# DTI in TBI: An exploratory study into a method enabling detection of White Matter changes in individuals following TBI

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## *Contents*

## *Acknowledgements and Declaration*

All Diffusion Tensor Imaging scans (patient and controls) were acquired at Cardiff University Brain Imaging Centre by staff/researchers based there. LJH was not involved in this aspect of data collection.

The neuropsychological tests taken by patient participants were administered and scored by the clinician involved in their care again not involving LJH

Patient participants were identified and recruited by Dr Martin Bunnage and his Assistant Psychologist

Matlab scripts for the production of the mean plots, histograms and cumulative frequency graphs were conceived and written by Prof Jones.

LJH was responsible for the recruitment of all control participants and the administration and scoring of all control neuropsychological testing

LJH analysed and interpreted and all neuropsychological data and was responsible for analysis of the DTI scan data

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And finally, as always, thank you to Jonny for being him and being with me throughout it all again. LJXX

## *List of Abbreviations*

**CSD** Constrained Spherical Deconvolution

**CT** Computed Tomography

**CUBRIC** Cardiff University Brain Research Imaging Centre

**DAI** Diffuse Axonal Injury

**DTI** Diffusion Tensor Imaging

**FA** Fractional Anisotropy

**GCS** Glasgow Coma Score

**LOC** Loss of consciousness

**MD** Mean Diffusivity

**mTBI** mild Traumatic Brain Injury

**MRI** Magnetic Resonance Imaging

**PTA** Post Traumatic Amnesia

**ROI** Region of Interest

**TBI** Traumatic Brain Injury

**UF** Uncinate Fasciculus

## *Abstract*

**Background:** For Diffusion Tensor Imaging (DTI) to become a clinically useful tool in the detection of traumatic brain injury (TBI) and prediction of functional outcome, a reliable method enabling the identification of likely injury in individual patients needs to be developed.

**Objective:** To explore different methods of analysing DTI measures to determine if individual TBI patients can be differentiated from a group of non-brain injured controls and if so, how these differences are associated with cognitive function.

**Method:** 4 participants with TBI and 11 control participants were scanned using DTI and completed a battery of neuropsychological tests. The DTI measures of Fractional Anisotropy (FA) and Mean Diffusivity (MD) in the uncinate fasciculus were compared across individual TBI patients and a control group using 3 different methods of analysis.

**Results:** The comparison of mean FA/MD from individual TBI patients with the overall mean FA/MD of the control group revealed that some TBI patients had lower values of FA whilst others had increased MD. This difference in FA may be associated with deficits in measures of attention. The histogram curves and cumulative frequency plots for individual TBI patients and the controls revealed subtle yet potentially significant differences in the distribution of FA/MD. However at this stage these differences could not be associated with cognitive function.

**Conclusion:** Initial findings indicate that individual TBI patients can be differentiated from a control group using different methods with differing degrees of sensitivity. These differences may be related to cognitive function but further research is warranted before firm conclusions can be drawn.

## *Introduction*

Traumatic brain injury (TBI) is a leading cause of disability worldwide [1]. In England the average yearly rate of reported TBI is 229 per 100,000 people [2]. The detection of TBI and determination of its severity is crucial to the accurate prediction of a patient's functional outcome and enables the most appropriate and timely intervention to be made.

TBI results from external mechanical or biomechanical forces that are great enough to permanently or temporarily impair neuronal function [3]. In severe cases of TBI, the forces involved result in the stretching of axons, which causes damage to the neurofilaments and microtubules running throughout them and often results in cell death. Cell death however is rare in milder forms of TBI (mTBI) and any damage caused to axons is thought to be largely reversible [4].

The classification of TBI severity is in part determined by an individual's Glasgow Coma Scale (GCS) at the time of first medical assessment. Additional scales such as length of time of unconsciousness and duration of post traumatic amnesia (PTA) are also used to improve classification of TBI severity [5], however whilst these assessment measures are helpful in the acute stages of a TBI, they are not accurate predictors of functional outcome i.e. cognitive ability, following TBI [4], [6], [7], [8],[9].

Brain imaging methods are therefore also employed to provide further information about the extent of injury. Computerised Tomography (CT) can differentiate between 'complicated' mild TBI defined by the presence of visible brain injury and 'uncomplicated' mTBI, which results in a scan lacking signs of pathology. However this differentiation also has poor predictive value for functional outcome [9]. Unlike CT, Magnetic Resonance Imaging (MRI) can detect focal structural lesions and is 25-30% more sensitive in identifying Diffuse Axonal Injury (DAI) [10], a key feature of 40-50% of the TBIs that require hospital treatment [11]. However, Schrader et al. [12] note that MRI scans of 1.0 Telsa (T) taken immediately or 3 months post injury are rarely, if at all, able to detect axonal injury resulting from ordinary concussion. Again there is poor correlation

between MRI and neuropsychological measures [13] or functional outcome [14].

The difficulties with predicting functional outcome are particularly prevalent in mTBI. In the vast majority of mTBIs, symptoms such as cognitive dysfunction, headache and dizziness have resolved within weeks of injury [15] and individuals do not develop any long-standing impairment. However Lannsjö et al. [16] revealed a significant number of people continue to experience related symptoms 3 months after their injury. Often in these cases CT and MRI scans are negative i.e. they do not show any areas of identifiable brain injury. In the absence of clear physiological explanation for the continued experience of symptoms, several psychological and social factors have been proposed to contribute to the persistence of symptoms including involvement in litigation [17] [18], the 'Good-Old-Days' bias [19] and a misinterpretation of symptoms [20].

However, with the development of Diffusion Tensor Imaging (DTI), an application of MRI which unlike traditional brain imaging methods permits the visualization of white matter tracts and therefore areas of probable diffuse axonal injury, the possibility has been raised that areas of brain damage resulting from TBI may be present but are as yet undetected by conventional methods. This has led to DTI being posited as a non-invasive tool in the improved detection of brain injury [21].

DTI utilises the principle of anisotrophy; in white matter water diffuses at a significantly faster rate along an axon rather than across it [22]. Commonly used measures derived from DTI include Fractional Anisotropy (FA), a scalar value between 0-1, which represents the directionality of the anisotropic water diffusion (1 is equal to fully anisotropic diffusion). FA is thought to represent the integrity of the axonal membrane and myelin sheath [23]. Mean Diffusivity (MD) is another commonly used DTI measure, which represents the average amount of water diffusion in a given region and is thought to be influenced by the integrity and size of the axon [24].

Various methods have been used in patient-control group studies looking for changes to white matter that can be revealed by the comparison of DTI measures between groups. Cercignani [25] describes 4 methods commonly used: a simple region of interest comparison between patient and control brains, whole brain histogram analysis which is considered useful where diffuse changes are likely to occur, the co-registration of patient and control brain into a standardised space and tractography, and the reconstruction of selected white matter pathways of interest.

Significantly the use of these methods has enabled the identification of changes in the diffusion of water which relate to potential underlying damage, in brain regions that appear normal on standard T2 scans in the acute [26][27] and chronic stages [28] of TBI. These stages are thought have a differential effect on FA values; in the acute phase of injury when inflammation and oedema are key features, FA is generally considered to increase, while the chronic stage of TBI is associated with decreased FA likely representing underlying degeneration and cell death [29] but see [30][31].

A number of studies that have compared groups of patients with TBIs of varying severity and a control group, have identified differences in DTI measures in a range of brain regions (see table 1 for summary).

To determine whether observed changes in DTI measures have a functional relevance, their relationship with cognitive function has also been explored. Kraus et al. [32] demonstrated that at 6 months post TBI, the number of areas of white matter damage was associated with increased severity and negatively correlated with performance across measures of attention, memory and executive function.

Table 1. Summary of white matter regions DTI studies have identified as significantly different from controls in patients with TBIs of varying severities

| Mild TBI | Moderate-Severe TBI |
|---|---|
| Anterior corona radiate [33] | Cingulum [32] |
| Cingulum [33] [34] | External capsule [32] |
| Cortico-spinal tract [32] | Forceps major/minor [32] [36] |
| Dorsolateral Prefrontal cortex [30] | Inferior fronto-occipital Fasciculus [32] |
| Corpus callosum [31][33][35] | Sagital striatum [32] |
| Inferior longitudinal fasciculus [33] | Perforant pathway [36] [37] |
| Sagital striatum [32] | Corpus callosum [32] [38] |
| Superior longitudinal Fasciculus [32] | Arcuate Fasciculus [38] |
| Uncinate Fasciculus [33] | Cortico-spinal tract [32] |
| Internal capsule [35] | Superior longitudinal Fasciculus [38] |
| | Fornix [38] |
| | Corona radiata [32] [36] |
| | Hippocampus [37] |
| | Thalamus [36] |
| | Superior Longitudinal Fasciculus [32] |

At 1 month following mTBI injury, Niogi [33] reported that the number of white matter lesions detected by DTI, but not the number of microhaemorrhages detected by 3T MRI, was correlated with mean reaction time on the Attention Network Task in people with post-concussion syndrome symptoms, thus suggesting that DTI is a better predictor of cognitive impairment in mTBI than measures obtained from MRI.

Several studies have specifically investigated groups of people who sustained mTBI and have cognitive impairment (as determined by neuropsychological assessment) several months following their injury, although it is unclear as to the specific nature of the impairment. Lo et al. [38] reported that patients with mTBI and persistent cognitive impairment had decreased FA in the genu of corpus callosum. Lipton et al. [30] also identified reduced FA in the corpus callosum but furthermore in subcortical white matter and bilateral internal capsules.

More specially, increased FA in the midbrain has been shown to relate to reduced executive function test performance 3 weeks following mild-moderate TBI and is able to differentiate a group of symptomatic patients i.e. those reporting symptoms relating to TBI, from an asymptomatic control group 6 months after injury [39]. In addition, decreased FA in the thalamic projection fibres is correlated with reduced performance on a number of executive functioning tasks in the chronic stages of recovery (12months+) following mild-moderate TBI [36] and areas of reduced FA in the dorsolateral prefrontal cortex 2 weeks after mTBI, have been shown to be significantly correlated with poor performance on executive function [30].

The evidence base for DTI as a valuable technique in identifying regions of likely white matter damage in groups of TBI patients is developing rapidly. However, to use DTI techniques as a clinical tool in the prediction of functional outcome for TBI patients, a reliable method that enables an individual with TBI to be differentiated from a non-brain-injured control group, needs to be established.

Singh et al. [40] recently described a novel technique enabling the identification of regions of white matter damage in individuals. By comparing normalised FA in regions of interest of individuals with mild-moderate injury and a control group, they describe changes in the hippocampus/fornix, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, corpus callosum (genu and splenium), cortico-spinal tracts and the uncinate fasciculus of the patients at 1 month following TBI. However it is unclear whether the observed changes correspond to any functional outcome in terms of performance on cognitive measures.

Lipton et al. [41] compared individual mTBI paitents with cognitive impairment but negative MRI scans, to a control group by using whole brain histogram analysis. They identified decreased FA in the corpus callosum and internal capsule in the individual TBI patients. Consequently the authors concluded that their findings provided evidence that DTI could be used as a clinical tool for the assessment of individuals. However it is unclear which aspects of cognitive

function were impaired in the mTBI patients and how any impairments were related to the observed change in FA. Furthermore, whole brain voxelwise analysis has been critised for rarely taking into account the substantial effects that regions that are not of interest but are difficult to exclude from the analysis (such as the cerebral spinal fluid), have on the measures obtained [42].

The aims of the present study were therefore to establish a method that enables an individual who has sustained a TBI to be differentiated from a non brain-injured control group based on measures obtained from DTI, and, to determine how these measures may be related to cognitive function following a TBI. Three methods of analysing individual TBI patient measures with a control group were explored; one which compared the means of DTI measures from a region of interest and two which analysed distributions of raw DTI measures between individuals and controls.

## ***Methods ...***

Participants

Participants formed 2 groups. The TBI patient group consisted of 4 participants (1 female, 3 male, age range 25-65 years) who had sustained a traumatic brain injury 12-24 months prior to invitation to participate in the study and were current or recent outpatients at a local community brain injury rehabilitation unit. The control group consisted of 11 right-handed participants (5 male, 6 female; age range 25-43 years). Control participants were recruited from a control database at Cardiff University Brain Imaging Centre. Participants who had been scanned using DTI in the preceding 3 years were considered eligible to participate. Demographic and clinical characteristics where applicable are found in Figure 1.

All eligible participants were screened to exclude those with previous or current significant mental heath problems, neurological problems, alcohol or substance abuse and physical impairment (see Appendix M for full exclusion/inclusion criteria). All control participants also confirmed no previous significant head injury. Two control participants did report a likely past concussion.

The study was approved by NHS ethics and the Research and Development committee of the local NHS trust. The School of Psychology ethics committee at the Universities of Cardiff and Exeter also approved the study. All participants were deemed to have capacity to consent to participate and provided written consent to participate in the research.

Table 2. Clinical and demographic characteristics of Participants (exact ages of TBI patients have not been provided for reasons of anonymity)

| | Gender | Age Range | TBI Patient/Control | Injury Severity |
|---|---|---|---|---|
| **1** | F | 25-30 | TBI Patient | Mod-Severe |
| **2** | M | 50-54 | TBI Patient | Mod-Severe |
| **3** | M | 60-65 | TBI Patient | Mod-Severe |
| **4** | M | 30-34 | TBI Patient | Mod-Severe |
| **5** | F | 31 | Control | - |
| **6** | F | 36 | Control | - |
| **7** | F | 25 | Control | - |
| **8** | M | 31 | Control | - |
| **9** | F | 32 | Control | - |
| **10** | F | 35 | Control | - |
| **11** | M | 43 | Control | - |
| **12** | M | 37 | Control | - |
| **13** | M | 38 | Control | - |
| **14** | M | 38 | Control | - |
| **15** | F | 37 | Control | - |

Neuropsychological Assessment

Participants who sustained a TBI were administered a range of neuropsychological tests as part of their routine care. The tests were selected by the Clinical Neuropsychologist involved in their assessment for clinical reasons prior to their involvement in the study. Tests that were completed by the majority of the TBI patient participants were included in the analysis. The neuropsychological tests selected for control participants were therefore based on this opportunistic sample and aimed to form a standardised battery covering key aspects of cognition comparable to those tested in patients. Time restraints and administrative error meant that some neuropsychological test data is missing for control participants. All tests are well established and commonly used in clinical neuropsychology settings. The core domains of verbal and visual memory, attention, executive function and processing speed were assessed. Executive Function is a complex All raw scores were converted to standardised scores before analysis.

- Verbal Memory

  Immediate and Delayed Verbal Memory was assessed using the Californian Verbal Learning Test (CVLT-II; [43].

- Visual Memory

  Immediate and Delayed Visual Memory ability was assessed by the Family Pictures and Visual Reproduction subtests of the Wechsler Memory Scale III (WMS-III; [44].

- Processing Speed

  The Digit-Symbol-Coding and Symbol Search subtests of the WAIS-II [45] and Trail making Test A were used to measure processing speed.

- Attention

  The Continuous Performance Test – 2 (CPT-2; [46] was used to assess attention.

- Executive Function

  Executive functioning is a complex concept of cognition which includes cognitive flexibility, planning, inhibition and rule acquisition. A range of tests would be necessary to fully characterise this domain. However for this study, the Trails B subtest was used to determine cognitive flexibility but it is also sensitive to processing speed [47].

Table 3. Summary of the neuropsychological tests completed by each participant

| **Neuropsychological test** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CPT-2 | * | * | | * | * | * | * | * | * | * | * | * | * | * | * |
| WAIS-III – Symbol Search | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| WAIS-III – Digit Symbol Coding | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| CVLT-2 | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| WMS-III – Family Pictures | * | * | * | | * | * | * | * | * | * | * | * | * | * | * |
| WMS-III – Visual Reproduction | * | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| Trails A and B | * | * | * | * | * | * | * | * | * | * | * | * | * | | * |

2.3 DTI Acquisition and analysis

Diffusion weighted MR data were acquired on a 3.0 Tesla HDx system (General Electric), using an 8 channel head coil. The pulse sequence was a twice-refocused spin-echo echoplanar imaging EPI sequence [48], acquired with data acquisition matrix = 96 × 96; field of view = 230 × 230 mm; in-plane resolution = 2.4 × 2.4 mm, parallel imaging factor = 2. Diffusion encoding gradients were applied in 30 non-collinear directions, isotropically distributed [49] with a b-value of 1200 s/mm$^2$. 6 MR images without diffusion weighting were also acquired.

2.4 DTI Processing

The DTI data were analysed and processed in Explore DTI [50]. Data were corrected for subject motion and eddy-current induced geometric distortions [51]. Using non-linear regression, a single diffusion tensor was applied to the raw diffusion data in each voxel. The diffusion data were then used to produce fractional anisotropy and mean diffusivity maps.

For whole brain tractography, DTI data were first co-registered to standarised anatomical space (Montreal Neurological Institute space). The uncinate fasciculus (UF) was chosen as the white matter tract of interest based on the finding of an in-house preliminary study, confidence in the accuracy of reconstruction and previous research evidence that has implicated the tract in TBI [33]. The UF was extracted using a validated in-house method based on the selection of 3 regions of interest (areas which were known to contain the matter tracts of the UF and eliminate fibres belonging to other tracts). A deterministic streamline method was used to visualise the white matter tract.

2.5 Analysis of DTI measures and Neuropsychological Testing

Where mean values of FA and MD of individual TBI patients were calculated and compared to the mean FA and MD of all control participants 95% confidence intervals (CI; equal to +/- 1.96 standard deviations) of the control mean were calculated. TBI patient values falling outside the 95% CI were

considered to be statistically significant. Histograms of the raw FA and MD data for each region of interest (ROI) were also plotted and overlaid using Matlab (v. 7.3.0) with overall control mean and 95% CI calculated.

For neuropsychological testing, all raw scores were converted into age-adjusted standardized scores. Using a case series approach similar to that used by Tonks et al. [52], the control participants' standardised scores were averaged. Scores from TBI patients which fell outside of the 95% CI of the control mean (+/- 1.96 standard deviations from the mean) were considered significantly different from controls.

To compare DTI measures with neuropsychological tests, mean FA/MD values for each participant were plotted against the age-adjusted standardised score in the test of interest and a Pearson's r correlation coefficient for the 2 variables was calculated. Only measures that appeared to be associated were compared in this way.

## *Results*

To develop a reliable method that enables the discrimination of individual TBI patients from a non-brain-injured control group, 3 different methods were explored to determine which may offer the greatest sensitivity in detecting differences in FA and MD in the UF.

**Method 1: Mean Plot Analysis**

The mean FA/MD of each individual participant was plotted against the mean FA/MD of each participant forming the control group. The average of the control FA/MD mean and the 95% confidence interval were calculated and represented on the mean plot graph.

In both the left and right UF, the mean FA of TBI patients 1 and 4 is lower than the control group average FA and fell outside of the 95% CI (Figure 1A and figure 1B) indicating that there is likely to be a significant difference in the FA values for these TBI patients compared to the control group. This difference may represent a decrease in the integrity of the left and right UF and underlying DAI resulting from their TBI. The mean FA for the left and right UF of TBI patients 2 and 3 however (Figure 1A and 1B), were located within the 95% CI of the control group's overall mean FA indicating that the left and right UF of these TBI patients appears to be no different from that of controls and may have been undamaged in their TBI.

Mean plots of individual and control average MD of the right and left UF were also produced and the control group average and 95% CI represented. A different pattern to that obtained for FA values in the UF can be observed for the measure of MD. TBI patients 3 and 4 have mean MD values higher than the 95% CI of the control mean MD in both the left and right UF (Figure 1C and 1D). Increased MD is another potential indicator of a loss of integrity to the white matter tract likely to result from TBI. Despite increased FA, TBI patient 1 together with TBI patient 2, had average MD values that fell within the 95% CI of the control group mean for both the left and right UF (Figure 1C and 1D).

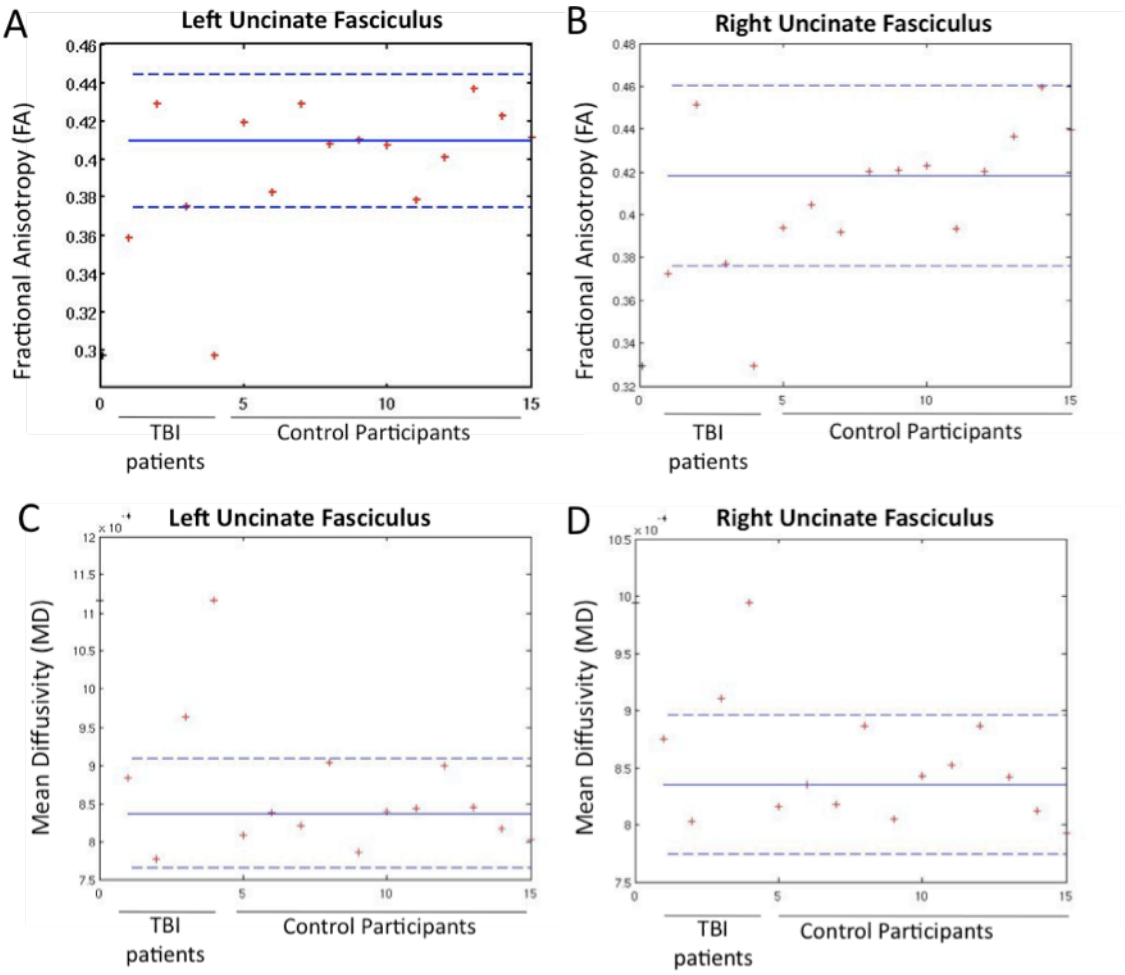


Figure 1. Mean plot analysis of FA/MD in the left and right Uncinate Fasciculus (UF) of TBI patients (1-4) and controls (5-15). Red cross represents mean FA value. Solid blue line represents mean of control FA/MD values and dashed blue line indicates 95% confidence interval (CI).

A. Mean FA in the left UF of TBI patients 1 and 4 falls below the control group 95% CI
B. Mean FA in the right UF of TBI patients 1 and 4 falls below the control group 95% CI
C. Mean MD in the left UF of TBI patients 3 and 4 falls above the control group 95% CI
D. Mean MD in the right UF of TBI patients 3 and 4 falls above the control group 95% CI

Table 4. Summary of significant findings for DTI measures using Method 1: Mean plot analysis (marked by '*') from right and left UF for T

| | FA | | MD | | Total |
|---|---|---|---|---|---|
| Patient | L UF | R UF | L UF | R UF | |
| 1 | * ↓ | * ↓ | | | 2 |
| 2 | | | | | 0 |
| 3 | | | * ↑ | * ↑ | 2 |
| 4 | *↓ | * ↓ | * ↑ | * ↑ | 4 |

**Method 2: Individual Histogram Analysis**

It is possible that the averaging of FA/MD raw values to calculate mean values for each participant as used in method 1, can obscure any subtle differences that may exist in the data. For example, a person with normally distributed FA that peaked at a value of 0.5 would have the same average value as a person whose FA was non-normally distributed and peaked twice at values of 0.25 and 0.75. Therefore, the averaging of values may occlude any difference in the distribution of FA that may represent changes in the integrity of the tracts being measured. To overcome this potential problem, histograms of the frequency of raw FA/MD values in the UF were produced for each TBI patient and control participant and overlaid (Figure 2). As for the mean plot method, the control average histogram curve was calculated together with the 95% CI, and represented on the histogram.

The histogram curves for the FA in the left UF supports observations from the mean plot analysis and reveals that the majority of points of the control participant curves fall within the 95% CI range of the control group mean FA curve (figure 2A). FA values in the control group peak at around 0.4. However,

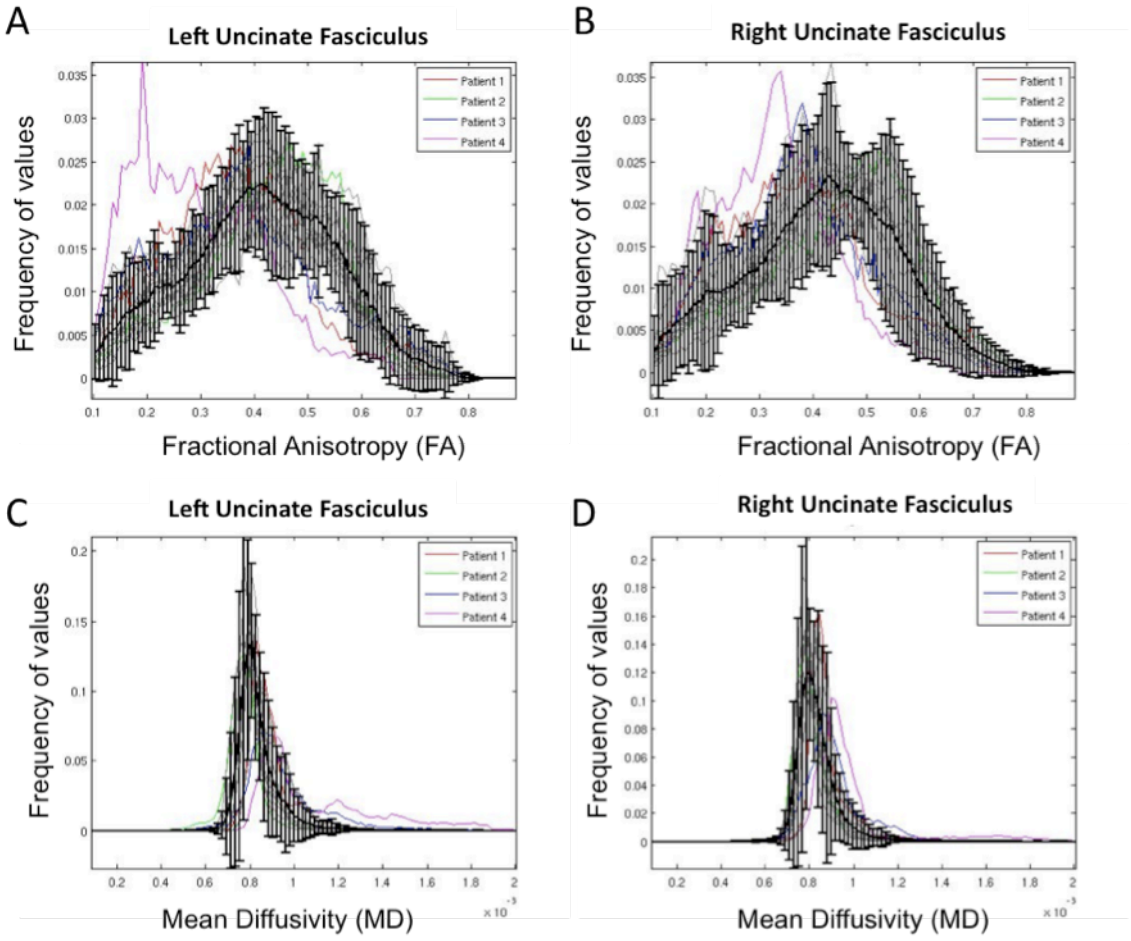


Figure 2. Histogram analysis of FA/MD in the Uncinate Fasciculus (UF) of TBI patients 1-4 (see colour key) and control participants (grey line). Black line represents control mean at each FA/MD value with error bars representing the 95% Confidence interval (CI).

A. FA in the left UF: FA frequency curves are shifted towards lower FA values in TBI patients 1,2 and 4 compared to controls. TBI patient 2 has a higher proportion on FA values at 0.45-0.6 than the controls
B. Mean FA in the right UF: FA frequency curves of TBI patients 1,3 and 4 fall outside of the 95% CI of the control mean.
C. Mean MD in the left UF: TBI patient 1 has a greater frequency of MD values between 0.8-1 whilst TBI patients 3 and 4 have a greater frequency of MD values above 1 when compared to the control group 95% CI. TBI patient 2 has a greater frequency of MD values between 0.4-0.7 compared to controls.
D. Mean MD in the right UF: MD frequency curves for TBI patients 3 and 4 are shifted towards higher MD values and reveal a greater frequency of values above 0.9 compared to controls.

the histogram curve for TBI patient 4 appears significantly shifted towards lower FA values with the highest frequency of values at 0.1-0.2. The frequencies of many other FA values also fall outside of the 95% CI curve. A similar, although less extreme pattern is observed for TBI patient 1; the highest frequency of FA values is positioned between 0.3-0.4 with the frequency of lower FA values being greater than in control participants and falling outside the 95% CI (figure 2A).

Interestingly, in addition to these observations, there are several points where the histogram curve for TBI patients 3 and 4 can also be seen to fall outside of the control 95% CI (figure 2A). TBI patient 3 has fewer FA values of 0.5-0.6 than the control group controls whilst TBI patient 2 has a greater frequency of FA values than the control group at this point (figure 2A).

A similar pattern can be observed for FA values in the right UF (figure 2B). Consistent with findings from the mean plot analysis, the histogram curves for TBI patients 1 and 4 fall outside of the 95% CI for the overall mean FA of control participants and in both instances are skewed towards a greater frequency of lower FA values (Figure 2B). However the histogram curve for TBI patient 3 can also be seen to shift towards a greater frequency of lower FA values than the control group. Again it is important to note that some control participants' FA values also fall outside of the 95% CI for controls in this region of interest.

Histograms of the distribution of MD frequencies in the UF of TBI patients and control participants were also produced. The histogram curves of both the left and right UF reveal that TBI patients 3 and 4 have a notably greater frequency of higher MD values than control participants but a reduced frequency of lower MD values when compared to controls (figure 2C and 2D). There is also a subtle shift in the distribution of TBI patient 1 towards a higher frequency of higher MD values in both the left and right UF. Interestingly in the left UF, TBI patient 2 has, unlike other TBI patients, a higher frequency of lower MD values than the control group (figure 2C).

The histogram analysis therefore appears to replicate the significant differences between TBI patients and control group participant that were revealed in the mean plot analysis, but also reveals that the distribution of FA and MD in the TBI patients that were indistinguishable from the control group by mean plot analysis, is subtly different from that of controls and may represent altered integrity of the UF that was previously unidentified in the mean plot analysis of method 1. However, it is also important to note that the histogram curves for control participants can occasionally also be seen to deviate by a small amount from the 95% CI for controls (Figure 2A, 2B and 2C). Interestingly in the left UF (Figure 2A) one of the participants who fell outside of the 95% CI was a control participant who reported previous concussion. However, they showed a slight increase in FA at values 0.55-0.65, similar to that of TBI patient 2. As increased FA values are generally thought to be associated with a greater integrity of white matter tracts, it is unclear whether the same mechanism may underlie the increased FA for the control and patient participant. Control participants without concussion also fall outside the 95% CI so it is not possible to draw any conclusion about the significance of the observation at this stage.

Table 4. Summary of significant findings using Method 2: Histogram analysis (marked by '*') for right and left UF for TBI. ↑ represents an increase in FA/MD value from mean, ↓ represents a decrease in FA/MD value from mean

| | **FA** | | **MD** | | **Total** |
|---|---|---|---|---|---|
| Patient | L UF | R UF | L UF | R UF | |
| 1 | * ↓ | * ↓ | * ↑ | * ↑ | 4 |
| 2 | * ↑ | | * ↓ | | 2 |
| 3 | * ↓ | * ↓ | * ↑ | * ↑ | 4 |
| 4 | * ↓ | * ↓ | * ↑ | * ↑ | 4 |

**Method 3: Cumulative Frequency Plot**

An alternative way of representing the distribution of FA and MD values is in the form of a cumulative frequency graph. This is a useful method that enables a visual representation of whether values fall outside those of a normally distributed group.

Using this method of analysis, TBI patients 1, 3 and in particular, TBI patient 4, are again shown to have a greater proportion of lower FA values than the control group in the left and right UF (Figure 3A and 3B). Interestingly in the left UF, the cumulative curve for TBI patient 2 can be seen to deviate from the control mean curve in the opposite direction to other TBI patients; the patient has fewer low FA values than the control group until approximately a value of 0.45 when the curve becomes more consistent with that the control mean curve (Figure 3A). This is the first time that TBI patient 2 appears to deviate from the control mean and suggests that cumulative frequency plot analysis may be more sensitive to differentiating TBI patients from controls than the mean plot or histogram analysis.

Cumulative frequency curves for the MD in the left and right UF indicate a similar change in MD distribution as revealed by histogram analysis; TBI patients 3 and 4 have fewer low MD values and a larger proportion of high MD values when compared to controls (figure 3C and 3D), this is particularly evident in the left UF (figure 3C).

However, it is important to note that there are also control cumulative curves that also deviate notably from the mean. Given the very large number of data points involved, a Kolmogorov-Smirnov test to determine statistical significance of these differences was not considered appropriate. With very large sample sizes such as those used, very small deviations from the control would likely produce a significant result [53]. Therefore a significant limitation of this method is that it is not possible to determine if the differences in cumulative curve for TBI patients, or indeed control participants.

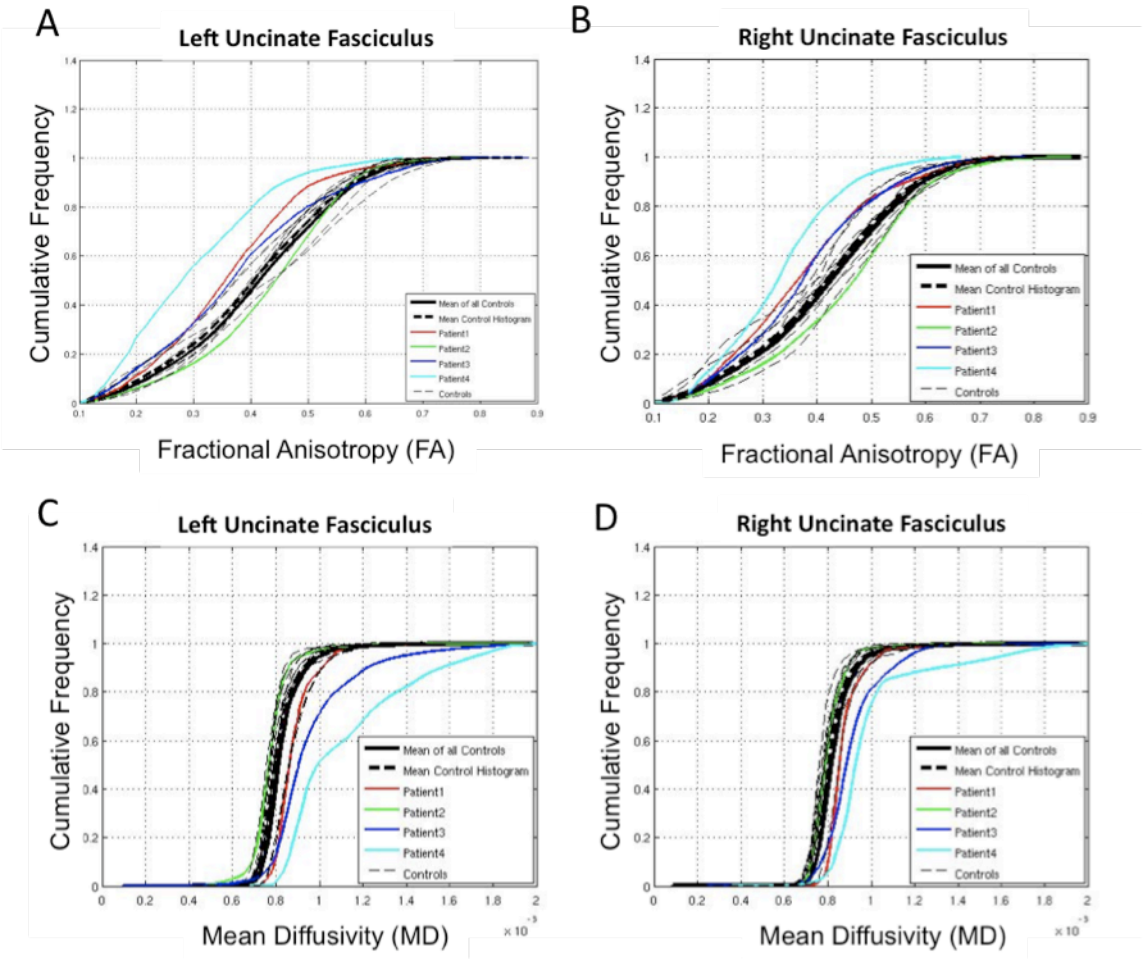


Figure 3. Cumulative frequency plots of the Uncinate Fasciculus of patients 1-4 (see colour key) and control participants (thin black dashed lines).

A. FA in the left UF: All TBI patient cumulative frequency curves fall outside of the control participant curves. TBI patients 1,3 and 4 have a greater cumulative frequency at lower FA values. TBI patient 2 has a lower cumulative frequency curve than controls.
B. FA in the right UF: All TBI patients have cumulative frequency curves that fall outside of control participant curve. Only TBI patient 4 can be seen to show a substantially greater frequency of lower FA
C. MD in the left UF: Cumulative frequency curves for TBI patients 3 and 4 have much fewer lower cumulative frequencies than control participants. Curves for TBI patients 1 and 2 did not appear to deviate from controls.
D. MD in the right UF: Cumulative frequency curves for TBI patients 3 and 4 have fewer low MD values than control participants

Despite this limitation, at this stage visual inspection of the cumulative frequency plots reveals subtle and large differences in the distribution of FA and MD in the UF of TBI patients when compared to controls that are generally consistent with findings from the histogram method of analysis. The exception occurs in the right UF of TBI patient 2 where FA values appear to be greater, a previously unobserved finding.

Functional significance of DTI Measures

The neuropsychological tests completed by control and TBI patient participants were broadly categorized into 5 domains of cognitive function: attention, processing speed, visual memory, verbal memory and executive function. Age-adjusted standarised scores were calculated for all neuropsychological tests completed by control participants. None of the scores obtained by the control participants were considered to be clinically significant.

The age-adjusted standardized scores from the control participants were then averaged and the 95% CI of the scores calculated. The age-adjusted standardised scores for each neuropsychological test completed by the TBI patients were obtained from their medical records and compared to the control group average in a case series approach previously demonstrated by Tonks et al. [52]. TBI patient neuropsychological test scores that fell outside of the control 95% CI, were considered to be significantly different from the controls. All TBI patients had at least 1 neuropsychological test score that fell below the 95% CI of the control group. When TBI patients had at least 1 neuropsychological test score which fell below the 95% CI of the controls, this was considered to reflect an impairment in the cognitive domain that the neuropsychological test assessed. All TBI patients therefore had at least 1 cognitive domain with impaired functioning (see Table 4). For clinical reasons, TBI neuropsychological tests results of TBI patients are not available for all cognitive domains assessed in controls.

Table 5. Summary of the cognitive domains shown to be impaired in TBI patients when comparing their standardised score to the 95% CI of the control group.
* denotes areas of impairment

| TBI Patient | Attention | Processing Speed | Visual Memory | Verbal Memory | Executive Function | Total impaired cognitive domains |
|---|---|---|---|---|---|---|
| 1 | * | | | | * | 2/5 (40%) |
| 2 | | * | * | * | | 3/5 (60%) |
| 3 | n/a | * | * | * | | 3/4 (75%) |
| 4 | * | * | n/a | * | | 3/4 (75%) |

To determine if the DTI measures obtained for the UF had any functional significance, the pattern of cognitive impairment found in the TBI patients seen in table 5 was compared to the DTI measures that were significantly different in TBI patients (table 3) when using the average FA/MD values calculated in method 1. The tables reveal that TBI patients 1 and 4 have significantly lower FA values in the left and right UF and are also impaired in the cognitive domain of attention. TBI patient 2 however does not deviate from the control group in measures of attention or mean FA in the UF. Unfortunately neuropsychological scores for TBI patient 3 were not available for the domain of attention to determine if an association similar to that for TBI patients 1 and 4 could also be observed.

To explore if there may be a relationship between scores on attention tests and average FA in the left and right UF, the standardised scores from all participants (TBI patients and controls) were correlated with the mean FA of either the left or right UF. However at this stage it was not possible to identify a significant correlation between the 2 measures.

With the existing data, the pattern of neuropsychological test results does not correspond to the pattern of average MD found in the UF i.e. TBI patient 3 and 4 have increased MD compared to controls but they do not exclusively show impairment in any cognitive domain when other TBI patients are unimpaired. It is important to highlight that without a complete neuropsychological test dataset,

it is not possible to draw any firm conclusions about the significance, or lack of, these findings.

The pattern of cognitive impairments for each participant (Table 5) was also compared to the pattern of results obtained from the histogram (Table 4). With an increasing number of identified significant differences in DTI measures in the UF using these methods, it was not possible to observe a clear relationship between significant DTI measures and areas of cognitive impairment. Again, this does not mean that a relationship does not exist, simply that at this stage it has not been possible to identify one.

## *Discussion* ...

The present study investigated the potential for 3 different methods of analysis to enable the differentiation of individual TBI patients from a control group using measures obtained from DTI.

It was possible to identify likely significant differences in the FA and MD measured in the Uncinate Fasciculus by comparing the mean of these values from the individual TBI patients with the control group mean. It was observed that for some TBI participants FA values decreased in the UF whilst for others MD values increased compared to the control group. These changes in FA/MD may indicate the compromised integrity of the white matter tracts of the UF that may have occurred as a result of TBI in these patients.

Apparently subtler differences in FA/MD that may exist between individual TBI patients and a control group were however revealed by using a different method of analysis. By displaying the frequencies of FA/MD values found in the UF in the form of histograms and cumulative frequency plots, it was possible to identify differences in their distribution that were occluded by averaging the values. Using these methods TBI patients who were not distinguishable from the control group when comparing mean FA/MD, were shown to have a distribution of FA/MD that was significantly different from controls. The cumulative frequency method was able to identify slightly more areas of likely differences in TBI patients compared to controls but as it was not possible to calculate if these differences were significant, it may be that the histogram method is most reliable. As previously, a logical interpretation of the differences in FA/MD is that they represent the presence of underlying white matter damage that is likely to have occurred in the TBI patients.

Although some previous studies have begun to investigate whether DTI measures from individual TBI patients with cognitive impairment can be differentiated from controls [41], it has yet to be determined how any of the observed changes may specifically relate to functional outcome. The present study sought to address this gap and has provided preliminary evidence to

suggest that there may be a relationship between DTI measures and cognitive function in the chronic stages of TBI when the mean plot analysis method was used. Although it was not possible to determine relationships between the neuropsychological test scores and the DTI measures for all the TBI patients, some interesting associations were observed. Impaired performance in tasks requiring attention may be related to reduced FA in the right and left UF in TBI patients. The UF is not well understood but is thought to be part of the limbic system and has recently been implicated in the retrieval of famous face names [54] and auditory-verbal memory ability [55].

These findings are significant because for DTI to be a useful clinical tool in the detection of TBI and for it to contribute to the improved prediction of functional outcome, a method is required that enables the reliable identification of diffuse axonal injury in individual patients that can be related to an outcome measure such as cognitive ability. The present study goes some way to providing a method that may enable the identification of areas of likely change to the integrity of white matter thought to represent DAI and cognitive outcome.

It is interesting to note that where significant differences were identified in the FA/MD of the UF in individuals with TBI, measures in the both the right and left UF were found to be significantly different from controls. This is particularly relevant given that information obtained from the non-diffusion weighted MRI scans usually suggests that for the majority of TBI, damage to one hemisphere is dominant. Thus the finding that analysis of the DTI measures indicates bilateral damage to the UF, suggests that the methods of analysis used may reveal otherwise undetected areas of damage and more accurately reflect the diffuse nature of TBI.

It is also the case however that clear evidence of significant brain damage can be seen on some of the TBI patients' non-diffusion weighted scans yet analysis of the DTI measures does not always represent this damage, i.e. using these methods the TBI patients appear no different from controls. It may be that by only selecting the UF as a region of interest, brain regions with greater damage, which may be more predictive of outcome, have been missed. A number of

other questions are also raised by the present findings such as whether a reorganization/regeneration of neuronal pathways in these areas may have occurred and results in only subtle changes in FA/MD in the chronic stages following TBI. The effects of premorbid characteristics such as education level and the age at which the TBI occurred are additional factors that may influence this effect.

Previous research findings comparing groups of people who sustained a TBI with a group of controls often observed decreased FA and increased MD in the same region. In the present study, the mean plot analysis method did not reveal this reciprocity in individual patients. However with the exception of the right UF in TBI patient 2, the histogram and cumulative frequency methods of analyses demonstrated it in all areas where significant differences between individual TBI patients and controls were found. It is questioned whether this supports the histogram and cumulative frequency plots as more sensitive measures of changes in FA/MD values.

There are however several limitations of the present study. The small number of participants and the incomplete neuropsychological test data prevents statistically significant conclusions to be drawn. A clear improvement in the study design would be to increase the number of TBI patient participants to enable the methods to be further tested for reliability in differentiating TBI patients from a control group. It would also be beneficial to include a wide range of TBI injury severities to explore potential relationships between TBI severity and the degree of change to FA/MD values in the UF and indeed in other brain regions of interest. An increased sample size would also permit the possibility of exploring the possible effects that age may have on the DTI measures and any potential differences there may be in the recovery process following TBI. Furthermore, the control group may also be unrepresentative of the general population, as the vast majority had scored above average in many domains in the neuropsychological tests. It is therefore a possibility that the observed differences in FA/MD in TBI patients are confounded by differences in pre-morbid intellectual ability rather than a result of the TBI. Furthermore the TBI patient participants were not matched in age to the control

group. It is known that FA values are thought to decrease with age [56]. With an older age range, some of the differences in the DTI measures of TBI patient participants could be attributable to effects of age rather than brain injury per se. By increasing the size of the control population to include a wider range of demographic backgrounds a more representative and reliable control group would be achieved.

A further limitation of the current design is that for both TBI patient and control participants, the time between neuropsychological testing and DTI scans acquisition varied considerably and in some instances was up to 2 years. As discussed DTI measures are known to be influenced by age so although observable, significant white matter changes attributed to aging would not be expected to occur over this time, it is not possible to rule out the possibility. Therefore future studies should seek to minimize the time between neuropsychological testing and brain imaging.

It is also important to note that one of the TBI patients has a preexisting medical condition that may in some instances affect the nervous system. To our current knowledge, there is no evidence that this is the case, however it remains possible that the medical condition may have resulted in or contributed to the observed differences in DTI measures indentified in this patient. In future studies participants should be screened for such medical conditions to exclude the possibility of any confounding variables.

A further limitation of the present study is the absence of conventional neuroimaging scans e.g. CT and MRI, for the TBI patient participants. This additional source of information would help to provide further evidence of the site of brain injury and also help to determine if the DTI analysis methods developed are able to identify areas of potential damage that were not otherwise visible by conventional scans.

Although commonly used in this field of research, deterministic tractograpy, the method of white matter tract visualisation employed in the present study, also has inherent limitations. The method becomes particularly problematic in

regions of crossing fibres [57], as the estimation of the direction of predominant diffusion and therefore the trajectory of the reconstructed pathway, will not necessarily follow the direction of the white matter tracts of interest [58] or may terminate erroneously [59]. Crucially it is not possible to know if errors have been made in the reconstruction of white matter tracts to be analysed [56] as the visual representation may appear to correspond to the tract of interest but it may also contain fibres from other tracts or may exclude fibres that do belong to it. Therefore additional tract visualisation methods such as Constrained Spherical Deconvolution should be used in additional studies to overcome this problem. The present study has also not taken into account Partial Volume Effects (the effects of the surrounding grey matter on the analysis of a white matter tract), which are known to influence DTI measures, therefore a future study should consider their effects on any findings.

To maximize the potential impact of developing the present study further, With a greater number of TBI patient participants it would also be interesting to explore the effect of demographic factors such as age and pre-morbid ability on DTI measures following TBI.

It is important to note however that the predictive validity of DTI is still uncertain. Although previous studies have shown relationships between DTI measures and cognitive performance, there is currently still insufficient data from group or individual studies, to indicate what effect any difference in DTI measures in any given white matter tract would have on functional outcome. Indeed the link with observable brain pathology and functional outcome is still poorly understood. For example, evidence from autopsy studies have indicated that up to 30% of brains have signs of Alzheimer's disease at autopsy but the symptoms of the disease were not present whilst the person was alive [60]. Furthermore in the case of TBI, it has been discussed that the traditional brain imaging measures of CT and MRI are shown to be poorly related to functional outcome. It may be that these methods are not as sensitive to certain types of pathology as DTI but it must also be considered that other factors may be involved in the level of functional outcome a person is able to achieve following a brain injury.

Functional outcome is not only determined by performance on neuropsychological tests and can include whether a person is able to return to work or reintegrate in their community. This in turn is thought to be influenced by many additional psychological and social factors such involvement and in litigation and beliefs about an illness.

To maximize the potential impact of developing the present study further, additional variables that may influence the potential relationship between DTI measures and cognitive function and consequently help determine the predicative validity of DTI, should therefore be included. For example depression and post-traumatic stress disorder are relatively common conditions following a TBI and have both been shown to be associated with reductions in FA [61][62]. Participant should be screened for these conditions and it may also be beneficial to include scales of assessing health beliefs (e.g. the Illness Perceptions Questionnaire-Revised [63]. Additional functional outcome measures such as an individual's return to work status and quality of life should also be included. With a greater number of TBI patient participants it would also be interesting to explore the effect of demographic factors such as age and pre-morbid ability on DTI measures following TBI.

Despite the limitations outlined above, the present study provides preliminary evidence that the use of DTI can enable the differentiation of individual TBI patients from controls by enabling the identification of regions of white matter that are likely to be damaged following TBI. To our knowledge this is the first study that has explored these methods of comparing the DTI measures of FA/MD obtained from a region of interest in individual TBI patients with those of a control group whilst seeking to establish how the observed changes in FA/MD may be related to specific cognitive functions.

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## Dissemination Statement

It is hoped that the findings from this work will be rewritten for submission to the Journal of Neurology, Neurosurgery and Psychiatry and presented at relevant forthcoming conferences.

Given the exploratory and potentially sensitive nature of the study i.e. the detection of otherwise undetected brain damage, detailed feedback will not be presented to participants. However, a letter providing a lay summary of the findings, explaining that a potentially new method of analysis of TBI using DTI has been explored with potentially interesting results, will be sent to TBI patient participants. Those control participants who expressed an interest in the findings of the study will also be provided with a similar summary.

The present study is considered to be exploratory and it is hoped that the results will form the basis of a grant proposal to permit further research in this area to consolidate findings.

## APPENDIX A: NHS ETHICAL APPROVAL – SUBSTANTIAL AMMEDMENT

**South West 5 REC**
formerly Frenchay REC
C/o North Bristol NHS Trust
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25 June 2010

Dr Martin Bunnage
Consultant Clinical Neuropsychologist
The Burden Centre
Frenchay Hospital
Bristol
BS16 1JB

Dear Martin

| | |
|---|---|
| **Study title:** | **Diffusion Tensor Imaging in patients with Traumatic Brain Injury: A pilot study of contemporary imaging methods.** |
| **REC reference:** | **08/H0107/69** |
| **Amendment number:** | **1** |
| **Amendment date:** | **17 June 2010** |

The above amendment was reviewed by the Sub-Committee in correspondence.

**Ethical opinion**

Favourable Opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation on the basis that all data going to the student is anonymised ie only nature of brain injury, gender, approximate age for NHS patients.

**Approved documents**

The documents reviewed and approved at the meeting were:

| Document | Version | Date |
|---|---|---|
| Summary/Synopsis | Pilot v1 | 14 June 2010 |
| Participant Consent Form: Student Pilot Study | 1 added by REC | 18 June 2010 |
| Participant Consent Form | 3 | 14 June 2010 |
| Participant Information Sheet: Student Pilot Study | 1 added by | 18 June 2010 |

| | REC | |
|---|---|---|
| Participant Information Sheet | 3 | 14 June 2010 |
| Protocol | 2 | 14 June 2010 |
| Notice of Substantial Amendment (non-CTIMPs) | 1 | 17 June 2010 |

**Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

**R&D approval**

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**08/H0107/69:** **Please quote this number on all correspondence**

Yours sincerely

**Mr Anthony Sack**
**Committee Co-ordinator**

E-mail: Anthony.Sack@nbt.nhs.uk

| | |
|---|---|
| *Enclosures:* | *List of names and professions of members who took part in the review* |

| | |
|---|---|
| *Copy to:* | *North Bristol NHS Trust R&D office* |

## APPENDIX B: NHS ETHICAL APPROVAL - ORIGINAL

**Frenchay Research Ethics Committee**
C/o North Bristol NHS Trust
Pembroke Room
Beaufort House
Southmead Hospital
Westbury-on-Trym
Bristol
BS10 5NB

Telephone: 0117 323 5211
Facsimile: 0117 323 2832

24 November 2008

Dr Martin Bunnage
Consultant Clinical Neuropsychologist
North Bristol NHS Trust
The Burden Centre
Frenchay Hospital
Bristol
BS16 1JB

Dear Dr Bunnage

| | |
|---|---|
| **Full title of study:** | **Diffusion Tensor Imaging in patients with Traumatic Brain Injury: A pilot study of contemporary imaging methods.** |
| **REC reference number:** | **08/H0107/69** |

Thank you for your letter of , responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Ethical review of research sites**

The Committee has designated this study as exempt from site-specific assessment (SSA). The favourable opinion for the study applies to all sites involved in the research. There is no requirement for other Local Research Ethics Committees to be informed or SSA to be carried out at each site.

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Participant Consent Form | 1 | 28 July 2008 |
| Participant Information Sheet | 1 | 01 August 2008 |
| GP/Consultant Information Sheets | 1 | 01 August 2008 |
| Letter of invitation to participant | 1 | 28 July 2008 |
| Questionnaire: Second Screening | 1 | 28 July 2008 |
| Questionnaire: Initial Screening | 1 | 28 July 2008 |
| Letter from Sponsor | | 10 July 2008 |
| Protocol | 1 | 27 August 2008 |
| Investigator CV | | |
| Application | | 01 August 2008 |
| MRI debriefing sheet | | |
| Response to Request for Further Information | | |
| Participant Consent Form | 2 | 08 October 2008 |
| Participant Information Sheet | 2 | 06 October 2008 |
| Covering Letter | | |
| Response to Request for Further Information | | |
| Participant Consent Form | 2.1 | 17 November 2008 |

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve

our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

| | |
|---|---|
| **08/H0107/69** | **Please quote this number on all correspondence** |

With the Committee's best wishes for the success of this project

Yours sincerely

**Dr Mike Shere**
**Chair**

Email: Anthony.Sack@nbt.nhs.uk

| | |
|---|---|
| *Enclosures:* | "After ethical review – guidance for researchers" *SL- AR2* |

| | |
|---|---|
| *Copy to:* | *North Bristol NHS Trust* |

North Bristol NHS
NHS Trust

Research & Innovation Office
Floor 3, Learning & Research Building
Southmead Hospital
Westbury on Trym
Bristol
BS10 5NB

**Tel**: 0117 323 6468
**Fax**: 0117 323 6192
**Email:** research@nbt.nhs.uk

25th August 2010

Dear Mr Bunnage

**Title: DTI in TBI: A pilot study of contemporary methods**
**R&D reference no: 2046**
**REC reference no: 08/H0107/69**
**Start date: 01/10/08**
**End date: 01/10/11**
**Amendment number: 1**
**Amendment date: 17 June 2010**

Thank you for notifying us of the above substantial amendment which includes the following changes to the protocol:

1) Comparison of measures obtained from DTI scans of brain-injured participants to DTI measures obtained from a control group

2) Investigation whether the measures obtained from DTI scans are related to neuropsychological measures of cognitive function

Following receipt of the amended study documentation and favourable opinion letter from the South West 5 Research Ethics Committee dated 25/June/2010, we are happy to offer our ongoing approval.

Please ensure that all members of the research team use the current versions of the approved documents. These should be kept in the Trial Master File for monitoring, audit and inspection purposes and previous versions should be clearly marked as void.

Yours sincerely

Helen Andrew
Senior Research Governance Officer
Research & Innovation
North Bristol NHS Trust

Floor 3 Learning & Research building Southmead Hospital Bristol BS10 5NB

T: 0117 323 5209

## APPENDIX D: NHS ETHICS APPROVAL – LOCAL R&D ORIGINAL

North Bristol NHS
NHS Trust

Research & Innovation Office
Floor 3, Learning & Research Building
Southmead Hospital
Westbury on Trym
Bristol
BS10 5NB

**Tel**: 0117 323 6468
**Fax**: 0117 323 6192
**Email:** research@nbt.nhs.uk

8th December 2008

Project Title:- Diffusion Tensor Imaging in patients with Traumatic Brain Injury: A pilot study of contemporary imaging methods

Project ID :- 2046
Start date :- 01/10/2008
End date :- 01/10/2010

I am pleased to tell you that the above project has been approved by North Bristol NHS Trust and that we will act as sponsor for this study.

We wish you every success with your study. We are keen to support good research at North Bristol NHS Trust and are pleased that you have decided to conduct your project here.

Approval is given on the understanding that this project be carried out according to Good Clinical Practice and within the guidelines of the NHS Research Governance Framework for Health and Social Care* and in particular:

- You have responsibility for ensuring that, all participants sign informed consent (whenever applicable) and that the protocol agreed by the local research ethics committee is adhered to by yourself and any co-workers.

- You are required to provide us with information about any amendments to the protocol, changes in funding, personnel or end date and any research-related adverse events.

- Any staff working on this study at this site must have been issued with a contract with NBT (honorary, substantive or bank) before they commence work on the study at this site

In addition, other information may be requested from time to time and lay summary of the results will be requested from you at the end of the study.

In accordance with the NBT Research Monitoring and Audit policy, this study may be subject to audit by the R&D Office.

Yours Sincerely

**Nicola Coe**
**Deputy Director**
**Research & Innovation**
**North Bristol NHS Trust**

## APPENDIX E: ETHICS APPROVAL FROM CARDIFF UNIVERISTY

**Re: Ethics feedback - EC.10.06.01.2487R**
Derek Jones

**Sent:** 15 July 2010 16:51
**To:** psychethics [psychethics@Cardiff.ac.uk]
**Cc:** Hanley, Laura

>>> psychethics 7/13/2010 12:33 PM >>>
Dear Derek,

The Ethics Committee has considered the further information you provided for your
staff project proposal: Investigating the relationship between diffusion tensor and
cognitive function (EC.10.06.01.2487R).

The project has now been approved.

Please note that if any other changes are made to the above proposal then you must
notify the Ethics Committee.

Regards,
Dominique Mortlock

School of Psychology Research Ethics Committee
Tower Building
Park Place
CARDIFF
CF10 3AT

Ffôn /Telephone: +44 (0) 29 2087 0360
Ffacs/Fax: +44 (0) 29 2087 4858

http://www.cardiff.ac.uk/psych/research/ethics/

## APPENDIX F: ETHICS APPROVAL EXETER UNIVERSITY

**To:** **Laura Jane Hanley**
**From:** **Cris Burgess**
**CC:** **Huw Williams, Martin Bunnage**
**Re:** **Application 2010/009 to Ethics Committee**
**DTI in TBI: A pilot study of contemporary methods**
**Date:** **09 November 2010**

The School of Psychology Ethics Committee met on 13/10/10 and your NHS Local Research Ethics Committee application and approval were reviewed. In line with our procedures, your project is now de facto approved.

The agreement of the Committee is subject to your compliance with the British Psychological Society Code of Conduct and the University of Exeter procedures for data protection (http://www.ex.ac.uk/admin/academic/datapro/). In any correspondence with the Ethics Committee about this application, please quote the reference number above.

I wish you every success with your research.

Yours sincerely,

Cris Burgess
Chair of School Ethics Committee

**RE: ethics approval query**
Burgess, Cris
You replied on 12/10/2010 17:01.
**Sent:** 12 October 2010 16:56
**To:** Hanley, Laura
**Cc:** Evans, Marilyn

Hi Laura,

I've had a chance to look through all your documentation now and can confirm that we are happy for you to carry out your proposed study. This approval is without conditions and applies for one year from today's date, thus almost coinciding with your proposed end date of 1st October 2011. I wish you all the best with your research.

I will be in touch more formally within the next week to provide you with an application/approval number, but in the meantime please treat this email as confirmation of our approval.

Best regards,
Cris (as Chair, Psychology REC).

---

Dr Cris Burgess
Psychology, College of Life & Environmental Sciences
University of Exeter

Deputy Director Undergraduate Psychology
Chair, Psychology Research Ethics Committee
Academic Exams Officer and Chair, Undergraduate Board of Examiners

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**Psychology Research Ethics Committee**
Burgess, Cris

**Sent:** 13 October 2010 14:41
**To:** Hanley, Laura

Hi Laura,

With respect to my emailed approval for your study yesterday, in future correspondence please can you use the Psychology REC reference 2010/09.

Many thanks,
Cris.

---

**Dr Cris Burgess**
Psychology, College of Life & Environmental Sciences
University of Exeter

*Deputy Director Undergraduate Psychology*
*Chair, Psychology Research Ethics Committee*
*Academic Exams Officer and Chair, Undergraduate Board of Examiners*

## APPENDIX G: CONTROL PARTICIPANT INFORMATION SHEET

Participants Information Sheet 09-11-10 (v4)

### Investigating the relationship between diffusion tensor imaging data and cognitive function

**Purpose of study**

We wish to obtain measures of cognitive function to explore their relationship with diffusion tensor imaging measures. This data would form a control dataset that would be used to compare with other populations.

**Who is conducting the Study?**

The study is a result of a collaboration between Dr Martin Bunnage of the Head Injury Therapy Unit at Frenchay Hospital, Bristol and Professor Derek Jones of CUBRIC. Laura Jane Hanley is a trainee Clinical Psychologist from the University of Exeter and will be conducting the research as part of her doctorate training. She is supervised by Dr Bunnage and advised by Professor Jones

**Why have I been chosen?**

You have been contacted because you have already provided brain images to the CUBRIC control database and at this time provided consent to be invited to further studies at CUBRIC. We would like you to contribute to the current study by completing a battery of neuropsychological tests. We would then like to compare the data obtained from these tests to that previously obtained from your DTI scan. This set of data would then contribute to a control CUBRIC dataset which would then be used as a control in comparison with other populations of people e.g. those who have had a brain injury. This is to enable possible relationships between measures of white matter integrity and cognitive function to be identified.

**Can I take Part?**

If you are aged 18-65 and have English as your first language, we would like you to consider you taking part in the study.

However if you have one of the following conditions or experiences then unfortunately you will not be able to take part in the current study at this stage:

* People who have sustained a previous brain-injury i.e. blow to the head associated with loss of consciousness and / or post-traumatic amnesia of at least 5 minutes duration

* People who have been diagnosed with or have a suspected neurological condition including epilepsy

* People who have had a neuropsychological assessment in the last 2

years

* People who have current or a history of moderate-severe mental health difficulties

* People with current or a history of alcohol/substance abuse

* People with current or a history of problems with aggression and anger control

At the beginning of the cognitive testing you will be asked to confirm that you do not have any of these conditions or experiences.

**Do I have to take part?**
No. Your participation in the study is completely voluntary. If you do agree to take part and then change your mind, you can withdraw from the study at any time.

**What will happen if I do take part?**
You will be contacted by a researcher from the study and a time will be arranged for you to take part in the neuropsychological testing. The testing will take place at Cardiff University at a time convenient for you. The testing will usually take around 2 hours and will include a number of commonly used neuropsychological measures of for example, memory, reasoning, planning, organisation and problem solving skills.

You will also be asked to provide simple demographic information that will be used in the analysis of the study. This will include your age, gender, highest level of education, handedness (determined by the completion of a brief questionnaire), socioeconomic status and whether you are colour blind/wear glasses. You will also be asked if you have experienced concussion in the past.

All data obtained from your participation will be kept confidentially and will be identified by a study number rather than your name. Steps will be taken to ensure that you will not be able to be identified from the publication of any findings using this data.

If you wish to ask further details about the study please contact Laura Jane Hanley on ljh219@exeter.ac.uk

**Possible Disadvantages**
There are no harmful effects of testing except for the possibility of some mental fatigue. Some find the tests enjoyable and others may find them a little frustrating.

**Can I find out the test results?**
The results of the cognitive testing, which are a series of numbers, will not be routinely provided. However you are welcome to request a full debrief of the test results and if after this debrief you have any further questions, access to the Consultant Clinical Neuropsychologist can be arranged.

**What if there is a problem?**

In the unlikely event that the neuropsychological test results appear to indicate something potentially out of the ordinary, the results will be discussed with the Consultant Clinical Neuropsychologist involved in the study for a professional opinion. If further action is advisable you will be contacted, the results discussed with you and you will be advised to contact your GP. A letter will also be sent to your GP advising them of the results, their potential implication and the Consultant Clinical Neuropsychologist's recommendations.

If you wish to make a complaint about the way you have been treated in the study, or the way in which it was contacted conducted, you should in the first instance contact:

Dr Martin Bunnage, Consultant Clinical Neuropsychologist
Telephone: 0117 340 6522
Email martin.bunnage@nbt.nhs.uk
Post: Dr Martin Bunnage, Consultant Clinical Neuropsychologist, The Head Injury Therapy Unit, Frenchay Hospital, Bristol, BS16 1JB

You may also contact:

Professor Derek Jones
Telephone: +44 (0)29 2087 9412
Email: jonesd27@CARDIFF.AC.UK
Post: Professor Derek Jones CUBRIC, School of Psychology, Cardiff University, Park Place, Cardiff, CF10 3AT

**Ethical Approval**

The study has been approved by the School of Psychology's Ethics Committee at Cardiff University

**What do I do if I want to take part?**

If you would like to take part in the study, please contact Laura Jane Hanley on ljh219@exeter.ac.uk or at the Head Injury Therapy Unit on 01179186522

Thank you for your time,

Dr Laura Jane Hanley Supervised by Dr Martin Bunnage
Trainee Clinical Psychologist Consultant ClinicalNeuropsychologist

Professor Derek Jones
Director of MRI, CUBRIC

## APPENDIX H: CONTROL PARTICIPANT CONSENT FORM

Investigating the relationship between diffusion tensor imaging data and cognitive function

### Consent Form

1. I confirm that I have read and understood the information sheet dated 09-11-10 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason. ☐

3. I agree that results from the neuropsychological tests and demographic information will be used confidentially together with measures obtained from the DTI scan data I previously contributed to the CUBRIC control database and that the data will form a control dataset that will be used for comparison with other populations of people ☐

4. I understand that results of neuropsychological test results will not be routinely be provided. However I understand that I can request a full debrief if I have questions about my performance and have access to the Consultant Clinical Neuropsychologist if questions still remain. ☐

5. I agree that, in the unlikely event that findings of the cognitive testing indicate something potentially out of the ordinary the results will be discussed with a professional psychologist in order to obtain an opinion. If appropriate, I understand that I will be contacted to discuss the results, and advised to contact my GP. I agree that a letter will be sent to my GP with the results and the recommendations of the Consultant Clinical Neuropsychologist. ☐

6. I agree to take part in the above study ☐

| _____ | _____ | _____ |
|---|---|---|
| **Name of Participant** | **Date** | **Signature** |
| _____ | _____ | _____ |
| **Name of person taking Consent** | **Date** | **Signature** |

One copy to the participant, one copy to the researcher

## APPENDIX I: CONTROL PARTICIPANT DEBRIEF SHEET

Debrief for Study 09-11-10 (v1)

Investigating the Relationship between diffusion tensor imaging data and cognitive function

Thank you very much for taking parting the above study.

The study is a result of a collaboration between Professor Derek Jones of Cardiff University Brain Imaging Centre and Dr Martin Bunnage of the Head Injury Therapy Unit, North Bristol NHS Trust, and was conducted by Dr Laura Jane Hanley, a trainee Clinical Psychologist from Exeter University. The research is contributing to Dr Hanley's Doctorate in Clinical Psychology.

The study seeks to explore potential relationships between diffusion tensor imaging measures and those of cognitive function. Today you completed a number of tests that measures your cognitive skills such as visual and verbal memory, attention, problem solving, planning and organisation. We will compare the measures obtained from these cognitive tests (which are a series of numbers), with those derived from the Diffusion Tensor Imaging scan you previously contributed to the CUBRIC database, to explore whether there are any relationships between cognitive measures and DTI measures in white matter areas of the brain. This data wil form a control dataset that will be used in comparison with data from other populations of interest.

The cognitive testing data will be kept confidentially and will the cognitive data will not be stored with your name, only a study identification number. You can decide to withdraw from the study ay any time.

If you have further questions please contact the researcher:

Dr Laura Jane Hanley
ljh219@exeter.ac.uk, 01179186522

Supervised by:
Dr Martin Bunnage, Head Injury Therapy Unit, Frenchay Hospital, Bristol
Martin.Bunnage@nbt.nhs.uk, 01179186522

Professor Derek Jones, CUBRIC, Cardiff
Jonesd27@cardiff.ac.uk, 02920 879412

If you wish to make a complaint you may do so by Dr Bunnage or Professor Jones or the Psychology Ethics Committee Secretary at:

Email: psychethics@cf.ac.uk
Phone: +44 (0)29 208 74007
Fax: +44 (0)29 2087 4858
Post: Psychology Ethics Committee Secretary
Cardiff University Tower Building Park Place Cardiff CF10 3AT

## APPENDIX J: PATIENT PARTICIPANT CONFORM FORM

**THE BURDEN CENTRE for**
**Neuropsychiatry, Neuropsychology and Epileptology**
Frenchay Hospital,
Bristol BS16 1JB

North Bristol NHS Trust

**Department of Neuropsychology**
**Tel. 0117 340 2235 (Child)**
**0117 340 2290(Adult)**

Martin Bunnage
Simon Gerhand
Emma Hale
Helen Miller
Margaret Newson
Helen Thorburn
Ingram Wright HoD

### Consent Form

### Diffusion Tensor Imaging in Traumatic Brain Injury

Version **3.0**
Date **14/06/2010**

7. I confirm that I have read and understood the information sheet dated 06/10/2008 Version 2.0 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
8. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
9. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from CUBRIC, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
10. I agree to provide my contact details so that the researchers can organize my trip to the scanner in Cardiff and my GP and Consultant's details should the researcher need to inform them of any relevant findings from the scan. ☐
11. I agree to my GP being informed of my participation in the study. ☐
12. I agree that, in the unlikely event that some abnormality is discovered on the scan, Cardiff University staff can show the scan to qualified medical professionals in order to obtain a medical opinion. If appropriate, I agree that my GP and treating Consultant (if I have one) can be contacted in writing with the results of the MRI scan. ☐
13. **I agree that results of neuropsychological tests I have already completed at HITU can be used anonymously in the analysis of the study** ☐
14. I agree to take part in the above study ☐

_____ _____ _____
**Name of Participant** **Date** **Signature**

_____ _____ _____
**Name of person taking Consent** **Date** **Signature**

One copy to the participant, One copy to the researcher, One copy to the medical notes

**My Contact Details**

**Address:**_____

**Telephone number:** _____

**My GP's Details**

**Address:**_____

**Telephone number:** _____

**My Consultant's Details**

**Address:**_____

**Telephone number:** _____

## APPENDIX K: PATIENT INFORMATION SHEET

**THE BURDEN CENTRE for**
**Neuropsychiatry, Neuropsychology and Epileptology**
Frenchay Hospital,
Bristol BS16 1JB

North Bristol NHS Trust

**Department of Neuropsychology**
**Tel. 0117 340 2235 (Child)**
**0117 340**
**2290(Adult)**

**Patient Information Sheet**

**Diffusion Tensor Imaging in Traumatic Brain Injury**

Version **3.0 14/06/2010**

Martin Bunnage
Simon Gerhand
Emma Hale
Helen Miller
Margaret Newson
Helen Thorburn
Ingram Wright HoD

Dr Martin Bunnage, Consultant Clinical Neuropsychologist,
Clinical Lead of the Head Injury Therapy Unit, Department of Neuropsychology, Frenchay Hospital

Professor Derek Jones, Director of MRI, CUBRIC, Cardiff University

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully. Talk to others about the research if you wish. Feel free to ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. You ongoing treatment from the Head Injury Therapy Unit will in no way be affected by whatever decision you choose to make.

**Part 1**

**Purpose of the Research**
Traumatic Brain Injury (TBI) results in brain damage. The more severe the injury, usually the more severe the damage. More severe damage is usually associated with greater problems with daily living, i.e. problems with thinking skills, emotions, and physical function. Traditional Magnetic Resonance brain Imaging (MRI) does not capture very well the damage caused to the connections between brain cells and between different brain regions that can happen following traumatic brain injury. Diffusion Tensor Imaging (DTI) is a recent development within the field of MRI which is exquisitely sensitive to the types of changes that can happen following traumatic brain imaging. This information, it is hoped, will be useful in making more reliable predictions about the outcome from TBI.

**Why have I been invited?**
You have been invited because you have sustained a traumatic brain injury. If you choose to participate you will be one of approximately ten people who will be scanned using the state-of-the-art brain imaging facilities at Cardiff University.

**Do I have to Take Part?**
Simply put, NO, you do not have to take part. This is a research trial and is not part of your ongoing treatment from the Head Injury Therapy Unit. It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason.

**What will happen if I take part?**
If you agree to take part in this research study you will need to travel to CUBRIC which is part of Cardiff University, in Cardiff. You will only need to attend this facility once and you will need to be there for about two hours, with approximately 50 minutes of your time being spent within the MRI scanning machine itself.

The precise day and time for the scan will be decided at some future point. This will be a day that is mutually convenient for both you and for CUBRIC. Scans will only happen on weekdays and only during normal working hours, i.e. 9am – 5pm.

This scan is not part of routine clinical care and as such is over and above that which you would normally be asked to do as part of your care.

Once you arrive at CUBRIC you will be met by Dr Martin Bunnage and Professor Derek Jones. We will talk you through the procedures for the day and you will be asked to complete some questionnaires that relate to safety and MRI. The procedures for the brain scan will be explained to you and you will have the opportunity to ask any questions you may have. You will then be asked to consent to having the scan done.

For the scan itself you will be asked to lie in on your back inside the (MRI) scanner tube while images are acquired. The scanner can be noisy while acquiring images and so we will give you earplugs to wear and there will be additional padding placed against your ears. A pulse-oximeter (a device that looks a bit like a clothes-peg) will be placed on the finger to synchronize the acquisition of the images to your heart beat. You will be given a bulb to squeeze which will alert the operator to pause / stop the scan. There is an intercom fitted so that you and the operator can talk with each other. You need only stay as still as possible during. You will not be required to wear a special gown, but rather will need only to ensure that there are no large metal parts on your clothing. You can, if you want to, watch a subtitled movie while in the scanner. It is possible to have the scanning broken up in to separate chunks if you are unable to stay still for that long. All scans are completely non-invasive and do not employ ionizing radiation.

It may be that you are at CUBRIC at lunchtime, if this is the case money for lunch will be provided.

Once you have been scanned you will attend a de−briefing with Dr Martin Bunnage and the Head of Structural Imagining at the centre, Professor Derek Jones. Once you have been de-briefed and had the chance to ask any questions you may have you will be free to return to Bristol.

We would also like to use the results of the neuropsychological tests (e.g. tests of memory, attention and problem solving skills) that you will have completed at HITU. This is so that we can investigate whether the findings from the scan taken at CUBRIC are related to

thinking skills and mood. You will not need to take any more tests than the ones that you will have already completed as part of your routine treatment at HITU.

**Expenses and Payments**
We aim to ensure that nobody is 'out of pocket' by taking part in this research project. This means we will pay for your travel to and from CUBRIC and will pay for lunch if you are at CUBRIC over lunch. We will also pay for any other reasonable costs associated with your involvement with the research. Money will be reimbursed either on the day of you scan or later by post. You will need to bring a receipt for your expenses to allow us to reimburse you.

**What will I have to do?**
You will need to travel to CUBRIC in Cardiff and spend about two hours at the centre. While at the centre you will need to complete some paperwork and then undergo an MRI brain scan. This will involve spending about 50 minutes in the MRI machine keeping as still as you can.

You will need to provide Dr Martin Bunnage with your contact details and the contact details of your GP. We need this information in order to organise the scans and so that we can tell your GP of your involvement with the study.

**What are the possible disadvatages and risks of taking part?**
There is a small risk of anxiety and feelings of panic associated with being in the scanner, a risk that staff at the centre are very familiar with. If at any time you feel uncomfortable you are free to stop the scan and if you wish withdraw from the study.

There is a small risk that the MRI scan may identify a new medical issue, not already known to you and your doctor. Some such 'discoveries' have the potential to impact upon an individual's ability to obtain life insurance, for example if a brain tumour were identified. You need to consider this before agreeing to take part in the study

The study may require up to a day of your time, i.e. to get to Cardiff, to have the scan, to be de-briefed and then to return to Bristol. This schedule is potentially very tiring. In addition, for those of you with orthopaedic and physical injuries there is the potential for pain and discomfort associated with the travelling and being in the scanner. You need to consider whether you are able to cope with this potential discomfort prior to agreeing to take part in the study.

**What are the side effects of the DTI scan**
None known

**What are the possible benefits of taking part?**
This study will not help you particularly but it is hoped that the information we gather from this research will help us to better understand the kind of damage that can occur to the brain following traumatic brain injury.

**What if there is a problem?**
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Please see Part 2.

**Will my taking part in the study be kept confidential?**
Yes. We will; follow ethical and legal practice and all information about you will be handled in confidence. Please see Part 2.

**Part 2**

What if relevant new information becomes available?
Sometimes we get new information about the methods used in this research. If this happens Dr Martin Bunnage will contact you and discuss with you what this knew iformation means in relation to your continued participation in the study. If you decide not to carry on with the research Dr Bunnage will make arrangements to remove you from the study and will ensure this does not impact upon the care you receive from the Head Injury Therapy Unit.

**What will happen if I don't want to carry on with the study?**
You are free to withdrawal from the study at any time. If you do decide you no longer want to be involved with the research. We will keep your MRI data in an anonymous form for use in the analysis part of the study unless you ask us to destroy. If you ask us to we will destroy all of the data we have collected from your participation in the study.

**What if there is a problem?**
If you have a concern about any aspect of this study, you should ask to speak to Dr Martin Bunnage who will do his best to help answer your question. He is contactable in the following ways.

Telephone: 0117 340 2290
Email martin.bunnage@nbt.nhs.uk
Post Dr Martin Bunnage, Consultant Clinical Neuropsychologist, The Burden Centre, Frenchay Hospital, Bristol, BS16 1JB

If you remain unhappy and wish to make a formal complaint you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital on Tel 0117 9701212

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against North Bristol NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

**Will my taking part in this study be kept confidential?**
Personal addresses, postcodes and telephone numbers will be used in communicating research arrangements with you.

A record will be kept securely on Frenchay Hospital's computer system of each volunteer in the study and will be accessible to Dr Martin Bunnage. You will each be allocated a "study number" which will be used to identify you, rather than using your actual name. This helps to keep your personal information safe.

The outcome of the MRI analysis undertaken by CUBRIC will be transferred electronically between Professor Jones and Dr Bunnage in an anonymous form so that you can not be identified from the information transferred.

Draft manuscripts pertaining to the publication of the data derived from this study will be electronically transferred between Dr Bunnage and Professor Jones. These manuscripts will not contain any personal identifying information.

The actual imaging data will be pseudo-anonymised and include a study date, and stored securely on the password protected University computer network at CUBRIC. Any data that leaves CUBRIC will be fully anonymised.

The imaging data analysis will take place at CUBRIC and will be undertaken by Professor Derek Jones.

The overall study analysis will take place both at CUBRIC and at Frenchay Hospital by both Professor Derek Jones and by Dr Martin Bunnage.

Your data may be stored for use in future research. It may be stored for up to 10 years. If any future use is intended for your stored data an application to Frenchay Research Ethics Committee will be made to ensure this data is handled in an appropriate way. If you do not wish for us to store your data please inform us in writing at any time and we will delete/destroy all your data.

**Involvement of the General Practitioner / Family Doctor (GP)**
We intend to inform your GP if you agree to take part in this study. We will only be telling your GP that you are enrolled in the study. We will not be routinely sharing any information obtained from your scan. If, however, an unexpected abnormality is found on your scan we will inform your GP so that they can make appropriate follow up arrangements.

**What will happen to the results of the research study?**
It is intended that the outcome of this research is published either in a scientific journal or presented at a conference. The results will be anonymised and it will not be possible for anyone to be identified from these published results. If you are interested a copy of this published work can be obtained from Dr Martin Bunnage upon request.

**Who is organising and funding the research?**
This research is being funded by Professor Derek Jones from his funds at Cadiff University. Dr Martin Bunnage is not being paid to be involved in this research

**Who has reviewed the study?**
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Frenchay Research Ethics Committee.

Yours sincerely

**Dr Martin Bunnage** BSc(Hon) M.Psych (Neuro) PhD C.Psychol
Consultant Clinical Neuropsychologist
Honorary Lecturer University of Bristol

## APPENDIX L: PATIENT PARTICIPANT DEBRIEF SHEET


# MRI Debriefing Sheet

**Study title**
Diffusion Tensor Imaging in Traumatic Brain Injury

**Thanks**
Many thanks for taking part in this study. We hope it was interesting. Please feel free to ask the Researcher any questions you have about what happened.

Please note that some of the information contained on this form is a repeat of what might be found on the Volunteer Information Sheet, which you should already have and can keep.

**What was the purpose of the study?**
We are a group of scientists performing research using a medical imaging technique called magnetic resonance imaging (MRI). Our work involves developing new ways of using MRI to take pictures of the brain. We hope the methods we are developing will lead to new techniques to be used in medical diagnosis as well as research studies.

**What happens if you find something on the scan?**
Very occasionally, when we look at MRI data, unexpected potential abnormalities are discovered. We are not medical practitioners but once we have looked at the data in some detail, we may ask a Medical Consultant to examine the data, and if appropriate a report can be forwarded to your GP and treating consultant if you have one. The researchers involved do not have expertise in medical diagnosis, as they are not medical doctors. You should not regard this research scan as a medical screening procedure.

**Are the procedure and results confidential?**
All information which is collected about you during the course of this research will be kept strictly confidential. We may share the data we collect with researchers at other institutions, for example with the researchers at Frenchay Hospital, but any information which leaves the Cardiff University Brain Repair and Imaging Centre MRI suite will have your name and address removed so you cannot be recognised from it. Any information about your identity obtained from this research will be kept private. In any sort of report we might publish we will not include information that will make it possible for other people to know your name or identify you in any way.

**What will happen to the results of the research study?**
Where appropriate, the results of this study will be presented at medical and scientific conferences and published in journals. You will not be identified in any report or publication. The results of this study will also help us to design future research projects, and possibly lead
to new methods of diagnosis for neurological conditions.

**What do I do if I am unhappy with the way I was treated or with something that happened to me?**

In the first instance, you should contact Mrs Lisa Kennedy; Email: KennedyLC@cardiff.ac.uk Tel: +44 (0)29 2087 6912.

**Who has reviewed the study?**
This study has been reviewed and approved by the Frenchay Research Ethics Committee.
**Contact for Further Information**

Prof. Derek Jones, telephone 029 2087 9412, or e-mail jonesd27@cardiff.ac.uk

Dr Martin Bunnage, telephone 0117 340 2290, or e-mail martin.bunnage@nbt.nhs.uk

# APPENDIX M: INCLUSION AND EXCLUSION CRITERIA FOR PATIENT POPULATION – FROM NHS ETHICS FORM

INCLUSION CRITERIA

1. Suffered a traumatic brain injury, i.e. blow to the head associated with loss of consciousness and / or post traumatic amnesia of at least 5 minutes duration. This is necessary to ensure that the study examines appropriate cases.

2. Suffered a traumatic brain injury between 12 months and 24 months ago. This time frame is optimum time to 'see' the full damage associated with a traumatic brain injury. Too soon and one would not see all the damage that takes time to evolve and too late and the picture may be confounded by other factors that can potentially influence the appearance of the brain, e.g. chronic alcohol misuse or the chronic use of antiepileptic medications

3. Medically stable and independent in personal care. Necessary because of the 'outpatient' nature of the study and because CUBRIC is not set up for the study of patients and does not have medical staff at hand in case of medical emergency.

EXCLUSION CRITERIA

1. History of other neurological disease/disorder because these, by virtue of their ability to effect brain
structure and function, have the potential to significantly confound the results of a study attempting to quantify the effects of TBI on brain integrity.

2. History of chronic alcohol/substance misuse because this, by virtue of its ability to effect brain structure and function, has the potential to significantly confound the results of a study attempting to quantify the effects of TBI on brain integrity.

4. History of mental illness because this, by virtue of the possibility it reflects abnormal brain development / function, has the potential to significantly confound the results of a study attempting to quantify the effects of TBI on brain integrity.

5. Current alcohol/substance misuse because this will likely impact negatively upon the level of cooperation and reliability of a participant as well as potentially exposing the research staff and other participants to unnecessary risks.

6. Current severe mental illness because this will likely impact negatively upon the level of cooperation and reliability of a participant as well as potentially exposing the research staff and other participants to
unnecessary risks.

7. A diagnosis of epilepsy because this exposes the research staff to an avoidable potential medical risk.

8. A history or current problems with aggression and anger control as this exposes the research staff and participants to an unnecessary risk.

9. The CUBRIC screening requirements in relation to contraindications to undergoing MRI will also be applied e.g. metal implants

10. Inability to provide informed consent.

## APPENDIX N: BRIEF SUMMARY OF KEY FACTORS IN RESEARCH STRATEGY

### Recruitment of participants

Sample size of possible control participants: 31
Number of control participants eligible to take part: 24
Number of control participants invited: 24
Number of control participants consented to take part: 12
Number of control participants tested: 11 (1 did not meet exclusion criteria)

Sample size of possible clinical participants: approx 60 per year
Number of control participants eligible to take part: approx 12
Number of clinical participants invited: approx 8
Number of clinical participants consented: 4
Number of clinical participants scanned: 4

### Timeline of Data Collection and analysis

July 2010 – Cardiff ethics approval granted

August 2010 – NHS ethics approval complete

October 2010 – Exeter ethics approval granted

November 2010 - taught how to use software to analyse DTI scans

December 2010 – February 2011: Technical problem with software preventing transfer and analysis of all DTI scans already acquired (13/15 participants)

March 2011 – Continuing software problems preventing analysis as before

mid March 2011 – Participant recruitment complete for control neuropsychological testing and patient DTI scans

end March 2011- Identified differences in data acquisition that took place in preliminary study before present study. Consequently all anaylsis completed up to this date required reprocessing

mid April 2011 - Reprocessing of scans to ensure consistency (completed by Prof Jones)

April 2011 – Request for extension approved

May 2011 – Analysis of reprocessed and new scans to be complete

June 2011 - draft to supervisors

July 2011 – submission

## APPENDIX O: BRIEF SUMMARY OF SKILLS LEARNT FOR RESEARCH PROJECT

- Basic use of LINEX/UNIX software programs inc MATLAB
- Understanding of basic principles of Diffusion Tensor Imaging (1 full day + 1.5 hour workshop attended)
- Training in DTI analysis using deterministic tractography
- Use of Neuropsychological tests in research setting