commonly reported following mild TBI (Lundin, de Boussard, Edman, & Borg, 2006; Orff, Ayalon, & Drummond, 2009) and examination of specific BDI items found a high frequency of these items endorsed in the mild TBI group *versus* endorsement of sadness or loss of pleasure. Further review, however, also determined the presence of seven individuals in the TBI group with BDI-II scores within the moderate range (above 20). Analyses of memory and DTI variables were conducted with and without these seven participants and demonstrated no effect on the pattern of results. As such, all participants were included in reported analyses.

The Post-Concussion Syndrome Checklist (PCSC) (Gouvier, Cubic, Jones, Phillip, & Cutlip, 1992) was used to rate subjective frequency of various post-concussive symptoms (PCS). Almost half (47.5%) of the TBI participants reported experiencing memory difficulties and 45.0% reported attention/concentration problems with high frequency. During clinical interview, participants were also asked if they experienced cognitive (e.g., memory, attention) or behavioral (e.g, irritability, fatigue) difficulties. The Frontal Systems Behavior Rating Scale-Self Version (FrSBe), a self-report behavior rating scale, was used to assess for the presence of postinjury behavioral syndromes of apathy, disinhibition and executive dysfunction (Reid-Arndt, Nehl, & Hinkebein, 2007). The TBI and control participants differed only on reported current level of apathy (Table 1) with TBI participants endorsing higher rates of apathy. Finally, TBI and control participants also completed two measures of effort (i.e., Test of Memory Malingering, Dot Counting) and all participants achieved scores in the valid range on the respective measure (Table 1).

DTI Data Acquisition

Imaging studies were conducted using a 3.0-Tesla whole body scanner (General Electric Medical Systems, Waukesha, WI) using a customized DTI pulse sequence with a quadrature head coil. The DTI sequence is based on a single-shot EPI with the capability of compensating eddy currents induced by the diffusion gradients *via* dynamically modifying the imaging gradient waveforms (Poonawalla & Zhou, 2004). The sequence used 27 diffusion gradient directions, b-values of 0, 750 s/mm^2, and voxel sizes of $1.5 \times 1.5 \times 5$ mm^3. A 3D high resolution anatomical scan was also acquired to allow coregistration with the DTI data and normalization to the Montreal Neurological Institute template (MNI) with a spatial resolution of $0.85 \times 0.64 \times 1.5$ mm^3 (Kraus et al., 2007, for additional details).

DTI Data Analysis

The 28 diffusion directions were used to calculate the fractional anisotropy (FA) as the primary indicator of white matter integrity. The images were reconstructed and FA calculated using DTI Studio (Wakana et al., 2004). The 28 diffusion weighted images were examined for image quality and head movement. Head movement was required to be less than 2 mm. Voxels with very low signal (indicating nonbrain voxels) were masked out of the analysis before calculation of pixelwise FA (background noise = 125). The FA map was then converted to ANALYZE. Statistical Parametric Mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) Was used to co-register the DTI with corresponding T1 images and then convert the DTI to normalized space (Montreal Neurologic Institute T1 template). None of the mild TBI in this investigation had significant atrophy or pathology making normalization to the MNI template accurate.

Region of Interest Analysis

All region of interest (ROI) analyses were carried out on data from each individual participant. The ROIs were drawn on a group averaged (including both controls and mild TBI) normalized FA map referencing not only the grayscale FA map but also a color-coded directionality map. This color-coded map allows visualization of intersecting fiber bundles and provides information as to where specific tracts begin and end. The masks were then overlaid on the FA maps from the

remaining participants and visually checked for accuracy. The specific ROIs included the following: anterior and posterior corona radiata, corticospinal tracts (including parts of the corticopontine tract and superior thalamic radiation), external capsule, cingulum, forceps minor, forceps major, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus, sagittal stratum, and body, genu, and splenium of the corpus callosum. Right and left were analyzed separately where appropriate and combined when no differences reached significance. Detailed descriptions of these regions of interest can be found in (Kraus et al., 2007).

These masks were then applied to the FA map from each individual participant. One concern when using ROI masks drawn on representative participants is that either gray matter or cerebral spinal fluid would be included in the calculation of mean FA. To ensure that FA was only calculated from white matter tissue, a threshold of FA = 0.20 was applied before extraction of FA for each ROI.

Statistical Analysis

For the CVLT-II, we examined group comparisons of the first trial of List A and the single List B learning trial using independent sample t tests We then conducted a mixed-design repeated-measure analysis of variance with Trial as the within-subject factor (recall on Trials 1, 2, 3, 4, 5) and Group (control, TBI) as the between-subject factor. We also conducted a mixed-design repeated-measures analysis of variance (ANOVA) of single trial learning as the within-subject factor (recall on Trial 1 and List B) and Group as the between-subject factor. In addition to raw rates of recall across trials, data from each individual were fitted to a power function (Equation 1). The power function, which is commonly applied in the behavioral learning literature (Anderson, 1982; Logan, 1998), was applied to data from each participant to allow extraction of both the y-intercept (represented by y in Equation 1) and slope (represented by b in Equation 1):

$$y = ax^b \qquad (1)$$

For the DTI data, tests of independent means were conducted between groups for the body, genu, splenium, and total corpus callosum. For the 11 remaining ROIs for which measurements could be taken for each hemisphere, we conducted repeated measures ANOVAs with the left/right ROI as the within-subject measures by Group (control *vs* TBI) as the between-subject comparison.

To determine the amount of unique variance accounted for by DTI variables in performance on single trial learning, ROIs that demonstrated group differences were entered into a stepwise regression analyses with CVLT Trial 1 as the dependent variable.

RESULTS

CVLT-II

To test the primary hypothesis that mild TBI show reductions in single trial learning (acquisition), an independent samples t test was used to compare TBI and control recall on Trial 1 of List A. The mild TBI group achieved lowers scores than the control group on the first trial of the CVLT-II (Figure 1A), $t(73) = 2.341$; $p = .020$; $\eta^2 = 0.070$.

Although there was a trend for reduced performance in TBI, a repeated-measures ANOVA demonstrated that the groups did not differ in performance across the five total immediate learning trials, $F(1,73) = 3.288$; $p = .074$; $\eta^2 = 0.043$. Additionally, there was no Group × Trial interaction. Unlike List A Trial 1, the groups did not differ on List B, $t(73) = 1.009$; $p = .317$; $\eta^2 = 0.014$ (Table 2) and repeated-measures revealed no Group × List interaction.

Further analyses of each CVLT-II trial demonstrated that the mild TBI participants were significantly different from controls on the first trial, but not on any subsequent trial (Trials 2–5) of List A. However, the analysis of slope (or

Fig. 1. California Verbal Learning Test-Second Edition (CVLT-II) learning analyses. A: CVLT-II raw recall findings across trials 1 through 5 for controls and patients with mild traumatic brain injury (TBI). Statistically significant difference between groups was only observed on the first learning trial. Lines represent best fit power function for each group. B: Average exponential rate of learning for controls and mild TBI patients. Error bars represent 1 ± SEM.

Table 2. Raw scores of California Verbal Learning Test-Second Edition (CVLT-II) performance

	Control (n = 35)		TBI (n = 40)			
	Mean	SD	Mean	SD	T value	p value
CVLT-II Raw Scores						
Trial 1	7.63	2.06	6.58	1.84	2.341	.022
Trial 2	10.77	2.54	9.63	2.82	1.839	.070
Trial 3	12.31	2.48	11.75	2.46	0.987	.327
Trial 4	13.26	2.57	12.35	2.65	1.501	.138
Trial 5	13.63	2.07	12.95	2.65	1.222	.226
Total Trials (T-Score)	57.60	9.84	53.25	10.80	1.813	.074
Trial B	7.11	2.82	6.50	2.46	1.009	.317
Short Delay Free Recall	12.17	3.32	11.48	2.95	0.961	.339
Short Delay Cued Recall	12.43	2.73	11.98	2.89	0.697	.488
Long Delay Free Recall	12.46	3.28	11.60	3.01	1.179	.242
Long Delay Cued Recall	13.14	2.40	12.45	2.89	1.119	.267

rate) from the individually fit power functions demonstrated a significant difference between the groups with reduced rate in the mild TBI group, $t(73) = 2.514$; $p = .014$; $\eta^2 = 0.080$ (see Figure 1B). As would be expected from the Trial 1 effect, there was also a difference in the y-intercept, $t(73) = 2.118$; $p = .038$; $\eta^2 = 0.058$ between groups. In terms of overall list learning, the groups did not differ on the total five-trial verbal learning composite score, $t(73) = 1.813$; $p = .074$; $\eta^2 = 0.043$, short-delay free recall, $t(73) = 0.961$; $p = .343$; $\eta^2 = 0.013$, or long delay free recall, $t(73) = 1.179$; $p = .242$; $\eta^2 = 0.019$. The groups performed similarly on both the cued short-delay $t(73) = 0.697$; $p = .488$; $\eta^2 = 0.007$ and long-delay, $t(73) = 1.119$; $p = .267$; $\eta^2 = 0.017$.

Analyses were also conducted comparing CVLT-II performance between TBI participants who reported memory complaints on the PCSC *versus* those who did not. As detailed in Figure 2, the TBI participants with reported memory complaints achieved lower scores on all trials of the CVLT-II
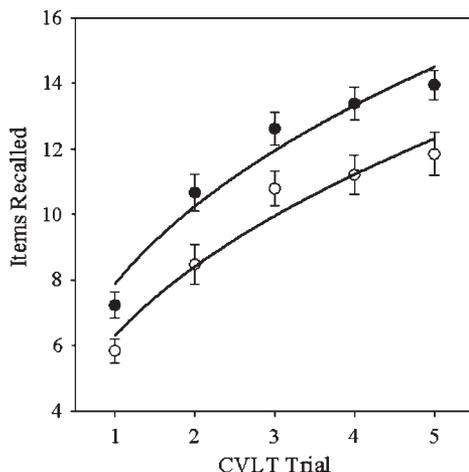

Fig. 2. California Verbal Learning Test-Second Edition (CVLT-II) learning by traumatic brain injury (TBI) with and without memory complaints. CVLT-II raw recall findings across trials 1 through 5 for TBI patients with (filled circles) and without (open circles) memory complaints as measured by the PCSC.

than TBI without complaints (all comparisons, $p < .05$). TBI patients with subjective memory complaints also achieved lower scores on List B and the delayed memory score ($p < .05$).

Relationship between Verbal Learning and Mood

Pearson product-moment correlations found no relationship between initial verbal learning with total BDI-2 depression score (r = −0.059; $p = .715$), frequency of PCS anxiety (r = −0.046; $p = .907$) and FrSBe ratings of apathy after injury (r = −0.133; $p = .420$). There was also no relationship detected between the composite total learning score or any delayed memory variables with depression, anxiety, or apathy (all p's > .05).

Neuroimaging-DTI Analysis

Consistent with earlier findings (Kraus et al., 2007) and as depicted in Figure 3A–C, the mild TBI group had significantly lower FA compared with controls in the superior longitudinal fasciculus, $F(1,73) = 4.608$; $p = .035$; $\eta^2 = 0.059$, sagittal stratum, $F(1,73) = 5.695$; $p = .020$; $\eta^2 = 0.072$, and uncinate fasciculus, $F(1,73) = 10.600$; $p = .002$; $\eta^2 = 0.127$. The TBI group did not differ from controls in any other ROI.

Relationship Between DTI and Single Trial Learning

Linear regression analyses were conducted to determine the amount of unique variance that FA in these ROIs could account for in the single-trial learning measure. These analyses demonstrated that only FA of the left uncinate fasciculus, $t(39) = 2.549$; $p = .016$ and left superior longitudinal fasciculus $t(39) = 2.059$; $p = .047$ accounted for a significant amount of variance (14% and 9%) in the first learning trial of the CVLT-II. However, neither ROI was a significant predictor of total learning, learning rate, or short or long
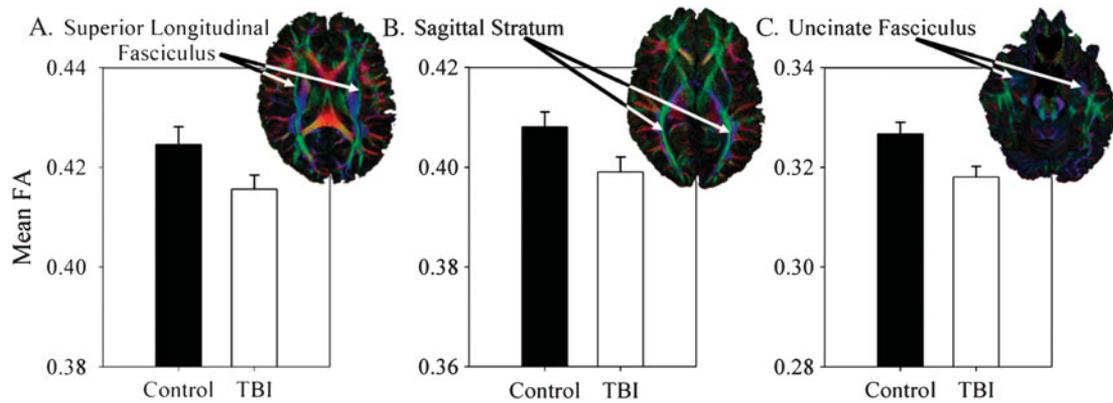
Fig. 3. Fractional anisotropy (FA) by group comparisons. Mean FA for the left/right superior longitudinal fasciculus (A), left/right sagittal stratum (B), and left/right uncinate fasciculus (C) for controls and mild TBI participants.

delay memory performance (all p's > .05). Table 3 details the Pearson-product moment correlations between the remaining ROIs, single-trial learning measures, sustained attention measures, and mood and behavior variables.

DISCUSSION

The individual components of memory (i.e., attend, acquire, encode, consolidate, and recall information) are likely not given much consideration by an individual who reports "memory" problems; an individual simply experiences a failure to remember. If an individual is unable to initially acquire information following one trial, the memory complaint is of the same verisimilitude as that experienced by an individual with an impaired ability to encode information over many trials. In daily interactions such as conversations, lectures, and work-place instructions, individuals are often presented with information one time, rather than being given the benefit of repeated "trials." For this reason and others, studies have questioned the ecological validity of composite learning and memory domain scores in elucidating the

nature of memory complaints following TBI (Silver, 2000; Silverberg & Millis, 2009; Wood, 2009; Yeates & Taylor, 2005)

Consistent with our hypothesis, participants with a history of chronic mild TBI did differ significantly from the control participants on a measure of initial verbal learning (acquisition). Furthermore, there was no significant group difference on the total composite learning score or delayed memory variables. Taken together, despite reported memory difficulties by 47% of the mild TBI participants, these findings suggest no generalized deficit in the broadly conceptualized memory system per se. The TBI participants were able to encode information over the five trials; what they did encode, they were able to recall. Given the objective finding of differences on Trial 1 and slower rate of overall learning, interpreting only the total immediate or delayed memory scores on the CVLT-II may not be ecologically valid. The mild TBI patients demonstrate an inefficiency when presented with information for the first time which could easily be exacerbated by the qualities of day-to-day interaction *versus* constitute a generalized encoding, consolidation, and/

Table 3. Significant bivariate correlation in regions of interest with cognitive and behavioral variables

	ACR		PCR		fMin	fMaj	EC	UF		CG	SS	CST	
Hemisphere	L	R	L	R	L	R	R	L	R	R	L	R	gCC
CVLT													
Trial 1					.452**			.336*		.316*			
Trial 2	.376*	.346*			.419**	.327*							
Trial 3	.321*												
Trial 4	.319*				.321*								
Trial 5													
List B	.324*	.353*			.446**								.386*
BDI Raw Score											.323*		
FrSBe Apathy							.419**	.	325*				
PCSC Total			.416*	.505**			−.355*					.373*	

**p = 0.01 level
*p = 0.05 level
Note. ACR = anterior corona radiata; PCR = posterior corona radiata; fMin = forceps minor; fMaj = forceps major; EC = external capsule; UF = uncinate fasciculus; CG = cingulum; SS = the sagittal stratum including the optic radiations; CST = corticospinal tracts, which included parts of the corticopontine tract and parts of the superior thalamic radiation; gCC = genu corpus callosum.

or retrieval-based "memory" deficit. These findings have translational value in that they support clinical recommendations such as rehearsal of information to facilitate encoding and recall.

While historically considered a "benign" injury with complete recovery expected within 3 months (Carroll et al., 2004; Lange, Iverson, & Franzen, 2009; Levin et al., 1987), it is believed that a minority of individuals experience postconcussive symptoms beyond this period (Pagulayan, Temkin, Machamer, & Dikmen, 2006; Rothweiler, Temkin, & Dikmen, 1998; Sterr, Herron, Hayward, & Montaldi, 2006; Vanderploeg, Berlanger, & Curtiss, 2009; Vanderploeg, Curtiss, & Belanger, 2005; Wood, 2004). That mild TBI is the casual factor underlying these complaints is controversial, especially given the inconsistent objective evidence supporting the complaints (e.g., evidence of neuropsychological impairment, observable lesions on MRI). Furthermore, in part because postconcussive symptoms are not specific to traumatic brain injury (Lees-Haley, Fox, & Courtney, 2001; Smith-Seemiller, Fow, Kant, & Franzen, 2003), some clinicians have suggested that the majority of complaints are complicated by or solely attributable to psychological or motivational factors rather than involve, at least in part, the pathophysiology of the injury itself (Bay & Bergman, 2006; Ettenhofer & Abeles, 2009; Jacobson, 1995; Karzmark, Hall, & Englander, 1995; Larrabee, 1997; Mooney & Speed, 2001; Mooney et al., 2005; Williams, Lees-Haley, & Brown, 1993). In fact, many studies demonstrate that psychiatric comorbidities influence PCS reporting and reports of memory complaints (Chamelian & Feinstein, 2006; Suhr & Gunstad, 2002; Vanderploeg et al., 2009). However, our data suggests Trial 1 differences exist independently of primary mood disturbance, apathy, or anxiety. Moreover, CVLT-II Trial 1 did not correlate significantly with any TBI grading parameters (e.g., duration of posttraumatic amnesia, duration of loss of consciousness, posttraumatic seizures, posttraumatic headache) as it has in other studies (MacKenzie et al., 2002). It is important to note that this lack of relationship may reflect the accuracy of self-report rather than a lack of true relationship. Most critically, the finding of diminished recall for Trial 1 was observed in well motivated (i.e., as assessed by effort measures), nonlitigating, nondepressed, and gainfully employed individuals many years after sustaining a mild TBI.

Of interest is the lack of significant difference between groups on the second word list (List B). Initially, we speculated that increased task familiarity would explain improved performance for both groups. However, this was not the case. In fact, as detailed in Table 2, the TBI participants performed at a comparable level on both Trial 1 of List A and List B where control participants declined slightly. One alternative explanation for the lack of improvement on List B may be attributed to proactive interference (PI) effects which are common in semantic clusters (Delis, Kramer, Kaplan, & Obers, 2000). Based on the performance of the normative sample of the CVLT-II and other patient populations (Ivory, Knight, Longmore, & Caradoc-Davie, 1999), PI effects are

expected and demonstrated when the number of words recalled on the single trial of List B is lower than what was recalled on the first trial of List A (Delis et al., 2000). In our sample, the lack of a significant difference between groups on List B may illustrate the expected modest PI effects demonstrated by the control participants and the lack of PI effects in the TBI participants. While the repeated measures analysis did not demonstrate a significant group by trial interaction effect, this may have been due to lack of power, but raises a question of whether there is a reduction in PI in mild TBI.

The question is then raised as to the underlying mechanism for slower acquisition on Trial 1. In mild TBI, acceleration–deceleration forces and related diffuse axonal injury is generally found to be the only significant pathology (Bazarian, Zhong, Blyth, Zhu, Kavcic, & Peterson, 2007; Inglese et al., 2005; Medina et al., 2006). Given the nature of diffuse axonal injury and its potential impact on distributed neurobehavioral networks, injury along these pathways could result in wide-spread cognitive and behavioral dysfunction. In examining ROIs which demonstrated differences in FA relative to controls, the left uncinate fasciculus accounted for a significant amount of variance in Trial 1. This specific tract has been implicated previously in studies of memory (Niogi et al., 2008). The uncinate fasciculus connects temporal and prefrontal areas so it is not surprising to find its involvement in learning and memory. The relationship between memory and FA of the uncinate fasciculus has been demonstrated in patients with TBI (Niogi et al., 2008) with poor memory performance being correlated with reduced FA. While our data did not demonstrate a significant difference between groups on overall memory performance or a relationship between memory performance and the uncinate fasciculus, our data did demonstrate a significant relationship between Trial 1 and the left uncinate fasciculus.

Similarly, the relationship between Trial 1 performance and FA in the superior longitudinal fasciculus is also to be expected as this tract is thought to be composed of three component parts and has been purported to play a role in visual awareness, maintenance of attention, initiation of complex motor behavior, phonemic and articulatory aspects of language, and lexical decision making (Gold, Powell, Xuan, Jiang, & Hardey, 2007; Schmahmann, Smith, Eichler, & Filley, 2008). Damage to this tract has also been reported previously in TBI (Bendlin et al., 2008; Cho et al., 2008; Kraus et al., 2007). In our study, FA of the left superior longitudinal fasciculus was a significant predictor of Trial 1 performance. To our knowledge, this is the first study to demonstrate the involvement of this tract in verbal learning in TBI. Integrity of this tract has also been reported to have a role in other verbally mediated tasks such as verbal repetition (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008), which may explain its involvement in the CVLT-II.

The slower rate of learning across trials in TBI warrants further investigation. Again, we would suspect that successful recall of items is influenced by how well one consistently uses a recall strategy (Chan, Kwoka, Chiub, Lamb, Pangb, & Chow, 2000; Gongvatana, Woods, Taylor, Vigil,

Table 4. California Verbal Learning Test-Second Edition (CVLT-II) standard scores

	TBI (*n* = 40)		% Participants	% Participants
	Mean	*SD*	1–2 *SD* below mean	>2 *SD* below mean
CVLT-II Z-scores				
Trial 1	−0.51	0.89	27.5%	—
Trial 2	−0.45	1.11	22.5%	7.5%
Trial 3	−0.23	0.99	12.5%	5.0%
Trial 4	−0.35	1.03	10.0%	5.0%
Trial 5	−0.33	1.28	12.5%	7.5%
Trial B	−0.22	0.87	12.5%	2.5%

Grant, & Group, 2007; Luek, 1976; Ribeiro, Guerreiro, & De Mendonça, 2007). It is possible that the TBI group was slow to recognize and then use a successful strategy, or they adopted a less efficient strategy (e.g., serial recall) across trials. Examining the strategic and arguably, higher-order (i.e., executive/frontal lobe), aspects of learning could be informative in appreciating the complexities of the initial verbal learning inefficiency (Wood, 2009). Our groups did not differ on formal neuropsychological measures of executive function. However, the administered executive tasks are partially externally facilitated (e.g., changing visual sorting contingencies, visual planning to match a model) and do not require the same internally derived strategy formation used in verbal list learning. However, without an analysis of the strategies used within trial and across trials on the CVLT-II, this contention is speculative. Future work will test the validity of this hypothesis.

Another concern in many TBI studies is the inclusion of participants with a history of mild TBI without witness confirmation of LOC or PTA. Given the reliance on retrospective report, it is possible that some of these individuals did not sustain a TBI. Indeed, *post hoc* analyses examining differences between control participants and the mild TBI subgroups (witness corroborated *vs* only subjective report of TBI) on the data presented herein found that significant differences on Trial 1 were only observed between controls and TBI patients with witness corroborated TBI. A study with restrictions to inclusion for only witnessed or objectively verified TBI parameters would be compelling. However, the inclusion of self-reported participants in this study only serve to increase the likelihood of supporting the null hypothesis rather than biasing in favor of finding group differences. Similarly, only approximately half of our mild TBI participants reported memory difficulties suggesting that the data presented may actually underestimate the magnitude of the effect. Consistent with this, when converted to standardized scores, these patients fall into the low end of normal performance (Table 4). Indeed, the 19 TBI participants, who reported experiencing memory difficulties, performed more poorly on all CVLT-II learning variables and likely represent the more severe end of the mild TBI continuum.

Finally, 14 TBI participants reported a history of multiple mild TBI. While analyses conducted without these individuals did not change the significance of the findings, their inclu-

sion raises the possibility that findings could be driven, in part, by changes attributable to multiple mild injuries as has been suggested by others (Weber, 2007).

To our knowledge, this is the first study to examine verbal learning with a focus on single-trial learning and white matter integrity in a nonlitigating, nondepressed, employed population with mild TBI. Our data suggest that chronic mild TBI patients demonstrate deficits in the acquisition of information which are supported by evidence of chronic damage to white matter microstructure. However, we collected no data regarding the functional significance of any cognitive complaints and as such it is unclear if initial trial learning difficulties relate to functional deficits. Future studies comparing initial learning and more specific outcome variables (e.g., difficulties at work/school) would prove especially informative in this regard.

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