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# White matter damage and cognitive impairment after traumatic brain injury

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**White matter disruption is an important determinant of cognitive impairment after brain injury, but conventional neuroimaging underestimates its extent. In contrast, diffusion tensor imaging provides a validated and sensitive way of identifying the impact of axonal injury. The relationship between cognitive impairment after traumatic brain injury and white matter damage is likely to be complex. We applied a flexible technique—tract-based spatial statistics—to explore whether damage to specific white matter tracts is associated with particular patterns of cognitive impairment. The commonly affected domains of memory, executive function and information processing speed were investigated in 28 patients in the post-acute/chronic phase following traumatic brain injury and in 26 age-matched controls. Analysis of fractional anisotropy and diffusivity maps revealed widespread differences in white matter integrity between the groups. Patients showed large areas of reduced fractional anisotropy, as well as increased mean and axial diffusivities, compared with controls, despite the small amounts of cortical and white matter damage visible on standard imaging. A stratified analysis based on the presence or absence of microbleeds (a marker of diffuse axonal injury) revealed diffusion tensor imaging to be more sensitive than gradient-echo imaging to white matter damage. The location of white matter abnormality predicted cognitive function to some extent. The structure of the fornices was correlated with associative learning and memory across both patient and control groups, whilst the structure of frontal lobe connections showed relationships with executive function that differed in the two groups. These results highlight the complexity of the relationships between white matter structure and cognition. Although widespread and, sometimes, chronic abnormalities of white matter are identifiable following traumatic brain injury, the impact of these changes on cognitive function is likely to depend on damage to key pathways that link nodes in the distributed brain networks supporting high-level cognitive functions.**

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**Keywords:** traumatic brain injury; diffuse axonal injury; diffusion tensor; brain behaviour and relationships; cognitive impairment
**Abbreviations:** DTI = diffusion tensor imaging; $D_{ax}$ = axial diffusivity; $D_{rad}$ = radial diffusivity; TBSS = tract-based spatial statistics

# Introduction

Traumatic brain injury often results in persistent disability, due particularly to cognitive impairments (Whitnall *et al.*, 2006). Most survivors are young and have near-normal life expectancy (Thornhill *et al.*, 2000). Hence, the burden on public health and social care is substantial (Thurman *et al.*, 1999). The cognitive domains of memory, executive function and processing speed are commonly affected (Ponsford and Kinsella, 1992; Levin and Kraus, 1994; Levin, 1995; Scheid *et al.*, 2006; Draper and Ponsford, 2008). Despite much previous work, the underlying pathophysiology of these persistent impairments remains poorly understood (Lowenstein, 2009).

Although focal brain injury often occurs as a result of traumatic brain injury, in many cases, the location and extent of this injury does not fully explain the patient's cognitive problems (Bigler, 2001). This is likely to be because damage to brain connectivity is a critical factor in the development of cognitive impairment after traumatic brain injury. Functions commonly impaired, such as memory and executive functions, depend on the coherent activity of widely distributed brain networks (Mesulam, 1998). 'Nodes' in these networks are connected by long white matter tracts that may be damaged in traumatic brain injury as a result of diffuse axonal injury. The pathology of diffuse axonal injury has been investigated in some detail (Povlishock and Katz, 2005), but, until recently, it has been difficult to study the location and extent of this damage, or its functional consequences *in vivo*.

Conventional CT and standard MRI underestimate the extent of white matter damage after traumatic brain injury (Rugg-Gunn *et al.*, 2001; Arfanakis *et al.*, 2002). Standard MRI of traumatic brain injury includes the use of gradient-echo imaging that allows the identification of microbleeds. These are surrogate markers of diffuse axonal injury (Scheid *et al.*, 2003) and their presence is associated with persistent cognitive impairment (Scheid *et al.*, 2006). However, pathological studies often show more extensive axonal damage (Povlishock and Katz, 2005), which is unlikely to be fully reflected in focal microbleed signal abnormalities.

Recently, it has become possible to study white matter damage using diffusion tensor imaging (DTI; Arfanakis *et al.*, 2002; Assaf and Pasternak, 2008). In the tensor model, DTI data are used to estimate the amount of water diffusion in a number of directions at each point (voxel) in the image. From this, metrics such as fractional anisotropy can be derived to quantify the degree of white matter disruption (Basser and Pierpaoli, 1996, 1998). Greater anisotropy, as indicated by a higher fractional anisotropy value, is believed to reflect more coherent tissue structure, whilst increased diffusivity suggests tissue damage (Rugg-Gunn *et al.*, 2001; Arfanakis *et al.*, 2002). Experimental models of axonal damage and demyelination have implicated axial and radial diffusivities as potential biomarkers of axonal and myelin loss, respectively (e.g. Song *et al.*, 2003; Budde *et al.*, 2008). Changes in fractional anisotropy persist after traumatic brain injury and predict functional outcome over and above patients' initial clinical state or focal lesion load (Sidaros *et al.*, 2008).

Previous work in patients with traumatic brain injury has typically focused on a limited number of brain locations defined as regions of interest (Kraus *et al.*, 2007; Niogi *et al.*, 2008*a*, *b*; Kennedy *et al.*, 2009). This approach is a sensitive way of identifying white matter damage, but as it is restricted to assessment of the *a priori* defined regions, only a small amount of the total white matter is usually investigated (e.g. Niogi *et al.*, 2008*a*). This is problematic for a number of reasons. Traumatic brain injury produces a complex pattern of diffuse axonal injury at variable locations across individuals and so it is difficult to decide *a priori* where to 'look' for the white matter disruption. The investigation of a small number of regions is likely to result in a failure to identify significant white matter damage elsewhere in the brain. As the cognitive functions commonly affected by traumatic brain injury depend on distributed network function, such an approach limits analysis of the structural causes of cognitive impairment. These issues are compounded by our limited knowledge of how tract structure relates to cognitive function in the normal brain, making it important to assess white matter structure after traumatic brain injury with as comprehensive spatial coverage as possible.

Tract-based spatial statistics (TBSS) is a new voxel-based technique for analysing white matter structure across the whole brain (Smith *et al.*, 2006). A voxel-based approach has previously provided important insights into long-term consequences for cognition of brain injury (Salmond *et al.*, 2006). TBSS allows complex patterns of white matter disruption to be identified and their relationships with cognitive function to be studied in a data-driven way. Statistical calculations are performed at each point within an individual's white matter 'skeleton', which has been registered to standard space using a two-stage process involving non-linear warping and subsequent alignment of individual white matter tracts across subjects. This allows a comprehensive analysis of tract structure to be performed in a way that is robust to effects of brain injury, such as brain atrophy. TBSS has been used to show a relationship between white matter structure and cognitive function in other neurological conditions (Ceccarelli *et al.*, 2009; Dineen *et al.*, 2009; Roosendaal *et al.*, 2009; Bosch *et al.*, 2010).

Here, we used TBSS for the first time to study the relationship between distributed white matter damage and cognitive impairment following traumatic brain injury. First, we investigated whether there were differences in white matter structure in a group of post-acute and chronic patients with traumatic brain injury and an age-matched control group. We then investigated whether the pattern of white matter structure predicts cognitive function in three domains commonly affected by traumatic brain injury, i.e. memory, executive function and information processing speed. Our prediction was that increased white matter disruption following traumatic brain injury will be associated with greater cognitive impairment, but that distinct types of impairment are

associated with particular patterns of white matter abnormalities. Memory function is highly dependent upon hippocampal–medial diencephalic interactions mediated through the fornices (Aggleton and Brown, 1999; Aggleton, 2008; Tsivilis *et al.*, 2008). Learning and memory is impaired in chronic traumatic brain injury (Draper and Ponsford, 2008) and white matter structure within the hippocampal formation has previously been shown to relate to associative memory performance (Salmond *et al.*, 2006). We, therefore, predict that white matter structure of the hippocampal connections will correlate with memory performance. Executive functions are widely thought to depend on interactions between the frontal lobes and more posterior brain regions (Miller and D'Esposito, 2005) and a relationship between executive dysfunction and age-related decline in white matter integrity within tracts connecting frontal regions has previously been demonstrated (O'Sullivan *et al.*, 2001; Davis *et al.*, 2009; Madden *et al.*, 2009; Perry *et al.*, 2009). Therefore, we predict that breakdown of these frontal connections following traumatic brain injury will similarly correlate with executive impairment. Finally, white matter organization has been shown to predict processing speed on a range of simple tasks in healthy individuals (Sullivan *et al.*, 2001; Madden *et al.*, 2004; Schulte *et al.*, 2005; Tuch *et al.*, 2005; Bucur *et al.*, 2008). Therefore, we expect white matter structure as measured by DTI to correlate with information processing speed.

# Materials and methods

## Participants

Twenty-eight patients with traumatic brain injury in the post-acute/chronic phase (21 males, mean age ± SD: 38.9 ± 12.2 years) and an age-matched group of 26 healthy controls (12 males, 35.4 ± 11.1 years) were recruited. All patients were recruited at least two months post-injury (average 25 months). Injury was secondary to assaults (36%), road traffic accidents (32%), falls (25%) and sports-related injury (7%). Patients were referred to their local traumatic brain injury service because of the presence of functional impairments following their head injury. There were 20 moderate or severe and eight mild (probable) cases based on the Mayo Classification System for Traumatic Brain Injury Severity, relating to the duration of loss of consciousness, length of post-traumatic amnesia, lowest recorded Glasgow Coma Scale in the first 24 h, and/or CT or MRI results (Malec *et al.*, 2007). Exclusion criteria were as follows: neurosurgery, except for invasive intracranial pressure monitoring ($n = 1$); a history of psychiatric or neurological illness prior to the head injury; a history of previous traumatic brain injury; anti-epileptic medication; current or previous drug or alcohol abuse; or contraindication to MRI. All participants gave written informed consent according to the Declaration of Helsinki (World Medical Association, 2008). The study was approved by the Hammersmith, Queen Charlotte's and Chelsea Research Ethics Committee.

## Neuropsychological assessment

All participants completed a standardized neuropsychological test battery sensitive to cognitive impairment associated with traumatic brain injury. The cognitive functions of specific interest were indexed by: (i) current verbal and non-verbal reasoning ability via the Wechsler Abbreviated Scale of Intelligence Similarities and Matrix Reasoning subtests (Wechsler, 1999); (ii) associative learning and memory via the immediate recall score on the People Test from the Doors and People Test (Baddeley *et al.*, 1994); (iii) the executive functions of set-shifting, inhibitory control, cognitive flexibility and word generation fluency via the Trail Making Test (Reitan, 1958) alternating-switch cost index (time to complete alternating letter and number Trails B—time to complete numbers-only Trail A) and two indices from the Delis–Kaplan Executive Function System (Delis *et al.*, 2001), namely the inhibition/switching minus baseline score from the Color–Word subtest (high scores indicating poor performance) and the total score on Letter Fluency; and (iv) information processing speed via the median reaction time for accurate responses on a simple computerized choice reaction task (see Supplementary Material for further details).

## Structural imaging

Each patient had standard high-resolution $T_1$ and gradient-echo ($T_2$*) imaging to assess focal brain injury and evidence of microbleeds. MRI was performed on Philips 3T Achieva scanner (Philips Medical Systems, The Netherlands) using a body coil. The $T_1$ and $T_2$*-weighted images were obtained prior to DTI. For DTI, diffusion-weighted volumes with gradients applied in 16 non-collinear directions were collected in each of the four DTI runs, resulting in a total of 64 directions. The following parameters were used: 73 contiguous slices, slice thickness = 2 mm, field of view 224 mm, matrix 128 × 128 (voxel size = 1.75 × 1.75 × 2 $mm^3$), $b$ value = 1000 and four images with no diffusion weighting ($b = 0$ s/$mm^2$). The images were registered to the $b = 0$ image by affine transformations to minimize distortion due to motion and eddy currents and then brain-extracted using Brain Extraction Tool (Smith, 2002) from the FMRIB Software Library image processing toolbox (Smith *et al.*, 2004; Woolrich *et al.*, 2009). Fractional anisotropy and mean diffusivity maps were generated using the Diffusion Toolbox (Behrens *et al.*, 2003), as well as images for each of the eigenvalues ($\lambda1$, $\lambda2$ and $\lambda3$) representing the magnitude of diffusion in the three principal directions. Axial ($D_{ax}$) and radial ($D_{rad}$) diffusivity images were then derived from the eigenvalues ($D_{ax} = \lambda1$, $D_{rad} = \lambda2 + \lambda3/2$).

## Diffusion tensor imaging data analysis

Voxelwise analysis of the fractional anisotropy, mean diffusivity and axial and radial diffusivity data was carried out using TBSS in the FMRIB Software Library (Smith *et al.*, 2004, 2006). Image analysis using TBSS involved a number of steps: (i) non-linear alignment of all subjects' fractional anisotropy images into common FMRIB58 fractional anisotropy template space; (ii) affine-transformation of the aligned images into standard MNI152 1 mm space; (iii) averaging of the aligned fractional anisotropy images to create a 4D mean fractional anisotropy image; (iv) thinning of the mean fractional anisotropy image to create a mean fractional anisotropy 'skeleton' representing the centre of all white matter tracts, and in this way removing partial-volume confounds; and (v) thresholding of the fractional anisotropy skeleton at fractional anisotropy $\geqslant 0.2$ to suppress areas of extremely low mean fractional anisotropy and exclude those with considerable inter-individual variability. Similar steps for processing non-fractional anisotropy images were then carried out to obtain the mean, axial and radial diffusivity images. Non-parametric permutation-based statistics were employed using randomize with threshold-free cluster enhancement and 5000 permutations (Nichols and Holmes, 2002; Smith and Nichols, 2009). A threshold of $P < 0.05$ was then applied on the results, corrected for multiple comparisons. Age and gender

were included as covariates of no interest in all TBSS analyses. In addition, patients with and without microbleed evidence of diffuse axonal injury were compared against each other (microbleed versus non-microbleed) and against the controls. Since severity of injury is also likely to impact upon the extent of white matter disruption, we carried out additional comparisons between patients classified as mild and moderate/severe and controls. As DTI changes are known to evolve after injury (Mac Donald *et al.*, 2007; Sidaros *et al.*, 2008), we also investigated the effects of time since injury on the group differences in white matter structure.

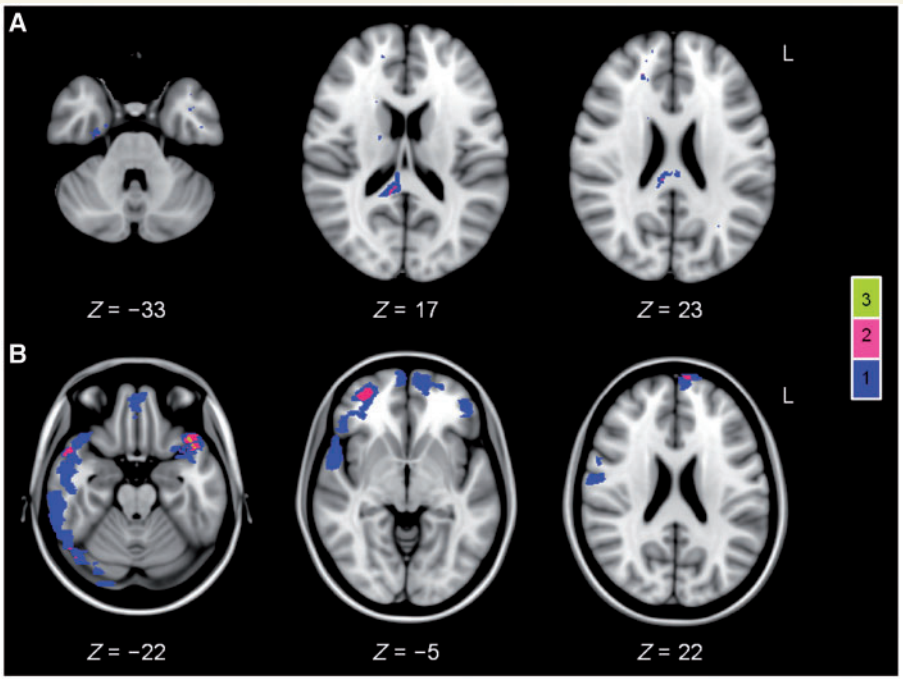


**Figure 1** Lesion probability maps of (**A**) white matter lesions visible on gradient echo imaging and (**B**) contusions. The colour bar indicates the number of patients who had lesions at each site. Green–yellow indicates where lesions were present in three (11%) of the 28 patients with traumatic brain injury, pink indicates where they were present in two (7%) and blue where a lesion was found in one patient only.

**Table 1 Neuropsychological test results by group**

| Cognitive domain | Cognitive variable | Traumatic brain injury Mean ± SD[a] | Control Mean ± SD[a] | Traumatic brain injury versus Control[b] (*t*) |
|---|---|---|---|---|
| Intellectual ability: verbal/non-verbal | WASI similarities | 39.7 ± 3.4 (*n* = 28) | 35.2 ± 5.7 (*n* = 26) | 2.98** |
| | WASI matrix reasoning | 29.0 ± 3.3 (*n* = 27) | 26.7 ± 4.2 (*n* = 26) | 2.84** |
| Memory: associative memory | People Test immediate recall | 24.8 ± 4.9 (*n* = 28) | 29.9 ± 4.0 (*n* = 24) | −4.03*** |
| Processing speed: visual search/complex | Trail Making Test Trail A (s) | 28.3 ± 9.5 (*n* = 27) | 19.8 ± 4.3 (*n* = 25) | 4.36*** |
| | Trail Making Test Trails B (s) | 70.2 ± 40.1 (*n* = 28) | 40.5 ± 10.5 (*n* = 23) | 3.74*** |
| Processing speed: naming/reading | Colour naming (s) | 34.2 ± 8.6 (*n* = 27) | 28.2 ± 5.6 (*n* = 26) | 3.30** |
| | Word reading (s) | 23.6 ± 4.0 (*n* = 27) | 22.5 ± 4.5 (*n* = 25) | 0.90[c] |
| Executive function: alternating-switch cost | Trail Making Test Trails B minus A (s) | 34.2 ± 26.5 (*n* = 26) | 22.2 ± 9.9 (*n* = 24) | 2.10* |
| Executive function: cognitive flexibility | Inhibition/switching (s) | 67.2 ± 18.8 (*n* = 27) | 54.1 ± 10.6 (*n* = 25) | 3.13** |
| | Inhibition/switching minus a baseline of colour naming and word reading (s) | 38.0 ± 15.4 (*n* = 27) | 27.9 ± 10.4 (*n* = 25) | 2.74** |
| Executive function: word generation fluency | Letter Fluency F + A + S total | 43.1 ± 9.8 (*n* = 28) | 49.6 ± 10.0 (*n* = 24) | −2.40* |
| Processing speed: choice reaction time | Choice reaction task median reaction time (ms) | 449 ± 75 (*n* = 27) | 393 ± 52 (*n* = 26) | 3.00** |

a Following Exploratory Data Analysis using boxplots, outlier scores ⩾1.5 × interquartile range outside the middle half of the sample were excluded variable-wise.
b Patients showed significantly better performance for intellectual ability, but for all other significant group differences controls outperformed patients.
c Not significant at the $P \leqslant 0.05$ level.
*$P \leqslant 0.05$; **$P \leqslant 0.01$; ***$P \leqslant 0.001$.
WASI = Wechsler Abbreviated Scale of Intelligence.

## Analysis of white matter structure and cognitive function

The relationship between white matter structure and cognitive function was investigated within the framework of a general linear model in the FMRIB Software Library. The effects of group and cognitive variables were modelled, allowing analysis of the relationship between white matter structure and cognitive function across voxels. Overall correlations across both groups, correlations within each group and group interactions were examined. Analysis was carried out using: (i) the People Test immediate recall total score to index associative learning and memory; (ii) the Trail Making Test Trails B – Trail A alternating switch-cost, the Delis–Kaplan Executive Function System Color-Word inhibition/switching minus a combined baseline of naming and reading speed, and the Delis–Kaplan Executive Function System Letter Fluency total for letters F, A and S to index the executive functions of set-shifting, cognitive flexibility and word generation fluency; and (iii) median reaction time for accurate trials on the choice reaction task to index information processing speed (Table 1). One control subject and one patient were extreme outliers on either the alternating-switch cost or the cognitive flexibility analyses and this was modelled in the design using separate regressors. Permutation-based significance testing was carried out as described above. For illustrative purposes, fractional anisotropy and diffusivity values from the peak voxels of the significant clusters of interest were then extracted for each participant from their skeletonized images and plotted against the cognitive scores.

# Results

## Standard magnetic resonance imaging

$T_1$ imaging was normal in 61% of patients and $T_2$* normal in 25%. Definite and possible intraparenchymal microbleeds indicative of diffuse axonal injury were found in 50% of the patients (11 males, mean age 38.9 ± 9.9 years, average time since injury 26 months; non-microbleed group 10 males, mean age 38.9 ± 14.5 years, average time since injury 25 months). The median number of microbleeds as identified using the Microbleed Anatomical Rating Scale (Gregoire *et al.*, 2009) was seven (range 1–19). Microbleeds were mainly found in frontal and temporal white matter bilaterally. There was little overlap in the location of white matter damage. Cortical lesions were found in 39% of all patients and were mainly seen in frontal and temporal regions. Again, there was a relatively small amount of lesion overlap (Fig. 1; see Supplementary Material for further details). Magnetic resonance signal abnormality indicative of superficial siderosis was found in 43% of the patients, mainly overlying bilateral frontal and right temporal cortices. This is likely to be secondary to chronic haemosiderin deposition as a result of subdural or subarachnoid haemorrhage at the time of injury.

## Cognitive function

The patient group outperformed the control group in terms of average current intellectual ability, as indexed by the Wechsler Abbreviated Scale of Intelligence Similarities and Matrix Reasoning, controlled for age. However, the patients showed a pattern of specific cognitive impairments characteristic of traumatic brain injury (Ponsford and Kinsella, 1992; Levin and Kraus, 1994; Levin, 1995; Scheid *et al.*, 2006; Draper and Ponsford, 2008). Thus, controlling for intellectual ability, they showed: (i) impaired associative learning and memory on the People Test; (ii) impaired executive functioning, as shown by inefficiencies on the Trail Making Test, Color–Word inhibition/switching and Letter Fluency; and (iii) impaired information processing speed on the choice reaction task and all other measures of processing speed, apart from word reading.

## Widespread white matter disruption following traumatic brain injury

Comparison of patients with traumatic brain injury and age-matched controls revealed that the majority of the white matter showed some evidence of disruption in the traumatic brain injury group. The between-group differences were most clear for fractional anisotropy and mean diffusivity, with less extensive but still marked differences seen for axial diffusivity and much more limited differences seen for radial diffusivity. Lower fractional anisotropy was found in the traumatic brain injury group in inter-hemispheric fibres (genu, body and splenium of the corpus callosum) and intra-hemispheric association fibres of the uncinate fasciculi, inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculi and the cingulum bundle. Lower fractional anisotropy was also found in projection fibres of the corticopontine and corticospinal tracts, as well as in the fornices, the anterior and posterior thalamic projections, the forceps major and minor, the anterior and posterior limbs of the internal capsule and the anterior corona radiata (Fig. 2A). The same contrast showed higher mean diffusivity for the patients in similar locations as the lower fractional anisotropy, but more extensively in the left superior longitudinal fasciculus and also in the external capsule bilaterally (Fig. 2B). Elevated axial diffusivity in the traumatic brain injury group was seen in several tracts including the corpus callosum, bilateral uncinate fasciculi, the right superior and inferior longitudinal fasciculi, the cingulum bundle bilaterally underlying the posterior cingulate cortex, the corticospinal tracts, the fornices, the anterior thalamic radiations bilaterally, the forceps major and minor and the anterior and posterior limbs of the internal capsule (Fig. 2C). Radial diffusivity was higher for the patients in the corpus callosum, the right superior longitudinal fasciculus, the right posterior/medial parietal white matter underlying the posterior cingulate and precuneus cortices, the fornices, bilateral anterior thalamic radiations and the forceps minor, but to a limited extent only (Fig. 2D). There were no white matter regions that showed either higher fractional anisotropy, or lower mean, axial or radial diffusivities in the patient group.

Next, we examined whether the time since injury influenced these group differences in white matter structure. Its influence was primarily seen in axial diffusivity and mean diffusivity. Elevated axial diffusivity was correlated with increasing time

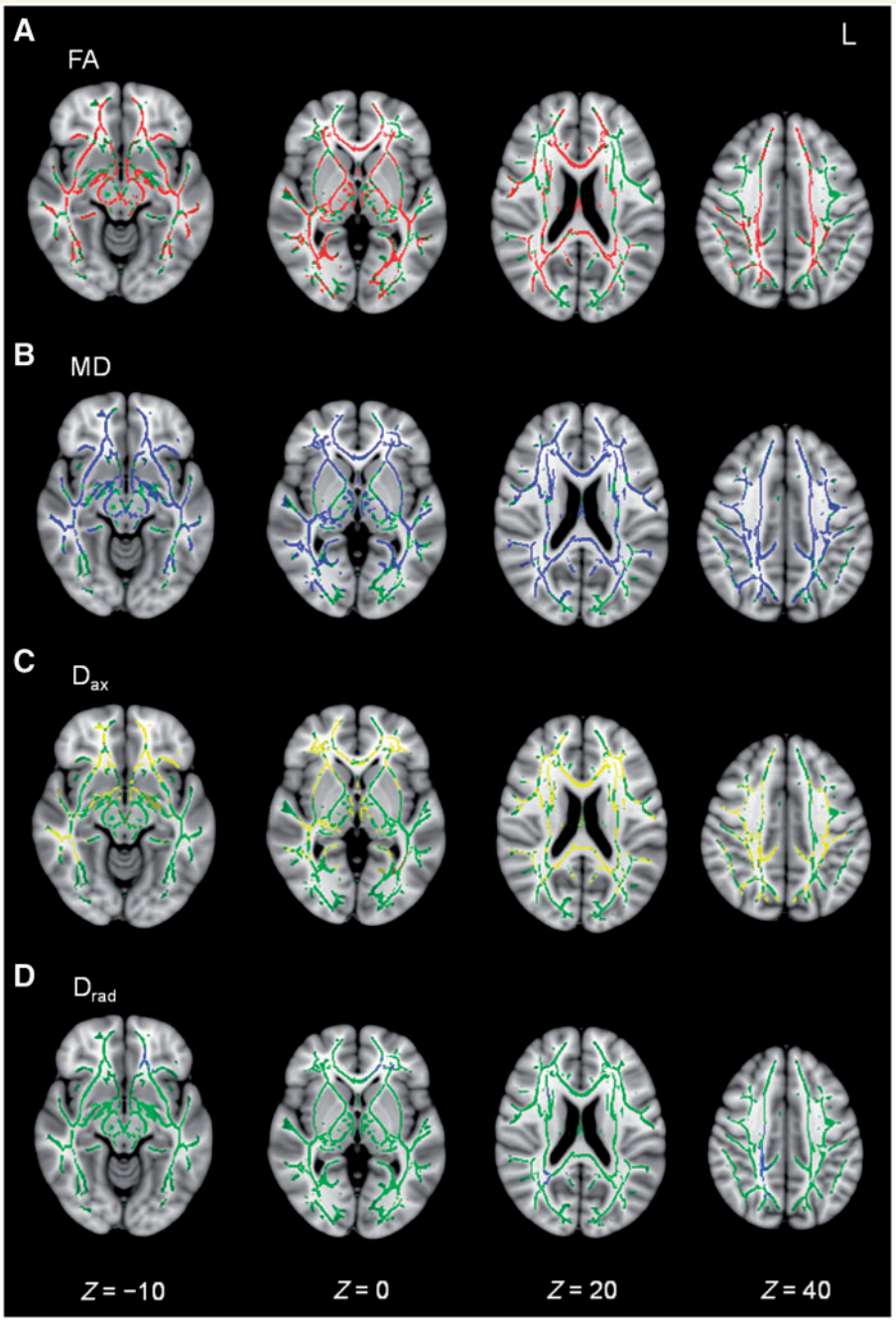


**Figure 2** Widespread white matter disruption following traumatic brain injury. Axial slices of the results of (**A**) fractional anisotropy (FA), (**B**) mean diffusivity (MD), (**C**) axial diffusivity ($D_{ax}$) and (**D**) radial diffusivity ($D_{rad}$) TBSS contrasts between traumatic brain injury and control groups. Fractional anisotropy (red): controls > traumatic brain injury; mean diffusivity (dark blue): traumatic brain injury > controls; $D_{ax}$ (yellow): traumatic brain injury > controls; and $D_{rad}$ (light blue): traumatic brain injury > controls. The contrasts are overlaid on a standard Montréal Neurological Institute 152 $T_1$ 1 mm brain and the mean fractional anisotropy skeleton (in green) with display thresholds set to range from 0.2 to 0.8. The results are thresholded at $P \leqslant 0.05$, corrected for multiple comparisons.

since injury ($R = 0.49$, $P < 0.01$), an effect that was present when controlling for patient age ($R_{partial} = 0.45$, $P < 0.05$). A similar result was found for mean diffusivity ($R = 0.55$, $P < 0.01$; $R_{partial} = 0.46$, $P < 0.05$). Time since injury was not correlated with either fractional anisotropy or radial diffusivity once patient age had been controlled.

## Patients with microbleed evidence of diffuse axonal injury show more extensive white matter damage

As expected, the comparison of patients with microbleeds and those without (non-microbleed) revealed evidence of more

severe disruption in the microbleed group in large parts of the white matter. Significantly lower fractional anisotropy for the contrast of microbleed versus non-microbleed patients was observed in the body and splenium of the corpus callosum, as well as bilaterally within the inferior longitudinal fasciculi, the corticopontine/corticospinal tracts, the fornices, the thalamic radiations, the internal and external capsules and within white matter structures of the midbrain (the decussation of the superior cerebellar peduncles; Fig. 3A). There was also higher mean diffusivity for the patients with microbleeds largely corresponding to the locations of the lower fractional anisotropy, including bilateral inferior longitudinal fasciculi, the corticospinal tracts bilaterally, the fornices, bilateral anterior thalamic radiations, the posterior limbs of the internal capsule and the external capsule. In addition, higher mean diffusivity was observed in the superior longitudinal fasciculi, the cingulum bundle bilaterally underlying the posterior cingulate and retrosplenial cortices and the forceps major and minor, but only in the posterior body and the splenium of the corpus callosum (Fig. 3B). The patients with microbleeds also showed significantly elevated radial diffusivity in several white matter tracts (Fig. 3C). These corresponded to the tracts showing either lower fractional anisotropy or higher mean diffusivity (or both), apart from the superior longitudinal fasciculi and the forceps minor on the right that showed higher mean diffusivity in the absence of elevated radial diffusivity. In axial diffusivity, there were no group differences between the patients with and without microbleeds. Again, there were no white matter regions that showed either elevated fractional anisotropy or lower mean, axial or radial diffusivities in the microbleed group.

## Patients without microbleeds also show evidence of white matter damage

To assess whether DTI is more sensitive to the presence of white matter damage than gradient-echo imaging, we compared patients without microbleeds (the non-microbleed group) with controls. Significantly lower fractional anisotropy was found in patients without microbleeds in the body and genu of the corpus callosum, both corticopontine tracts and the right forceps major (Fig. 4A). Mean diffusivity was significantly elevated in the non-microbleed group in several tracts, including the corpus callosum, the cingulum bundle bilaterally, the corticopontine/corticospinal tracts, the fornices, the forceps major and minor and the anterior and posterior limbs of the internal capsule, more so on the right (Fig. 4B). Axial diffusivity was higher for the patients without microbleeds in locations largely corresponding to those in which mean diffusivity was also elevated, including the corpus callosum (apart from the rostrum), the fornices and the cingulum bundle bilaterally, but not in the internal capsule or

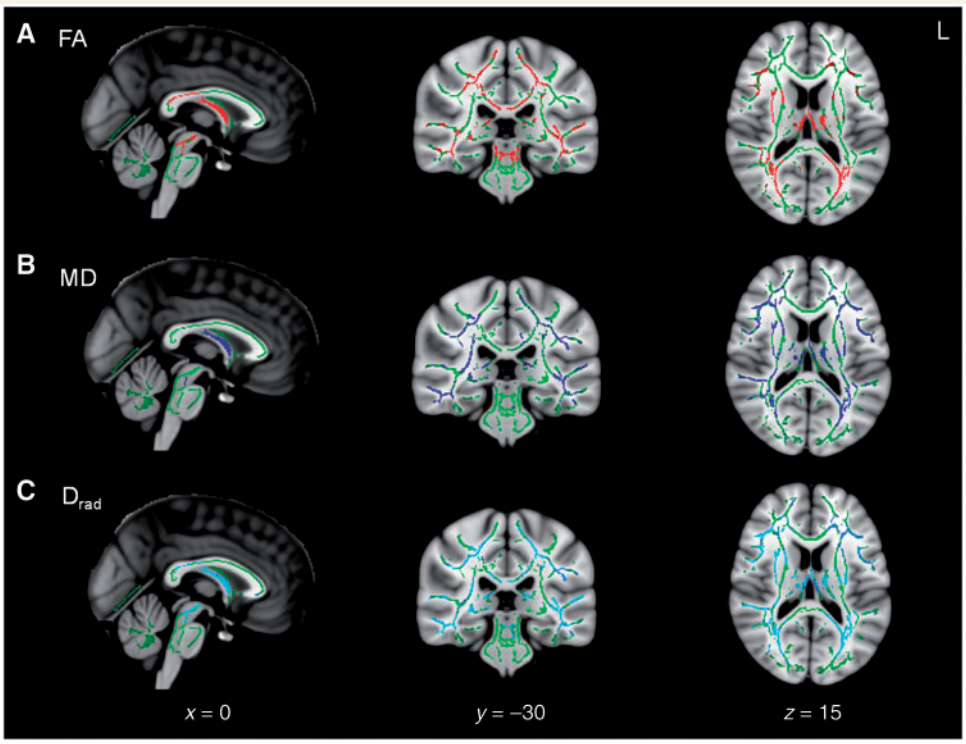


**Figure 3** Patients with microbleed evidence of diffuse axonal injury show more extensive white matter damage. The results of (**A**) fractional anisotropy (FA), (**B**) mean diffusivity (MD) and (**C**) radial diffusivity ($D_{rad}$) TBSS contrasts between patient groups with and without microbleed evidence of diffuse axonal injury. Fractional anisotropy (red): non-microbleed > microbleed; mean diffusivity (dark blue): microbleed > non-microbleed; and $D_{rad}$ (light blue): microbleed > non-microbleed. The contrasts are overlaid on a standard Montréal Neurological Institute 152 $T_1$ 1 mm brain and the mean fractional anisotropy skeleton (in green). The results are thresholded at $P \leqslant 0.05$, corrected for multiple comparisons.

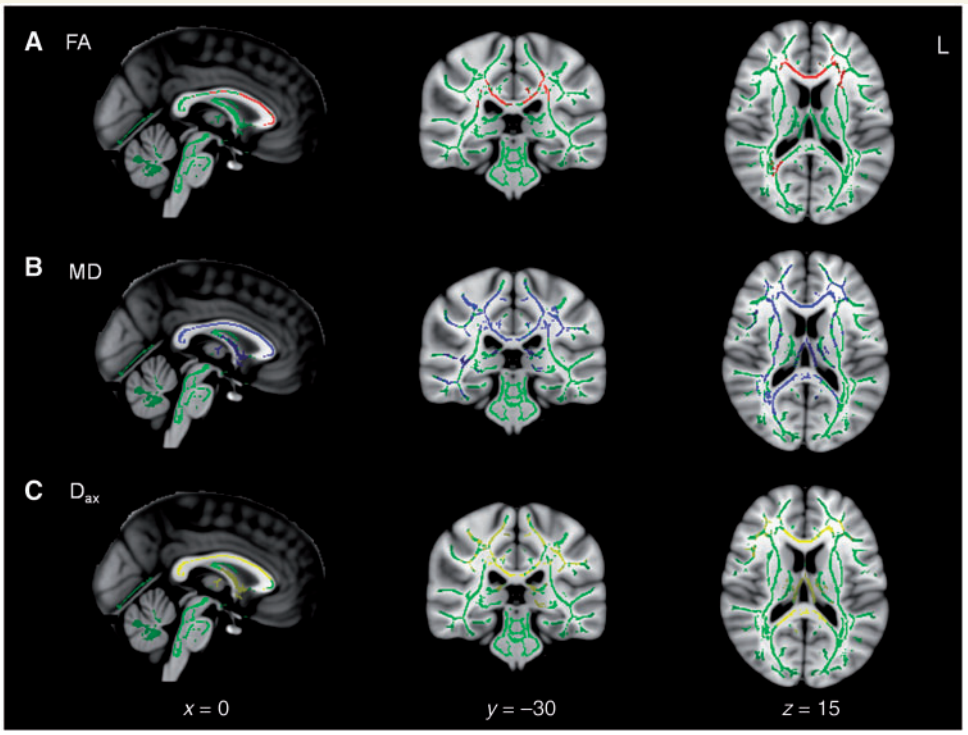


**Figure 4** Patients without microbleeds also show evidence of white matter damage. The results of (**A**) fractional anisotropy (FA), (**B**) mean diffusivity (MD) and (**C**) axial diffusivity ($D_{ax}$) TBSS contrasts between patients without microbleed evidence of diffuse axonal injury (non-microbleed) and controls. Fractional anisotropy (red): controls > non-microbleed, mean diffusivity (dark blue): non-microbleed > controls; and $D_{ax}$ (yellow): non-microbleed > controls. The contrasts are overlaid on a standard Montréal Neurological Institute 152 $T_1$ 1 mm brain and the mean fractional anisotropy skeleton (in green). The results are thresholded at $P \leqslant 0.05$, corrected for multiple comparisons.

the forceps major and minor (Fig. 4C). There were no significant group differences in radial diffusivity. There were also no regions where fractional anisotropy was elevated, or mean, axial or radial diffusivities lower in the non-microbleed group as compared with controls. These results demonstrate the presence of white matter abnormalities in patients with no microbleeds on gradient-echo imaging. As expected, the same contrasts between patients with microbleeds and healthy controls showed extensive white matter abnormalities in the patients (Supplementary Fig. 1).

## Patients classified as having sustained a 'mild' traumatic brain injury show white matter abnormalities

We also examined the relationship between traumatic brain injury severity as defined using the Mayo classification system (Malec *et al.*, 2007) and white matter damage. Although the mild group consisted of only eight patients, they showed lower fractional anisotropy compared with controls in a wide range of tracts (Supplementary Fig. 2A). These included the fornices, the cingulum bundle bilaterally, the corpus callosum, the anterior limb of the right internal capsule, the left external capsule, the inferior fronto-occipital fasciculi, the left superior longitudinal fasciculus, the forceps major and minor bilaterally, the anterior thalamic radiations bilaterally and the corticospinal tracts. The mild patients also showed elevated mean diffusivity in similar, but more widespread tracts, with additional differences seen in the internal and external capsules bilaterally and the superior longitudinal fasciculi (Supplementary Fig. 2B). Axial diffusivity was higher for the mild patients than controls in the corpus callosum, the inferior fronto-occipital fasciculi, the posterior cingulum bundles, the left superior longitudinal fasciculus, the posterior limbs of the internal capsule, the corticospinal tracts and both anterior thalamic radiations (Supplementary Fig. 2C). The mild patients had higher axial diffusivity than the moderate/severe patients in the body and genu of the corpus callosum, a difference that was still present after controlling for time elapsed since the injury. There were no other differences in any of the DTI metrics between the mild and moderate/severe patients. As expected, there were very widespread differences in fractional anisotropy (controls > patients) and mean and axial diffusivities (patients > controls) between moderate/severe patients and controls. These differences were seen within the fornices, the corpus callosum, all major intrahemispheric association and projection fibres, the internal and external capsules and the superior and anterior corona radiata. Radial diffusivity measurements were not different between any of the three groups.

## The relationship between white matter structure and cognitive function

### Associative memory

Across both patients and controls, we found evidence that the structure of the fornices predicted associative memory performance. As expected, fractional anisotropy within the fornix was positively correlated with memory, showing that individuals with more anisotropic white matter within the fornix had better performance. This relationship between fractional anisotropy and associative memory was observed in both patient and normal groups (Fig. 5A). Using the stringent permutation test we employed, this relationship was of borderline significance, when corrected for multiple comparisons across the whole brain ($P < 0.06$ in the right fornix, peak voxel: $x = 7$, $y = -5$, $z = 9$ and $P < 0.07$ in the left fornix, peak voxel: $x = -2$, $y = -16$, $z = 17$). In the peak voxel within the fornix, fractional anisotropy was significantly correlated with our measure of associative learning and memory across both groups ($R^2 = 0.25$, $P < 0.001$). TBSS tests for linear relationships between white matter structure and cognitive variables, but this relationship may not be best modelled linearly, as suggested by Fig. 5B. For this reason, we fitted a second-order polynomial regression slope, which models the data more accurately ($R^2 = 0.33$, $P < 0.0001$). This relationship was specific to the hippocampal formation as there were no significant regions outside it where fractional anisotropy was correlated with the measure of memory function. The relationship was also present when controlling for intellectual ability ($R_{partial} = 0.48$, $P < 0.001$), and an ANCOVA with severity as the between-subjects factor showed no significant interaction between severity and fractional anisotropy in the peak voxel from the fornix/memory relationship. No significant correlations between associative learning and memory and white matter structure were observed for any of the three diffusivities.

### Executive function

A more complex relationship between white matter structure and executive function was observed. There was no relationship between our executive function measures and fractional anisotropy, but a significant relationship was observed between set-shifting, as measured by the Trail Making Test alternating switch-cost index and both mean and radial diffusivity. Increases in mean and radial diffusivities have previously been reported after traumatic brain injury (Kraus *et al.*, 2007; Sidaros *et al.*, 2008; Kennedy *et al.*, 2009) and are thought to indicate axonal injury. In the whole-brain analysis, the patient group showed an expected correlation between elevated mean diffusivity and executive

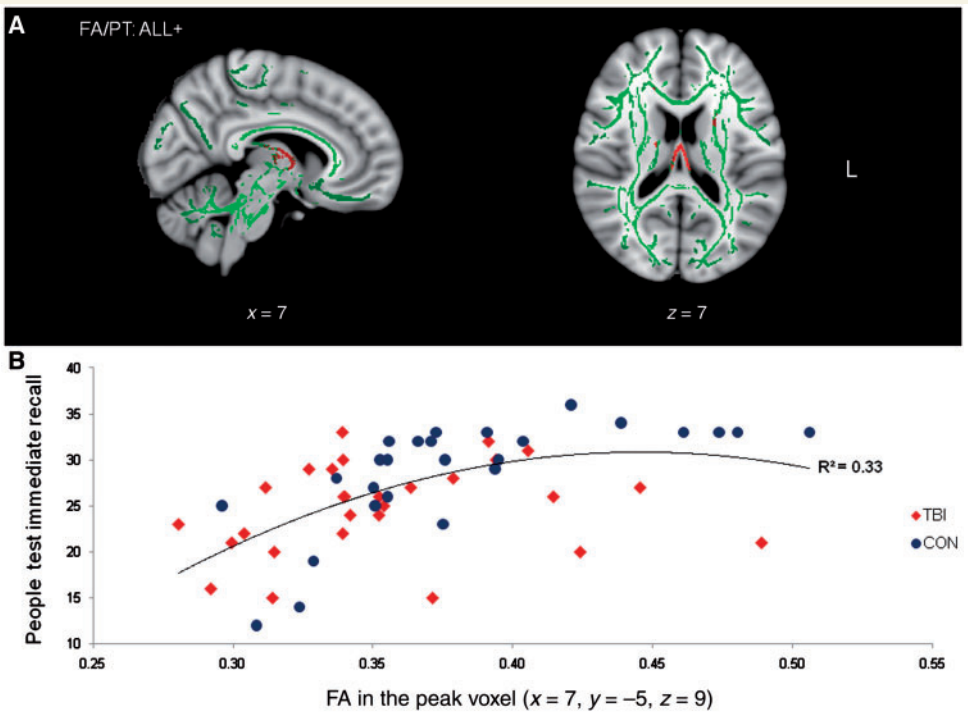


**Figure 5** The results of TBSS regression analysis of associative learning and memory (People Test immediate recall total) by fractional anisotropy (FA) across the traumatic brain injury and control groups. (**A**) Areas where fractional anisotropy is positively correlated with People Test (PT) recall score across the two groups are indicated in red (FA/PT: ALL+). The result is overlaid on a standard Montréal Neurological Institute 152 $T_1$ 1 mm brain and the mean fractional anisotropy skeleton (in green). For display purposes the result is displayed with a multiple comparisons threshold of $P \leqslant 0.1$. (**B**) Graph showing individual data points in both groups for People Test recall score against fractional anisotropy in the peak voxel (Montréal Neurological Institute $x = 7$, $y = -5$, $z = 9$). A second-order polynomial regression slope is shown, which provides a more accurate fit than the linear regression identified by the whole-brain general linear model analysis. CON = control; TBI = traumatic brain injury.

dysfunction. Patients with high mean diffusivity in the left superior frontal white matter showed worse performance. A subsequent analysis within all significant voxels confirmed this relationship ($R_{partial} = 0.75$, $P < 0.001$), controlling for intellectual ability. There was no such relationship in the healthy control group, in the groups combined or in the interaction between the groups.

A highly significant group interaction was observed between radial diffusivity and alternating-switch cost (whole brain corrected at $P < 0.01$). This was in striking contrast to our result for the relationship between fractional anisotropy and associative learning and memory, where a similar effect was seen across the groups. The voxels where the two groups showed distinct relationships with executive function were seen particularly in frontal white matter connections, including the cingulum bundle, the body and genu of the corpus callosum, the right superior longitudinal fasciculus and the right corticospinal tract (Fig. 6A). The peak effect intensity was found in a voxel in the right posterior/medial parietal white matter, between the superior longitudinal fasciculus and the cingulum bundle. In this voxel, there was a positive correlation between the variables in the patient group ($R^2 = 0.30$, $P < 0.01$), but no significant relationship in the control group (Fig. 6B). A similar result emerged when we examined all voxels showing the significant interaction effect, with a positive relationship observed between the variables in the patient group ($R^2 = 0.17$, $P < 0.05$), but no relationship was found for the controls. Therefore, patients with higher radial diffusivity in these white matter regions had more executive impairment. This relationship in the patient group remained significant after controlling for intellectual ability ($R_{partial} = 0.53$, $P < 0.01$ in the peak voxel and $R_{partial} = 0.43$, $P < 0.05$ across all significant voxels). An ANCOVA with severity as the between-subjects factor showed no significant interaction between severity and radial diffusivity in the peak voxel, or across all significant voxels.

We also analysed each group separately. In the control group, an unexpected negative relationship was found between executive function and radial diffusivity, in that increasing radial diffusivity was related to better executive function. This relationship was seen within parts of the corpus callosum, the superior longitudinal fasciculus and the cingulum bundle. This analysis identified a set of voxels that was only partially overlapping with the results of the interaction analysis. There was no significant relationship between executive function and radial diffusivity in the patient group alone in the whole-brain analysis, but the pattern of correlation was reverse to the control group. These two analyses show that a complex relationship exists between executive function and white matter structure, with voxels in different parts of the white matter showing different structure–function relationships in the healthy and damaged brain.

Fractional anisotropy and axial diffusivity were not associated with set-shifting as indexed by alternating-switch cost on the Trail Making Test. In addition, the other two executive functions investigated (i.e. cognitive flexibility and word generation fluency)

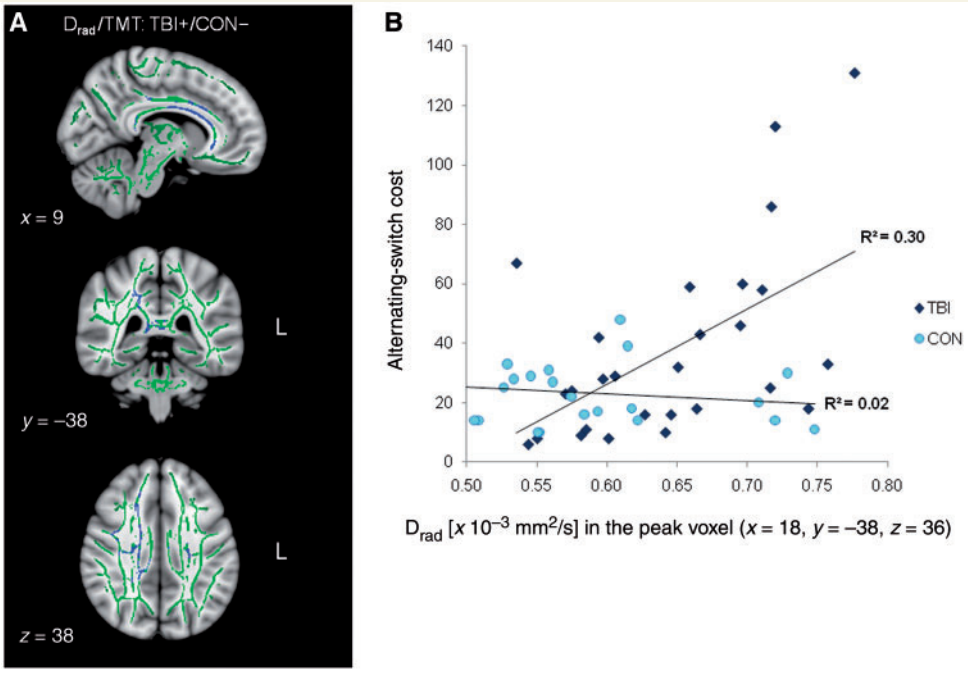


**Figure 6** The results of TBSS regression analysis of the group interaction between alternating-switch cost (Trail Making Test Trails B minus Trail A) and radial diffusivity ($D_{rad}$) in the traumatic brain injury and control groups. (**A**) Results of the whole-brain analysis with significant areas of the interaction effect for $D_{rad}$ (TBI + /CON −) shown in light blue. The results are thresholded at $P \leqslant 0.01$, corrected for multiple comparisons and overlaid on a standard Montréal Neurological Institute 152 $T_1$ 1 mm brain and the mean fractional anisotropy skeleton (in green). (**B**) Graph illustrating linear regression slopes for each group and individual data points for alternating-switch cost against $D_{rad}$ in the peak voxel (Montréal Neurological Institute $x = 18$, $y = -38$, $z = 36$) of the interaction effect. $D_{rad}$ values are expressed as $mm^2/s \times 10^{-3}$ for convenience of display. CON = control; TBI = traumatic brain injury.

did not show a significant relationship with any of the DTI measures.

### Information processing speed

In the whole-brain analysis, information processing speed, as measured by median reaction time for accurate responses on the choice reaction task, was not found significantly associated with any index of white matter structure.

## Elevated axial diffusivity after traumatic brain injury and cognitive function

It has been demonstrated previously that patients who show relatively large increases in axial diffusivity in the first year following their head injury have a more favourable outcome (Sidaros *et al.*, 2008). This raises the possibility that elevated axial diffusivity post-traumatic brain injury is a marker of axonal recovery. Sidaros *et al*. (2008) observed increases in the posterior limb of the internal capsule, a descending motor pathway with a well-known normal structure and architecture (Pierpaoli *et al.*, 2001). This prompted us to perform a focused analysis of axial diffusivity within this part of the white matter. We tested for partial correlations between axial diffusivity and the five cognitive variables described above, controlling for age, time since traumatic brain injury and current intellectual ability. Processing speed was negatively correlated with axial diffusivity ($R_{partial} = -0.55$, $P < 0.01$), such that patients with the highest axial diffusivity in the posterior limb of the internal capsule had the fastest reaction times. None of the other four cognitive variables showed a significant relationship with axial diffusivity.

# Discussion

We have demonstrated the relationship between white matter abnormalities and cognitive function in two domains commonly affected by traumatic brain injury, memory and executive function. The work builds on previous studies, which show that DTI is a sensitive technique for imaging white matter damage in traumatic brain injury (Inglese *et al.*, 2005; Salmond *et al.*, 2006; Kraus *et al.*, 2007; Niogi *et al.*, 2008*b*; Sidaros *et al.*, 2008; Kennedy *et al.*, 2009). In general, these studies have used a region of interest approach. This involves the investigation of a relatively small amount of white matter, within regions that are defined on the basis of *a priori* judgements. Here, for the first time, we used tract-based spatial statistics (a voxel-based approach) to explore the relationship between white matter structure and cognitive function following traumatic brain injury in a data-driven manner. This is particularly important, as the cognitive deficits commonly observed after traumatic brain injury, such as executive impairment, are likely to depend upon the disruption of distributed brain networks by diffuse axonal injury.

Our results show that widespread white matter abnormalities persist following traumatic brain injury and that the pattern of damage to specific white matter tracts predicts some aspects of the profile of cognitive deficits that are present. Variability in cognitive function in our patients cannot be explained by the limited, and largely non-overlapping, pattern of focal cortical damage. In contrast, across both patients and controls, the structure of the fornices was related to the efficiency of associative learning and memory. Previous work has shown the importance of the fornix for memory function (Aggleton, 2008; Tsivilis *et al.*, 2008). In humans, damage to the fornices produces memory deficits (Gaffan and Gaffan, 1991; McMackin *et al.*, 1995; Park *et al.*, 2000; Kesler *et al.*, 2001) and, in the monkey, the fornix has been shown to be critical for the rapid learning of new spatial and non-spatial associations (Brasted *et al.*, 2002, 2003; Kwok and Buckley, 2010). Following traumatic brain injury, the extent of damage to the hippocampi is known to predict memory impairment (Tate and Bigler, 2000), and mean diffusivity within the hippocampal formation has been shown to predict associative memory function (Salmond *et al.*, 2006).

We extend these observations by showing that the structure of the fornices is specifically correlated with the efficiency of certain aspects of memory function. Previous region-of-interest studies have not examined the effect of traumatic brain injury on the fornix in terms of memory. Using TBSS, we were able to investigate individual white matter tracts and can be confident that our result is specific to the hippocampal formation. Although widespread white matter abnormality was present, we found no other areas that significantly correlated with memory function. The results also suggest that the relationship between fornix structure and memory is not limited to patients with traumatic brain injury. As we have used a cross-sectional study design, we cannot completely exclude the possibility that there may have been pre-morbid differences in fornix structure between the two groups. However, this seems a highly unlikely explanation for our results, particularly when one considers that the patients show a specific pattern of cognitive impairment typical for traumatic brain injury, in association with better current intellectual functioning than the control group. Instead, the results suggest that fractional anisotropy within the fornix is positively correlated with associative memory performance in the healthy brain. Traumatic brain injury appears to modulate this existing relationship by disrupting white matter structure, thereby shifting patients along an existing continuum into a less efficient structure-function relationship. Mechanical factors may be important in explaining the prevalence of this type of memory impairment after traumatic brain injury, as the fornix is likely to be particularly susceptible to shearing and tearing forces due to its arch-like shape and long fibre tracts (Tate and Bigler, 2000).

In contrast, the patient and control groups showed distinct relationships between white matter structure (radial diffusivity) and one of our three indices of executive function. Our voxel-wise approach made it possible to explore this complex relationship. Standard DTI analysis involves the placement of regions of interest. This requires *a priori* knowledge of the likely location of effects of interest, which is both difficult and restrictive, as current understanding of structure-function relationships is limited and white matter damage diffuse. The TBSS approach allows the relationship between variables to be modelled in the framework of a general linear model and does not require the placement of specific regions of interest. Using a region of interest approach Niogi and colleagues (2008*a*) previously reported a correlation

between fractional anisotropy in a small part of the anterior corona radiata and executive function following mild traumatic brain injury. Their analysis focused on two small regions that showed white matter/cognitive function relationships in controls. We extend these findings by investigating a more severely affected group and using a different DTI metric to demonstrate that patients with more executive impairment have more white matter damage in a number of tracts that connect the frontal lobes to more posterior brain regions. This is consistent with the proposal that executive dysfunction following brain injury is, partly, the result of frontal lobe disconnection (Miller and D'Esposito, 2005).

Also in contrast to Niogi and colleagues (2008*a*), we did not observe a significant relationship between fractional anisotropy and executive function, although it is possible that the higher general intellectual function in the patients might obscure an overall correlation of fractional anisotropy and executive function across the two groups. However, this was not the case for our fornix/memory result and the IQ difference did not impact on the within-group patient analysis of executive function. The presence of widespread differences in the relationship between radial diffusivity and executive function in the uninjured brain and after traumatic brain injury suggests that using normal structure/function relationships to guide investigation of the effects of traumatic brain injury may not always be appropriate. A similar relationship between frontal connectivity and executive function has been observed in studies of normal ageing, where, in older adults, reduced integrity in tracts connecting frontal regions predicts executive dysfunction (O'Sullivan *et al.*, 2001; Davis *et al.*, 2009; Perry *et al.*, 2009). This suggests that different pathologies can produce similar cognitive impairments through damage to the same tracts.

DTI is extremely sensitive to white matter damage following traumatic brain injury. Reductions in fractional anisotropy and axial diffusivity emerge in the first few hours after a cortical contusion in experimental models of traumatic brain injury (Mac Donald *et al.*, 2007), and these early changes reflect axonal damage (Song *et al.*, 2003; Budde *et al.*, 2008, 2009). Tissue injury evolves over time with the development of macrophage infiltration, tissue oedema and demyelination and these pathological changes are reflected in DTI measurements (Mac Donald *et al.*, 2007; Sidaros *et al.*, 2008). In general, low fractional anisotropy persists over time, accompanied by an increase in radial diffusivity that leads to high mean diffusivity, whilst changes in axial diffusivity are more dynamic (Sidaros *et al.*, 2008).

We also provide direct evidence that DTI can detect white matter damage not seen using the standard magnetic resonance techniques. We stratified our analysis by investigating white matter abnormalities in patients with and without microbleeds. The presence of microbleeds on gradient-echo imaging is a marker of diffuse axonal injury and so indicates the presence of more severe white matter injury (Scheid *et al.*, 2003). As expected, patients with microbleeds showed widespread white matter abnormalities as compared with age-matched controls, but patients without microbleeds also showed significant white matter abnormalities. This highlights the limitation of relying on the presence of microbleeds as a marker of subtle white matter damage and demonstrates that significant white matter abnormality may be present following traumatic brain injury even when gradient-echo MRI is normal. We further stratified the patient analysis on the basis of severity, defined based on the Mayo system (Malec *et al.*, 2007). This, again, demonstrated the sensitivity of DTI in identifying white matter abnormalities in patients classified as 'mild'. Unlike the microbleed analysis, however, the comparison of mild and moderate/severe patients failed to show a difference in fractional anisotropy or mean diffusivity measurements. Although the Mayo system includes some aspects of structural brain damage in its criteria, it does not integrate sensitive magnetic resonance measures of white matter damage. Three of the eight 'mild' patients had microbleeds on gradient echo imaging. Therefore, although the 'mild' group was small, it is likely that the null results reflect the inclusion in this group of patients with significant diffuse axonal injury. This highlights the limitation of existing severity classifications for traumatic brain injury that fail to include specific measures of white matter damage.

Our results also show an overall increase in axial diffusivity, which was positively correlated with time since traumatic brain injury and greater in the 'mild' group of patients. Previous work has tended to show that traumatic brain injury produces early reductions in axial diffusivity that gradually normalize over time (e.g. Sidaros *et al.*, 2008; Wang *et al.*, 2009). On average, we scanned patients longer after their injury than Sidaros and colleagues (2008). Hence, our results suggest that axial diffusivity continues to rise well after the acute phase of traumatic brain injury. The pathological significance of these dynamic changes in axial diffusivity remains unclear, in part due to a lack of relevant animal studies (although see Wang *et al.*, 2009). The normalization of axial diffusivity could reflect reorganization within the white matter, due to axonal recovery or even regrowth (Voss *et al.*, 2006; Sidaros *et al.*, 2008). We found some support for this proposal by specifically examining the posterior limb of the internal capsule, where a large increase in axial diffusivity has been previously shown to be predictive of functional outcome (Sidaros *et al.*, 2008). This region contains descending corticospinal fibres and here, higher axial diffusivity in the posterior limb of the internal capsule was associated with faster processing speed on the choice reaction task. This result, therefore, provides support for the proposal that increased axial diffusivity reflects adaptive axonal recovery, but should be interpreted cautiously as our whole-brain analysis did not reveal a significant relationship for any region.

In our patients with traumatic brain injury, DTI changes were generally seen in the expected directions. In contrast, higher radial diffusivity in certain white matter tracts of the healthy controls was associated with more efficient executive function. This was unexpected, because one determinant of radial diffusivity is the degree of axonal myelination (Beaulieu, 2002) and, as this increases, one might expect reduced radial diffusivity, faster nerve conduction times (Jack *et al.*, 1983) and more efficient executive function. However, the relationship between DTI measures of white matter structure and cognitive function appears not to be this simple. Significant relationships between cognitive function and white matter structure in an unexpected direction have been reported previously (Tuch *et al.*, 2005). These results

emphasize that further work is needed to determine how changes in different aspects of white matter microstructure in specific tracts are related to cognitive function in the uninjured brain and how the DTI metrics are affected by brain injury. Further animal studies will also be needed to determine in detail the complex relationships between different DTI measures and the pathological effects of traumatic brain injury.

A possible limitation of DTI analyses is the presence of partial volume effects. This is potentially problematic for investigating patients with traumatic brain injury in the chronic phase, as patients frequently show some degree of brain atrophy. This means that the changes in DTI measures, such as lower fractional anisotropy, may reflect partial volumes, resulting from contamination of measurements by cerebrospinal fluid. Our approach limits the impact of this problem as the TBSS analysis involves 'skeletonization' of the white matter and focuses on the centres of the tracts (Smith *et al.*, 2006). This removes the white matter at the junctions with cerebrospinal fluid and grey matter that is prone to partial volume effects. Hence, our approach to investigating group differences is more robust to brain atrophy.

To conclude, we found widespread fractional anisotropy, mean diffusivity and axial diffusivity differences between patients with traumatic brain injury and healthy controls using TBSS. The distribution of white matter abnormality correlated with individual differences in associative learning and memory and one of our three indices of executive function. White matter disruption in the fornices predicted associative memory performance across both groups, whereas a more distinct pattern was observed for the relationship between frontal disconnection and executive function in the two groups. Our approach reveals the complexity of the relationships between indices of white matter structure and cognition and shows the importance of flexibly analysing patterns of disruption across the whole brain.

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# Supplementary material

Supplementary material is available at *Brain* online.

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