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BRAIN RESEARCH REVIEWS

Review

Traumatic brain injury, major depression, and diffusion tensor imaging: Making connections☆

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ABSTRACT

It is common for depression to develop after traumatic brain injury (TBI), yet despite poorer recovery, there is a lack in our understanding of whether post-TBI brain changes involved in depression are akin to those in people with depression without TBI. Modern neuroimaging has helped recognize degrees of diffuse axonal injury (DAI) as being related to extent of TBI, but its ability to predict long-term functioning is limited and has not been considered in the context of post-TBI depression. A more recent brain imaging technique (diffusion tensor imaging; DTI) can measure the integrity of white matter by measuring the directionality or *anisotropy* of water molecule diffusion along the axons of nerve fibers. *Aim:* To review DTI results in the TBI and depression literatures to determine whether this can elucidate the etiology of the development of depression after TBI. *Method:* We reviewed the TBI/DTI (40 articles) and depression/DTI literatures (17 articles). No articles were found that used DTI to investigate depression post-TBI, although there were some common brain regions identified between the TBI/DTI and depression/DTI studies, including frontotemporal, corpus callosum, and structures contained within the basal ganglia. Specifically, the internal capsule was commonly reported to have significantly reduced fractional anisotropy, which agrees with deep brain stimulation studies. *Conclusion:* It is suggested that measuring the degree of DAI by utilizing DTI in those with or without depression post-TBI, will greatly enhance prediction of functional outcome.

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Contents

1. Introduction

The famous case of Phineas Gage in 1868 was the first to clearly illustrate that behavior and emotion can change after traumatic brain injury (TBI) (Harlow, 1868). Major depressive disorder (MDD) is common in the subacute aftermath of mild TBI and exerts a deleterious effect on psychosocial function and certain indices of cognition (Fann, 1997; Feinstein, 2006; Jorge et al., 2004). Posttraumatic behavioral disorders (including hyperactivity, agitation, mood swings, irritability, excitation, and lack of inhibition, hostility, and distrust) constitute major problems with respect to the management, rehabilitation, and social and family reintegration of these patients (Guetin et al., 2009). Although there is a decreased probability of having an Axis I diagnosis many years after a TBI (Ashman et al., 2004), it is not uncommon for a state of disability and/or hardship involving the entire familial nucleus to persist (Inzaghi et al., 2005).

Depression and diminished life satisfaction among survivors of traumatic brain injury (TBI) are persistent problems that require the close attention of medical and rehabilitation professionals (2003). In Victoria, Australia, nearly half of the approximately 73,000 people who have experienced TBI need personal assistance or supervision (Snaith and Zigmond, 1994). In the United States, direct and indirect costs of TBI exceed $80 billion annually (NDC, 2003). The reported frequency of major depression post-TBI is variable (Whelan-Goodinson et al., 2009), but may be present in up to 77% of patients (Alfano, 2006; Ashman et al., 2004; Deb et al., 1999; Fann et al., 1995; Fedoroff et al., 1992; Hibbard et al., 1998; Holsinger et al., 2002; Jorge et al., 1993a, 1993b, 2004; Jorge and Starkstein, 2005; Koponen et al., 2002; Kraus and Sorenson, 1994; Pagulayan et al., 2008; van Reekum et al., 2000) and, along with related anxiety disorders, is associated with poorer recovery (Gordon et al., 2006; Jorge and Starkstein, 2005).

Contributing factors to these complications in recovery is that conceptualization and potential treatment of post-TBI depression is not well understood. The evidence for a benefit of 'standard' antidepressant strategies in post-TBI patients is underwhelming (Gordon et al., 2006), suggesting that these depressive syndromes are not simply the result of a 'typical' depressive response to a significant life stressor. Of reported TBI cases, approximately 85% are classified as mild TBI (Bazarian et al., 2005). Hence, mild TBI is one of the most common causes for admission to trauma centers (Ucar et al., 2006). Even in "mild" cases where there is generally no fracture of the skull, associated loss of consciousness, or amnesia, TBI often leads to a variety of physical, emotional, and cognitive difficulties (Duncan et al., 2005; Kraus et al., 2005). Up to 30% of mild TBI patients will suffer permanent sequelae of their injury and up to 20% will be unable to return to work (Nolin and Heroux, 2006). Suicide rates are also higher post-TBI than in the general population (Fleminger et al., 2003). Across the broader TBI population, there does not appear to be a significant relationship between Glasgow Coma Scale (GCS) scores, duration of post-traumatic amnesia (PTA), ongoing cognitive functioning, and the degree of post-TBI depression. Post-TBI depression is therefore not just related to injury severity. These observations suggest a strong likelihood of a specific pattern in brain changes that may result from TBI leading to substantially higher risk of subsequent development of depression.

Just over a decade has now passed since the 1998 National Institutes of Health (NIH) consensus conference, which identified a lack of scientifically rigorous TBI research and areas of important TBI research that remained largely

unexplored. For example, while major depression is the most common and hence the most studied psychiatric disorder after TBI (Koponen et al., 2002; Pagulayan et al., 2008), it has not been often approached from a neuroimaging perspective (Koponen et al., 2006). Unfortunately, there is a lack of quality studies examining psychiatric consequences of TBI and potential related brain changes (Gordon et al., 2006). While there is a consensus that underlying the brain changes is a compromise of neural tissue referred to as diffuse axonal injury (DAI), this can be subtle and difficult to detect. The aim of this paper is to review the post-TBI and depression literatures in the context of MRI, specifically focusing on studies that have applied an advanced neuroimaging acquisition sequence (diffusion tensor imaging) which can evaluate white matter (WM) integrity as an indicator of DAI by measuring water movement and restriction ("anisotropy"). By studying anisotropy maps in detail, neural models and networks can be elucidated so that links between depression and post-TBI brain changes may be evaluated.

1.1. *TBI mechanisms and gross imaging findings*

Traumatic brain injury commonly results from a simple blow to the head, or in biomechanical terms, a rapid 'linear deceleration.' In such a scenario, the brain strikes the inside surface of the skull at the point of impact. Conventional wisdom proposes that the brain then subsequently rebounds to collide with the opposite side of the skull, producing what is called the 'contre-coup' injury (Ommaya and Gennarelli, 1974). Some authors have disputed this theory, however, suggesting that cavitation effects due to rapid deceleration (Courville, 1942) or the relative movement of brain tissue against skull bone (Shatsky et al., 1974) are responsible for this secondary injury to the brain tissue. Nonetheless, a simple linear head-strike, although common, represents the minority of primary brain injuries, and it is rare that an impact is purely linear or for that matter rotational (King et al., 2003). When an injury involves rapid rotation of the head, the tissues of the brain and brainstem are placed under significant shear stress. In fact, in the early 1940s, it was proposed that angular rather than linear acceleration of the head would result in more serious brain injuries (Holbourne, 1943). Using the 'bowl of porridge' analogy, it is easy to visualize how rotational shearing might result in severe tissue damage.

Bayly et al. (2005) provided a comprehensive description of the temporal order of mechanical forces during TBI and reported clear deformation of brain matter due to occipital deceleration in humans during mild, rapid deceleration of the head, with notable compression in frontal regions and stretching in posterior regions. It is this more diffuse, microstructural damage resulting from physical deformation of brain tissue that constitutes the pathophysiological entity known as DAI.

In animal models, it has been shown that mild neurotrauma that neither breaks the dura mater nor produces a widespread hematoma is expected to produce little or no neuropathology in the hippocampus and other brain regions (Baldwin et al., 1996), when compared with the damage associated with severe TBI (Chen et al., 2003). Variation in the involvement of cortex and in the degree of hippocampal damage reported for fluid percussion models is likely to be related to severity and lateralization of injury (Floyd et al., 2002; Grady et al., 2003; Obenaus et al., 2007; Thompson et al., 2005).

In the acute phase, imaging findings can often provide insights into the mechanism of injury. Purely focal traumatic lesions such as extradural and subdural hematomas not only pinpoint the site of injury but also suggest that the injury may have arisen due to more linear acceleration without significant rotational component (King et al., 2003). DAI is typically associated with more subtle changes that simple computerized tomography (CT) scans (the first-line imaging modality in assessing TBI; Lee et al., 2008) are frequently unable to detect (Jenkins et al., 1986; Mittl et al., 1994). MRI will often demonstrate lesions at the grey matter (GM) white matter (WM) junction, with additional hemorrhagic lesions occurring in the corpus callosum (CC), rostral brainstem, and basal ganglia as the severity of injury increases (Alsop et al., 1996; Arfanakis et al., 2002; Assaf et al., 1999; Barzo et al., 1997; Han et al., 2007; Hanstock et al., 1994; Ito et al., 1996; Marmarou et al., 2000; Miles et al., 2008; Sidaros et al., 2008; Takayama et al., 2000; Teasdale and Hadley, 2005; Vorisek et al., 2002; Xu et al., 2007; Yasokawa et al., 2007). The CC, which is the largest collection of commissural fibers in the brain, is especially vulnerable to TBI because of its unique location (Gorrie et al., 2001). Not all types of the brain cells are equally vulnerable; the most susceptible cellular components are axons and the most resistant structures are blood vessels (Besenski, 2002). A comprehensive review of the neurophysiology of brain injury is presented in Gaetz (2004), although an understanding of many aspects of the mechanisms of TBI is still lacking (Ragnarsson, 2006).

Neuroimaging-based volumetric studies, the number of which has grown exponentially since the 1980s (Gordon et al., 2006), have provided many useful insights into alterations in brain functioning post TBI. Both human and animal TBI studies have shown reduced brain volumes, either as total or its primary constituents (GM and WM) or as specifically vulnerable regions of interest (ROIs). Frontal, temporal (hippocampus, amygdala, and parahippocampal gyrus), and occipital regions (e.g., Anderson and Bigler, 1994; Ariza et al., 2006; Bayly et al., 2005; Bendlin et al., 2008; Bigler et al., 1997; Ducreux et al., 2005; Gale et al., 2005; Hicks et al., 1993; Kotapka et al., 1991; Levine, 2006; Maxwell et al., 2003; Tate and Bigler, 2000; Tomaiuolo et al., 2004; Wilde et al., 2005). For example, reduced right hippocampal volume after childhood TBI is a common finding (Di Stefano et al., 2000; Tasker et al., 2005; Tomaiuolo et al., 2004). An altered CC shape or reduced cross-sectional area is also a common finding among TBI survivors (e.g., Beauchamp et al., 2008; Strich, 1970; Tomaiuolo et al., 2004). From a neuropsychological standpoint, reductions in volumes have been related to reduced cognitive performance, particularly attention and memory (e.g., Bigler et al., 1997; Bigler, 2001; Ewing-Cobbs et al., 2006; Gale et al., 1995, 2005; Hopkins et al., 2005; Wilde et al., 2006). Serra-Grabulosa et al. (2005) reported that severe TBI in childhood resulted in hippocampal atrophy and WM loss even 10 years after the injury and that hippocampal damage may contribute towards memory impairment post-TBI. The authors suggest that due to the limbic circuitry involving hippocampal output, a number of WM pathways may be damaged in TBI and may be responsible for TBI memory sequelae. Sugiyama et al. (2007)

found in two survivors of chronic TBI that the interruption of the fornix (which involves the circuit of Papez) potentially correlates with the memory disorder. In addition to the diffuse WM volume loss, there is probably WM loss in the fornix and mammillothalamic track, as well as the anterior thalamus projections to cortex and cingulate gyrus, which may be just as disruptive to memory as a specific hippocampal volume loss (Gale et al., 1995; Tate and Bigler, 2000). The study by Avants et al. (2008) supports this suggestion.

Despite these and other findings, the relationship between volume reduction and injury severity is equally unclear. The heterogeneity of the underlying injuries, radiological findings and postinjury clinical course across the TBI population is likely to be the culprit, as it is in many other negative studies involving the general TBI population (Belanger et al., 2007). Furthermore, it is difficult to determine prognosis until 12 to 24 months or more have passed following the injury (Lew et al., 2006). Hence, a more thorough investigation of the underlying pathophysiology resulting from the TBI is warranted.

1.2. *Detection of DAI after TBI*

Under the microscope, DAI is characterized by disruption of the cytoskeletal network and axonal membranes in the first few hours after TBI (Arfanakis et al., 2002; Benson et al., 2007; Liu et al., 1999), which ultimately results in axonal disconnection. This progressive functional and structural deterioration is thought to be brought about by a combination of altered membrane permeability with concomitant calcium ion influx, proteolysis, mitochondrial dysfunction, and, subsequently, Caspase-mediated apoptosis. Subsequent to axonal disconnection, the formation of axonal 'retraction balls' is observed, which is thought to be the result of the accumulation of axoplasm at the site of axonal disconnection (Bullock and Nathoo, 2005).

Adams (1982) was among the first to report DAI in head injury from a theoretical perspective, and then perform an analysis of a number (N=45) of cases (Adams et al., 1982). A report of 78 post-TBI patients was published a few years later (Cordobes et al., 1986), which focused on assessing DAI from CT; all patients had detectable DAI, but each had sustained a very severe TBI. When patients with less severe grades of TBI (i.e., mild or moderate) are assessed with CT, DAI is less detectable. The detection of lesions suspicious of DAI is important as their presence in the acute stage of TBI is related to outcome (Paterakis et al., 2000; Schaefer et al., 2004), and associated cognitive sequelae have been described for the chronic stage (Scheid et al., 2007; Wallesch et al., 2001).

Gentry et al. (1988) and Kelly et al. (1988) were the first to report on the comparative evaluation of closed head trauma via both MRI and computerized tomography (CT); they found that MRI was more useful than CT for detecting nonhemorrhagic lesions. Many similar studies have since been published with comparable findings, e.g., Mittl et al. (1994) demonstrated that MRI shows evidence of DAI in some patients with normal head CT findings after mild head injury.

While these, and many other investigations (e.g., Anderson et al., 1996; Gale et al., 1995), consistently showed that standard structural MRI sequences, usually T1- or T2-weighted, are more sensitive to detecting DAI than CT, the pathophysiology underlying DAI resulting from TBI remained elusive regardless of injury severity. T2 relaxation times in ROIs correlate precisely with tissue water content and can provide an estimate of vasogenic edema following brain injury (Kato et al., 1986). In the neuropathology literature, DAI is typically accompanied by small hemorrhages or so-called tissue tear hemorrhages (Scheid et al., 2007). Most blood products, such as deoxyhemoglobin, methemoglobin, and hemosiderin, are often undetected on conventional MR images alone. Iron deposits can be detected with T2*-weighted sequences, and the gradient recalled echo (GRE) technique is the most commonly used (Topal et al., 2008). However, even T2*-weighted sequences (for emphasizing hemosiderin deposits) do not detect DAI in every patient (Scheid et al., 2007). Images acquired at 3 T are superior to those acquired 1.5 T in revealing DAI in the chronic phase of TBI (Scheid et al., 2007) since T2* signal intensity loss, for example, depends on the magnetic field strength (Atlas et al., 1988). However, standard T1- and T2- and T2*-weighted sequences are simply not sensitive enough to detect DAI in every patient regardless of field strength (Lee et al., 2008). Consequently, conventional MRI underestimates the extent of DAI, possibly accounting for much of the transient clinical pathologic conditions following TBI and perhaps explaining the residual neurologic and cognitive deficits that are associated with TBI (Arfanakis et al., 2002; Sugiyama et al., 2007).

Note, however, that increased susceptibility at 3 T may not only be advantageous. Firstly, due to artifacts caused by air from sinuses and mastoid bone, the 3-T gradient echo images are not suitable for the evaluation of frontobasal and temporobasal/temporopolar brain structures (Scheid et al., 2007). Secondly, the increased sensitivity of 3 T MRI also to potential nontraumatic microbleeds, possibly resulting in differential diagnostic uncertainties (Fiehler, 2006).

1.3. *Diffusion neuroimaging to detect DAI after TBI*

A sequence based on Brownian movement (diffusion) of water through WM tracts was developed in 1991 (Le Bihan et al., 2001), aptly named diffusion-weighted imaging (DWI), and permitted the study of change in the random motion of proton in water in vivo (Liu et al., 1999). Restricted proton motion results in a decrease of the apparent diffusion coefficient (ADC) of water and increased signal intensity in diffusion-weighted images (Shanmuganathan et al., 2004). In a novel study by Nakahara et al. (2001), ADC maps generated from DWI data were used in the evaluation of four deeply comatose patients with severe TBI; ADC values in GM and WM were significantly different in the one patient with fatal outcome shortly after MRI examination. In another DWI study, Shanmuganathan et al. (2004) found whole-brain ADCs to correlate significantly with GCS scores in TBI patients. While DWI can detect DAI in some patients (e.g., Galloway et al., 2008; Hergan et al., 2002; Liu et al., 1999) where CT or standard MRI sequences do not (e.g., Arfanakis et al., 2002; Assaf et al., 1999; Blamire et al., 2002; Chan et al., 2003; Huisman et al., 2003; Huisman et al., 2004; Inglese et al., 2005; Jones et al., 2000; Nakayama et al., 2006; Ptak et al., 2003; Rugg-Gunn et al., 2001; Salmond et al., 2006b; Shanmuganathan et al., 2004; Suh et al., 2001; Topal et al., 2008), it cannot detect DAI in all instances: this was a strong motivating force behind the development of diffusion *tensor* imaging (DTI). Unlike conventional DWI (Le Bihan et al., 2001), where diffusion-weighted

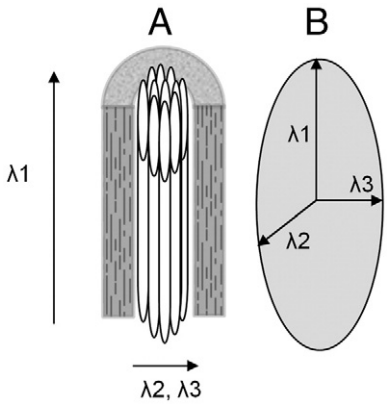

Fig. 1 – Illustration of principles involved in diffusion tensor imaging. (A) Microtubules of an axon encased in myelin sheath. (B) Eigenvectors represent main axes directions. Water diffusion is restricted along the longitudinal axis (λ_1) and/or perpendicular to the longitudinal axis of the axons (radial diffusion, eigenvalues λ_2, λ_3) due to axonal microstructure.

images are used to calculate the scalar ADC, DTI characterizes diffusive transport of water by an effective diffusion tensor *D*. The eigenvalues of *D* are the three principal diffusivities, and the eigenvectors define the local fiber tract direction field (Basser et al., 1994) (Fig. 1). Moreover, one can derive from *D* rotationally invariant scalar quantities that describe the intrinsic diffusion properties of the tissue. The most commonly used (Arfanakis et al., 2002) are the trace of the tensor, which measures mean diffusivity, and fractional anisotropy (FA) and lattice index, which characterize the anisotropy of the fiber structure, i.e., how much higher the diffusivity is along some directions compared with others. FA of water molecules ranges from 0 (anisotropic, i.e., random motion) to 1 (isotropic, i.e., nonrandom motion). In the cerebral WM, FA values should be high. A decrease in FA may indicate that a certain type of brain damage is present.

1.4. *Neuroimaging to investigate brain changes in depression*

It was elucidated a number of years ago that regions of hyperintense signal (hyperintensities) are associated with chronicity of mild-adult and geriatric/late-onset depression (e.g., Hickie et al., 1995; Jorm et al., 2005; Nobuhara et al., 2006; Sheline et al., 2008; Yamashita et al., 2001), suggesting abnormalities in the WM, and it has been found that WM hyperintensities also contribute to poor treatment outcome. Strictly speaking, late-life depression refers to depressive syndromes defined in the *International Classification of Diseases* (*ICD-10*; World Health Organization, 1992), which arise in adults aged over 65 years. The most commonly reported sites of WM hyperintensities in the context of late-life depression are in the frontal gyri that contain fibers of the anterior cingulate and the dorsolateral pathways (Middleton and Strick, 2001). Two medial temporal structures of the major efferent prefrontal WM tracts, the amygdala and hippocampus, are also implicated in major depressive disorder (MDD) in a plethora of volumetric and shape analysis studies (e.g., Bergouignan et al., 2009; Bouix et al., 2005; Egger et al., 2008; Frodl et al., 2002; Kronmuller et al., 2008; Mervaala et al., 2000; Posener et al., 2003; Tamburo et al., 2008; Zhao et al., 2008). Two meta-analyses (Campbell et al., 2004; McKinnon et al., 2009) found reduced amygdala and hippocampal volumes to be related to MDD. Specifically, the findings suggest that a relatively small hippocampal volume may be a vulnerability factor for a poor treatment response. For example, MacQueen et al. (2008) found that MDD patients who remitted had larger pretreatment hippocampal body/tail volumes bilaterally compared with those who were not in remission at 8 weeks. Furthermore, Maller et al. (2007) found the hippocampi in patients with MDD to be significantly smaller compared to age- and sex-matched controls, but particularly in the posterior tail. This suggests that a relatively small dorsal hippocampus may be a marker of MDD. In addition, the patients had a treatment-resistant form of MDD, which suggests not only that MDD may be related to reduced hippocampal volume but also that the tail segment is most reduced in those who are treatment-resistant. Studies have elucidated that this part of the hippocampus is rich in 5-HT (serotonin) receptors (Adams et al., 2008; Joca et al., 2003), which are primary targets for a number of antidepressant therapies (Drevets et al., 2000; Lambas-Senas et al., 2009). As the majority of patients with depression post-TBI do not respond to typical antidepressant treatment, the study raises the question of whether the post-TBI depression is developed as a result of the same activity occurring in the brains of patients with treatment-resistant MDD without a history of TBI. As both the hippocampus and prefrontal region are often implicated following TBI, it is possible that the symptoms of depression are reflective of an underlying pathophysiological change occurring at, and between, these two regions. This raises a number of possible models for treatment-resistant MDD and for the development of MDD post-TBI. For example, treatment-resistant MDD may be a result of the same underlying problems as in the brains of patients with MDD post-TBI; that is, prefrontal and hippocampal dysfunction in addition to a dysfunctional connection between them. By contrast, treatment-responsive MDD may be a consequence of a dysfunctional prefrontal and/or hippocampal regions, but the connection between them is not dysfunctional. It is of prime importance to acknowledge that neural circuits and connectivity are critical to our understanding of cognitive and emotional information processing; hence, WM provides the framework and anatomical basis of neural connectivity and circuitry in the central nervous system (Kumar and Cook, 2002).

In addition to frontotemporal studies in MDD patients, there is a growing body of literature suggesting that a smaller volume of the caudate nucleus may be related to the pathophysiology of MDD and may account for abnormalities of the corticostriatal–pallidothalamic loop in MDD. For example, Butters et al. (2009) reported greater caudate volume reduction, particularly in the anterior region, to be associated with more severe late-life depression. Kim et al. (2008) reported reduced caudate GM in women with MDD, no group differences in WM, and no significant correlations between GM volumes and symptom severity within the MDD group.

There are also a number of reports of altered CC areas in those with MDD, but results are not consistent. For example,

Table 1 – Studies reporting DTI results in individuals with TBI.

Study	Total (M/F), age, time since injury, controls	ROI	Severity (GCS)	Tesla/ directions	Main findings
Werring et al. (1998)	1 M penetrating right orbit (21 y, 18 months post)+5 controls	2×2	LOC then conscious at ER	1.5 (g)/7	Pt had hemiplegia: Directionality of anterior limb on affected side but not uninjured side
Wieshmann et al. (1999)	1 M blunt-head (42 y, 9 y post)+22 controls	0	Sev	ns (ns)/7	Widespread increase of the magnitude of diffusion. Decrease of the directionality of diffusion in myelinated structures including the right optic radiation and the forceps major of the CC
Jones et al. (2000)	4 M (52 y, 18 h post; 42 y, 34 h post; 26 y, 22 h post; 17 y, 14 h post)/1 F (52 y, 20 h post)	0	Mod-Sev 10, 4, 5, 8 12(F)	1.5 (g)/7	Narrow band of tissue observed in periphery of focal lesions, characterized by selective reduction in the diffusion tensor, without any associated increase in the T2-weighted signal intensity
Rugg-Gunn et al. (2001)	2 M (29 y, 11 m post; 31 y, 18 m post)	0	Sev	1.5 (g)/7	Abnormalities of diffusion in patients with head injuries and unremarkable MRI
Arfanakis et al. (2002)	5 (3 M/2 F 35.6±14.8 y), ≤24 h post admission, +30 d post+10 controls [b]	2×5 [a]	Mild 13–15	1.5 (ns)/23	WM regions (internal capsule, CC, and less often in external capsule) with reduced FA were detected in the first 24 h post-TBI. Follow-up in two xpatients revealed that in some regions with initially reduced FA, the changes were partially, or completely, corrected 30 d after injury
Ptak et al. (2003)	15 (8 M/7 F; mean=54 y; 21–83 y), ≤7 d post+30 controls	12	Sev < 8	1.5 (g)/ns	Lower FA in CC genu and splenium, right and left internal capsule (except right limb), and right and left centrum semiovale
Huisman et al. (2004)	20 (15 M/5 F; 31±10 y), ≤7 d post+15 controls	4	Mod–Sev 8.7±3.7	1.5 (ns)/6	Lower FA in internal capsule and CC splenium. No difference in FA of putamen and thalamus
Naganawa et al. (2004)	1 F (27 y), 4 d, 24 d, 2 m post+1 control	2×1+1 [a]	Sev (initially) 6, 11, 11	1.5 (s)/6	CC: some fibers extending to right frontoparietal WM were spared. On the second DTI data set, however, those fibers disappeared, and no fiber extending to upper frontal and parietal WM was seen
Ducreux et al. (2005)	2 M (19 y, 2 d; 19 y, 1 d post)	2	Sev 7,4	1.5 (s)/6	Pt 1: DTI and FT pattern consistent with broken WM tracts Pt2: Discrepancy between DTI and FT data that showed unaltered WM tracts in the presence of intracellular edema
Inglese et al. (2005)	46 (29 M/17 F, mean=36 y; 18–58 y), 4.05 d to 5.7 y post+29 controls	4	Mild 13–15	1.5 (s)/6	No difference between controls and patients for the whole brain analysis, but CC, internal capsule, and centrum semiovale had significantly lower FA for the patients
Le et al. (2005)	1 M blunt (22 y), 3 d + 12 w post+1 control	1 [a]	Sev 9, 6	1.5 (ns)/6	DTI at 3 d post-TBI: CC splenial lesion with reduced FA at 3 d had partially recovered as shown by DTI 12 w post-TBI
Ahn et al. (2006)	2 (1 M: 33 y, 10 w post; 1 F: 27 y, 6 w post)+6 controls [b]	2×5	Sev (LOC=2–3 w)	1.5 (p)/32	DTI with FT: focal lesions detected in the left brainstem of Pt 1 and in the right pons and the left and right medulla of Pt 2. The patients showed significantly decreased FA values in the focal lesions compared to normal controls
Nakayama et al. (2006)	23 nm, (19 M/4 F; 27.4±12.1 y), 14 y post+23 controls	8	Sev (LOC=7.2±8.6 d)	1.5 (g)/6	FA values of the genu, stem, splenium, and the column of the fornix were lower in patients with nmTBI than in healthy controls
Salmond et al. (2006b)	16 (12 Sev, 3 Mod, 1 Mild (13 M/3 F; 32 ±3.1 y)), ≥6 m post+16 controls	0	Mild–Mod–Sev 6.6±2.8	3 (o)/ns	Significant bilateral decreases in anisotropy, in major WM tracts and association fibers in the temporal, frontal, parietal, and occipital lobes. Statistically significant increases in diffusivity were also found in widespread areas of the cortex. A significant positive correlation was found between diffusivity and impairment of learning and memory in the left posterior cingulate, left HC and left temporal, frontal, and occipital cortex
Tisserand et al. (2006)	8 (ns; 20–40 y), ≥9 m post+6 controls	9	Mod–Sev 6.42	ns (ns)/10	FA was lower in the TBI patients than in healthy controls in the middle–posterior brain region bilaterally. FA lower in CC but only significantly in splenium
Voss et al. (2006)	2 M (39 y: 19, 20.5 y post, 24 y: 6 y post) +20 controls	0 (focus on CC) [a]	Sev (emerged from long-term comas)	3 (g)/ns	Pt1: Decreased anisotropy in the damaged WM+large, bilateral regions of posterior WM with significantly increased anisotropy that reduced over 18 months. In contrast, notable increases in anisotropy within the midline cerebellar WM in the second study correlated with marked clinical improvements in motor functions.

					Pt2: Aberrant WM structures on DTI but not clinically correlated
Bazarian et al. (2007)	6+6 controls: 8 M/4 F (21.7 y, 18–31 y), <72 h post	1 and 5	Mild 13–15	3 (s)/60	DTI detected significantly lower trace and elevated FA values in mild TBI subjects compared to controls. Quantile analysis revealed these abnormalities to occur in WM areas where trace is low and FA is high, while ROI analysis suggested the presence of axonal injury in the internal capsule and posterior CC
Benson et al. (2007)	20 [6 Mild, 14 Sev], (13 M/7 F; 35.5 ±14.6 y 11–57 y), 3 d to 15 y post+14 controls	1 and 2	Mild+Sev 13–15+3–8	1.5 (s)/6	WM-only FA histograms revealed a shift to the left, i.e., decreased FA, of the entire distribution of FA values for the TBI patients compared with controls
Han et al. (2007)	1 F (47 y), 0 w+24 m post+6 controls	2×5[a]	Sev (LOC=11 days)	1.5 (p)/32	10 w: Decreased FA in both sides of brainstem compared to controls 24 m: Significantly increased FA in both side of brainstem (in parallel with motor function improvement)
Kraus et al. (2007)	39 (20 Mild [8 M/12 F]/17 Mod–Sev [8 M/9 F]; mean=35 y), ≥6 m (mean=107 m) post+18 controls	0 and 13	Mild+Mod–Sev (LOC=0.11±0.5 h + 237 ±111.5 h)	3 (g)/27	Decreased FA in all 13 ROIs (anterior and posterior corona radiata, corticospinal tracts, cingulum fibre bundles, external capsule, forceps minor and major, genu, body and splenium of the CC, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and sagittal stratum) for mod–sev TBI group, but only in the corticospinal tract, sagittal stratum, and superior longitudinal fasciculus for the mild TBI group. WM load negatively correlated with all cognitive domains. Analysis of λ values suggested all TBI severities can result in a degree of axonal damage, while irreversible myelin damage only apparent for mod–sev TBI
Mao et al. (2007)	1 F (45 y), 8.5 m post+10 controls	2×4	ns	3 (p)/16	FA and FT revealed a reduction of WM integrity in the left frontal and medial temporal areas. WM damage identified by DTI was correlated with the patient's language impairment as assessed by fMRI and a neuropsychological exam
Newcombe et al. (2007)	33 (20 M/13 F, 34.6±15.4 y), 46±34 h (7–132 h) post+28 controls	1 and 3	Mod–Sev 3–11 (6.1±2.5)	3 (b)/12	Global burden of whole brain WM injury: Reduced FA in patients. Eigenvalue analysis suggested that the early imaging changes seen in WM are consistent with axonal swelling rather than axonal truncation
Skoglund et al. (2008)	1 F (22 y), 6 d+18 m post	1[a]	Sev 7	1.5 (p)/15	6 days after injury: severe FA reduction in rostral pons containing the corticospinal tract (correlated to the patient's severe hemiparesis). 18 months after injury: complete recovery completely and conventional MRI showed no pathology, and although FA values in the rostral pons had increased, they were still not normalized
Sugiyama et al. (2007)	2 M (26 y, 6 m post; 34 y, 20y post)+3 controls	1 (CC fibre tracking)	Sev	1.5(g)/17	In both patients, DTI fiber tractography revealed interruption of WM fibers in the CC and the fornix, while no lesions found on conventional MRI
Xu et al. (2007)	9 M (26.4±4.9 y (21–36 y)), 2–6 y (mean=4 y) post+11 controls	Many	Sev <7	3 (p)/32	Reduced FA values and increased ADC values for the TBI patients clustered in the large WM tracts of the telencephalon, including the CC, the internal and external capsules, periventricular WM, and the superior and inferior longitudinal fascicles
Yasokawa et al. (2007)	52 (30 M/22 F; 17–70 y [mean=32.2 ±13.5 y), ≥6 m post (21.8±10.7 m)+17 controls	6	Sev (GOS: 19 in vegetative state, 33 severe disability)	1.5 (g)/6	Lowest FA in midbrain and medulla oblongata. These values correlated with motor dysfunction
Avants et al. (2008)	12 (7 M/5 F, 35.0±12.1 y), post ns+9 controls	2×2	ns	ns (ns)/30	Patients with TBI had significantly reduced volume and increases in mean diffusion at coincident locations in the mediodorsal thalamus and anterior hippocampus
Bendlin et al. (2008)	35 (26 M/9 F; mean=30.54±11.37 y), 2 m+12.7 m post+36 controls	0	In ER: <13 Post-resuscitation: >6	3 (g)/12	TBI group had lower FA compared to controls in several WM tracts, including the CC, forceps major and minor, the anterior region of the corona radiata, the anterior limb and retrolenticular part of the internal capsule, the cerebral peduncles, external capsule, cingulum, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus, the corticopontine tract, and portions of the thalamus
Greenberg et al. (2008)	13 (10 M/3 F; 34.5±13 y), 4.5 m to 2.5 y post (no controls)	2×2+2	Mod–Sev m=7.67±4.16	1.5 (g)/25	FA significantly decreased in frontal and temporal tracts. No significant changes were in the CC

(continued on next page)

Table 1 *(continued)*

Study	Total (M/F), age, time since injury, controls	ROI	Severity (GCS)	Tesla/ directions	Main findings
Lipton et al. (2008)	17 (8 M/9 F; 26–70 y), 8 m to 3 y post +10 controls	1+0	Mild 13–15	1.5 (g)/25	Significantly decreased FAs ($p<0.005$) were found in the subject group in CC, subcortical WM, and internal capsules bilaterally. Colocated elevation of mean diffusivity was found in the patients within each region
Miles et al. (2008)	17 (11 M/6 F; mean=33.44 y (18–59 y)), mean=4 d (1–10 d) post+29 controls	2×4	Mild 13–15	1.5 (s)/6	FA significantly lower in centrum semiovale, the genu and the splenium of the CC, and the posterior limb of the internal capsule
Niogi et al. (2008)	43 (28 M/15 F, mean=32.3±10.6 y; 17–61 y), ≥1 m (mean=16.9 m,1–53 m) post+23 controls	2×6	Mild 13–15	3 (g)/55	In both groups: correlation between attentional control and FA in left hemisphere anterior corona radiata, as well as correlation between memory performance and FA in the uncinate fasciculus
Rutgers et al. (2008b)	21 (12 M/9 F; mean=32±9 y), 0.1–109 m (median=5 m) post+11 controls	13[b]	Mild >13	1.5 (s)/25	Patients had on average 9.1 regions with reduced FA, with a mean region volume of 525 mm^3, predominantly found in cerebral lobar WM, cingulum, and corpus callosum. These regions mainly involved supratentorial projection fiber bundles, callosal fibers, and frontotemporo-occipital association fiber bundles. Internal capsules and infratentorial white matter were relatively infrequently affected.
Rutgers et al. (2008a)	39 (27 M/12 F; mean=34±12 y), 24 Mild/9 Mod/6 Sev, <3 m post vs >3 m post+10 controls	3	Mild+Mod+Sev >13, 9–12, ≤8	1.5 (s)/25	Mild TBI associated with DTI abnormalities in genu <3 months after trauma. In more severe TBI, both the genu and splenium are affected. DTI suggests a larger contribution of vasogenic edema in the genu than in the splenium in TBI
Sidaros et al. (2008)	30 (23 M/7 F; 34.1±14.3 y, 18–65 y; $n=23$ at follow-up) 5–11 w, 9–15 m post+30 controls	5[a]	Sev <8	1.5 (s)/6	Initial scan: reduced FA in all investigated WM regions in patients compared to controls. FA in cerebral peduncle correlated with ~1 year GCS score ($r=0.60$, $p<0.001$) and in this sample predicted dichotomized outcome with 76% accuracy when taken alone, and with 100% accuracy in combination with clinical evaluation by functional independence measure at the time of the first scan. Follow-up DTI, FA in patients had increased in the internal capsule and centrum semiovale ($p\leq0.01$) due to an interval increase of λ with unchanged λ. In these regions, FA and λ reached normal or supranormal levels, primarily in patients with favourable outcome. In the cerebral peduncle and in CC, λ and λ both increased during the scan interval and, particularly in patients with unfavourable outcome, FA remained depressed
Wang et al. (2008a)	12 (8 M/4 F; 26±8.1 y), 6.7±4.2 d, 8.2±1.6 m post+12 controls	10	Sev 3–8 (mean=4.4±2.1)	3 (g)/19	At least 1 fiber variable of each region (CC, fornix, penduncular projections) showed DAI-associated alterations. At least 1 fiber variable of the anterior body and splenium of the CC correlated significantly with the GOS-extended scores
Kennedy et al. (2009)	8 (6 M/2 F; 39.1±12.4 y), 7±8.6 y post+8 controls	3	Sev (LOC=5–90 d, mean=21.75±28.69 d)	3 (s)/unclear	Lower FA in centrum semiovale, the superior frontal (SPF), and the inferior frontal (INF) gyri. Time since injury, but not age, was associated with WM changes in the SPF ROI, whereas age, but not time since injury, was associated with WM changes in the INF ROI, suggesting that the effects of WM on time since injury may interact with age
Kumar et al. (2009)	38 (hemorrhagic DAI (H-DAI, n=8), non-hemorrhagic DAI (Nh-DAI, $n=7$), and no apparent DAI on conventional MRI (NA-DAI, $n=23$) (26 M/12 F, 30 y,18–55 y), 5–14 d+6 m post+30 controls	11[a]	Mod 9–13 (m=10.8)	1.5 (g)/[b]	All patients had reduced FA in anterior and posterior limbs of internal capsule and H-DAI group also had reduced FA in the CC at time 1 and at time 2.

M=male, F=female, b=Bruker, g=General Electric, o=Oxford, p=Philips, s=Siemens, n=number, ns=not stated, d=days, m=months, y=years, nm=nonmissile, CC=corpus callosum, post=time after injury, Mod=moderate, Sev=severe, GCS=Glasgow Coma Score, GOS=Glasgow Outcome Scale, LOC=period of loss of consciousness, ER=on arrival at the emergency room. ROI (number of regions of interest analysed): 0=voxel-based analysis of entire brain, 1=one region of interest, e.g., FA of whole brain or brainstem, ×2=regions were analysed bilaterally.

[a] Longitudinal study.

[b] No English translation available or not stated.

while Husain et al. (1991) found no statistically significant group differences in measurements of CC and septum pellucidum, MDD patients had a larger CC area compared to healthy controls. Wu et al. (1993) reported that the anterior and posterior quarters of the CC were significantly larger in MDD patients, and similarly, Lacerda et al. (2005) reported that patients with familial MDD had a significantly larger middle genu area compared to healthy controls, and significantly larger middle genu, anterior splenium, and middle splenium areas compared to patients with nonfamilial MDD. This difference was more pronounced in females. Walterfang et al. (2009) reported expansions in the thickness of the CC's posterior body and isthmus in MDD patients when compared to controls; this was *not* seen in remitted patients. That is, the CC was expanded in regions connecting frontal, temporal, and parietal regions in currently depressed patients only, suggestive of state-related changes in WM in MDD that may reflect the effects of state-related factors on WM structure. Parashos et al. (1998), examining MDD patients and controls, found smaller callosal area in patients, not reaching statistical significance. The inconsistencies in results across these studies could be explained at least in part by distinct factors, such as (1) differences in patient sample characteristics (age, gender, handedness, length of illness, age at onset, and severity), (2) methodological differences in MRI acquisition as well as in callosal measurements, and (3) insufficient statistical power of studies presenting negative findings (Lacerda et al., 2005).

2. Methods

2.1. Subjects

Articles were defined through a review of the literature conducted via MedLine searches (until February 2009) using the phrases "traumatic brain injury," "closed head injury," "head injury," "brain injury," "depression," "depressive disorder," "mdd," "unipolar," "imaging," "neuroimaging," "MRI," "magnetic resonance imaging," "magnetic resonance," "diffusion tensor imaging," "DTI," "diffusion," "tensor," "Brownian," "tensor imaging," "diffuse axonal injury," "traumatic axonal injury." Additional articles were identified from reference lists of key articles. Articles were only included in the review if they reported the DTI findings. Postmortem studies were excluded. DWI findings (i.e., ADCs) were also excluded. To exclude the influence of changing FA values over time, only studies that recruited adult subjects were included (current research suggests that FA values are relatively stable from 20 to 50 years and then undergo a more rapid decline, Charlton et al., 2006; Ota et al., 2006; Persson et al., 2006; Pfefferbaum et al., 2006; Salat et al., 2005; Sullivan et al., 2006; Sullivan and Pfefferbaum, 2006).

3. Results

Forty articles presenting DTI findings from TBI subjects (Table 1) were identified through database searches, and a separate 17 articles presenting DTI findings from subjects with depression (Table 2). No articles were identified which used DTI to investigate depression in TBI patients.

3.1. Demographics

A total of 596 patients (392 males and 204 females) were represented among the 40 DTI–TBI articles. Ages ranged from 17 to 83 years, with a weighted mean of 32.3 years. TBI subjects had classifications ranging from Mild (Glasgow Comas Scale [GCS]≥13), Moderate (GCS=9–12), and Severe (or Chronic, GCS≤8), although not all articles stated GCS, GOS (Glasgow Outcome Score), or LOC (period of Loss Of Consciousness). Approximately half of these studies used only patients who had sustained a severe TBI, another seven only included those with mild TBI, and one study only included those with moderate TBI. The remaining studies (of those which stated GCS, GOS, or LOC) included TBI subjects with a range of severities. The vast majority of patients had Severe TBI and were DTI scanned within 14 hours to 20 years after injury.

A total of 503 patients (197 males and 306 females) were represented by the DTI depression articles. Ages ranged from 18 to 85 years, with a weighted mean of 56.5 years. All patient subjects in the DTI depression articles had a diagnosis of major depression (majority were late-onset/geriatric).

3.2. Brain regions identified

In TBI patients, DAI was reported in a large number of brain regions using the DTI technique that are consistent with histological findings. DAI was most often reported in frontotemporal regions and within the major WM tracts that connect them, including the corpus callosum and WM fibers of the anterior cingulate and watershed region, particularly the internal capsule (Table 3). This was most evident when only studies on mild or moderate TBI patients were presented (Table 4).

In patients with depression, DAI was reported in a smaller number of areas than was identified in the TBI literature. The frontotemporal regions were most consistently reported as having reduced FA in depression patients and/or associated with nonremission, as well as fibers passing through the cingulate.

Table 5 summarizes the ROIs most commonly reported as having reduced FA in TBI and MDD samples. As can be seen, the corpus callosum and the internal capsule were the most commonly reported regions with reduced FA after TBI and also among articles investigating MDD. A visual representation of these results is given in Fig. 2.

4. Discussion

Depression is the most frequently reported mood disorder among survivors of TBI (Jean-Bay, 2000; Pagulayan et al., 2008; van Reekum et al., 2000). By carefully reviewing the literature of DTI findings in people who sustained a TBI, and in those with a diagnosis of major depression, we have been able to decipher the similarities and differences between these groups of people. By considering these overlapping findings, we are a step closer towards understanding the underlying involvement of white matter in major depression, and therefore further towards

Table 2 – Studies reporting DTI results in those with depression.

Study	Group(s) M/F, time since injury	ROI	Tesla/ directions	Main findings
Taylor et al. (2001)	14 (4 M/8 F, 69±1.66 y)+19 controls	2×7	1.5 (g)/6	Hyperintensities showed higher ADC and lower anisotropy than normal regions. GM exhibited similar trends. There was no significant difference in diffusion characteristics of hyperintensities between subjects and control subjects
Alexopoulos et al. (2002)	13 (ns, 60–77) (no controls)	2×5	1.5 (s)/6	Lower FA of the right and the left frontal WM regions 15 mm above the AC–PC plane (approximately anterior cingulate) was associated with a low remission rate after age was considered. Remission was not significantly associated with FA of lower frontal regions or a temporal region
Nobuhara et al. (2004)	8 (1 M/7 F; 62.9±5.8 y)+12 controls	6[a]	1.5 (g)/ns	Significant WM FA reduction in widespread frontal and temporal brain regions in patients with depression before ECT treatment compared with controls. A significant increase in frontal WM FA was seen following ECT treatment. A course of bilateral ECT ameliorated WM integrity in frontal brain regions.
Taylor et al. (2004)	17 (7 M/10 F, 67.5±6.1 y)+16 controls	5	1.5 (g)/6	Even after controlling for age, sex, hypertension, and heart disease, the authors found significantly lower FA values in the right superior frontal gyrus WM of depressed patients than comparison subjects
Steele et al. (2005)	15 (4 M/11 F, 45.9 y)+14 controls	1	1.5 (g)/6	No reduced FA in the brainstem
Bae et al. (2006)	106 (33 M/73 F, 70.4±6.4 y, 60–85 y)+84 controls	2×4+1	1.5 (g)/6	Depressed subjects had significantly lower FA values in WM of the right ACC, bilateral superior frontal gyri, and left middle frontal gyrus
Nobuhara et al. (2006)	13 (4 M/9 F, 62.8±6.6 y)+13 controls	8	1.5 (g)/6	Significant FA reduction in widespread frontal and temporal lobe of MDD patients. Evidence that WM FA in inferior frontal is inversely related MDD severity
Li et al. (2007)[b]	19 (4 M/15 F, 28.1±7.4 y, 20–41 y)+20 controls	2×7	1.5 (g)/13	Compared with healthy controls, patients with MDD showed significantly lower FA values in prefrontal WM at bilateral 20 mm, right 16 mm, and right 12 mm above the AC–PC. Furthermore, there was no significant correlation between the FA value of any ROI and illness course as well as severity of depression
Ma (2007)[b]	14 (2 M/12 F, 28.9±8.0 y, 20–41 y) treatment-naive+14 controls	0	1.5 (g)/13	Patient group exhibited significantly lower FA values than healthy comparison subjects in WM of the right middle frontal gyrus, the left lateral occipitotemporal gyrus, and the subgyral and angular gyri of the right parietal lobe
Xia (2007)	18 (10 M/8 F, 36.08±10.81 y)+13 controls	[c]	1.5 (g)/25	Subjects with MDD who failed to respond to treatment had a significantly lower FA in frontal WM those successful responders, and healthy controls
Yang (2007)	31 (11 M/20 F, 64.6±5.21 y)+15 controls	3×2+2	1.5 (g)/25	FA values were significantly decreased in the frontal (superior and middle frontal gyrus), and temporal (right parahippocampal gyrus) regions of elderly patients with depression compared with healthy controls
Yuan (2007)	16 remitted (7 M/9 F, 66.9±7.0 y)+14 controls	0	1.5 (g)/25	Lower FA in WM in patients than in controls at the right superior frontal gyrus, left inferior frontal gyrus, left middle temporal gyrus, right inferior parietal lobule, right middle occipital gyrus, left lingual gyrus, right putamen, and right caudate
Alexopoulos et al. (2008)	25 remitted vs 23 nonremitted (ns, 70.1±5.5 y)	0	1.5 (s)/8	Subjects who failed to achieve remission (N=23) had lower FA in multiple frontal limbic brain areas, including the rostral and dorsal anterior cingulate, dorsolateral prefrontal cortex, genu of the CC, WM adjacent to the hippocampus, multiple posterior cingulate cortex regions, and insular WM, relative to those who achieved remission (N=25). In addition, lower FA was detected in the neostriatum and midbrain as well as select temporal and parietal regions
Gutman et al. (2009)[d]	13 (9 M/4 F, 26.7±5.2 y, 20–36 y) nondepressed	2	1.5 (s)/60	Two DBS WM targets suggest distinct neural networks with areas of overlap in regions implicated in depression and antidepressant response: (1) Subcallosal cingulate WM: consistent ipsilateral connections to the medial frontal cortex, the full extent of the anterior and posterior cingulate, medial temporal lobe, dorsal medial thalamus, hypothalamus, nucleus accumbens, and the dorsal brainstem (2) Anterior limb of internal capsule: widespread projections to frontal pole, medial temporal lobe, cerebellum, nucleus accumbens, thalamus, hypothalamus, and brainstem COMMON to both (1) and (2): connections to frontal pole, medial temporal lobe, nucleus accumbens, dorsal thalamus, and hypothalamus

Table 2 (*continued*)

Study	Group(s) M/F, time since injury	ROI	Tesla/ directions	Main findings
Hoptman et al. (2008)	41 (16 M/25 F, 70.1±6.3 y, 60–86 y) (no controls)	0	1.5 (s)/8	High blood pressure is associated with microstructural WM abnormalities (lower FA) in the dorsal anterior cingulate and multiple frontostriatal and frontotemporal WM regions in geriatric depression
Taylor et al. (2008)	37 remitted (21 M/16 F, 65.8±5.7 y)+ 37 nonremitted (19 M/18 F, 70.5± 8.0 y)	3×2+1	1.5 (g)/6	Subjects who did not remit to sertraline exhibited higher FA values in the superior frontal gyri and anterior cingulate cortices bilaterally
Zou et al. (2008)	45 (15 M/30 F, 33.2±8.9 y, 18–52 y)+ 45 controls	0	3 (g)/15	Significant decrease in FA in the left hemisphere, including the anterior limb of the internal capsule and the inferior parietal portion of the superior longitudinal fasciculus, in patients with MDD compared with healthy controls. DTI measures in the left anterior limb of the internal capsule were negatively related to the severity of depressive symptoms (controlled for age and sex)

M=male, F=female, WM=white matter, GM=grey matter, CSF=cerebrospinal fluid, TBV=total brain volume, ICV=intracranial volume, HC=hippocampus, OC=until the opening of the crus of the fornix, Atrophy=CSF/ICV.
ROI (number of regions of interest analysed): 0=voxel-based analysis of entire brain, 1=one region of interest, e.g., FA of whole brain or brainstem, ×2=regions were analysed bilaterally.
[a] Longitudinal study.
[b] First-episode, treatment-naïve; DTI studies employing PTSD subjects were excluded.
[c] NoEnglish translation available.
[d] Although this did not employ subjects with depression, this study investigated tracts involved in DBS for treatment of depression.

elucidating whether detection of DAI can help predict who will develop depression post-TBI as well as guide future treatment protocols.

4.1. *TBI, DAI, and DTI*

Early DTI studies by Werring et al. (1998) and Wieshmann et al. (1999) on single subjects who had sustained blunt-head trauma indicated reduced FA and increased diffusivity at least 6 months after injury. Arfanaskis et al. (2002) investigated the association between DTI and DAI in groups of TBI survivors and found that DAI may be detected by means of reductions in diffusion anisotropy. This may explain why conventional DWI studies have not effectively detected DAI by using only measures of mean diffusivity. For example, Rutgers et al. (2008a) reported reduced FA but not significant ADC change in moderate to severe TBI patients less than 3 months after injury. In all patient groups (mild, moderate, severe), FA reduction in the genu was accompanied by significant ADC increase, whereas FA reduction in the splenium occurred in the absence of significant ADC change. This indicates that the type of microstructural change was different in both locations.

In a novel experimental study, Mac Donald et al. (2007) demonstrated significant correlations between DTI and histology of DAI. Ducreux et al. (2005) showed that DTI FA analysis and fiber tracking analysis may be able to differentiate between traumatic cytotoxic edema and broken fibers in the case of DAI post-TBI. Similarly, Le et al. (2005) reported recovered FA in the CC splenium of a blunt head injury victim at 12 weeks after injury, whereas three-dimensional tractography revealed an interruption in the WM fibers in the posteroinferior aspect of the splenium that correlated with the patient's left hemialexia (a functional deficit caused by disconnection of the right visual cortex from the language centers of the dominant left hemisphere). Significantly lower FA values in the patients were also found in the splenium.

Forty studies have reported on DAI in TBI patients using DTI sequences (Table 1) with a steady increase since 2004 (Fig. 3). In general, TBI has been associated with a global FA decrease in WM (Benson et al., 2007; Huisman et al., 2004; Newcombe et al., 2006; Newcombe et al., 2007; Ptak et al., 2003). Severe TBI has often been reported to result in reduced FA in most regions including the lower areas (such as the brainstem). The most frequently reported sites in all severities of TBI of DAI are in the CC (e.g., Adams et al., 1980; Ewing-Cobbs et al., 2006; Kumar et al., 2009; Lipton et al., 2008; Miles et al., 2008; Rutgers et al., 2008a; Sidaros et al., 2008; Takayama et al., 2000; Voss et al., 2006), particularly splenium, and fornix (e.g., Nakayama et al., 2006; Sugiyama et al., 2007; Tisserand et al., 2006; Wang et al., 2008a), even in mild TBI (Blumbergs et al., 1995; Tomaiuolo et al., 2004; Wilde et al., 2006). Frontotemporal regions were often implicated, as too the centrum semiovale and internal capsule. Interestingly, a study by Greenberg et al. (2008) reported reduced FA in frontotemporal regions, but not in the CC post-TBI. Hemispheric WM, brainstem, and cerebellum are affected less frequently but more often in severe TBI (Ahn et al., 2006; Blumbergs et al., 1995). In a group of 43 mild TBI patients (1–53 months after injury), Niogi et al. (2008) found reduced FA in some of the major WM tracts (in this case, the corona radiata and uncinate fasciulus) which also correlated with performance in attention and memory, respectively. Similarly, Kumar et al. (2009) reported reduced FA in the acute stage, as well as at secondary stages, at 6 months after injury (moderate TBI) in the CC and periventricular WM (other ROIs were not seeded) which correlated with neuropsychological performance. Le et al. (2005) present an interesting visual representation of DTI measurements in the CC post-TBI compared to a healthy control.

A recent study (Kennedy et al., 2009) found that adults with TBI seven years earlier had lower FA (and higher mean diffusivity) than controls, specifically in the centrum semiovale, superior frontal, and inferior frontal regions. Bendlin et al. (2008) reported

Table 3 – Main findings of DTI–TBI studies (all TBI patients).

Study	Severity (GCS)	Reduced FA regions						
		Frontal	Temp	CC	Cing	Centrum Semiovale	Internal Capsule	Other
Werring et al. (1998)	LOC then conscious at ER						*	
Wieshmann et al. (1999)	Sev			*				Right optic radiation
Jones et al. (2000)	Mod–Sev 10, 4, 5, 8 12(F)							Periphery of focal lesions
Rugg-Gunn et al. (2001)	Sev	*					*	
Arfanakis et al. (2002)	Mild 13–15			*			*	Less often in external capsule
Ptak et al. (2003)	Sev <8			*		*	*	
Huisman et al. (2004)	Mod–Sev 8.7±3.7			*			*	No difference in putamen and thalamus
Naganawa et al. (2004)	Sev (initially) 6, 11, 11			*				No CC fibers extending to upper frontal and parietal WM
Ducreux et al. (2005)	Sev 7, 4			*				
Inglese et al. (2005)	Mild 13–15			*		*	*	
Le et al. (2005)	Sev 9, 6			*				
Ahn et al. (2006)	Sev (LOC=2–3 w)			*				Pons, medulla, cerebral peduncle (brainstem)
Nakayama et al. (2006)	Sev (LOC=7.2±8.6 d)			*				Fornix
Salmond (2006a)	Mild–Mod–Sev 6.6±2.8	*	*		Posterior			Major WM tracts and association fibers in parietal and occipital lobes
Tisserand et al. (2006)	Mod–Sev 6.42			*				"middle–posterior brain region" (as opposed to ventral/dorsal and anterior)
Voss et al. (2006)	Sev (emerged from long-term comas)			*				In the damaged WM+large, bilateral posterior regions; cerebellar vermis
Bazarian et al. (2007)	Mild 13–15			*			*	
Benson et al. (2007)	Mild+Sev 13–15+3–8							Entire distribution of FA values
Han et al. (2007)	Sev (LOC=11 days)							Pons, medulla, cerebral peduncle, (brainstem)
Kraus et al. (2007)	Mild+Mod–Sev (LOC=0.11±0.5 h+ 237±111.5 h)	*	?	*	*			Anterior and posterior corona radiata, corticospinal tracts, cingulum fibre bundles, external capsule, forceps minor and major, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and sagittal stratum for mod–sev TBI group, but only in the corticospinal tract, sagittal stratum, and superior longitudinal fasciculus for the mild TBI
Mao et al. (2007)	ns	*	*					
Newcombe et al. (2007)	Mod–Sev 3–11 (6.1±2.5)	*	*	*	*			Global WM reduction
Skoglund et al. (2008)	Sev 7							Rostral pons (containing the corticospinal tract)
Sugiyama et al. (2007)	Sev			*				Fornix
Xu et al. (2007)	Sev <7			*			*	External capsule, periventricular WM, and the superior and inferior longitudinal fascicules

Table 3 (*continued*)

Study	Severity (GCS)	Reduced FA regions						
		Frontal	Temp	CC	Cing	Centrum Semiovale	Internal Capsule	Other
Yasokawa et al. (2007)	Sev (GOS: 19 in vegetative state, 33 severe disability)							Midbrain and medulla oblongata
Avants et al. (2008)	ns		*					Mediodorsal thalamus
Bendlin et al. (2008)	In ER: <13 Post-resuscitation: >6	*	*	*	*		*	Forceps major and minor, anterior corona radiata, cerebral peduncles, external capsule, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus, corticopontine tract, thalamus
Greenberg et al. (2008)	Mod–Sev m = 7.67 ± 4.16	*	*					
Lipton et al. (2008)	Mild 13–15			*			*	Subcortical WM
Miles et al. (2008)	Mild 13–15			*		*	*	
Niogi et al. (2008)	Mild 13–15		*					Anterior corona radiata and uncinate fasciculus
Rutgers et al. (2008a)	Mild >13	*	*	*	*		* (infrequent)	Cerebral lobar WM. Infratentorial WM relatively infrequently affected
Rutgers et al. (2008b)	Mild + Mod + Sev >13, 9–12, ≤8			*				
Sidaros et al. (2008)	Sev <8			*		*	*	Cerebral peduncles
Wang et al. (2008a)	Sev 3–8 (mean = 4.4 ± 2.1)			*				Fornix, penduncular projections
Kennedy et al. (2009)	Sev (LOC = 5–90 d, mean = 21.75 ± 28.69 d)	*				*		Superior and inferior frontal gyri
Kumar et al. (2009)	Mod 9–13 (m = 10.8)			*			*	

Ahn et al. (2006) and Han et al. (2007) are the same research group.

that TBI affected virtually *all* of the major fiber bundles in the brain of 35 post-TBI patients, including the CC, cingulum, the superior and inferior longitudinal fascicules, the uncinate fasciculus, and brain stem fiber tracts. Similar findings were reported by Xu et al. (2007). Other regions affected included the internal and external capsule, the corticospinal tract and thalamus, which is consistent with findings of many studies (Table 1). The results suggested that while GM and WM degeneration are significant contributors to brain volume loss in the months following brain injury, WM volume loss was not always detectable on T1-weighting where there existed reduced FA. This suggests that DTI measures may be more useful than high-resolution anatomical images in assessment of group differences after TBI, and there is now a general consensus that DTI is more sensitive than conventional MRI for detecting DAI in acute and chronic stages of TBI (Kennedy et al., 2009). However, while FA reduction is attributed to a change in parenchymal structure (Arfanakis et al., 2002; Inglese et al., 2005; Nakayama et al., 2006; Ptak et al., 2003), which may include misalignment of fibers, edema, fiber disruption, or axonal degeneration, the exact cause of posttraumatic DTI changes in WM remains to be elucidated (Rutgers et al., 2008b).

Many of the DTI–TBI studies reported on severe TBI, so it is sensible that many studies reported widespread areas of reduced FA. However, if those studies are removed from the analyses to leave only patients with mild or moderate degrees of TBI, the findings become clearer (Table 4). That is, reduced FA in frontal and temporal WM was commonly reported among those studies, but more often in the CC (although this may be because it was the most commonly seeded region) and also in the internal capsule. The internal capsule separates the internal segment of globus pallidus and substantia nigra pars reticulata, i.e., regions targeted in deep brain stimulation (DBS) for antidepressant treatment (for review, see Fitzgerald, 2008).

4.2. *Depression and DTI*

Compared with the TBI literature, there are a limited number of DTI studies in individuals with MDD (Table 2 and Fig. 3). Yet, together with functional imaging studies, they demonstrate that depression is characterized by functional disconnection between frontal and temporal regions; those individuals where this disconnection is related to structural changes as detected by

Table 4 – Main findings of DTI–TBI studies (only mild or moderate TBI patients).

Study	Severity (GCS)	Reduced FA regions						
		Frontal	Temp	CC	Cing	Centrum semiovale	Internal capsule	Other
Arfanakis et al. (2002)	Mild 13–15			*			*	Less often in external capsule
Inglese et al. (2005)	Mild 13–15			*		*	*	
Bazarian et al. (2007)	Mild 13–15			*			*	
Bendlin et al. (2008)	In ER: <13 Post-resuscitation: >6	*	*	*	*		*	Forceps major and minor, anterior corona radiata, cerebral peduncles, external capsule, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus, corticopontine tract, thalamus
Lipton et al. (2008)	Mild 13–15			*			*	Subcortical WM
Miles et al. (2008)	Mild 13–15			*		*	*	
Niogi et al. (2008)	Mild 13–15		*					Anterior corona radiata and uncinate fasciculus
Rutgers et al. (2008a)	Mild >13	*	*	*	*		* (infrequent)	Cerebral lobar WM. Infratentorial WM relatively infrequently affected
Kumar et al. (2009)	Mod 9–13 (m=10.8)			*			*	

DTI may be less likely to respond to antidepressants. For example, Alexopoulos et al. (2002) reported lower FA lateral to the anterior cingulate region at the level of the middle frontal gyrus to be associated with low remission rate (citalopram) in late-life MDD. Taylor et al. (2001) reported reduced FA in the right superior frontal gyrus in patients with geriatric depression, and Taylor et al. (2008) found that MDD patients who remitted to sertraline exhibited higher FA values in the superior frontal gyri and anterior cingulate cortices bilaterally (there were no statistically significant associations between ADC measures and remission). More generally, Xia et al. (2007) found that depressed subjects who failed treatment had reduced FA in frontal WM compared to responders and healthy controls. Furthermore, Nobuhara et al. (2004) reported significant WM FA reduction in widespread frontal and temporal brain regions in patients with depression before electroconvulsive therapy (ECT) compared with controls and that, after repetitive ECT sessions, patients showed a significant decrease in depressive symptom severity. All of the eight patients were considered treatment responders, and WM FA in all frontal regions increased significantly in depressed patients and did not differ significantly from controls after ECT. While treatment response was not assessed in the context of DTI in the study by Yang et al. (2007), they also found significantly reduced FA in the middle and superior frontal regions as well as in the bilateral parahippocampal gyri (i.e., temporal lobe) in their group of depressed patients when compared to control subjects.

In some patients, remission of MDD has been associated with metabolic increases in dorsal cortical regions (e.g., Drevets, 2000) and decreases in ventral limbic and paralimbic structures (e.g., Mayberg, 2001). Consistent with Taylor et al. (2008), Vasic et al. (2008) reported a disconnectivity of dissociable prefrontal and cingulate regions in MDD patients. Bae et al. (2006) support these findings in a large sample ($N=106$ MDD patients), as do those of Li et al. (2007) in a sample of young adults with MDD, and the studies of Kim et al. (2005, 2006) in individuals with posttraumatic stress disorder. Hoptman et al. (2008) reported a significant association between FA in the anterior cingulate and multiple frontostriatal and frontotemporal regions, and blood pressure in geriatric

Table 5 – Frequencies at which ROIs displayed reduced FA within 40 TBI and 17 MDD studies.

ROI	Frequency		Proportion (%) of frequencies		Most commonly reported ROI of reduced FA in TBI	Most commonly reported ROI of reduced FA in MDD
	TBI	MDD	TBI	MDD		
Frontal	9	2	22.5	11.8	3	3
Temporal	8	3	20	17.6	4	2
CC	25	8	62.5	40	1	1
Cingulate	5	2	12.5	11.8	5	3
Centrum Semiovale	4	2	10	11.8	6	3
Internal capsule	14	8	35	40	2	1
Other	≥20	4	≥50	20		

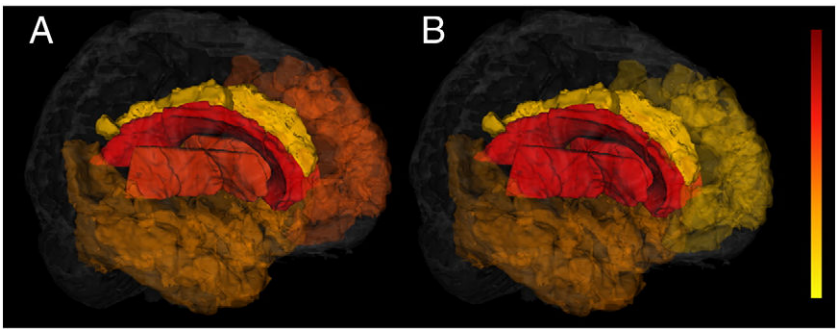

Fig. 2 – Visual representation of the results of Table 5. The structure color represents the frequency at which it is implicated in studies examining reduced FA in TBI (A) and in MDD (B), ranging from yellow (less frequent) to red (most frequent). Note the overlap in the structures most frequently reported as having reduced FA in TBI and MDD (as collated in Table 5).

depression. Yang et al. (2007) reported reduced FA to be significant in frontotemporal regions but not in the CC. These studies add to a growing body of literature suggesting that a disturbance of these dynamic networks is characterized by a simultaneously increased connectivity of the dorsal lateral prefrontal cortex during task-induced activation and increased connectivity of the anterior cingulate during task-induced deactivation (Ebmeier and Kronhaus, 2002). This is logical since the cingulum bundle is the most prominent WM tract in the limbic system (Kim et al., 2006), connecting to the anterior cingulate gyrus and entorhinal gyrus (where reduced FA was found by Yang et al., 2007, for example), projecting intensively to and from the amygdala (Hamner et al., 1999).

The majority of MRI depression research, including the use of DTI, is conducted using elderly subjects, in contrast to DTI–TBI research that employs patients of a lower mean age, which is consistent with the gender ratio frequencies of TBI and depression in the community. In the current review, the mean age of TBI patients was 32.3 years, and 54.5 years for patients with depression. In late-life depression, the most consistent finding has been the greater regions of high-intensity lesions (hyperintensities) on T2-weighted scans in patients with MDD when compared against healthy nondepressed controls. These lesions are commonly observed in WM mainly around and within frontal (periventricular) regions and deep WM, although sometimes in subcortical nuclei as well (Kumar and Cook, 2002, see Butters et al., 2009), and are related to neuropsychological function (Murphy et al., 2007). Using DTI, Taylor et al. (2001) reported lower FA in areas of

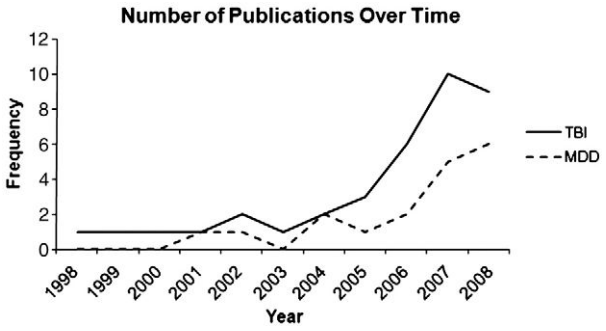

Fig. 3 – Frequency of DTI publications relating to TBI or depression (MDD) in adults.

hyperintensities compared to 'normal' regions, but no difference in diffusion characteristics between patients and controls. That is, the hyperintensities in older people with MDD are no different from the hyperintensities in older people without MDD. Magnetic resonance spectroscopy (MRS) has revealed increases in choline levels in subcortical regions that include GM and WM (e.g., Hamakawa et al., 1998; Kato et al., 1986; Mervaala et al., 2000).

Only 3 of the 17 DTI studies we found that employed patients with depression used patients that were younger than geriatric or mid-life (Li et al., 2007; Ma et al., 2007; Zou et al., 2008). While the body of MRI depression literature is growing, the problem with mostly utilizing an elderly population is that the 'abnormal' magnetic resonance signal commonly observed in those with late-onset depression, for example, may not be able to be differentiated from the naturally occurring phenomena within an aging brain. That is, although a collection of 'abnormal' signal representing WM hyperintensities (e.g., periventricular leukomalacia) may be reported as related to depression on a group level, for example, it must be considered that the onset of WM hyperintensities is a naturally occurring event in the aging brain (Sachdev et al., 2006; Wen and Sachdev, 2004). Furthermore, FA changes over time, with a linear reduction by the age of 20 years (Sullivan et al., 2006) that becomes accelerated after the age of 50 (Charlton et al., 2006). A predilection of loss occurs for thin, unmyelinated fibers, which are in greatest abundance in the frontal lobes and callosal genu (Aboitiz et al., 1996; Bartzokis, 2004), which are also commonly identified areas of reduced FA post-TBI and reduced cross-sectional area post-TBI and in those with depression. Hence, to elucidate magnetic resonance signal resulting from a natural event (i.e., aging), rather than an external event (e.g., a TBI), and to utilize that information effectively for rehabilitation (both physical and mental), would be invaluable to survivors of TBI and their families.

Unfortunately, the overrepresentation of older patients is not the only weakness in MDD research. Konarski et al. (2007) conducted a literature search of English-language articles using the search terms major depressive disorder and bipolar disorder, cross-referenced with available neuroimaging technologies and analytical approaches. They found that although an impressive variety of approaches are used to investigate depression, including MRI, positron emission tomography (PET), single photon emission computerized tomography (SPECT), DTI, voxel-based morphometry (VBM), and MRS, there is a lack of

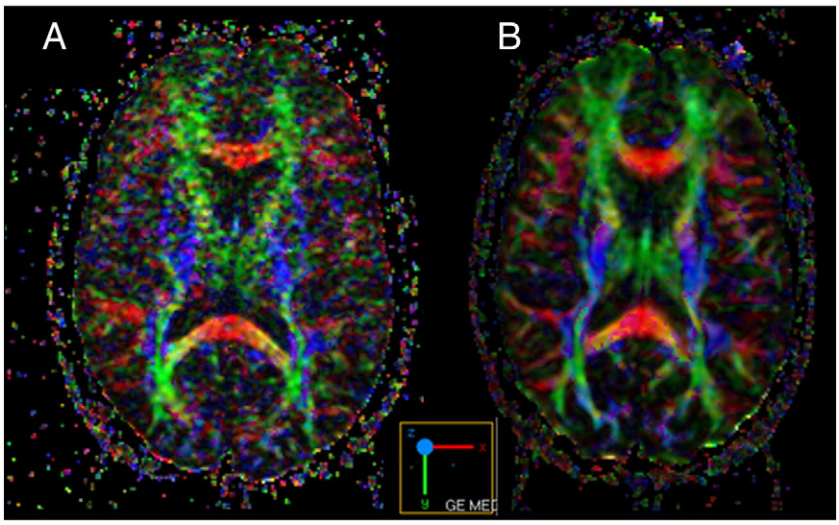

Fig. 4 – Axial display of color FA maps from a single subject DTI scanned with (A) 12 noncollinear directions (b = 1000 sec/mm^2; 3 mm slice thickness) and (B) 35 directions (b = 1000 sec/ mm^2; 5 mm slice thickness; single scanner for both scans [Signa 1.5 T (General Electric Medical Systems, Milwaukee, WI). Parallel imaging was used (ASSET; array spatial sensitivity encoding technique) during both acquisitions. A 35-direction scan was acquired immediately following the 12-direction scan. Subject is a patient of J.J.M. who had treatment-resistant MDD at the time of scanning.

multivariate analysis of functional and structural neuroimaging data, longitudinal analysis in the depressed and remitted states, and inclusion of representative patients with medical and psychiatric comorbidities. Taking up these suggestions, along with future developments in neuroimaging acquisition and analysis, will enhance the clinical translation of future research findings.

4.3. *Post-TBI depression and structural brain imaging*

While structural brain imaging in research has helped to recognize degrees of DAI in the WM as being related to TBI extent, prediction of long-term functioning is limited. This is due mainly to studies using small and heterogeneous samples. For example, focal damage has different consequences to nonfocal damage, whereby the former is associated with cognitive and personality syndromes and not to the development of depression or anxiety disorders (Koponen et al., 2006). The association between psychiatric disorders after TBI and traumatic lesions detectable with post-acute MRI was weak. In a separate study of 43 subjects with moderate-to-severe TBI, no MRI-based anatomical differences were found between depressed and nondepressed survivors (Salmond et al., 2006a). However, a large and systematic study (Jorge et al., 2004) suggests a relationship between frontal brain volume and the development of depression post-TBI, and this is consistent with other studies. For example, Fujii and Ahmed (1996) found right and left temporal and left frontal lesions to be most prevalent in TBI patients who developed psychiatric conditions, and Jorge et al. (1993a) used CT in 66 patients post-TBI and reported a connection between depression and the lesions of the left dorsolateral frontal region and the left basal ganglia, but only during the first month after the injury. However, this pattern is not apparent for each patient. Hence, while a frontal–temporal model of post-TBI depression is slowly

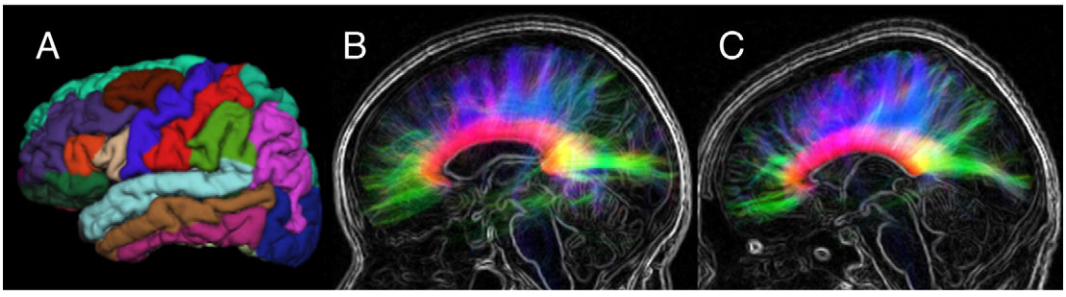

Fig. 5 – Representative images showing (A) parcelation of the cortical mantle using Freesurfer and the major commissural tracts projecting through the corpus callosum for a control participant (B) and a patient with TBI (C). The interhemispheric WM trajectories were generated for each cortical parcelation and shown as a whole brain tractogram. The red streamlines project in the left–right orientation, the green in the anterior–posterior direction, and blue within the inferior–superior plane. The reduced number of streamlines connecting frontal lobe regions is clearly evident for this patient. (Images courtesy of K.P.).

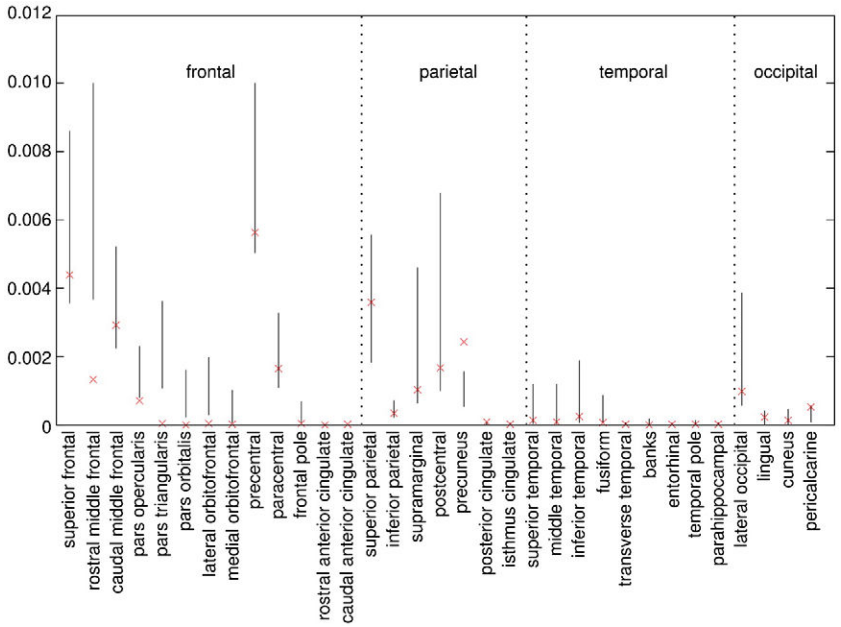

Fig. 6 – A connectivity profile showing loss of connectivity of frontal lobe structures for this patient compared to analogous data generated from a normative cohort. Normalized connectivity measures are plotted for each cortical parcelation. The lines represent the range of connectivity measures for the normal population; while the red cross signifies measures for the TBI patient. Significant reduction in connectivity is evident within the rostral middle frontal gryus, pars orbitalis, lateral, and frontal orbitofrontal regions. The advantage of the connectivity profile is that it enables quantitative assessment of connectivity measures. (Data courtesy of K.P.).

developing, no clear consensus has emerged from standard structural neuroimaging studies of the brain changes associated with post-TBI depression.

Chen et al. (2008) presented a study on the neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. Using fMRI- and voxel-based morphology, they found that athletes with concussion with depression symptoms showed reduced activation in the dorsolateral prefrontal cortex and striatum and attenuated deactivation in medial frontal and temporal regions. The severity of symptoms of depression correlated with neural responses in brain areas that are implicated in major depression. Voxel-based morphology confirmed GM loss in these areas. Furthermore, in patients who have suffered mild rotational acceleration/deceleration, the lesions may be confined to the WM of the frontal and temporal lobes at the GM/WM junction, owing to different inertial response of the two components with disruption of axons from the neuronal cell bodies (Ducreux et al., 2005). These results may reflect an underlying pathophysiology consistent with a limbic–frontal model of depression (Mayberg, 1997; Seminowicz et al., 2004).

As stated previously, brainstem structures are often affected in TBI, particularly in severe cases. It is interesting to note that two transcranial ultrasound studies of unipolar depressive non-TBI patients reported reduced echogenicity of the brainstem midline (Becker et al., 1994, 1995). This may be consistent with disruption of WM tracts, including the medial forebrain bundle, and it has been suggested that the effect of such disruption could be reversed by antidepressants (Becker et al., 2001). This is a sensible finding as nuclei of cells that synthesize serotonin, noradrenaline, and dopamine (i.e., key components implicated in depression) are located in the brainstem (Yadid and Friedman, 2008). However, in a replication of these studies with DTI in a group of MDD patients (Steele et al., 2005), no FA reduction in the brainstem was reported.

4.4. *DAI, DTI, and post-TBI depression*

Of the 17 studies that used DTI to investigate MDD (Table 2), none was in the context of post-TBI. It is of note, however, that one DTI study of DAI post-TBI (Salmond et al., 2006a) reported areas of low FA to be almost identical to those identified in a separate DTI study of a group of young adults with first-episode treatment-naive MDD (Ma et al., 2007) and very similar to the findings of Yuan et al. (2007) from a group of first-episode remitted geriatric depression. That is, Ma et al. (2007) showed that patients with MDD had significantly lower FA values in four brain WM regions (right middle frontal gyrus, left lateral occipitotemporal gyrus, the subgyral WM of the right parietal lobe (near the sulcus callosomarginalis and partially in the precuneus), and the right angular gyrus), and Yuan et al. (2007) also reported reduced FA in a number of those regions (right superior frontal gyrus, left inferior frontal gyrus, left middle temporal gyrus, right inferior parietal lobule, right middle occipital gyrus, left lingual gyrus, right putamen, and right caudate). Alexopoulos et al. (2008) reported similar, multiple regions of reduced FA (in MDD patients who did not achieve remission). The similarities between the findings of these studies suggest a common underlying

neuropathology, which is more widespread than some studies that limit their studies to one of two ROIs may indicate. Although not a study of depressed patients, Gutman et al. (2009) showed with DTI that the targets for deep brain stimulation when used to treat depression (subcallosal cingulate WM and/or anterior limb of the internal capsule) have distinct and widespread projections to frontal and temporal poles as well as the cingulate, thalamus, hypothalamus, nucleus accumbens, and brainstem; 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 MDD subjects (Zou et al., 2008), which is also one of the few studies reviewed that did not employ an older-age group of patients. It is therefore of note that Zou et al. (2008) reported reduced FA restricted to the internal capsule (and parietal region). The majority of DTI studies reviewed in Tables 1 and 2 employed an ROI method of analysing FA only in regions decided upon *a priori*, based on their interest in a particular area, usually based on clinical and/or research findings at that point in time. In addition, the placement of the ROI is subjective and manual errors may occur when defining the anatomical area. By contrast, few studies (such as those above) have investigated a larger number of regions or use a whole-brain approach, by use of voxel based morphology, for example. Even studies of TBI patients with known regions of damage (e.g., Ahn et al., 2006; Han et al., 2007; frontal damage TBI patients) do not always measure FA in those regions. It is only with these latter techniques that multiple regions can be identified as related or not related to MDD. In the context of tractography, it must be acknowledged that there are situations in which it can identify spurious pathways or fail to trace pathways that are known to exist (Dauguet et al., 2007; Dyrby et al., 2007; Pierpaoli et al., 2001).

The implication of prefrontal region involvement post-TBI and in those with MDD is sensible given that this region has profuse afferent and efferent axonal connections with multiple neocortical, subcortical, and limbic regions (Fuster, 2001; Mesulam, 1985). The DLPFC circuit is known for its central involvement in modulating mood regulation and cognitive ability (Taylor et al., 2004), projecting to the dorsolateral head of the caudate nucleus, then continuing to the lateral dorsomedial globus pallidus and, finally, to the ventral anterior and mediodorsal thalamus. The mediodorsal thalamus then sends fibers back to the DLPFC (Tekin and Cummings, 2002). Another DLPFC tract projects to the cingulum bundle and then to the temporal lobe. Furthermore, ventral hippocampal neurons project axons simultaneously to the prefrontal cortex and amygdala in rats and humans (Davidson et al., 2009; Ishikawa and Nakamura, 2006); the thalamus, caudate nucleus, nucleus accumbens, amygdala, and hippocampus all receive direct projections from the cortex (but not the globus pallidus; Wang et al., 2008b). In addition, the middle longitudinal fasciculus links associative and paralimbic cortices in the inferior parietal lobule, cingulate, and prefrontal regions with multimodal parts of the superior temporal region and the parahippocampal gyrus. There is also a major band of WM fibers (uncinate fasciculus) coursing between the rostral temporal region and the orbital and medial prefrontal cortex (Schmahmann et al., 2007). The elucidation from this review of the internal capsule as a major region implicated in MDD is therefore a sensible one, given its afferent and efferent connections to the two other major regions suspected as being involved in the development of MDD post-TBI (i.e., frontal and temporal regions).

4.5. *Technical factors relating to DTI*

As DTI data can only be obtained through postprocessing other than direct scanning, a set of MRI scanning image data including one T2-weighted image without gradient ($b=0$) and at least six diffusion-weighted images are required to solve the six independent parameters in each 3×3 tensor matrix (Ou and Wyatt, 2005). Hence, at least six directions are required. DTI resolution can be enhanced by increasing field strength and/or number of encoding gradient directions; hence, subtle DAI is more likely to be detected as field strength and/or number of directions acquired increases because these parameters alter estimations of anisotropy and diffusivity (Jones, 2004). It is therefore of interest to note that the studies reviewed in Tables 1 and 2 did not use consistent sequences. For example, a number of studies used the sequence as detailed in the original publication by Basser et al. (1994) (i.e., 1.5 T with six noncollinear directions), whereas others (e.g., Bazarian et al., 2007; Kraus et al., 2007; Yang et al., 2007) used a greater number of directions (up to 60) and/or a higher-field MRI scanner (up to 3 T). Fig. 4 shows an example of the difference in resolution when DTI is acquired with 12 and 35 directions.

As mentioned above, FA declines as MDD increases with age (Charlton et al., 2006; Ota et al., 2006; Persson et al., 2006; Pfefferbaum et al., 2006; Salat et al., 2005; Sullivan et al., 2006; Sullivan and Pfefferbaum, 2006), although regions differ in terms of when their FA begins to change. For example, Persson et al. (2006) reported older adults with a declining memory performance to have reduced FA in the anterior part of the CC compared to their stable counterparts, a finding supported by previous DTI studies that indicate this region to be specifically susceptible to age-related atrophy, while posterior regions are relatively spared (Head et al., 2004; Madden et al., 2004; O'Sullivan et al., 2001; Pfefferbaum et al., 2000; Pfefferbaum et al., 2005). Bhagat and Beaulieu (2004) reported CSF-suppressed DTI to demonstrate significant increases in FA of 3–12% in the young (21–25 years) and 2–14% in the elderly groups (61–74 years) with the largest changes being in the subcortical WM of the gyri. Furthermore, FA decreased by 10–19% in the subcortical WM of the gyri of the elderly subjects relative to the young. Collectively, FA appears to be relatively stable between the ages of 20 and 50 years.

Immature WM has less water restriction than mature tissue (hyperintense ADC signal relative to adult brain) and injured tissue typically has increased water restriction (hypointense ADC signal relative to uninjured immature brain tissue, Suh et al., 2001). This is supported, for example, by transcranial magnetic stimulation studies, indicating that motor thresholds in children are generally higher than for adults, that is, motor thresholds correlate negatively with age (Bender et al., 2005), although this is partly due to increasing cortical atrophy creating a greater scalp-to-cortex distance (Stokes et al., 2005). A recent study (Herbsman

et al., 2009) confirmed this, reporting that two parameters—skull-to-cortex distance and the anterior component of the principal diffusion direction of the corticospinal tract as it passes the internal capsule—are highly predictive of motor threshold in a linear regression model and account for 82% of the variance observed.

4.6. *Cognitive reserve, brain reserve, and depression post-TBI*

Investigations have found support for a cognitive reserve, and/or brain reserve, as a resilience factor against a number of psychiatric conditions, including dementia (e.g., Christensen et al., 2007; Perneczky et al., 2007; Sole-Padulles et al., 2009) and TBI (Kesler et al., 2003; Ropacki and Elias, 2003). For example, a recent systematic review of the effect of education on survival in Alzheimer's disease (Paradise et al., 2009) found that education delays the onset of the dementia syndrome in Alzheimer's disease (but does not lead to earlier death after diagnosis). Green et al. (2008) reported that recuperative affects of younger age post-TBI may be attributable to greater reserve capacity (as indexed by WM integrity) and that estimated premorbid IQ was associated with higher cognitive functioning outcome. In a large 10-year retrospective study of the effect of premorbid demographic factors on the recovery of neurocognitive function in 293 TBI patients (228 males and 65 females), Jeon et al. (2008) found that a higher level of education was a good prognostic factor for intelligence regardless of GCS score and younger age group showed a better result for memory with an exception of severe TBI group. In a study of a cohort of survivors of moderate–severe head injury at least 6 months after injury, Salmond et al. (2006a) found a significant difference between depressed and nondepressed survivors, with higher intelligence associated with lower rates of depression. The results suggest that premorbid intelligence may provide a resilience factor against depression in head injury survivors. Future DTI studies may be contributory in this context as a positive correlation has been reported between intelligence and FA (e.g., Jung and Haier, 2007; Yu et al., 2008).

4.7. *Fiber tracking and structural connectivity: limitations and future directions*

As previously outlined, many TBI studies have employed region-of-interest (ROI) type analyses of diffusivity maps (MD and FA) to measure diffuse axonal injury. One limitation of this approach is the difficulty of accurately placing ROIs within specific WM pathways contained within a complex network of fiber tracts. A solution to this problem is the use of fiber tracking algorithms that determine the trajectory of anisotropic structures, namely, WM fiber bundles, for extracting target neural networks. An excellent review of fiber tracking technology or "tractography" has been published by Jones (2008). This approach has been extensively used to investigate WM injury associated with TBI (Ducreux et al., 2005; Singh et al., 2010; Sugiyama et al., 2007; Wang et al., 2008a; Wilde et al., 2008).

However, fiber tracking also has a number of constraints when applied in neuroimaging research. A major concern is the use of the standard diffusion tensor model, utilizing either deterministic (Conturo et al., 1999; Mori et al., 1999) or probabilistic (Behrens et al., 2003; Parker et al., 2003) fiber tracking approaches, which is unable to resolve multiple fiber populations (Tournier et al., 2007). This is a significant issue considering more than one-third of voxels contained within the diffusion image have multiple fiber orientations (Behrens et al., 2007). A number of elegant approaches have been developed to reduce this problem. These strategies include the use of high-angular resolution diffusion imaging (HARDI) first proposed by Tuch et al. (2002), Q-ball imaging (Tuch, 2004), and diffusion-spectrum imaging (Wedeen et al., 2005). To achieve resolution of crossing fibers, these techniques normally require lengthy acquisition times involving high diffusion-encoding gradient strengths and a larger number of diffusion-encoding directions. The current challenge is the development of robust fiber tracking technologies with scan acquisition times that are suitable for clinical populations (less than 15 minutes). Such techniques have yet to be applied to study diffuse axonal injury.

A weakness lies in the fact that the same brain regions implicated in both TBI and spontaneous depression in the current review have also been shown to be abnormal in structure and in FA in a number of other psychiatric disorders. For example, reduced FA in these ROIs has been reported in patients with Rett syndrome, mild cognitive impairment, obsessive–compulsive disorder, autism, and ADHD (Chua et al., 2009; Mahmood et al., 2010; White et al., 2008). We therefore suggest that future FA research in TBI and MDD should attempt to also include other psychiatric disorders.

As brain injury effects interhemispheric communication, new strategies based on measuring structural connectivity within the brain may provide improved markers of damage to functional networks and enable the investigation of possible reorganization or recovery mechanisms. This approach is based on the concept that cortical regions have specific connection profiles that can be determined using the probabilistic tractography framework (Johansen-Berg and Rushworth, 2009; Perrin et al., 2008; Zalesky and Fornito, 2009). Normally, the cortical mantle is parcelated into a number of functionally discrete regions with connections or streamlines between these regions generated using a HARDI or Q-ball fiber acquisition. A connectivity matrix or profile can be generated, yielding quantitative information about the number of connections or streamlines anatomically linking cortical parcellations (see Figs. 5 and 6). This approach has been successfully used to subdivide the corpus callosum based on functional cortical anatomy (Park et al., 2008). Such technology shows considerable promise in the study of TBI, as many of the commissural WM fiber bundles that link the hemispheres of the brain are susceptible to diffuse axonal injury. Importantly, structural connectivity has the potential to provide a unique insight into the relationship between injured neural networks, particularly within frontal and temporal lobe structures and the chronic development of depression often associated with TBI.

4.8. *Summary and implications*

Current opinion regarding the etiology of depression is that it appears to relate to the connectivity and efficiency of connections linking anatomically divergent brain regions (Filley, 2005). Hence, DAI-related changes in WM tracts are likely to be associated with the development of depression.

Structural or functional disconnection between brain regions is likely to result in the type of functional abnormalities observed in patients with non-TBI-related mood disorders.

As DAI-related injury is poorly visualized on conventional structural MR images, only limited assumptions can be made about a brain region's role in the etiology. Recent developments in brain imaging, particularly DTI, have provided the capability to assess the integrity of WM tracts. DTI is based on the characteristics of water diffusion ('anisotropy') in the myelinated neuronal axon pathways; altered anisotropy results from pathological processes that change the microstructural environment, such as neuronal swelling or shrinkage, increased or decreased extracellular space, and loss of tissue organization (Anderson et al., 1996). This advanced technique is being applied to study TBI because it can detect substantial WM changes not seen with structural imaging (Rugg-Gunn et al., 2001; Xu et al., 2007). Most TBI–DTI studies conducted to date have been in the acute injury state, and while some have begun to explore the relationship between WM changes and cognition in the more chronic state, they have not yet explored the relationship between WM abnormalities and psychiatric disorders such as depression. Given the increasing recognition of the relevance of abnormalities of WM and connectivity in depression in the noninjured brain and the increasing availability of DTI yet its lack of use (as revealed by this review), this is clearly an area on which future research should focus (Filley, 2005). Improved understanding of the pathophysiology of post-TBI depression should also enhance the development of new targeted treatment interventions and increase our capacity to identify patients at-risk. Ultimately, prediction of outcome and requirement for early intervention will be greatly enhanced through this review.

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