Published in final edited form as:

Transl Neurosci. 2012 March 1; 3(1): 9–14. doi:10.2478/s13380-012-0003-3.

Diffuse Disconnectivity in tBi: a resting state fMRI and DTI study

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Abstract

Diffuse axonal injury is a common pathological consequence of Traumatic Brain Injury (TBI). Diffusion Tensor Imaging is an ideal technique to study white matter integrity using the Fractional Anisotropy (FA) index which is a measure of axonal integrity and coherence. There have been several reports showing reduced FA in individuals with TBI, which suggest demyelination or reduced fiber density in white matter tracts secondary to injury. Individuals with TBI are usually diagnosed with cognitive deficits such as reduced attention span, memory and executive function. In this study we sought to investigate correlations between brain functional networks, white matter integrity, and TBI severity in individuals with TBI ranging from mild to severe. A resting state functional magnetic resonance imaging protocol was used to study the default mode network in subjects at rest. FA values were decreased throughout all white matter tracts in the mild to severe TBI subjects. FA values were also negatively correlated with TBI injury severity ratings. The default mode network showed several brain regions in which connectivity measures were higher among individuals with TBI relative to control subjects. These findings suggest that, subsequent to TBI, the brain may undergo adaptation responses at the cellular level to compensate for functional impairment due to axonal injury.

Keywords

Traumatic Brain Injury (TBI); Functional magnetic resonance imaging (fMRI); DTI; Cognitive Function

1. introduction

The pathophysiology of Traumatic Brain Injury (TBI) is complex and not well understood. Imaging research has shown that the primary mechanisms of injury are bleeding and diffuse axonal injuries (DAI) [1-3]. Cognitive impairment including diminished attention, memory and executive function are observed in individuals with TBI with injuries at all severity levels [4-6]. Routine radiologic exams of people who suffered mild to moderate TBI do not always show positive readings that correlate with their cognitive impairments [7,8].

Abnormal white matter as well as gray matter has also been correlated with TBI severity. Using Diffusion Tensor Imaging (DTI), DAIs have been shown as multifocal hyperintensities on T2 weighted sequences as well as reduced Fractional Anisotropy (FA), a measure of white matter integrity [9]. Cognitive impairments have been correlated with reduced FA in white matter in several brain regions [10,11]. Functional imaging studies based on blood flow measures [12] have shown aberrant activation patterns in the attention and memory circuitry in individuals with TBI, with TBI subjects showing higher activity compared to control subjects [13-16]. These functional studies are consistent with the notion that reduced efficiency consequent to brain injury results in a need to recruit additional neuronal resources to accomplish a task [17,18]. One limitation of these task driven functional imaging studies is that differences in task performance among individuals with TBI and controls may confound the findings. Since most TBI subjects suffer from cognitive impairments, it can be difficult to determine whether imaging findings are attributable to differences in cognitive abilities, structural changes, or true functional differences. Resting state functional magnetic resonance imaging (fMRI) is an alternative functional imaging technique that circumvents this potential confound, as resting state sequences do not require the subject to perform any cognitive task while undergoing the fMRI scan [19-21]. To date there have been limited resting state studies in TBI, limited to case studies [22] or to a very small number of subjects [23].

Results from most of the imaging studies are consistent in demonstrating a global disconnect in the brains of TBI subjects. Given that TBI subjects have white matter abnormality and functional differences in brain activation studies, we sought to investigate gender effects in the correlates between structural connectivity and functional connectivity using DTI and resting state fMRI. In this study we have limited our TBI patient selection to those with mild to severe TBI and limited or no visible anatomical lesions based on assessments using conventional imaging protocols.

2. experimental Procedures

2.1 Subjects

Twelve subjects diagnosed with mild to severe TBI and eleven age- and gender-matched controls were recruited for this imaging study. Mean age was 39.82 (Controls=40.1, TBI=39.6). All participants were assessed using the Brain Injury Screening Questionnaire " (BISQ, Brain Injury Research Center of Mount Sinai School of Medicine 1997, 2001), the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI). The BISQ is a self report of cognitive, physical, and emotional symptoms, and the BDI is a self-reported measure of depression (Table 1). The BAI is a self-report measure of anxiety. Injury severity was classified using a 7-point scale ranging from 1 (No loss of consciousness, no confusion (i.e., no TBI)) to 7 (Loss of consciousness greater than 4 weeks in duration).

2.2 Imaging

All images were acquired on a Philips 3.0 T Achieva (Best, The Netherlands) scanner. A proton density/T2-weighted, dual echo sequence was used to screen for incidental pathology (TR = 2500 ms, TE = 10, 80 ms, FOV = 23.0 cm, FA = 90°, 36 axial slices, thickness = 3 mm, skip = 1 mm, Matrix size = 400 × 312). One fMRI rest scan was acquired using a field echo EPI sequence with the following parameters: TR = 2000 ms, TE = 27 ms, FOV = 21.0 cm, FA = 90°, 38 slices, skip = 0.8 mm, Matrix size = 88 × 86, 120 dynamics. A diffusion-weighted spin echo sequence was used to acquire the DTI image (TR = 5682 ms, TE = 70, FOV = 21.0 cm, FA = 90°, 54 axial slices, thickness = 2.5, no skip, matrix size = 104 × 106, *b*-factor = 1200 s/mm², 32 gradient directions plus *b*₀, 2 averages). A high resolution 3D T1-weighted structural image with good grey/ white matter differentiation was acquired

using a fast-field echo sequence for coregistration and normalization purposes (TR = 7.5 ms, TE = 3.4 ms, FOV = 22.0 cm, FA = 8°, 172 sagittal slices, thickness = 1 mm, no skip, Matrix size = 220 × 204 × 172). For the resting state fMRI we used a GE-EPI sequence with TR=2000ms, TE=27ms, 38 slices, thickness = 2.5mm, skip =0.8mm, FOV 20.8cm, Matrix size = 88×86, 120 time points for a total of 4 mins.

2.3 Data Analysis

2.3.1 Diffusion Tensor Imaging—Diffusion Tensor Images were eddy-current-corrected. FA and mean diffusivity maps (MD) were calculated using the FSL comprehensive library of analysis tools for brain imaging data (www.fmrib.ox.ac.uk/fsl). Exploratory whole brain group comparisons of the diffusion parameters were performed. First, FA images were spatially normalized to the International Consortium for Brain Mapping (ICBM) brain template using Tract Based Spatial Statistics (TBSS) [24]. The procedure involves a skeletonization of the FA images to obtain centers of white matter tracts. Voxel-wise statistics are performed only on the white matter skeleton in order to reduce the chance of type I errors due to imperfections in normalization. The parameters used to warp the FA images to the ICBM template and the white matter skeleton were applied to the MD images for statistical comparison. Randomize is an FSL routine for permutation based inference testing that was used for voxel-wise general linear modeling to test for group differences in FA and MD (separately). Clusters were identified using the TFCE (Threshold-Free Cluster Enhancement) that is optimized for permutation based inference testing of skeletonized images [25]. FA values of whole brain and several individual tracts were also extracted for further statistical analysis using Statistica V9 (Statsoft Inc., Tulsa, OK). In addition, the corpus callosum (CC) as visualized on a midsagittal slice was analyzed separately. In-house software developed in Matlab 2009 was used for tracing of the CC. Tracing was performed on an edge enhanced FA image using a Sobel filter. The average FA of the CC was calculated. T-tests were used to determine group differences in FA and self-reported depression, and correlational analyses were used to assess relationships between injury severity and outcomes among individuals with TBI.

2.4 Resting State Analysis

Preprocessing of the functional images was performed in FSL and included motion correction (MCFLIRT), coregistration to the high resolution T1 images (FLIRT) and non-linear registration to the standard Montreal Neurological Institute (MNI) template (FNIRT). Independent component analysis (ICA) was used to identify 18 unique networks of resting state activity using MELODIC [26] as implemented in FSL. The default mode network (DMN) consisting of the Anterior and Posterior Cingulate Cortex (ACC & PCC) and the bilateral parietal cortices (PC) has been consistently reported before by other studies [19-21]. The DMN was identified for each subject and z-statistic images were extracted and entered higher-level analyses. General linear modeling and permutation-based inference testing (RANDOMISE) were used to test for group differences and symptom correlates of the default mode network.

3. Results

3.1 DTI

Whole brain group comparisons using TBSS showed diffuse reduction of fractional anisotropy throughout the brain in subjects with TBI (Figure 1a). Whole brain TBSS derived mean FA showed reduced FA in TBI compared to the control group ($p=0.009$). MD values were increased in mild to severe TBI subjects ($p=0.004$). Voxel by voxel correlation analysis of the TBSS FA data showed significant differences in most white matter areas between TBI and control subjects (Figure 1b). Whole brain TBSS derived mean FA in TBI was

significantly correlated with injury severity ($r=-0.774$, $p=0.005$, age corrected). Whole brain MD values were positively correlated with TBI severity scores ($r=0.638$, $p=0.035$, age corrected).

Region of Interest analysis (Figure 2a) of the mid-sagittal corpus callosum showed that the TBI group has significantly reduced FA in the mid-cross sectional area of the corpus callosum (HC:580.3, TBI:495.9, $t=2.990$, $p=0.007$). After age correction, mean FA of mid-sagittal corpus callosum was significantly correlated with severity scores ($r=-0.7630$, $p=0.006$) (Figure 2b). Age corrected whole brain FA as well as mean FA in the corpus callosum was correlated with self-reported depression as measured by the Beck Depression Inventory ($r=-0.585$, $p=0.005$) and ($r=-0.514$, $p=0.017$) respectively. FA was not correlated with self-reported anxiety as measured by the Beck Anxiety Inventory.

3.2 Resting state fMRI

Group maps showed the default mode network spanning the brain regions that are consistent with the literature. Voxel by voxel comparison between TBI and control cases showed significant differences in connectivity with the TBI group showing a higher z-score than controls in the frontal, left parietal and superior temporal regions of the default mode network (Figure 3). Correlation analysis of the DMN networks did not render any significant findings.

4. Discussion

Our DTI data demonstrated very convincingly a significant structural disconnection in the TBI subjects group but not in the healthy control group. This is consistent with what has been reported in the literature [1,10,27,28]. We used both a region of interest approach focused on the corpus callosum as well as a technique that assesses the whole brain (TBSS). These results were consistent for the two approaches we used in the data analysis, showing diffuse reduction of FA throughout the brain. This structural disconnection measured by FA throughout the majority of the white matter tracts was also correlated with TBI severity measure, suggesting a relationship between initial severity of injury and subsequent white matter damage. Consistent with the FA maps, voxel by voxel TBSS based MD measurements showed diffuse increases in MD in the white matter regions among TBI subjects (images not shown), possibly suggesting that demyelization or axonal shrinkage may occur in response to TBI.

The significant correlation of FA with self-reported depression is also consistent with previous reports of abnormal white matter in patients with late life depression [29,30]. It is not unreasonable to assume that the trauma experienced by the individuals with TBI has both psychological as well as pathological (white matter damage) consequences that lead to depressive symptoms.

Previous resting state fMRI studies in clinical populations show reduced functional connectivity in the DMN. Decreased DMN connectivity has been reported in various psychiatric disorders, including Alzheimer's disease [31,32], schizophrenia [33] and autism [34]. Our resting state fMRI analysis showed an increase in connectivity in various regions of the DMN in the mild to severe TBI patient population. This can be explained by the efficiency model as follows. The connectivity measures represent signaling between the different components (brain regions) of the network. The communication between the different regions of the DMN is supported by the underlying axonal bundles. When the axonal bundles are defective, as shown in our DTI results, signaling efficiency will be reduced. The resulting diffuse connectivity and inefficient networks that form over time represent a form of *functional compensation* [18,35,36], though this compensation requires

the neurons to work harder to accomplish the same task. Disruption of these signaling pathways will cause both direct as well as feedback signals to be weakened, leading to hyperactivity in the signaling neurons. The previously mentioned reports of decreased connectivity studied in patients with disorders such as schizophrenia and autism may have genetic or developmental origins where the axonal wiring is already dysfunctional at the time of diagnosis. The patient population in our study consisted of mild to severe TBI cases. We hypothesize that in this population, signaling axonal bundles were not completely destroyed by the shearing forces of the injury, but some axons are still intact and are able to provide connectivity albeit less efficiently. Indeed, one recent Alzheimer's study showed that during the early phase of the disease the anterior and ventral systems are more connected than matched controls, but as the disease progresses this increase eventually also deteriorates [37]. An earlier study on patients characterized by amnesic mild cognitive impairment (MCI) compared with healthy controls showed increased connectivity in the prefrontal as well as medial temporal regions; these are the same regions where we found increased activity [38]. Although we detected a significant correlation between FA and TBI severity, we did not find any significant differences in any of the DMN regions as a function of TBI severity. In summary, in this study we showed a relation between white matter damage and the functional disconnection in the DMN. We suggest that the damage to the axonal bundles leads to aberrant functional connectivity, which is also reflected by cognitive impairment and possibly provides novel targeted therapies in TBI. Our studies for the first time suggest that the TBI brain may undergo adaptation responses at the cellular level over time to compensate for functional impairment due axonal injury. The studies support further translational studies by providing a potential mechanism through which novel therapeutic approaches could be developed to facilitate compensatory responses in subjects with mild to severe TBI.

Acknowledgments

The study was supported by discretionary funding to GMP and Grant Number #UL1RR029887, National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). The authors would also like to thank the Image Analysis Core of the Mount Sinai Translational and Molecular Imaging Institute.

List of abbreviations

ACC	Anterior Cingulate Cortex
BDI	Beck Depression Inventory
BISQ	Brain Injury Screening Questionnaire
CC	Corpus Callosum
DAI	Diffusion Axonal Injuries
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
fMRI	Functional Magnetic Resonance Imaging
ICA	Independent Component Analysis
ICBM	International Consortium for Brain Mapping
MCI	Mild Cognitive Impairment
MD	Mean Diffusivity Maps

MNI	Montreal Neurological Institute
PC	Parietal Cortices
PCC	Posterior Cingulate Cortex
TBI	Traumatic Brain Injury
TBSS	Tract Based Spatial Statistics
TFCE	Threshold-Free Cluster Enhancement

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Figure 1.

(a) FA comparisons between control and mild to moderate TBI subjects using voxel by voxel TBSS analysis ($p < 0.05$). Yellow: Control $>$ mild to moderate TBI. (b) Correlation analysis of FA and severity scores using voxel by voxel TBSS results in mild to moderate TBI subjects ($p < 0.05$). Blue: significant negative correlations between FA and severity.

Figure 2.
 (a) Sobel filtered sagittal MRI illustrating outline of mid-sagittal corpus callosum. (b)
 Correlation analysis of FA in mid-sagittal corpus callosum and severity.

Figure 3. Group Default Mode Network illustrated in green superimposed on anatomical MRI. Significant differences between mild to moderate TBI and Control subjects illustrated in red (mild to moderate TBI>Control) and blue (Control>mild to moderate TBI). Bottom: Close up of 3 representative axial planes.

Table 1

Neuropsych assessment for mild to moderateTBI subjects.

Clinical Assessment	Mean Control	Mean TBI	t-value	df	p	n controls	n TBI
BDI	1.60	12.67	-3.42	20	0.0027	10	12
BAI	1.64	6.5	-2.69	21	0.0137	11	12
Severity	1	4.54	-	-	-	11	12