

Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury

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Memory and attentional control impairments are the two most common forms of dysfunction following mild traumatic brain injury (TBI) and lead to significant morbidity in patients, yet these functions are thought to be supported by different brain networks. This 3T magnetic resonance diffusion tensor imaging (DTI) study investigates whether microstructural integrity of white matter, as measured by fractional anisotropy (FA) within a small set of individually localized regions of interest (ROIs), is associated with these cognitive domains in normal adults and adults with mild TBI. Results in a sample of 23 normal controls reveal a significant correlation between attentional control and FA within a ROI in the left hemisphere anterior corona radiata. Furthermore, the controls demonstrate a correlation between memory performance and FA in a ROI placed in the uncinate fasciculus. Next, to examine whether these relationships are found in the pathological ranges of attention, memory and microstructural white matter integrity associated with mild TBI, these analyses were applied to a group of 43 mild TBI patients. Results, which generally demonstrated a wider range of attention, memory and FA scores, replicated the correlation between attentional control and FA in left hemisphere anterior corona radiata, as well as the correlation between memory performance and FA in the uncinate fasciculus. These two sets of brain-behaviour relationships were highly specific, as shown by a lack of correlation between attention and uncinate fasciculus FA and the lack of correlation between memory performance and anterior corona radiata FA. Furthermore, a 'correlational double dissociation' was demonstrated to exist between two distinct frontal structures independently associated with attention and memory, respectively, via a series of multiple regression analyses in both normal controls and adults with mild TBI. The results of the multiple regression analyses provide direct evidence that tract-specific variation in microstructural white matter integrity among normal controls and among mild TBI patients can account for much of the variation in performance in specific cognitive domains. More generally, such findings suggest that diffusion anisotropy measurement can be used as a quantitative biomarker for neurocognitive function and dysfunction.

Keywords: diffusion tensor imaging; traumatic brain injury; executive function; executive attention; memory

Abbreviations: ACR = anterior corona radiata; ANT = attention network task; CB = cingulum bundle; CVLT-II = California verbal learning test, second edition; DTI = diffusion tensor imaging; FA = fractional anisotropy; ICC = intraclass correlation coefficient; ILF = inferior longitudinal fasciculus; LDFR = long delay free recall; ROI = region of interest; SDFR = short delay free recall; SLF = superior longitudinal fasciculus; TBI = traumatic brain injury; UF = uncinate fasciculus

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Introduction

Sub-systems of executive function such as attention and memory are among the most significant human brain processes impacting overall cognitive function. A variety of approaches have been used to better understand these anatomical and functional components. On one end of the spectrum are neuropsychological focal lesion studies in patient populations linking gross frontal lobe damage to executive dysfunction and focal retrograde and anterograde amnesia (Stuss and Benson, 1984; Milner *et al.*, 1985; Levine *et al.*, 1998; Stuss and Alexander, 2000). Neuropsychological data clearly highlight the central role of the frontal lobes in executive attention (Stuss *et al.*, 1981; Vendrell *et al.*, 1995). Yet, there are notable limitations of these methods for isolating and dissociating their functional components. Focal lesions are often quite large and variable in spatial extent which limits the precision of findings to gross divisions of the brain. Additionally, focal lesion studies are restricted to studying categorical damage (impaired versus normal) when, in fact, many injuries may exist on a spectrum of severity that may systematically relate to the degree of cognitive impairment.

Functional magnetic resonance imaging (fMRI) studies have also provided insights into sub-systems of executive function. Such studies provide evidence that response conflict in Stroop and Flanker tasks involve the anterior cingulate gyrus (Casey *et al.*, 2000; Gruber *et al.*, 2002; Fan *et al.*, 2005) while working memory processes involve bilateral prefrontal and temporal regions (Landfield, 1988; Cabeza and Nyberg, 2000; Shu *et al.*, 2003). Yet fMRI faces challenges when applied to patients who exhibit deficits on the very tasks required to activate the regions under investigation and is also restricted to studying cortical grey matter.

Magnetic resonance diffusion tensor imaging (DTI) can be used to assess microstructural white matter integrity on a continuous scale and can be used to examine the anatomical connectivity within functional networks (Basser *et al.*, 1994; Basser and Pierpaoli, 1996). Fractional anisotropy (FA), a normalized DTI measure of the degree of directionality of water diffusion, has been shown to be sensitive to white matter microstructural integrity and is known to correlate with a wide range of cognitive skills (Moseley *et al.*, 2002; Medina *et al.*, 2005; Schmithorst *et al.*, 2005; Mabbott *et al.*, 2006; Niogi and McCandliss, 2006). Even after controlling for age-related development, DTI studies have shown that performance in specific cognitive functions is associated with white matter organization and integrity (Catani, 2006; Durston and Casey, 2006; Niogi and McCandliss, 2006).

Such methods may shed new light on functional dissociations between prefrontal brain circuitry associated with attentional control and memory. It is plausible that examining normal FA variation in white matter tracts and associated cognitive function can provide evidence to determine which pathways impact memory and which

pathways impact attentional control. Moreover, variation in white matter integrity, whether due to normal development or pathology, should account for differences in cognitive function. A convenient population to examine a larger range of variation in white matter integrity, memory function, and executive function skills, is those affected by mild traumatic brain injury (TBI). Mild TBI is a potential model human system to study the relative contributions of white matter tracts to executive and memory functions, as the mechanism of damage has been linked primarily to diffuse axonal injury (DAI) (Gennarelli and Graham, 1998; Medana and Esiri, 2003; Povlishock and Katz, 2005). Due to the variable nature of head injury, certain tracts may be damaged to different degrees while other tracts may be relatively spared. Furthermore, attention and memory are the two most commonly affected cognitive domains in mild TBI (Lundin *et al.*, 2006; Malojcic *et al.*, 2008). It is likely that the same tracts that are responsible for normal inter-individual differences in memory and attentional control are selectively damaged in mild TBI, producing these chronic cognitive dysfunctions with different degrees of severity.

In this study, we first conduct an exploratory analysis in normal adults to test potential associations between white matter tracts and individual differences in two cognitive domains: memory and attentional control. After determining the two white matter tracts primarily associated with memory and attentional control in normal adults, we test whether these structure–function relationships extend to the damaged range in mild TBI patients. We then examine whether impairment is categorical or whether cognitive dysfunction exists on a continuous spectrum of severity related to the extent of white matter injury. Furthermore, regional heterogeneity of injury in mild TBI provides a means to establish specificity of the role these particular white matter tracts have in cognitive function. We test the specificity of these structure–function relationships in mild TBI subjects by establishing a quantitative double dissociation. Such evidence would clarify the white matter networks required in memory and attentional control which may be subtly and independently impacted in mild TBI, causing chronic disability. Damage to these white matter pathways may be predictive of dysfunction in the corresponding cognitive domain, thus extending the utility of DTI to the diagnosis of cognitive sequelae in mild TBI.

Methods

Participants

Subjects in this study included 43 patients prospectively recruited with mild TBI (28 males, 15 females), defined as having a Glasgow Coma Scale score of 13–15 at the time of presentation to the Emergency Department following head trauma as well as post-traumatic amnesia. All mild TBI subjects were imaged at least 1 month post-injury (mean 16.9 months, range 1–53 months). Exclusion criteria included age <17 years or >65 years, any prior

Table 1 Demographic data for subjects with mild traumatic brain injury and summary of conventional clinical MRI findings

Patient	Age (Years)	Sex	GCS	Time since TBI (months)	Conventional clinical MRI findings
1	25	F	15	7	TMH
2	40	M	15	18	R+L frontal CHC; R+L temporal CHC
3	35	F	15	12	Normal
4	45	M	15	51	NWMH
5	25	M	15	38	R inf. frontal CHC
6	29	F	15	29	Normal
7	37	M	15	20	L frontal CHC; L temporal CHC; R frontal CHC
8	31	F	15	35	L temporal CHC; R frontal CHC; TMH in L thalamus
9	26	M	15	10	Normal
10	50	M	15	44	NWMH
11	44	M	15	40	NWMH
12	52	F	15	53	Normal
13	37	M	15	10	Normal
14	49	F	15	35	Normal
15	20	M	15	1	R temporal CHC
16	43	M	15	6	R+L frontal CHC; L temporal CHC
17	32	M	15	3	R temporal CHC; L temporal CC
18	40	M	14	13	R+L frontal CC; R+L temporal CC
19	36	F	14	12	L temporal CHC, L parietal CHC
20	27	M	15	12	TMH
21	46	F	14	8	R temporal CC; NWMH
22	61	F	15	19	R+L frontal CHC; L temporal CHC; R parietal CHC; NWMH
23	27	M	15	12	R frontal CHC; R temporal CHC
24	35	M	14	12	L frontal CHC; B frontal + L temporal TMH
25	29	M	15	12	R+L frontal CHC; L temporal CHC; R frontal, R parietal, L temporal TMH
26	22	F	15	12	R temporal CHC
27	27	M	15	12	R frontal CHC; R frontal TMH
28	23	M	13	12	R+L frontal CHC; L temporal CHC
29	23	F	15	12	R+L frontal CHC; R temporal CHC
30	18	M	15	12	Normal
31	37	M	14	12	Normal
32	17	M	15	12	L frontal TMH; L temporal TMH; R parietal TMH
33	18	M	15	12	Normal
34	26	M	13	12	R temporal CHC; R occipital TMH; L frontal TMH
35	17	F	15	12	Normal
36	36	M	15	12	R temporal CHC
37	26	F	15	12	R temporal CHC; L frontal TMH; L parietal TMH
38	26	M	15	12	R+L frontal CHC; R temporal CHC
39	27	F	15	12	Normal
40	23	M	15	12	R+L frontal TMH; R temporal TMH; TMH in splenium; TMH in L midbrain
41	34	M	15	12	L frontal TMH
42	46	F	14	12	R frontal TMH; TMH in body of corpus callosum
43	24	M	15	12	Normal

GCS = Glasgow Coma Scale; TMH = traumatic microhaemorrhages, L = Left; R = Right; CHC = chronic haemorrhagic contusion; CC = Chronic (non-haemorrhagic) contusion; NWMH = non-specific white matter hyperintensities.

history of TBI, any history of neurological or psychiatric illness including drug or alcohol abuse, psychotropic medications that would affect cognitive testing or any contraindication to MR imaging such as pregnancy or ferromagnetic implants. The average age was 32.4 years (range 17–61 years). Table 1 summarizes demographic information for the TBI patients. Normal adult control subjects in this study included 23 healthy volunteers (17 males, 6 females) with an average age of 29.9 years (range 18–58 years). There was no significant difference in mean age, gender, handedness (only one normal control was left-handed) or level of education between the mild TBI group and the control group. Written informed consent was obtained from all subjects in accordance with protocols approved by the Internal Review Board of Weill

Cornell Medical College or the Committee on Human Research at the University of California, San Francisco.

MRI and DTI acquisition and analysis

Magnetic resonance imaging was acquired on two 3 Tesla (3T) GE Signa EXCITE scanners (GE Healthcare, Waukesha, WI, USA) each equipped with 8-channel phased-array head coils. Identical MR imaging hardware, pulse sequences and acquisition protocols were used at the two sites. Whole-brain DTI was performed with a multislice single-shot spin echo echoplanar pulse sequence (TE = 63 ms, TR = 14 s) using 55 diffusion-encoding directions, isotropically distributed over the surface of a sphere with

electrostatic repulsion, acquired at $b = 1000 \text{ s/mm}^2$, 1 acquisition with $b = 0 \text{ s/mm}^2$, 72 interleaved slices of 1.8 mm thickness each with no gap between slices, a 128×128 matrix that is zero-filled during reconstruction to 256×256 and a field of view (FOV) of 230 mm. Parallel imaging was employed using the Array Spatial Sensitivity Encoding Technique (ASSET) with an acceleration factor of 2. Images were post-processed offline using DTIstudio software (Jiang *et al.*, 2006) to obtain FA maps, apparent diffusion coefficient (ADC) maps and directionally encoded colour FA maps.

The following conventional 3T MR imaging sequences were acquired: (i) axial 3D inversion recovery fast spoiled gradient-recalled echo (FSPGR) T_1 -weighted images (TE = 1.5 ms, TR = 6.3 ms, TI = 400 ms, flip angle of 15°) with 230 mm FOV, 156 1.0 mm contiguous partitions at a 256×256 matrix, (ii) axial T_2 -weighted fluid-attenuated inversion recovery (FLAIR) images (TE = 126 ms, TR = 10 s, TI = 2200 ms) with 220 mm FOV, 47 to 48 3.0 mm contiguous slices at a 256×256 matrix, (iii) axial magnetization prepared gradient echo (MPGR) T_2^* -weighted images (TE = 15 ms, TR = 500 ms, flip angle of 20°) with $220 \times 170 \text{ mm}^2$ FOV, 47 to 48 3.0 mm contiguous slices at a 256×192 matrix. All conventional MR images were interpreted by attending neuroradiologists certified by the American Board of Radiology. None of the control subjects had any clinically significant abnormal findings on their MR scans of the brain.

Region of interest analysis

To avoid several confounds associated with spatial normalization of white matter tracts, a manual ROI approach was adopted to test specific structures throughout the brain selected *a priori*. Each ROI was placed in an anatomically identifiable white matter tract on the directionally encoded colour FA images, as illustrated in Fig. 1. The ROI procedure consisted of using standard ellipse-shaped ROIs. Selection and analysis was implemented with software written in Interactive Data Language v6.0 (IDL, ITT Visual Information Solutions, Boulder, CO, USA). Ellipses were prescribed on axial directionally encoded anisotropy maps at the centre of each structure in normal-appearing white matter, as assessed from the conventional MR imaging sequences. The size and dimensions of the ellipse were kept constant for each tract across subjects. Subsequently, the anatomical accuracy of the ROI placement was validated by a board-certified neuroradiologist. The selected structures, following the nomenclature of Mori *et al.* (2005), and corresponding ROI size in voxels included the: (i) uncinate fasciculus (UF, 41 voxels), (ii) anterior corona radiata (ACR, 20 voxels), (iii) the anterior aspect of the inferior longitudinal fasciculus (ILF, 27 voxels), (iv) genu of the corpus callosum (55 voxels), (v) the cingulum bundle (CB, 52 voxels) and (vi) the superior longitudinal fasciculus (SLF, 27 voxels). These ROIs were selected based on previous literature associating these structures with memory or attention (Landfield, 1988; Casey *et al.*, 2000; Levin, 2003; Fan *et al.*, 2005; Sperling, 2007). Mean and standard deviation (SD) of FA values for each ROI were recorded.

Inter-rater and intra-rater reliability were assessed using the intraclass correlation coefficient (ICC). Two raters measured FA of ROIs in the ACR bilaterally and in the UF bilaterally for 15 normal control subjects and 15 TBI subjects to test inter-rater reliability in the two tracts found to have statistically significant correlation with memory and attention performance. One of these

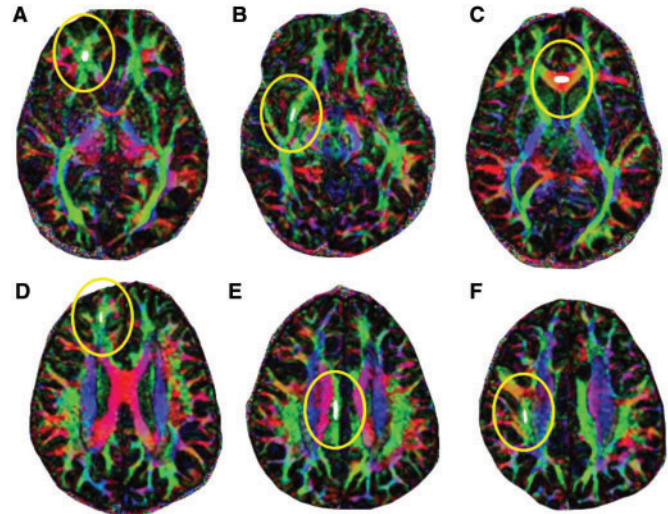


Fig. 1 Region of interest placement for DTI analysis. Shown are corresponding ROIs for the right hemisphere. The solid ellipse within yellow outline indicates the location and size of the ROI. (A) UF, (B) ILF, (C) genu of corpus callosum, (D) ACR, (E) CB and (F) SLF.

raters repeated these measurements to determine intra-rater reliability. The ICC was first calculated separately for measurements on normal subjects and TBI subjects for both inter- and intra-rater reliability. Subsequently, an overall ICC was determined by pooling the normal and TBI subjects together.

Assessment of attentional control

The Attention Network Task (ANT) (Fan *et al.*, 2005) was used to provide a quantitative assessment of attentional control. The test consists of three cue conditions with two target conditions. The three cue conditions were no-cue (baseline), centre-cue (temporally informative) and a spatial-cue (temporally and spatially informative). Briefly, stimuli consisted of a row of five visually presented arrows each individually pointing either leftward or rightward, against a gray background. The subjects were to indicate the direction of the central arrow by pressing a button with the index finger of the left hand for the left direction or the right hand for the right direction. Either all five arrows pointed in the same direction (the congruent target condition) or the flanking arrows pointed in the opposite direction of the centre arrow (the incongruent condition). Reaction times were recorded and the difference in reaction times between the incongruent and congruent conditions, the conflict score, was used as the measure of attentional control (i.e. congruent reaction time minus incongruent reaction time). Since incongruent trials elicit longer reaction times than congruent trials, the conflict score is expected to be negative-valued. A shorter difference in reaction times of the two trials indicates better attentional control performance and therefore a 'less negative' conflict score.

Assessment of memory performance

The California Verbal Learning Test, Second Edition (CVLT-II) was administered to measure memory performance (Delis *et al.*, 2000). An examiner orally presented two word lists (list A and list B) that each contained 16 items, comprised of four words

from each of four semantic categories. First there are five presentations of list A, each immediately recalled orally by the examinee. This is followed by a presentation of list B once followed by an immediate recall by the examinee. After a 20-min delay during which non-verbal tasks are administered, the examinee is asked to recall as many words as possible from list A. This last trial, the long delay free recall trial (LDFR), was used as the primary measure of memory performance. A greater number of correctly recalled words indicates better memory performance. The short delay free recall test (SDFR), which entails immediately recalling the list of words, was used to differentiate between encoding and retrieval mechanisms. Raw scores from the CVLT-II were used for each of the memory measures.

Statistics

Non-parametric statistical tests with an alpha of 0.05 were used to determine significance. The Spearman's rho statistic was used to test for significance of correlations. A Bonferroni correction was used to account for multiple comparisons. The alpha corrected for multiple comparisons is reported in the 'Results' section. Additionally, partial correlations were used to control for time since injury in the TBI group and age in both the normal control and TBI subjects. These included correlations in normal control subjects between FA (of various structures) and LDFR and FA and conflict score. One normal control subject was removed from any statistical tests pertaining to LDFR because he was a statistical outlier on the memory measure. In the TBI patients, correlations were computed for FA and LDFR, FA and conflict score, lateralization and conflict score, LDFR and SDFR, and finally, FA and SDFR. Subsequently, a partial correlation between UF FA and LDFR was performed while controlling for SDFR. The Mann-Whitney U-test was used to test statistical significance when comparing FA and cognitive performance between the normal control group and mild TBI group.

A multiple linear regression analysis was used to establish a correlational double dissociation, as shown previously for reading skill and digit recall in children (Niogi and McCandliss, 2006). This is done using a series of multiple regression analyses. The aim of the analysis was to assess the unique variance accounted for by attentional control in the left ACR (the dominant hemisphere contributing to attention) after controlling for age and memory performance. This same approach was then applied to the UF to assess the unique variance of memory accounted for by the average FA of the bilateral UF after controlling for age and attentional control. Since both hemispheres of the UF had significant association with memory, the bilateral average was used for this test.

In more detail, each multiple regression analysis consisted of two blocks of independent variables and FA as the dependent measure. The first block contained age and the presumptively irrelevant cognitive measure as independent variables. In the case of the left ACR, the control measures were age and LDFR. In the case of the bilateral UF, the control measures were age and conflict score. The second block contained these control variables with the addition of the pertinent parameter that loads onto the specific region. In the case of the left ACR, the pertinent cognitive measure was conflict score, while, in the bilateral UF, the pertinent parameter was LDFR. Significance of the ΔR^2 change was computed using an *F*-statistic.

Post hoc, the previous correlational tests in both the normal and TBI groups were repeated substituting ADC for FA. All statistical tests were performed using SPSS v.14 (SPSS Inc., Chicago, IL, USA).

Results

Structure–function relationships in normal adults I: memory domain

Conventional MRI findings were normal for all control subjects. MRI findings for the TBI patients are summarized in Table 1.

The ICC for inter-rater reliability of ROI measurements in normal subjects was 0.84. For TBI subjects, the inter-rater ICC was 0.84 as well. The ICC for intra-rater reliability of ROI measurements in normal subjects was 0.93. In TBI subjects, the intra-rater ICC was 0.88. When assessing overall reliability across all subjects (normal and TBI), the ICC for inter-rater reliability was 0.84 and for intra-rater reliability was 0.91. As these ICC values were each greater than 0.80, they constitute excellent agreement for both inter- and intra-rater reliability.

The goal of the first analysis was to determine which white matter tract is primarily associated with the memory domain. To do so, we tested whether normal variation of white matter microstructural integrity accounts for inter-individual differences in the Long Delay Free Recall (LDFR) sub-test of the California Verbal Learning Test, Second Edition (CVLT-II) (Delis *et al.*, 2000). The LDFR sub-test measures verbal memory, specifically the ability to recall a list of 16 words after 20 min of non-verbal testing. In this test, the number of correctly recalled words is an index of memory performance. Previous literature suggests that the memory domain is associated with the hippocampus and prefrontal cortex (Landfield, 1988; Levin, 1990; Sperling, 2007). As such, major tracts associated with these areas including the UF, ILF and the genu of the corpus callosum (Fig. 1A–C) were subject to ROI analysis on FA maps from the DTI scan.

We tested whether FA correlates with the LDFR score in normal adults. We found that the average FA of the right and left UF correlated significantly with memory performance ($r=0.61$, $P=0.003$, Fig. 2A). Additionally, the FA of the right UF significantly correlated with memory performance ($r=0.66$, $P=0.001$). While the left hemisphere UF did not have a statistically significant correlation, a trend existed ($r=0.42$, $P=0.054$). The ILF and genu failed to correlate significantly with LDFR in these subjects (left ILF: $r=-0.17$, $P=0.45$; right ILF: $r=-0.053$, $P=0.81$; genu $=-0.01$, $P=0.97$). Table 2 summarizes these results and shows correlations controlling for age. Controlling for multiple comparisons using a Bonferroni corrected alpha level, correlations below $P<0.01$ are significant. Using this criterion, a significant correlation exists between the right UF and LDFR.

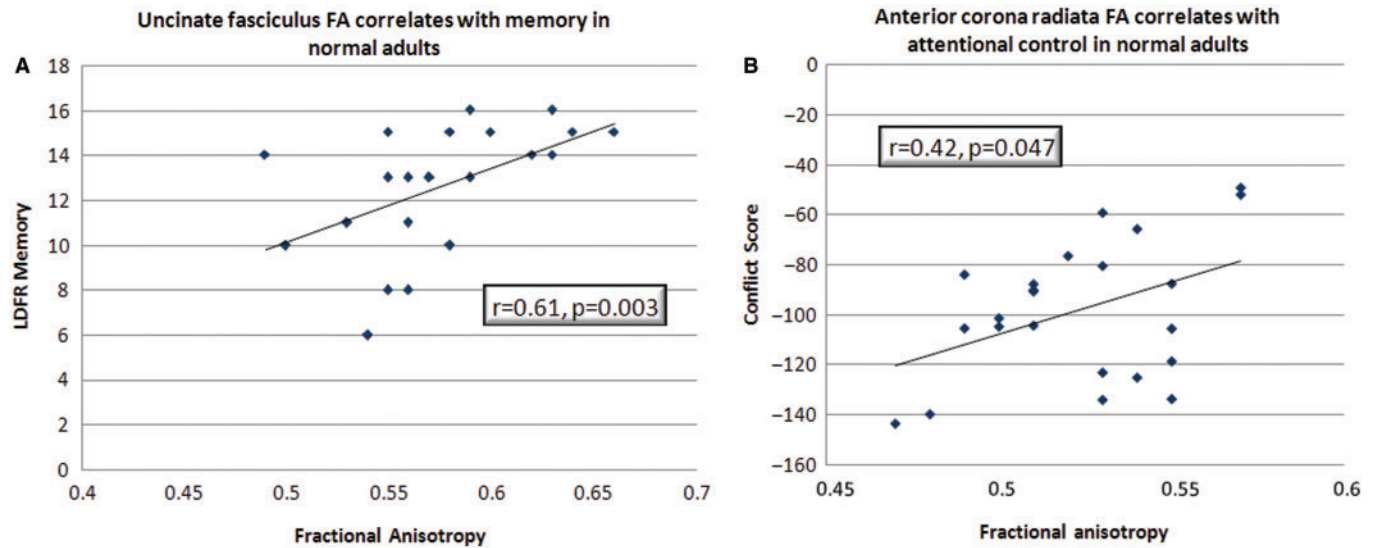


Fig. 2 Cognitive function is significantly associated with white matter microstructure in normal adults. **(A)** Correlation of Long delay-free recall (LDFR) memory and average bilateral UF fractional anisotropy (FA) in both hemispheres ($r = 0.61$, $P = 0.003$). **(B)** Correlation of attentional control measured by conflict score and the left anterior corona radiata FA ($r = 0.42$, $P = 0.047$).

Table 2 Correlations in normal control subjects between memory and FA in the UF, ILF, and genu (Partial correlations control for age)

	UF left	UF right	ILF left	ILF right	Genu
Zero order	0.42 ($P = 0.054$)	0.66 ($P = 0.001$)	-0.17 ($P = 0.45$)	-0.053 ($P = 0.81$)	-0.053 ($P = 0.97$)
Partial correlation	0.33 ($P = 0.140$)	0.558 ($P = 0.009$)	-0.074 ($P = 0.75$)	-0.017 ($P = 0.94$)	0.20 ($P = 0.40$)

Structure–function relationships in normal adults II: attentional control domain

In this analysis, we test which white matter tract is primarily associated with attentional control. Attentional control was measured using the ANT described in detail in the Methods section (Fan *et al.*, 2002). Briefly, the conflict score is the difference in reaction times between congruent and incongruent flanking arrow trials and serves as an index of attentional control. Conflict scores are expected to be negative to reflect the cost of cognitive conflict, thus greater cognitive conflict is reflected in lower values.

In contrast to the first analysis, we selected ROIs in white matter tracts associated with the anterior cingulate gyrus, which is associated with attentional control (Casey *et al.*, 2000; Fan *et al.*, 2005). We correlated the FA from ROIs in the anterior corona radiata (ACR), the cingulum bundle (CB) and the superior longitudinal fasciculus (SLF) with the conflict scores in normal adults (Fig. 1D–F). Attentional control performance correlated significantly with FA of the left hemisphere ACR ($r = 0.42$, $P = 0.047$, Fig. 2B). However, the right hemisphere ACR FA and the bilateral average failed to correlate significantly (right ACR: $r = 0.21$, $P = 0.332$; bilateral ACR: $r = 0.32$, $P = 0.138$). The other ROIs also did not approach significance (left CB: $r = -0.070$, $P = 0.751$; right CB: $r = -0.32$, $P = 0.135$; left SLF: $r = 0.31$,

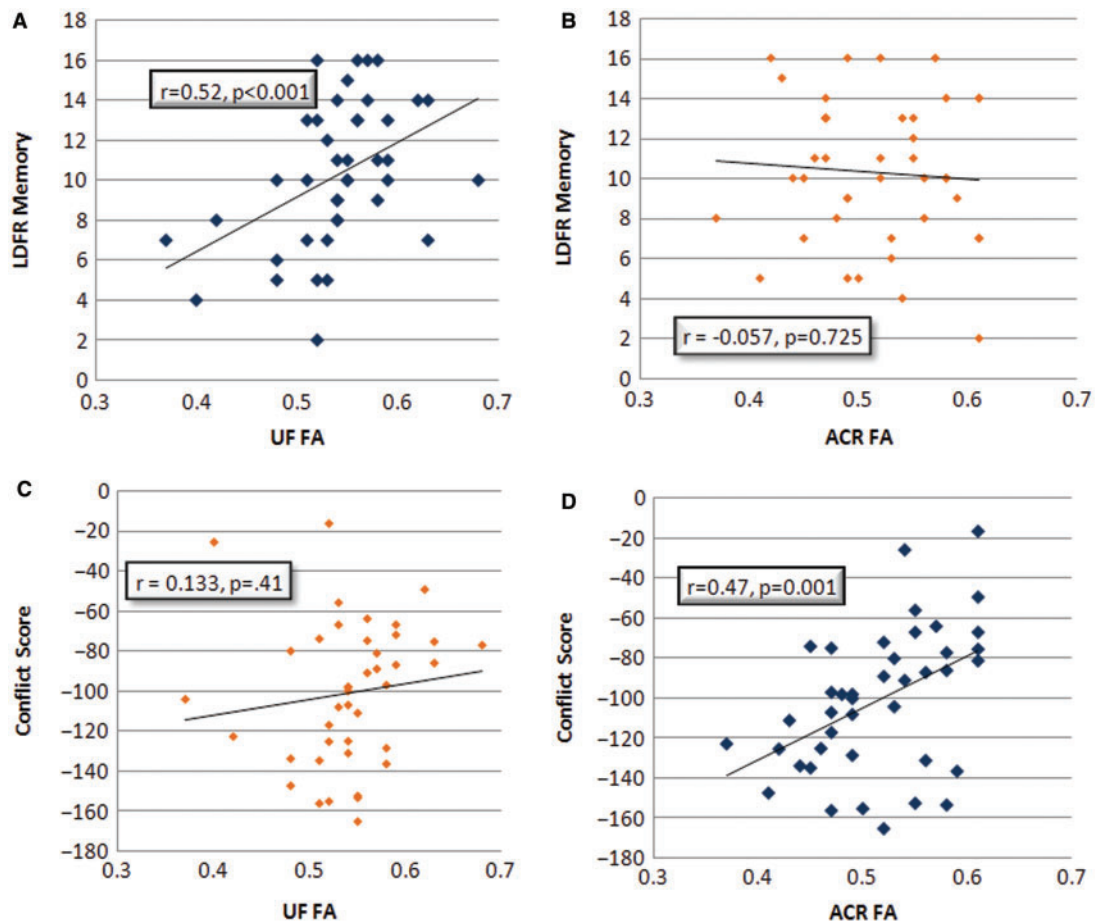
$P = 0.149$; right SLF: $r = 0.061$, $P = 0.783$). Table 3 summarizes these results and shows correlations controlling for age. Controlling for multiple comparisons using a Bonferroni corrected alpha level of $P < 0.0083$, only nonsignificant trends remain, suggesting a potential relationship between attentional control and the left hemisphere ACR.

Structure–function relationships in mild TBI subjects: memory and attentional control

In the next phase of the study we aimed to test whether these results extend to the damaged range. To do so, we first compare the TBI patient group to the normal controls to test whether certain TBI patients perform outside the normal range in memory and attention performance and whether they have FA below the normal range in the UF and ACR. A Mann–Whitney U-test shows that, as a group, the LDFR score and average UF FA are significantly reduced compared with the normal control group (LDFR: $U = 278$, $P = 0.007$; UF: $U = 276$, $P = 0.003$). While the TBI group was not significantly different than the normal control group in attentional control (conflict score: $U = 451$, $P = 0.56$) or bilateral average ACR FA ($U = 383$, $P = 0.11$), individual patients within the TBI cohort performed outside the normal range. Eight TBI patients had ANT

Table 3 Correlations for normal control subjects between attention (ANT conflict scores) and FA in the ACR, CB, and SLF (Partial correlations control for age)

	ACR left	ACR right	CB left	CB right	SLF right	SLF left
Zero order	0.42 ($P=0.047$)	0.21 ($P=0.15$)	-0.07 ($P=0.75$)	-0.32 ($P=0.14$)	0.31 ($P=0.15$)	0.061 ($P=0.78$)
Partial Correlation	0.42 ($P=0.054$)	0.22 ($P=0.33$)	-0.097 ($P=0.67$)	-0.396 ($P=0.068$)	0.254 ($P=0.25$)	0.022 ($P=0.92$)

**Fig. 3** Two cognitive functions are specifically associated with white matter microstructure in two distinct regions in adults with mild TBI. (A) Correlation of memory performance and average bilateral uncinate fasciculus (UF) fractional anisotropy (FA) in both hemispheres ($r = 0.52, P < 0.001$). (B) The ACR FA does not correlate significantly with LDFR memory ($r = -0.057, P = 0.725$). (C) The UF FA does not correlate significantly with attentional control ($r = 0.133, P = 0.41$). (D) Correlation of attentional control measured by conflict score and the left anterior corona radiata (ACR) FA ($r = 0.47, P = 0.001$).

conflict scores outside the range of the normal controls. Two of these subjects and an additional six TBI patients had FA values outside the normal bilateral average ACR FA range (15 patients when the right and left ACR are considered separately which include all eight TBI patients with conflict scores outside the normal range).

Given that certain patients within the TBI cohort perform below the normal range in the cognitive domains and have FA below the normal range, we test whether the aforementioned significant relationships shown in normal adults extend to the broader range of scores exhibited by adults with mild TBI. Driven by the results of the preceding experiments in normal adults, only the UF and ACR were

examined in the mild TBI subjects. Again, memory and attention were assessed using the LDFR sub-test of the CVLT-II and the ANT conflict score, respectively.

The results indicate that the relationships seen in normal adults extend into the damaged range. First, FA of the UF in both hemispheres correlated significantly with memory performance in mild TBI subjects (bilateral average UF: $r = 0.52, P < 0.001$, Fig. 3A; right UF: $r = 0.50, P = 0.001$; left UF: $r = 0.46, P = 0.002$). Table 4 summarizes these results and shows correlations controlling for age and time since injury. Controlling for multiple comparisons using a Bonferroni corrected alpha level of $P < 0.025$, the left and right and left UF remain significantly correlated with LDFR.

Table 4 Correlations for TBI subjects between LDFR memory performance and FA in the UF (Partial correlations control for age and length of time post injury)

	UF left	UF right	UF bilateral average
Zero order	0.46 ($P=0.002$)	0.50 ($P=0.001$)	0.52 ($P=0.001$)
Partial correlation	0.29 ($P=0.071$)	0.36 ($P=0.023$)	0.35 ($P=0.030$)

Table 5 Correlations for TBI subjects between attention performance and FA in the ACR (Partial correlations control for age and length of time post injury)

	ACR left	ACR right	ACR bilateral average
Zero order	0.47 ($P=0.001$)	0.11 ($P=0.49$)	0.36 ($P=0.022$)
Partial correlation	0.45 ($P=0.004$)	0.16 ($P=0.45$)	0.39 ($P=0.014$)

Secondly, the attentional control and ACR FA relationship also existed in the mild TBI population. The bilateral average ACR FA correlated significantly with the conflict score in mild TBI subjects ($r=0.36$, $P=0.022$). A closer examination of the contributions of each hemisphere shows that the left ACR FA is the primary contributor to this relationship ($r=0.47$, $P=0.001$, Fig. 3D). The right hemisphere ACR FA did not correlate with conflict significantly ($r=0.11$, $P=0.492$). To test whether the effect was left lateralized in the mild TBI subjects, a lateralization score was calculated for the ACR FA, which did not correlate with conflict in mild TBI ($r=-0.22$, $P=0.160$). Table 5 summarizes these results and shows correlations controlling for age and time since injury. Controlling for multiple comparisons using a Bonferroni corrected alpha level of $P<0.025$, the left ACR remains significantly correlated to conflict.

Specificity of structure–function relationships: a double dissociation

The final goal of the study was to test the specificity of the cognitive domains associated with the ACR and UF by attempting to establish a correlational double dissociation within the normal controls and mild TBI subjects, as shown previously for reading skill and digit recall in children (Niogi and McCandliss, 2006). This is done using a series of multiple regression analyses. The aim of the analysis was to assess the unique variance accounted for by attentional control in the left ACR after controlling for age and memory performance. This same approach was then applied to the UF to assess the unique variance of memory accounted for by the average FA of the bilateral UF after controlling for age and attentional control. This technique is described in detail in the ‘Statistics’ sub-section

Table 6 Multiple regression analysis of the ACR

Block	R	R ²	Adjusted R ²	R ² Change	Sig. Change
Normal adult subjects					
1	0.062 (a)	0.004	−0.096	0.004	0.962
2	0.450 (b)	0.202	0.076	0.198	0.043
TBI patients					
1	0.072 (a)	0.005	−0.047	0.005	0.906
2	0.457 (b)	0.209	−0.144	0.203	0.004

1) Predictors: (Constant), LDFR memory, age.

2) Predictors: (Constant), LDFR memory, age, Attentional control. The first block controls for the variables age and the proposed “irrelevant” measure, LDFR memory. The final block contains the previous independent variables and the addition of the “pertinent” parameter that loads on to the ACR, attentional control. There only exists a significant R² change when including attentional control in the regression analysis.

Table 7 Multiple regression analysis of the UF

Block	R	R ²	Adjusted R ²	R ² Change	Sig. Change
Normal adult subjects					
1	0.204 (a)	0.042	−0.059	0.042	0.668
2	0.518 (b)	0.269	0.147	0.227	0.03
TBI patients					
1	0.354 (a)	0.125	0.079	0.125	0.079
2	0.500 (b)	0.25	0.189	0.124	0.018

1) Predictors: (Constant), attentional control, age.

2) Predictors: (Constant), attentional control, age, LDFR memory. The first block controls for the variables age and the proposed “irrelevant” measure, attentional control. The final block contains the previous independent variables and the addition of the “pertinent” parameter that loads on to the UF, LDFR Memory. There only exists a significant R² change when including LDFR memory in the regression analysis.

of the ‘Methods’ section. Briefly, each multiple regression analysis consisted of two blocks of independent variables and FA as the dependent measure. The first block contained age and the presumptively irrelevant cognitive measure as independent variables. The second block contained these control variables with the addition of the pertinent cognitive measure associated with the specific region.

There was only a significant R² change in the final blocks after adding the pertinent cognitive measure in each case. After the addition of conflict in the multiple regression scheme for the left ACR, there was a significant R² change (Normal: $\Delta R^2=0.20$, $P=0.043$; TBI: $\Delta R^2=0.20$, $P=0.004$, Table 6). This implies that, even after controlling for age and memory, attentional control still loaded heavily on the left ACR. Likewise, after the addition of LDFR in the multiple regression scheme for the bilateral UF, there was a significant R² change (Normal: $\Delta R^2=0.23$, $P=0.03$; TBI: $\Delta R^2=0.12$, $P=0.018$, Table 7). Therefore, in

this case, differences in UF integrity are specifically related to memory performance even after controlling for age and differences in attentional control.

Post hoc analysis: is injury in the UF linked to encoding or retrieval problems in memory?

The aforementioned results suggest that damage to the UF is associated with decreased memory performance in adults with mild TBI. However, the cognitive deficit could either be due to inability to encode the information or difficulties in retrieving the information. To address this, a *post hoc* analysis was performed on the mild TBI subjects.

Memory was assessed using the LDFR measure of the CVLT-II. To distinguish between encoding and retrieval, one can investigate the ability of subjects to immediately recall the same list of words, measured in the SDFR sub-test of the CVLT-II. If subjects perform well in the SDFR test, but poorly in the LDFR test, then the subjects likely have deficits in memory retrieval because the lists were properly encoded for the immediate recall trials. However, if subjects perform poorly on both the LDFR and SDFR, then the deficit may be in either encoding or both long- and short-term retrieval.

There was no significant correlation of SDFR and LDFR scores in the mild TBI subjects ($P = -0.11$, $P = 0.488$). SDFR also does not correlate with FA of the UF (bilateral average UF: $r = -0.30$, $P = 0.851$; left UF: $r = -0.010$, $P = 0.953$; right UF: $r = -0.108$, $P = 0.500$). Additionally, after controlling for SDFR, a partial correlation between the bilateral FA of the UF and LDFR is significant (0.441 , $r = 0.006$). Furthermore, 75% of mild TBI subjects that scored above 90% in the SDFR test also had LDFR scores below 50%. The data suggest that the deficit in memory performance due to damage in the UF is likely due to difficulties in long-term retrieval, not encoding or short-term retrieval.

Post hoc analysis: structure–function correlations with apparent diffusion coefficient

Structure–function correlations that were statistically significant using FA were repeated using ADC as an exploratory follow-up analysis to better understand the nature of the diffusion changes in the TBI subjects. In normal subjects, no significant correlations existed between ACR ADC and conflict (right ACR: $r = -0.32$, $P = 0.14$; left ACR: $r = -0.34$, $P = 0.11$; bilateral average: $r = -0.38$, $P = 0.70$) nor UF ADC and LDFR (right UF: $r = -0.27$, $P = 0.23$; left UF: $r = -0.18$, $P = 0.44$; bilateral average: $r = -0.25$, $P = 0.26$).

Similarly, in TBI subjects no significant correlations existed between in the structure–function correlations using ADC (right ACR: $r = -0.043$, $P = 0.79$; left ACR: $r = -0.13$, $P = 0.44$; bilateral average: $r = -0.10$, $P = 0.54$) nor UF ADC and LDFR (right UF: $r = -0.20$, $P = 0.22$; left UF: $r = -0.061$, $P = 0.70$; bilateral average: $r = -0.16$, $P = 0.33$).

Discussion

The major finding in this 3T DTI study was that microstructural white matter integrity of bilateral UF is associated with memory performance while integrity of the left ACR is associated with attentional control. Interestingly, these associations account for individual differences of attentional control and memory performance in normal adults. Furthermore, damage to these tracts due to mild TBI is associated with greater deficits in the corresponding cognitive domain. In the final phase of this study, the specificity of these relationships was confirmed by establishing a double dissociation separately in the normal adult group and the TBI patient group. The specificity of these structure–function relationships in both groups suggests DTI can be used as a microstructural imaging biomarker for cognitive function and dysfunction.

Microstructural white matter correlates of memory and attentional control

The presence of such a correlational double dissociation argues strongly for a link between individual differences in specific domains of cognitive performance, such as attention and memory, and individual microstructural differences in specific white matter tract circuitry. This double dissociation excludes potentially confounding factors that might cause spurious correlations between white matter microarchitecture and behavioural measures, such as increased motion artifacts in the DTI scans of subjects who perform poorly on the cognitive tests. The fact that the same relationship was found in normal adults and in TBI also rules out possible sources of bias in comparing the two groups, such as systematic differences between controls and patients in ROI placement within normal-appearing white matter. The dissociation depends on the microstructural integrity of white matter and thus challenges classical notions of purely cortical modules of function. Rather, these findings suggest networks of function comprised of separable sub-systems. In the case of executive function, memory and attentional control are revealed to be two dissociable sub-systems.

Given the role both the frontal lobe and temporal lobe play in memory, it is plausible that the microarchitecture of the UF, which connects the prefrontal cortex and parahippocampal gyrus, would affect memory performance. Other DTI studies have also showed a similar relationship. In patients with schizophrenia, loss of white matter integrity along the UF was associated with verbal memory deficits (Nestor *et al.*, 2004). Additionally, our findings suggest deficits in memory performance attributed to UF microstructural injury in both hemispheres is due to retrieval mechanisms under the context of longer delays. The hemispheric encoding/retrieval asymmetry (HERA) model similarly proposes that both right and left prefrontal cortex are involved in retrieval, while encoding primarily activates the left prefrontal cortex (Kapur *et al.*, 1994).

A prior longitudinal study of mild TBI using the ANT showed that deficits in the executive component of attention, as assessed by the conflict score, persist for at least a month post-injury even when the orienting component had recovered (Haltermann *et al.*, 2006). We demonstrate that the integrity of the left ACR, which runs adjacent to and also synapses in the anterior cingulate gyrus, was found to account for specific variation in the executive component of attention in both normal volunteers and in mild TBI patients, while the right ACR only produced a non-significant trend. We do not, however, interpret this as direct evidence for a laterality effect as the degree of laterality between left and right ACR was unrelated to attention measures, and the current study may lack sufficient power to resolve similar trends implicated in the right ACR.

Implications for DTI in the study of TBI

TBI is a growing public health concern which affects nearly 1.5 million Americans each year. Worldwide, approximately 57 million individuals worldwide have been hospitalized by one or more episodes of TBI (Langlois *et al.*, 2006) and this number is only expected to increase as the average age of the population rises and as the number of motor vehicles rises around the world. Despite the high incidence of mild TBI, there exists a disproportionately small number of research studies of mild TBI patients with post-concussive syndrome (PCS) (Bigler, 2004). As such, there are a number of contemporary issues in mild TBI that remain unanswered. Most of these issues fall under a common category of how to evaluate and diagnose mild TBI. Findings on conventional non-invasive neuroimaging techniques such as computed tomography (CT) and MR imaging have not reliably correlated with symptoms and are inconsistent at best for predicting functional outcome following mild TBI (Hammoud and Wasserman, 2002; Inglese *et al.*, 2005). The insensitivity of conventional MR imaging in evaluating DAI underscores the need to use more sensitive techniques such as DTI to measure white matter microstructure.

Accurate diagnosis of TBI is a challenge for conventional neuroimaging because of the microstructural nature of the damage. The primary form of injury is DAI, the mechanism of which is unequal rotational and acceleration forces that induce a shear-strain deformation (Gennarelli and Graham, 1998; Medana and Esiri, 2003; Povlishock and Katz, 2005). These forces cause disruptions of axolemma and neurofilament organization which are thought to impair axonal transport (Blumbergs *et al.*, 1989; Arfanakis *et al.*, 2002; Smith *et al.*, 2003). The resulting DAI is difficult to visualize using MRI or CT (Mittl *et al.*, 1994; van der Naalt *et al.*, 1999). Furthermore, focal lesions associated with DAI that are visualized by conventional MR imaging, even at 3T, are not associated with long-term patient functional outcome or neurocognitive status (Scheid *et al.*, 2003; Hughes *et al.*, 2004;

Scheid *et al.*, 2006; Niogi *et al.*, 2008). These studies suggest that conventional MR imaging techniques cannot identify mild TBI patients who will have delayed recovery or persistent post-traumatic symptoms. Recent investigations have shown, however, that DTI is more sensitive to axonal injury than conventional MR imaging techniques in TBI patients (Arfanakis *et al.*, 2002; Huisman *et al.*, 2004; Inglese *et al.*, 2005; Newcombe *et al.*, 2007) and in a mouse model of TBI (Mac Donald *et al.*, 2007).

Perhaps it is not surprising that the two most common cognitive impairments in mild TBI, attentional control and memory, are associated with the ACR and UF, respectively. Both the ACR and UF are very susceptible to rotational shear injury because these rostrally located tracts are subject to the highest rotational forces (Gennarelli and Graham, 1998; Povlishock and Katz, 2005). In a recent study, Niogi *et al.* found in a cohort of 34 mild TBI patients that the ACR and UF were the two most commonly damaged white matter tracts out of 22 examined throughout the brain (Niogi *et al.*, 2008). The results of the present investigation suggest that the reason memory and executive dysfunction dominate cognitive sequelae after mild TBI is because these cognitive domains are associated with the most frequently damaged white matter structures. A recent neurocognitive study of mild TBI (Malojcic *et al.*, 2008) also demonstrated persistent deficits in both visual attention and short-term memory; however, the authors attributed the results in both cognitive domains to a slowing of general information processing. In contradistinction, our data show that deficits in visual attention and short-term memory are separable and are associated with distinct information processing networks subserved by different white matter pathways. In a previous DTI study, we have shown that the global extent of white matter injury throughout the brain correlates with the speed of general cognitive processing, as measured by simple reaction times to visual stimuli (Niogi *et al.*, 2008). Our current study extends this finding to provide evidence that DTI can be used to differentiate long-term impairments in separable cognitive domains, further validating DTI as a potential biomarker for cognitive dysfunction in TBI.

It was postulated by Fork *et al.* (2005) that memory deficits should be interpreted as executive dysfunction because there was no indication of deficits in encoding new items. In contrast, our results suggest that rather than implicating a global executive dysfunction syndrome, LDFR memory impairment is more specific and independent of attentional dysfunction. In subjects where there was damage to the left ACR and sparing of the bilateral UF, attentional control impairments tend to predominate. Similarly, in cases where there was relatively more damage to the bilateral UF than the left ACR, memory deficits were more severe.

In a recent DTI study of TBI, Kraus *et al.* (2007) examined a group of 20 mild TBI patients and demonstrated that these subjects had reduced FA in the cortico-spinal tract, sagittal stratum, and superior

longitudinal fasciculus. In their study, a 1 SD threshold below the control mean FA was used to indicate reduced anisotropy. Using this criterion, Kraus *et al.* (2007) found the number of structures with reduced FA correlated with executive, attentional and memory cognitive measures. While Kraus and colleagues demonstrated that the global extent of damage impacts these cognitive domains, our current study demonstrates that injury to specific networks impairs memory and attentional control domains separately and that normal variation in the microstructure of these tracts also influences cognitive performance. Furthermore, these cognitive deficits exist on a continuous spectrum of severity that is dependent on the degree of microstructural white matter injury, as opposed to categorical loss of function.

Methodological considerations

Numerous studies have established FA as a marker for white matter integrity in TBI, demyelinating diseases, and as a correlate of cognitive function in normal populations (Tuch *et al.*, 2005; Mabbott *et al.*, 2006; Mukherjee and McKinstry, 2006; Newcombe *et al.*, 2007; Grieve *et al.*, 2007; Kraus *et al.*, 2007; Niogi *et al.*, 2008). To limit the number of multiple comparisons, only one DTI measure was used for the *a priori* analysis. Given the strong association between FA and white matter integrity in previous studies, FA was used as the primary index of white matter microstructural integrity. It is important to note that there are other DTI measures as well that may have been employed. The diffusion ellipsoid can be reduced to radial diffusivity (average of the secondary and tertiary eigenvalues) and axial diffusivity (primary eigenvalue). Additionally, the average of all three eigenvalues is the average diffusion coefficient (ADC) which has been shown to increase in TBI (Goetz *et al.*, 2004; Huisman *et al.*, 2004; Shanmuganathan *et al.*, 2004; Newcombe *et al.*, 2007).

As an exploratory *post hoc* analysis, significant structure–function correlations were repeated with ADC. Interestingly, no significant correlation existed when using ADC although trends approaching significance were apparent in correlations within the normal control group. Perhaps the current study lacks sufficient power to resolve trends implicated by FA. However, these trends did not exist in the TBI population suggesting that FA may be a more sensitive biomarker of diffuse axonal injury.

There are some limitations to this study worth noting for future investigations. First, premorbid functioning is not known for mild TBI patients, although patients with multiple episodes of TBI or with known neuropsychiatric illnesses, alcohol or drug abuse were excluded. Thus, it is not clear whether their cognitive function and white matter FA reflect the effects of mild TBI or existed prior to the injury. While attention, memory and processing speed are cognitive domains that are particularly vulnerable to the effects of mild TBI, gross deficits of intelligence are seldom present. Unfortunately, in almost all cases of persistent PCS, the patients also suffer from

depression which will exacerbate commonly noted symptoms such as headaches, attention problems and memory loss (Arcia and Gualtieri, 1994; Hellawell *et al.*, 1999; Bigler, 2004).

Second, it is important to note that many of our subjects that had damage to the left ACR also had damage to the bilateral UF. These subjects tended to have impairments in both the memory and attentional control domains. Yet, the independence of memory and attentional control impairment was established by the double dissociation and was particularly notable in cases for which there was preferential damage to one structure and relative sparing of the other. It is known that TBI produces heterogeneous loci of damage. It is possible that other structures also may have been injured and are implicated in either memory or executive attention performance.

Third, manual ROIs were used to measure FA in white matter tracts. These are limited in that they can only sample a small portion of the fibre pathway. They also suffer from intra-rater and inter-rater variability in placement of ROIs. However, despite these limitations, manual ROI measurements are widely accepted and remain the most commonly used method for DTI quantitation. Of the alternatives, standard methods for spatial normalization of MR imaging data to perform group comparisons in an unbiased fashion do not work for DTI (Jones *et al.*, 2005). No universally accepted method for automated group analysis of DTI has yet been devised. Three-dimensional DTI tractography can sample a larger portion of the white matter pathway than manual ROIs; however, this technique also requires manual ROI placement to define the tracts. Thus, the method is not unbiased. Also, the ACR and UF are technically difficult to define in their entirety with fibre tracking because both course through regions of crossing pathways for which the tensor model of diffusion is not valid (Hess and Mukherjee, 2007). Moreover, focal haemorrhages or cavities in these tracts due to DAI would also adversely affect fibre tractography (Le *et al.*, 2005). In this study, portions of these tracts were chosen for ROI quantitation that were separate from the regions of major crossing fibres and which appeared normal on conventional 3T MR imaging.

Fourth, our goal was to examine TBI subjects with chronic symptoms and as a result we assessed TBI patients at least 1 month post-injury. The timeline regarding changes in neuropathology (recovery or progression) after TBI is unclear due to a paucity of longitudinal studies. Certain reports suggest that resolution normally occurs within a few days to 3 months post-injury, and a subset continue to have long-term symptoms (Dikmen *et al.*, 1986; Ponsford *et al.*, 2000; Povlishock and Katz, 2005; Kashluba *et al.*, 2008). It is worth noting that the subjects were scanned within a large range of time post-injury (1–53 months). However, correlations did not change significantly after controlling for time elapsed post-injury. Thus, it is likely that those with chronic symptoms have stable lesions

that did not resolve. Similarly, the study includes a wide age range (17–61 years). Controlling for age did not significantly alter the correlations, suggesting that chronic memory and attention deficits following TBI are independent of age-related changes in white matter microstructure.

Conclusion

White matter microstructural integrity of the left ACR is associated with attentional control performance in both normal adults and adults with mild TBI. In addition, the bilateral UF is associated with memory function in both normal adults and adults with mild TBI. Furthermore, results demonstrate domain specificity of these structure–function relationships that reflect a continuous scale of severity rather than a categorical loss of modular function. This study provides evidence that DTI may serve as a microstructural imaging biomarker for cognitive dysfunctions and variations within normal cognitive functions.

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