The (Eigen)Value of Diffusion Tensor Imaging to Investigate Depression After Traumatic Brain Injury

Jerome J. Maller,^{1*} Richard H.S. Thomson,¹ Kerstin Pannek,²
Stephen E. Rose,³ Neil Bailey,¹ Philip M. Lewis,⁴ and Paul B. Fitzgerald¹

¹Monash Alfred Psychiatry Research Centre, The Alfred & Monash University School of Psychology and Psychiatry, Melbourne, Victoria, Australia

²The University of Queensland, Centre for Advanced Imaging, Centre for Clinical Research, School of Medicine, Brisbane, Queensland, Australia

³Centre for Magnetic Resonance, Centre for Clinical Research, Centre for Medical Diagnostic Technologies in Queensland University of Queensland, Brisbane, Queensland, Australia

⁴Department of Neurosurgery, Alfred Hospital, Melbourne, Victoria, Australia

Abstract: *Background:* Many people with a traumatic brain injury (TBI), even mild to moderate, will develop major depression (MD). Recent studies of patients with MD suggest reduced fractional anisotropy (FA) in dorsolateral prefrontal cortex (DLPFC), temporal lobe tracts, midline, and capsule regions. Some of these pathways have also been found to have reduced FA in patients with TBI. It is unknown whether the pathways implicated in MD after TBI are similar to those with MD without TBI. This study sought to investigate whether there were specific pathways unique to TBI patients who develop MD. *Methods:* A sample of TBI-MD subjects ($N = 14$), TBI-no-MD subjects ($N = 12$), MD-no-TBI ($N = 26$), and control subjects (no TBI or MD, $N = 23$), using a strict measurement protocol underwent psychiatric assessments and diffusion tensor brain Magnetic Resonance Imaging (MRI). *Results:* The findings of this study indicate that (1) TBI patients who develop MD have reduced axial diffusivity in DLPFC, corpus callosum (CC), and nucleus accumbens white matter tracts compared to TBI patients who do not develop MD and (2) MD patients without a history of TBI have reduced FA along the CC. We also found that more severe MD relates to altered radial diffusivity. *Conclusions:* These findings suggest that compromise to specific white matter pathways, including both axonal and myelination aspects, after a mild TBI underlie the susceptibility of these patients developing MD. *Hum Brain Mapp* 35:227–237, 2014. © 2012 Wiley Periodicals, Inc.

Key words: depression; magnetic resonance imaging; diffusion; dorsolateral prefrontal cortex; longitudinal fasciculus; white matter

INTRODUCTION

Previous volumetric investigations of patients with major depression (MD) have revealed smaller volumes compared with controls in areas such as the hippocampus,

frontal lobe, and corpus callosum [CC; Geuze et al., 2005; Lacerda et al., 2005; Maller et al., 2007]. Similar regions have also been found to be reduced in volume in patients who have sustained a mild to moderate traumatic brain

*Correspondence to: Jerome J. Maller, Monash Alfred Psychiatry Research Centre, The Alfred & Monash University School of Psychology and Psychiatry, Melbourne Victoria, Australia. Level 1—Old Baker Building PO Box 315 Prahran 3181, Commercial Road Melbourne, Victoria, Australia. E-mail: j.maller@alfred.org.au

Received for publication 5 October 2011; Revised 21 June 2012; Accepted 10 July 2012

DOI: 10.1002/hbm.22171

Published online 24 September 2012 in Wiley Online Library (wileyonlinelibrary.com).

injury (TBI), as a result of the impact of the brain against the inside of the skull which leads to stretching and thinning of the white matter, often referred to as diffuse axonal injury [DAI; Beauchamp et al., 2009; Tasker et al., 2005]. Mild TBI (mTBI) cases constitute ~ 85% of reported TBI cases [Bazarian et al., 2005]. Although this finding is not always consistent, it may be the result of studies potentially being confounded by age, sex, and other demographic factors as well as heterogeneous protocols developed for estimating volumetric values [von Gunten et al., 2000]. This could also result from not taking into account behavioral conditions such as MD which has been reported in up to 77% of patients post-TBI [Alderfer et al., 2005; Gordon et al., 2006; Jorge, 2005; Silver et al., 2009]. The few volumetric studies that have considered post-TBI MD have found reduced volume in prefrontal and temporal structures such as the dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex, cingulate gyrus, and hippocampus [e.g., Chen et al., 2008; Hudak et al., 2011; Jorge et al., 2004], when compared with TBI-no-MD or controls.

Diffusion tensor imaging [DTI; Basser et al., 1994] is a technique that is more sensitive to axonal damage than conventional structural MR imaging [Kennedy et al., 2009; Provenzale, 2011]. White matter integrity can be assessed using the fractional anisotropy (FA) index, a value between 0 and 1 with higher value indicating greater anisotropy and hence white matter integrity. We recently reviewed the literature of published articles reporting FA values in samples of patients with TBI or MD [Maller et al., 2011] and found no studies that used DTI to investigate depression post-TBI, although there were some common brain regions identified between the TBI/DTI and MD/DTI studies, including fronto-temporal connections, CC, right parietal lobe, and structures contained within the basal ganglia. The internal capsule was commonly reported to have significantly reduced FA.

During processing of diffusion tensor magnetic Resonance Imaging (MRI) data we estimate a tensor, D , that inherently contains intravoxel structural and dynamic information [Basser et al., 1994]. The eigenvalues of D are the diffusion coefficients in these orthotropic directions. Of the three eigenvalues (λ) measured by the DTI technique, the principal eigenvalue λ_1 (also referred to as axial or parallel diffusivity) is thought to relate more to axonal morphology and degradation rather than myelin injury, which relates more to radial diffusivity [average of the second and third eigenvalues; Li et al., 2011; Song et al., 2002]. As MD outcomes of TBI are currently thought of as system-diseases, rather than limited to a single region of interest, it is sensible to investigate white matter integrity in this population on a whole-brain basis. Therefore, we sought to use a consistent imaging protocol and FA and eigenvalues estimation procedure in a sample of subjects with mTBI who developed MD, subjects with mTBI who did not develop MD, subjects with MD with no history of TBI, and controls with no history of

MD or TBI, to examine whether regions of different FA and diffusivity values are consistent with our review.

Our specific aims and hypotheses were

1. To investigate whether there is a specific relationship between changes in structural and functional integrity and the presence of post-TBI depression (Hypothesis 1: Patients with post-TBI depression will display significantly reduced anisotropy in prefrontal cortical-sub cortical white matter tracts compared with patients post-TBI who have no depression);
2. To investigate whether changes in structural and functional integrity are specific to post-TBI depression (Hypothesis 2: Patients with post-TBI depression will display significantly reduced anisotropy in prefrontal cortical-sub cortical white matter tracts compared with patients with depression not related to TBI);
3. To explore the structural and functional integrity specific to depression without TBI (Hypothesis 3: Patients with depression not related to TBI will display significantly reduced anisotropy in prefrontal cortical - sub cortical white matter tracts compared to healthy controls with no history of TBI or depression); and
4. To explore the functional implications of changes in integrity (Hypothesis 4: There will be a correlation between anisotropy in prefrontal cortical-sub cortical white matter tracts and depressive symptoms in patients with post-TBI depression).

MATERIALS AND METHODS

Subjects

A total of 78 subjects were recruited. 26 patients with MD without a history of TBI (MD-no-TBI), 15 patients with a history of mTBI who developed MD (TBI-MD), 12 patients with a history of mTBI who did not develop MD (TBI-no-MD), and 25 controls were included in this study. All participants underwent psychiatric and MRI assessments (Table I). Patients were recruited through public notices and through the clinical services of the Alfred Hospital, Melbourne, Victoria and were required to have no history of pre-TBI depression and TBI-MD patients were required to have developed MD between 6 weeks and 12 months post-TBI. All subjects with TBI were required to have a Glasgow Coma Scale score of 13 or 14 on ambulance arrival at the accident scene. Loss of consciousness among mTBI subjects ranged from 15 min to 2 h, and post-traumatic amnesia ranged from 10 min to 48 h, according to formal hospital records. One TBI patient had a very large head whose whole brain could not fit into the MRI field of view, hence their data were excluded from analyses (reducing the number of TBI-MD subjects to 14). Another TBI participant had a low volume subarachnoid hemorrhage over the left parietal lobe. Their data were included as their white matter skeleton registered well during the TBSS

TABLE I. Demographics of the four groups included in the DTI analyses

Variable	Group			
	TBI-MD	TBI-no-MD	MD-no-TBI	Control
Number (M:F)	14 (6:8)	12 (10:2)	26 (17:9)	23 (9:14)
Age mean (SD)	48.00 (9.92)	33.08 (12.69)	44.08 (12.99)	38.35 (13.00)
MADRS mean (SD)	28.77 (7.68)	2.25 (2.38)	32.27 (4.11)	N/A
	Range: 16–43	Range: 0–6	Range: 25–39	

MADRS, Montgomery–Åsberg Depression Rating Scale; MD, major depression; N/A, not applicable; TBI, traumatic brain injury.

preprocessing steps with no misalignments in the region of the hemorrhage. No participants had destructive white matter lesions on FLAIR images. All patients underwent CT scanning in the acute phase with all but one patient having a negative finding (as described above).

Twenty-five controls were recruited from notices and word of mouth. Two control scans were discarded due to incidental abnormalities, hence total control sample size was 23 (nine males). All MD patients (the MD only and TBI-MDD groups) were required to have a diagnosis of major depressive disorders made by a treating psychiatrist and confirmed with the Mini-International Neuropsychiatric Interview [MINI; Sheehan et al., 1998] and a score of at least 16 on the Montgomery–Åsberg Depression Rating Scale [MADRS; Montgomery and Åsberg, 1979]. Exclusion criteria for controls included a current or previous DSM-IV [SCID; First et al., 2001] axis I diagnoses, current active medical problem, and subjects were required to have no known neurological disease or a contraindication to MRI scanning. In addition, control subjects were required to have no history of psychiatric illness. All subjects provided written informed consent on a form approved by the Alfred Human Subjects Research and Ethics Committee.

Image Acquisition

A 1.5 T GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI) was used to acquire contiguous AC-PC aligned sagittal SPGR T1-weighted sequence (TR = 100, TE = 450, matrix size = 224×224 , NEX = 1, slice thickness = 1.4 mm), following a T2-FLAIR. A diffusion-based sequence was then acquired (slice thickness = 3 mm, in-plane resolution = 0.90 mm^2 , TR/TE = 17 s/86.6 ms, b value = $1,000 \text{ mm}^2/\text{s}$ along 12 noncollinear directions, and two images at $b = 0$, NEX = 1). All scan files were deidentified so that FA and eigenvalue analyses occurred blind to subject group.

Image Processing and Analysis

Diffusion-weighted images were corrected for eddy current distortions using tools provided with FMRIB's Diffusion Toolbox (FDT, part of FMRIB Software Library FSL; [Smith et al., 2004]; <http://www.fmrib.ox.ac.uk/fsl>; ver-

sion 4.1). The diffusion tensor, its three eigenvalues, and FA images were then calculated using FSL. Voxel-wise analysis was performed using TBSS [Smith et al., 2006].

All participants' FA images were registered nonlinearly to FMRIB's FA template (supplied with FSL). The results of this registration step were visually checked for accuracy for each participant. Using the average of all participants' registered FA images, an FA "skeleton" was generated which best represents the centers of all white matter tracts common to all participants' brains [Smith et al., 2006]. An FA threshold of 0.2 was applied to the resulting skeleton. Each participant's aligned FA and eigenvalue images were then projected onto this common FA skeleton. The resulting images were analyzed using the permutation-based non-parametric statistical technique "randomize" [Nichols and Holmes, 2002]. A total of 5,000 random permutations were applied for each analysis. Differences between groups were assessed using a two-tailed test. P -values are reported at the 0.05 significance level, corrected for multiple comparisons using threshold-free cluster enhancement [Nichols and Holmes, 2002]. Analysis of radial eigenvalues ($\lambda_2/3$) will identify anatomical locations within white matter tracts where there is increased diffusion of water perpendicular to the principal axonal direction (λ_1); such a measure may better highlight axonal injury within white matter pathways.

In TBI patients who developed MD, the white matter pathways that significantly correlated with a clinical measure of the MD severity (MADRS score) were identified. This offers an alternative approach for identifying the affected white matter pathways that relate to the development of MD after TBI. Hence, a regression analysis was performed, correlating diffusivity measures with the severity of depression using age as a confounding regressor. To assist with localization of white matter tracts for all TBSS analyses, the MRI Atlas of Human White Matter [Mori et al., 2005] was consulted.

Statistical Analysis of Demographic Data

All demographic data were statistically analyzed using SPSS for Windows version 19.0 (SPSS, Chicago, IL). Analyses were two-tailed and evaluated for significance at the 0.05 alpha level. Simple t -tests and analysis of variance (ANOVA) were used to compare demographics between groups.

Figure 1.

Voxels in red-yellow represent those which have significantly reduced radial diffusivity at $P = 0.05$ (corrected) in TBI compared with controls. The six slices are coronal with their positions represented by Y co-ordinates (MNI space) and white lines in the midsagittal slice (right side of figure). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

RESULTS

Demographics

There were more males in the MD-no-TBI and TBI-no-MD groups ($P = 0.04$). The ANOVA revealed a significant difference between the mean age of subjects in the TBI-MD and TBI-no-MD groups ($P = 0.035$), therefore age was covaried for in the TBSS analysis between these two groups. Time since injury varied from 6 weeks to 10 years. The number of medications that each MD subject was taking was between three and eight, and length of depression ranged from 1 year to 50 years. Preliminary TBSS analyses of medications (number) and length of depression (years) demonstrated that these two variables were not related to FA or its constituents.

TBSS Differences in FA and Eigenvalues

All TBI vs. controls

An exploration of the differences in diffusivity between all TBI subjects ($N = 26$) and controls ($N = 23$) was first performed to determine whether this patient population was consistent with previous DTI mTBI research. Although reduced FA in the TBI sample was not statistically significant ($P = 0.10$, corrected), radial diffusivity was greater in the TBI sample at the $P = 0.05$ level (corrected) across widespread areas including the CC, bilateral PFC, superior longitudinal fasciculi, and right internal capsule (Fig. 1).

TBI-MD vs. TBI-no-MD

We identified a decrease in axial diffusivity ($P < 0.007$) in the bilateral DLPFCs, anterior CC, right nucleus accum-

bens, right internal capsule, right inferior and superior longitudinal fasciculi, and brainstem for TBI-MD patients compared with TBI-no-MD patients (Fig. 2 and Table II). This indicates that there is widespread white matter damage unique to the development of MD after a TBI. FA and radial diffusivity did not differ significantly between groups.

TBI-MD vs. MD-no-TBI

We found no significant differences between TBI-MD and MD-no-TBI. There were reductions in FA in the MD-TBI group compared with the MD-no-TBI group, although these differences between groups did not reach significance at the 0.05 level for the corrected analyses. No trends were found for non-FA values.

MD-no-TBI vs. controls

To statistically match MD-no-TBI and control groups by age and sex, 26 MD-no-TBI and 22 control subjects were compared. MD-no-TBI subjects had significant ($P < 0.05$) reduction in FA values along the anterior and midbody of the CC (Fig. 3) in this corrected TBSS analysis. There was a significant increase ($P < 0.05$) in λ_2 located only along the CC and right SLF, and a trend toward increased radial diffusivity in these two regions at $P = 0.09$. No trends were found for the other diffusion metrics under investigation.

Depression severity and DTI

In an exploration of the functional implications of changes in integrity among the 14 patients those who developed MD post-TBI, TBSS showed that radial

Figure 2.

Reduced axial diffusivity voxels (red-yellow) at $P = 0.007$ (corrected) in those with post-TBI MD compared with TBI-no-MD. Numbers represent Y co-ordinates. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

diffusivity was significantly correlated with MADRS scores ($P < 0.05$) along the CC, bilateral nucleus accumbens, bilateral internal capsule, bilateral cingulate gyri, superior longitudinal fasciculi, and brainstem. At a significance level of $P = 0.028$ (corrected) the λ_3 TBSS analysis showed voxels along these same white matter pathways (Fig. 4). Although the corrected analyses for axial diffusivity, λ_2 , and mean diffusivity did not reach significance, they all

suggested a trend of voxels of reduced values being located along only the CC.

DISCUSSIONS

This study is the first to investigate the development of MD after mild traumatic brain injury (mTBI) using DTI. It

TABLE II. Regions of different FA and non-FA values as identified by TBSS

Region	TBI-MD vs. TBI (no-MD)		MD (no-TBI) vs. TBI-MD	MD (no-TBI) vs. controls			MADRS (TBI-MD)		Analysis frequency	Frequency order
	FA ^a	Axial ^b	Axial ^c	FA ^b	λ_2^b	Radial ^d	λ_3^b	Radial ^b		
PFC (R)		*	*						2	3
PFC (L)		*							1	4
Cing (R)			*				*	*	2	3
Cing (L)							*	*	1	4
CC		*		*	*	*	*	*	3	2
IC (R)		*	*				*	*	3	2
Nucl Acc (R)		*					*	*	2	3
Nucl Acc (L)		*							1	4
SLF (R)	*	*	*		*	*	*	*	4	1
SLF (L)							*	*	1	4
ILF (R)		*							1	4
Brainstem		*					*	*	2	3

“*” denotes that the region had significantly different values as identified by TBSS between the two groups compared.

^a $P = 0.14$ (corrected).

^b $P < 0.05$ (corrected).

^c $P = 0.17$ (corrected).

^d $P = 0.09$ (corrected).

CC, corpus callosum; FA, fractional anisotropy; IC, internal capsule; ILF, inferior longitudinal fasciculus; L, left; λ , eigenvalue; MD, major depression; Mean Diff, mean diffusivity; Nucl Acc, nucleus accumbens; PFC, prefrontal cortex; R, right; SLF, superior longitudinal fasciculus; TBI, traumatic brain injury; Axial, axial diffusivity; Radial, radial diffusivity.

Figure 3.

TBSS results of MD ($N = 26$) compared against controls ($N = 22$) at $P = 0.05$ (corrected). **A:** FA and **B:** λ_2 . Numbers represent Y co-ordinates. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

reports the finding of reduced FA and axial diffusivity values in the CC (specifically the anterior aspect) and right superior longitudinal fasciculus in MD patients without a history of TBI and further reduced FA in this region and bilateral PFCs in those who developed MD after a TBI.

Furthermore, significantly increased λ_3 was seen along white matter pathways directly related to regions implicated in fronto-temporal models of MD and consistent with those elucidated from our recent review [Maller et al., 2011].

Figure 4.

TBSS corrected analyses of correlations between MADRS scores in patients with post-TBI MD and radial diffusivity ($P = 0.05$, corrected). The top row of coronal slices from posterior (left of screen) to anterior (right of screen) and midsagittal slice, illustrates the locations of voxels (red-yellow) which were significant in this analysis. The three-dimensional rendering of this set of

significant voxels from an anterior-dorsal perspective is presented on the left of the figure, and on the right is a representation of those voxels from a right-side dorso-lateral perspective. Numbers represent Y co-ordinates. A = anterior; P = posterior; I = inferior; S = superior. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Consistent with previous mTBI research, there were a number of regions with reduced white matter integrity in subjects with mTBI, when compared with those without a history of TBI (or MD), including the prefrontal cortices and midline tracts. To investigate Aim 1 (whether there is a specific relationship between changes in structural and functional integrity and the presence of post-TBI depression), post-TBI MD and TBI participants with no depressive syndrome were initially studied. Significant microstructural changes in the frontal-parietal and fronto-temporal white matter tracts were investigated by the voxelwise comparison of FA and non-FA measures between the two groups. In an exploration of Aims 2 and 3 (to investigate whether changes in structural and functional integrity are specific to post-TBI depression, and to investigate the structural and functional integrity specific to depression without TBI), we found that those with MD-no-TBI had widespread reduction in FA (and axial diffusivity), mostly along the same tracts identified in the TBSS analysis between TBI-MD and TBI-no-MD.

Depression is common after a TBI [Silver et al., 2009]. Hudak et al. [2011] recently reported depressive symptoms in post-TBI patients to significantly correlate with volumetrics of three brain regions (left rostral anterior cingulate and bilateral orbitofrontal cortex); regions reported by previous studies of volumetric assessment in patients with depression post-TBI [Chen et al., 2008; Jorge, 2005; Jorge et al., 2004] include the PFC, DLPFC, hippocampus, and anterior cingulate. As these areas have also been implicated by a number of studies linking depression not related to TBI (reviewed by Koolschijn et al. [2009]), they support a common link between spontaneous and non-spontaneous (e.g., post-TBI) MD models; that is, involvement of fronto-limbic pathways. However, structure size does not necessarily reflect underlying function or integrity [e.g. Foster et al., 1999]. Hence, this study is the first to investigate post-TBI MD in the context of function by using measures of diffusion as biomarkers. We found reduced FA and axial diffusivity among similar regions to those reported from volumetric studies, but we also found reduced anisotropy in the CC, an area commonly reported as reduced in MD patients and TBI patients. The right inferior and superior longitudinal fasciculi were also implicated in the TBSS results, which is consistent with other studies which have found similar regions, and only on the right, to have reduced FA and/or axial diffusivity in MD or post-TBI in human and animal models [e.g., Kinnunen et al., 2011; Li et al., 2011]. More importantly, we found FA in post-TBI MD, when compared with post-TBI without MD, was most reduced (as supported by the axial diffusivity reduction and MD difference) in two of the most widely-reported regions reported as relevant to the development of MD, which are the CC and DLPFCs. The CC has been reported in many publications as reduced in size among post-TBI patients [Bigler and Maxwell, 2011] and MD patients without a history of TBI [Maller et al., 2011]. Furthermore, we found the internal capsule and nucleus

accumbens to have significantly reduced axial diffusivity in TBI-MD when compared against TBI-no-MD. This is supported by a main analysis which also found MD severity to significantly relate to radial diffusivity of the internal capsule and nucleus accumbens. These are important findings as they are consistent with DTI studies in deep brain stimulation (DBS) MD patients in which the nucleus accumbens (via the internal capsule) is often the target of the electrodes. [Gutman et al., 2009] showed with DTI that the targets for DBS when used to treat depression have distinct and widespread projections to frontal and temporal poles as well as the cingulate, thalamus, hypothalamus, nucleus accumbens, and brainstem, which was also implicated in our TBSS results; these are regions implicated in antidepressant response mechanisms [Airan et al., 2007; Schlaepfer et al., 2008; Tanis et al., 2007]. Very similar tracts were identified as having reduced FA in a separate study of MD subjects [Zou et al., 2008] which reported reduced FA restricted to the internal capsule (and parietal region). This is relevant because DBS is used for MD only in patients whose MD is highly treatment-resistant (i.e., nonresponsive to medication, electroconvulsive therapy, and often other forms of neurostimulation as well). That we found this region to be of reduced integrity in those who develop MD after TBI, and related to the severity of their MD, is consistent with the anecdotal findings of these patients' MD often being treatment-resistant.

The final set of analyses found that diffusivity values were related to MD severity in regions reported by the literature in other groups of MD patients, as recently reviewed [Maller et al., 2011]. Specifically, the CC, medial frontal gyri, nucleus accumbens, cingulate bundles, internal capsules, brainstem, and longitudinal fasciculi (Table II). These are among the majority of regions identified in fronto-temporal models of MD. Importantly, the radial diffusivity values were implicated. This finding could suggest an issue relating to myelination rather than axonal integrity, which could in turn suggest that a degenerative process in addition to DAI is the precursor for the development of MD after mTBI. Although it is difficult to speculate about whether increased radial diffusivity relates to DAI or a myelination problem, DAI probably leads to Wallerian degeneration of multiple neural circuits, which will involve cortical degeneration (atrophy) at some stage.

The decrease in FA and axial diffusivity along the right superior longitudinal fasciculus in subjects with MD post-TBI relative to TBI patients who did not develop MD, as well as in those with MD (no TBI) compared with matched controls (with no history of MD or TBI) is consistent with the literature. For example, the low FA regions reported in a DTI study of post-TBI patients [Salmond et al., 2006] are very similar to those found in a study of patients with first-episode treatment-naïve MD [Ma et al., 2007] and from a group of patients with first-episode remitted depression [Yuan et al., 2007], which include the right parietal lobe and right frontal gyri. Furthermore, Alexopoulos et al. [2008] found similar regions to have

reduced FA in a group of MD patients who did not achieve remission.

That axial and radial diffusivity analyses showed higher significance levels suggest that compared with FA, they are more sensitive markers of DAI. It is also consistent with rat studies [e.g., Li et al., 2011; Song et al., 2002] which tracked the changes in FA and its eigenvalue constituents from the acute phase to months afterward validated by histological investigation such as optical immunochemical staining. The group differences in TBI-MD vs. TBI-no-MD were in axial diffusivity, whereas MD severity was significantly related to radial diffusivity. Collectively, these results suggest that MD is related to both types of reduced white matter integrity, i.e., from both radial and axial perspectives.

Although the underpinnings of the difference(s) between lambda 2 and lambda 3 are currently unexplored, the results of our study and others [e.g., Thomalla et al., 2004] which report such examples of where only one of the two constituents of radial diffusivity is significant whilst the other is not, suggest that lambda 2 and 3 have different meanings, i.e., they do not represent identical aspects of radial diffusivity. We also performed separate lambda 2 and lambda 3 analyses to investigate whether radial diffusivity per se was related to TBI and/or depression, hence to accomplish this aim comprehensively we analyzed not only the radial diffusivity conglomerate but its constituents as well. That is, we wanted to investigate whether either of its constituents was significant even if the conglomerate was not. Our results suggest that lambda 2 and 3 are not simple reflections of one another, but rather, tell different parts of the radial diffusivity story, which may be found in future research to represent quite distinct aspects of FA which may represent discrete white matter damage and/or are the basis for targeted treatment and therapy.

TBSS is a widely used program specifically designed to compare groups on a voxel-by-voxel basis for differences in FA and its constituents. The program's authors suggest that it should not be used on scans of brains that have sustained major damage as the white matter skeletons of those patients may not align accurately with that of the template. This study was consistent with this advice as only one of our patients had a positive CT finding which was very minor, superficial, and distal to white matter, hence unlikely to influence the white matter skeleton registrations (this was confirmed by visual checks for accurate registration of each subject's white matter skeleton before group analyses proceeded).

Chronic primary or secondary dysfunction in dopaminergic, noradrenergic, and serotonergic systems seem to be relatively common consequences of TBI [Arciniegas and Silver, 2006; McAllister et al., 2006]. It is well established that these systems are also compromised in MD patients [Bennett, 2010; Drevets et al., 2000; Muller et al., 2011; Wagner et al., 2010]. In humans, MD is a common sequelae of TBI [Bombardier et al., 2010], even when mild [Ryan and Warden, 2003]. The symptom overlap between MD and the

common "post concussion syndrome" is substantial [Bryant, 2008; Hoge et al., 2008]. Furthermore, there is evidence that late-life MD can be precipitated by accumulated small silent cerebral infarctions that appear as white matter hyperintensities on MRI scans [Alexopoulos et al., 1997; Sheline et al., 2010; Thomas et al., 2002]. The overlap between brain regions implicated in traumatic and nontraumatic MD is discussed in a recent comprehensive review by Wager-Smith and Markou [2011]. The authors propose stress-induced "microdamage" to the brain as a putative trigger for subsequent cellular repair and neuroinflammation leading to symptoms of depression. In susceptible individuals, impaired cellular repair mechanisms may lead to a chronic cycle of neuroinflammation, presenting as persistent depression. As examples, they offer some preliminary studies in experimental animals, which have noted that depressive-like behaviors follow traumatic or ischemic brain injury, although the studies are not well controlled for confounds [Kato et al., 2000; Milman et al., 2005; Pandey et al., 2009; Shapira et al., 2007]. Moreover, they describe previous findings of reduced hippocampal volume in depression, for which there is evidence the degree of volume loss is related to the number of depressive episodes experienced. This again supports the theory that volume loss, secondary to stress-induced cellular damage, precipitates depressive symptoms. This general hypothesis fits well with our findings, wherein we describe reduced FA (indicating neuronal damage) in CC, DLPFC, and basal ganglia in both the TBI-MD and MD-no-TBI groups alike.

It is notable that there was some predominance of right-sided changes in the depression analyses. The implication of right-sided involvement in depression post-TBI is consistent with much of the existing MRI and EEG depression literature. For EEG, depression is associated with a shift toward greater right than left activity, consistent with findings for unpleasant emotion [Herrington et al., 2010]. It was recently reported that in subjects at high-risk for developing depression, alpha power correlated inversely with cortical thickness particularly over the right posterior region [Bruder et al., 2012] and another group [Shankman et al., 2011] recently found relatively lower right posterior alpha activity in patients with melancholic depression. In general, alpha power is found to be reduced and fMRI activation more right-lateralized in patients with depression [Gordon et al., 2010; Saletu et al., 2010] depression. That is, there is often left hemisphere underactivation at rest and right hemisphere overactivation during tasks. In an fMRI study, for example, Garrett et al. [2011] found patients with MD to show hyperactivation in the right temporoparietal region associated with orienting to unexpected stimuli. Heller's [1993] model of emotion processing predicts that depression would be related to greater right than left frontal neural activity, combined with low levels of right temporo-parietal activity. In the context of structural MRI, a reduction of right hippocampal-entorhinal cortex volume with voxel-based morphometry in patients with depression is often reported [e.g., Ahdidan et al., 2011; Bell-McGinty et al., 2002] and

relative to the left hemisphere, depressed individuals have smaller right-parietal viable brain volumes than nondepressed individuals [Schonberger et al., 2011]. In general, there seems to be something specific about right-sided changes and the development of depression post-TBI, and although less likely, it is possible that developing depression leads to greater right-sided dysfunction. Only a study examining subjects before and after a TBI can suitably address this question.

A limitation of this study is that the time since injury was very broad; previous research indicates FA is most reduced during the acute post-TBI phase, hence, it is possible that patients whose TBI was more recent had the most reduced white matter integrity along the tracts revealed to have reduced white matter integrity, when compared with subjects without MD. Longitudinal research is required to understand how these pathways are affected over time and whether deficits accumulate or ameliorate over time. As TBI subjects were recruited and not prospectively retained, there must be unevenness in data collection with regards to day-of-injury clinical information. It is possible that 48 h of truly documented post-traumatic amnesia would not be a mild TBI, but move it into the moderate range. Likewise, loss of consciousness of greater than 1 h, for some would move the injury into the moderate category. Depending on how many these clinical features apply to, there may need to be a modification in using the mild TBI moniker in follow-up studies of these patients. It is likely, however, that the use of more homogeneous groups in terms of the mechanism of injury would produce clearer or more consistent results. Finally, without longitudinal data, it is difficult to make a cause and effect judgment as to the relationship between white matter changes and symptoms. Injury related loss of white matter integrity may cause depression. However, it is also possible that the development of a depressive illness, through other mechanisms, may result in reduced intercortical connectivity which over time reduces white matter integrity. This study enrolled a greater portion of women in the TBI-MD than the TBI-no-MD, and although there is a higher incidence of depression in women, the gender difference was not addressed as this was beyond the scope of the study's aims. This is an area which we aim to address in future investigations.

Although this study focused on MD, other psychiatric disturbances have also been related to TBI. For example, Hart et al. [2011] reported minor depression and MD to each be present in approximately a quarter of their TBI patients ($N = 1,570$), and [Koponen et al., 2011] recently reported both Axis I and II psychiatric disorders to be common among patients with TBI. Our future investigations will consider this.

CONCLUSION

Previous DTI studies of TBI patients (whether TBSS or other techniques were applied) have not considered the

degree of depression among their samples, hence, this is the first study to attempt an investigation of the development of MD after TBI in the context of anisotropy. Consistent with a recent review, we have shown in mild TBI patients that the development of MD is related to compromised FA and axial and radial diffusivity in the prefrontal, CC, cingulate, internal capsule, and parietal regions, supporting models of MD without TBI. Reduced integrity in these regions may therefore be a biomarker for the development of MD post-TBI. Future studies should address this important issue.

ACKNOWLEDGMENTS

The authors thank all the patients and volunteers who agreed to participate in this study, Research Nurses at the Monash Alfred Psychiatry Research Centre, and the staff of the MRI facility at the Alfred Hospital, Melbourne, Victoria.

REFERENCES

- Ahdidan J, Hviid LB, Chakravarty MM, Ravnkilde B, Rosenberg R, Rodell A, Stodkilde-Jorgensen H, Videbech P (2011): Longitudinal MR study of brain structure and hippocampus volume in major depressive disorder. *Acta Psychiatr Scand* 123:211–219.
- Airan RD, Meltzer LA, Roy M, Gong Y, Chen H, Deisseroth K (2007): High-speed imaging reveals neurophysiological links to behavior in an animal model of depression. *Science* 317:819–823.
- Alderfer BS, Arciniegas DB, Silver JM (2005): Treatment of depression following traumatic brain injury. *J Head Trauma Rehabil* 20:544–562.
- Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M (1997): "Vascular depression" hypothesis. *Arch Gen Psychiatr* 54:915–922.
- Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S, Lim KO, Hoptman MJ (2008): Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatr* 165:238–244.
- Arciniegas DB, Silver JM (2006): Pharmacotherapy of posttraumatic cognitive impairments. *Behav Neurol* 17:25–42.
- Basser PJ, Mattiello J, LeBihan D (1994): MR diffusion tensor spectroscopy and imaging. *Biophys J* 66:259–267.
- Bazarian JJ, McClung J, Shah MN, Cheng YT, Flesher W, Kraus J (2005): Mild traumatic brain injury in the United States, 1998–2000. *Brain Inj* 19:85–91.
- Beauchamp MH, Anderson VA, Catroppa C, Maller JJ, Godfrey C, Rosenfeld JV, Kean M (2009): Implications of reduced callosal area for social skills after severe traumatic brain injury in children. *J Neurotrauma* 26:1645–1654.
- Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds CF III, Becker JT. (2002): Brain morphometric abnormalities in geriatric depression: Long-term neurobiological effects of illness duration. *Am J Psychiatr* 159:1424–1427.
- Bennett MR (2010): Synapse regression in depression: The role of 5-HT receptors in modulating NMDA receptor function and synaptic plasticity. *Aust NZ J Psychiatr* 44:301–308.
- Bigler ED, Maxwell WL (2011): Neuroimaging and neuropathology of TBI. *NeuroRehabilitation* 28:63–74.

- Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS (2010): Rates of major depressive disorder and clinical outcomes following traumatic brain injury. *JAMA* 303:1938–1945.
- Bruder GE, Bansal R, Tenke CE, Liu J, Hao X, Warner V, Peterson BS, Weissman MM (2012): Relationship of resting EEG with anatomical MRI measures in individuals at high and low risk for depression. *Hum Brain Mapp* 33:1325–1333.
- Bryant RA (2008): Disentangling mild traumatic brain injury and stress reactions. *N Engl J Med* 358:525–527.
- Chen JK, Johnston KM, Petrides M, Pitto A (2008): Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. *Arch Gen Psychiatr* 65:81–89.
- Drevets WC, Frank E, Price JC, Kupfer DJ, Greer PJ, Mathis C (2000): Serotonin type-1A receptor imaging in depression. *Nucl Med Biol* 27:499–507.
- First MB, Spritzer RL, Gibbon M (2001): Structured Clinical Interview for DSM-IV-TR Axis 1 Disorders-Research Version. New York: NY State Psychiatric Institute.
- Foster JK, Meikle A, Goodson G, Mayes AR, Howard M, Sunram SL, Cezayirli E, Roberts N (1999): The hippocampus and delayed recall: Bigger is not necessarily better? *Memory* 7: 715–732.
- Garrett A, Kelly R, Gomez R, Keller J, Schatzberg AF, Reiss AL (2011): Aberrant brain activation during a working memory task in psychotic major depression. *Am J Psychiatr* 168:173–182.
- Geuze E, Vermetten E, Bremner JD (2005): MR-based in vivo hippocampal volumetrics: 1. Review of methodologies currently employed. *Mol Psychiatr* 10:147–159.
- Gordon E, Palmer DM, Cooper N (2010): EEG alpha asymmetry in schizophrenia, depression, PTSD, panic disorder, ADHD and conduct disorder. *Clin EEG Neurosci* 41:178–183.
- Gordon WA, Zafonte R, Cicerone K, Cantor J, Brown M, Lombard L, Goldsmith R, Chandna T (2006): Traumatic brain injury rehabilitation: State of the science. *Am J Phys Med Rehabil* 85:343–382.
- Gutman DA, Holtzheimer PE, Behrens TE, Johansen-Berg H, Mayberg HS (2009): A tractography analysis of two deep brain stimulation white matter targets for depression. *Biol Psychiatr* 65:276–282.
- Hart T, Brenner L, Clark AN, Bogner JA, Novack TA, Chervoneva I, Nakase-Richardson R, Arango-Lasprilla JC (2011): Major and minor depression after traumatic brain injury. *Arch Phys Med Rehabil* 92:1211–1219.
- Heller W (1993): Neuropsychological mechanisms of individual differences in emotion, personality, and arousal. *Neuropsychology* 7:746–789.
- Herrington JD, Heller W, Mohanty A, Engels AS, Banich MT, Webb AG, Miller GA (2010): Localization of asymmetric brain function in emotion and depression. *Psychophysiology* 47: 442–454.
- Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA (2008): Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* 358:453–463.
- Hudak A, Warner M, Marquez de la Plata C, Moore C, Harper C, Diaz-Arrastia R (2011): Brain morphometry changes and depressive symptoms after traumatic brain injury. *Psychiatr Res* 191:160–165.
- Jorge RE (2005): Neuropsychiatric consequences of traumatic brain injury: A review of recent findings. *Curr Opin Psychiatr* 18:289–299.
- Jorge RE, Robinson RG, Moser D, Tateno A, Crespo-Facorro B, Arndt S (2004): Major depression following traumatic brain injury. *Arch Gen Psychiatr* 61:42–50.
- Kato N, Isomura Y, Tanaka T (2000): Intracellular calcium releases facilitate induction of long-term depression. *Neuropharmacology* 39:1107–1110.
- Kennedy MR, Wozniak JR, Muetzel RL, Mueller BA, Chiou HH, Pantekoe K, Lim KO (2009): White matter and neurocognitive changes in adults with chronic traumatic brain injury. *J Int Neuropsychol Soc* 15:130–136.
- Kinnunen KM, Greenwood R, Powell JH, Leech R, Hawkins PC, Bonnelle V, Patel MC, Counsell SJ, Sharp DJ (2011): White matter damage and cognitive impairment after traumatic brain injury. *Brain* 134(Pt 2):449–463.
- Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS (2009): Brain volume abnormalities in major depressive disorder: A meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp* 30:3719–3735.
- Koponen S, Taiminen T, Hiekkanen H, Tenovu O (2011): Axis I and II psychiatric disorders in patients with traumatic brain injury: A 12-month follow-up study. *Brain Inj* 25:1029–1034.
- Lacerda AL, Brambilla P, Sassi RB, Nicoletti MA, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2005): Anatomical MRI study of corpus callosum in unipolar depression. *J Psychiatr Res* 39:347–354.
- Li J, Li XY, Feng DF, Gu L (2011): Quantitative evaluation of microscopic injury with diffusion tensor imaging in a rat model of diffuse axonal injury. *Eur J Neurosci* 33:933–945.
- Ma N, Li L, Shu N, Liu J, Gong G, He Z, Li Z, Tan L, Stone WS, Zhang Z, Xu L, Jiang T (2007): White matter abnormalities in first-episode, treatment-naïve young adults with major depressive disorder. *Am J Psychiatr* 164:823–826.
- Maller JJ, Daskalakis ZJ, Fitzgerald PB (2007): Hippocampal volumetrics in depression: The importance of the posterior tail. *Hippocampus* 17:1023–1027.
- Maller JJ, Thomson RH, Lewis PM, Rose SE, Pannek K, Fitzgerald PB (2011): Traumatic brain injury, major depression, and diffusion tensor imaging: Making connections. *Brain Res Rev* 64:213–240.
- McAllister TW, Flashman LA, McDonald BC, Saykin AJ (2006): Mechanisms of working memory dysfunction after mild and moderate TBI: Evidence from functional MRI and neurogenetics. *J Neurotrauma* 23:1450–1467.
- Milman A, Rosenberg A, Weizman R, Pick CG (2005): Mild traumatic brain injury induces persistent cognitive deficits and behavioral disturbances in mice. *J Neurotrauma* 22:1003–1010.
- Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatr* 134:382–389.
- Mori S, Wakana S, Nagae-Poetscher LM, van Zijl PC (2005): MRI Atlas of Human White Matter. Amsterdam, The Netherlands: Elsevier.
- Muller N, Myint AM, Schwarz MJ (2011): Inflammatory biomarkers and depression. *Neurotox Res* 19:308–318.
- Nichols TE, Holmes AP (2002): Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Hum Brain Mapp* 15:1–25.
- Pandey DK, Yadav SK, Mahesh R, Rajkumar R (2009): Depression-like and anxiety-like behavioural aftermaths of impact accelerated traumatic brain injury in rats: A model of comorbid depression and anxiety? *Behav Brain Res* 205:436–442.
- Provenzale JM (2011): Imaging of traumatic brain injury: A review of the recent medical literature. *AJR Am J Roentgenol* 194:16–19.

- Ryan LM, Warden DL (2003): Post concussion syndrome. *Int Rev Psychiatr* 15:310–316.
- Saletu B, Anderer P, Saletu-Zyhlarz GM (2010): EEG topography and tomography (LORETA) in diagnosis and pharmacotherapy of depression. *Clin EEG Neurosci* 41:203–210.
- Salmond CH, Menon DK, Chatfield DA, Williams GB, Pena A, Sahakian BJ, Pickard JD (2006): Diffusion tensor imaging in chronic head injury survivors: Correlations with learning and memory indices. *Neuroimage* 29:117–124.
- Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodessa D, Axmacher N, Joe AY, Kreft M, Lenartz D, Sturm V (2008): Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33:368–377.
- Schonberger M, Ponsford J, Reutens D, Beare R, Clarke D, O'Sullivan R (2011): The relationship between mood disorders and MRI findings following traumatic brain injury. *Brain Inj* 25:543–550.
- Shankman SA, Sarapas C, Klein DN (2011): The effect of pre- vs. post-reward attainment on EEG asymmetry in melancholic depression. *Int J Psychophysiol* 79:287–295.
- Shapira M, Licht A, Milman A, Pick CG, Shohami E, Eldar-Finkelman H (2007): Role of glycogen synthase kinase-3 β in early depressive behavior induced by mild traumatic brain injury. *Mol Cell Neurosci* 34:571–577.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatr* 59(Suppl 20):22–33; quiz 34–57.
- Sheline YI, Pieper CF, Barch DM, Welsh-Bohmer K, McKinsty RC, MacFall JR, D'Angelo G, Garcia KS, Gersing K, Wilkins C, Taylor W, Steffens DC, Krishnan RR, Doraiswamy PM (2010): Support for the vascular depression hypothesis in late-life depression: Results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatr* 67:277–285.
- Silver JM, McAllister TW, Arciniegas DB (2009): Depression and cognitive complaints following mild traumatic brain injury. *Am J Psychiatr* 166:653–661.
- Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004): Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* 23(Suppl 1):S208–S219.
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE (2006): Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31:1487–1505.
- Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002): Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17:1429–1436.
- Tanis KQ, Newton SS, Duman RS (2007): Targeting neurotrophic/growth factor expression and signaling for antidepressant drug development. *CNS Neurol Disord Drug Targets* 6:151–160.
- Tasker RC, Salmond CH, Westland AG, Pena A, Gillard JH, Sahakian BJ, Pickard JD (2005): Head circumference and brain and hippocampal volume after severe traumatic brain injury in childhood. *Pediatr Res* 58:302–308.
- Thomas AJ, Perry R, Barber R, Kalaria RN, O'Brien JT (2002): Pathologies and pathological mechanisms for white matter hyperintensities in depression. *Ann NY Acad Sci* 977:333–339.
- Thomalla G, Glauche V, Koch MA, Beaulieu C, Weiller C, Röther J (2004): Diffusion tensor imaging detects early Wallerian degeneration of the pyramidal tract after ischemic stroke. *Neuroimage* 22:1767–1774.
- von Gunten A, Fox NC, Cipolotti L, Ron MA (2000): A volumetric study of hippocampus and amygdala in depressed patients with subjective memory problems. *J Neuropsychiatr Clin Neurosci* 12:493–498.
- Wager-Smith K, Markou A (2011): Depression: A repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition? *Neurosci Biobehav Rev* 35:742–764.
- Wagner G, Koch K, Schachtzabel C, Sobanski T, Reichenbach JR, Sauer H, Schlosser RG (2010): Differential effects of serotonergic and noradrenergic antidepressants on brain activity during a cognitive control task and neurofunctional prediction of treatment outcome in patients with depression. *J Psychiatr Neurosci* 35:247–257.
- Yuan Y, Zhang Z, Bai F, Yu H, Shi Y, Qian Y, Zang Y, Zhu C, Liu W, You J (2007): White matter integrity of the whole brain is disrupted in first-episode remitted geriatric depression. *Neuroreport* 18:1845–1849.
- Zou K, Huang X, Li T, Gong Q, Li Z, Ou-Yang L, Deng W, Chen Q, Li C, Ding Y, Sun X (2008): Alterations of white matter integrity in adults with major depressive disorder: A magnetic resonance imaging study. *J Psychiatr Neurosci* 33:525–530.