Brain white matter in the context of traumatic stress: a diffusion tensor imaging study

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Brain White Matter in the Context of Traumatic Stress: a Diffusion Tensor Imaging Study

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Originality Statement

I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at UNSW or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom I have worked at UNSW or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Signed:

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Abstract

This body of research investigated brain white matter integrity in the context of Post-traumatic Stress Disorder (PTSD) and mild traumatic brain injury (mTBI). The overarching aim of this project was to identify and describe neural mechanisms associated with these two conditions. In order to achieve this, diffusion tensor imaging (DTI) was used to study microstructural profiles in four participant groups: (a) mTBI, (b) PTSD, (c) trauma-exposed controls, and (d) non-trauma-exposed controls. DTI is a structural imaging technique that provides information about the anatomical position, orientation and anisotropy of brains white matter neural tracts. Previous studies that have investigated neural mechanisms of traumatic stress have largely used healthy individuals with no prior exposure to psychologically traumatic events as a comparison group. Apart from including a group of healthy, non-trauma exposed volunteers, the present project also incorporated a group of participants with a history of trauma in order to control for the potential confounding effects of such prior experience. Based on past research, this study selected three white matter tracts that have been previously implicated in PTSD, mTBI or both. Study 1 investigated microstructure of the corpus callosum. This tract was characterized by compromised integrity in both PTSD and mTBI. Study 2 examined the underlying structure of the cingulum bundle. mTBI showed aberrant changes that were not observed in PTSD. Study 3 investigated white matter coherence within the uncinate fasciculus. Neither mTBI nor PTSD were associated with microstructural alterations within this tract. Finally, Study 4 explored individual contributions of PTSD severity and history of mTBI to the observed microstructural damage within the corpus callosum and cingulum. Global anisotropy changes within the corpus callosum were shown to be associated with both factors. Alterations within the cingulum, however, were only predicted by a history of mTBI. Overall, the findings from this thesis indicated that while the corpus callosum showed vulnerability to the effects of both PTSD and mTBI, changes within the cingulum bundle appeared to be only mediated by a history of mTBI.

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Abbreviations

ACC	anterior cingulate cortex
BAI	Beck anxiety inventory
BDI	Beck depression inventory
BIRU	brain injury rehabilitation unit
CAPS	clinician administered PTSD scale
CBT	cognitive behavioural therapy
CC	corpus callosum
CT	computerized tomography
DSM	diagnostic statistical manual of mental disorders
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
ERP	event related potentials
FA	Fractional Anisotropy
fMRI	functional magnetic resonance imaging
GAD	generalized anxiety disorder
GCS	Glasgow coma scale
MD	Mean Diffusivity
MDD	major depressive disorder
M.I.N.I.	mini international neuropsychiatric interview
MFC	medial frontal cortex
mPFC	medial prefrontal cortex
MRI	magnetic resonance imaging
mTBI	mild traumatic brain injury

MR	magnetic resonance
MS	multiple sclerosis
NTEC	non-trauma exposed controls
OCD	obsessive compulsive disorder
PCC	posterior cingulate cortex
PCS	post-concussive syndrome
PFC	prefrontal cortex
PTA	post-traumatic amnesia
PTSD	post-traumatic stress disorder
rCBF	regional cerebral blood flow
RF	radio frequency
ROI	region-of-interest
SAD	social anxiety disorder
TBI	traumatic brain injury
TEC	trauma exposed controls
TSC	traumatic stress clinic
UF	uncinated fasciculus
vmPFC	ventromedial prefrontal cortex
WM	white matter

Chapter 1

Introduction to Traumatic Stress

Epidemiological studies indicate that most people will experience a psychologically traumatic event in their life (Breslau, Davis, Andreski, & Peterson, 1991). These range from events such as a car accident to being deployed to a war zone. In the case of a positive outcome, a traumatic event does not have any long-lasting effects and individuals can resume their pre-trauma level of functioning. In less favourable circumstances, however, the result can be life-changing with severely disabling consequences for the affected person.

Certain traumatic events can result in injuries to the brain. While these are most commonly observed after motor vehicle accidents due to the acceleration-deceleration forces, they may also occur following assaults, falls, and industrial accidents. In the context of combat, recent attention has also focused on the effects of blast injuries (Ropper, 2011). Traumatic brain injuries (TBI), even of mild severity, can result in ongoing psychological problems. The context in which mild traumatic brain injuries (mTBI) occur represents a threat to an individual's physical integrity, thereby putting them at a risk of developing post-traumatic stress disorder (PTSD).

One of the core debates in the field of traumatic stress over the past decade has been the nature of mTBI. Whereas some have argued that it is a potentially debilitating condition arising from neurological insult, others posit that the effects of mTBI are more accurately attributed to the stress reactions that occur in the wake of the traumatic experience. Although there is emerging evidence pertaining to the contributing influence of PTSD symptoms on mTBI-related sequelae, there is a dearth of evidence pertaining to neural mechanisms that may moderate the intersection of these two conditions. Accordingly, the overarching goal of this research program is to investigate mTBI in the context of PTSD symptoms, with a particular focus on white matter integrity of neural fibres.

1.1 Mild Traumatic Brain Injury

TBI is a neurological event which results from a strong mechanical or biomechanical force applied to the brain (Vasterling, Verfaellie, & Sullivan, 2009). TBI ranges in severity from very severe cases characterized by considerably reduced ability to autonomously function on a day to day basis, to very mild cases. mTBI is the most prevalent type of TBI (Zatzick, 2010). It is currently estimated that approximately 1.7 million people in the US alone are diagnosed with TBI, with 75% of all injuries classified as mild (Fitzgerald & Crosson, 2011). According to the most recent international survey conducted by the World Health Organization (WHO), the incidence of hospital-treated mTBIs in Australia is estimated to be approximately 75-96 per 100,000 population (Motor Accidents Authority NSW, 2008). Although there is an ongoing debate over the definition of mTBI, some of the most commonly agreed on symptoms required for the diagnosis are injury to the head, alteration or loss of consciousness for up to 30 minutes, post-traumatic amnesia that does not exceed 24 hours, and focal neurological deficits (Ruff, 2005). Other definitions include Glasgow Coma Scale (GCS) score of 13-15, indicating minimal alteration to awareness (Teasdale & Jennett, 1974).

Most mTBIs resolve within a few weeks after the traumatic incident without any ongoing issues. In 40-50% of all mTBI cases, however, patients report experiencing three or more symptoms one year after the injury (Vasterling et al., 2009). These persistent symptoms, commonly termed Post Concussive Syndrome (PCS), encompass subjective cognitive difficulties, physiological complaints and emotional problems (McMillan, 2001; Vasterling et al., 2009). The underlying causes of PCS symptoms have been widely debated. Some researchers believe that PCS is caused by microscopic brain damage that cannot be detected by conventional imaging techniques (Niogi et al., 2008). Using diffusion tensor imaging (DTI), Niogi et al. (2008) observed a positive correlation between cognitive deficits associated with PCS and diffuse axonal injury in a number of white matter (WM) regions, including the anterior corona radiata, the uncinate fasciculus, the inferior longitudinal fasciculus, cingulum bundle and the genu of the corpus callosum (Niogi et al., 2008). Similarly, Smits et al.'s (2010) study revealed an association between the severity of PCS and the microstructural injuries in the uncinate fasciculus, the inferior fronto-occipital fasciculus, the internal capsule and the corpus callosum, as well as in the parietal and frontal subcortical WM (Smits et al., 2011). These findings imply that PCS could be a result of organic changes within the brain WM.

An alternative theory is that PCS is accounted for by pre-existing or concurrent psychological conditions. In fact, Clarke et al. (2012) have shown that mTBI patients who scored highly on affective factors, such as depression, anxiety and neuroticism also reported more PCS symptoms (Clarke, Genat, & Anderson, 2012). Specific to anxiety, a number of studies have demonstrated that PTSD is the strongest factor associated with PCS after controlling for overlapping symptoms (Dean, O'Neil, & Sterr, 2012; Hoge et al., 2008; King, 1996; King, Caldwell, & Wade, 1999; Schneiderman, 2008). In a longitudinal study, Meares and colleagues reported that both acute and persistent PCS was predicted only by PTSD and pain levels, and was independent of having sustained a mTBI (Meares et al., 2011).

1.2 Post-Traumatic Stress Disorder (PTSD)

1.2.1 Diagnostic Statistical Manual of Mental Disorders- 5 Definition

Along with mTBI and PCS, another possible condition that may develop following a traumatic event is PTSD. According to the *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* (*DSM-5*; American Psychiatric Association, 2013), PTSD is present when a complex array of criteria are satisfied, the first of which is the exposure to a traumatic event during which an individual either experiences or witnesses their own or someone else's life being in danger. The second PTSD symptom is re-experiencing of the traumatic event in a form of intrusive memories, nightmares, and/or flashbacks. The third cluster of symptoms involves persistent avoidance of people and places associated with the traumatic event. The fourth criterion is the presence of negative alterations to mood and cognitions. The fifth criterion describes changes in arousal and reactivity. These symptoms must persist for at least one month causing significant distress and impaired functioning and cannot be explained otherwise. The 12-month prevalence of PTSD in a general population is estimated to be approximately 4-5% (Kessler, Sonnega, Hughes, & Nelson, 1995; Slade, 2009).

1.2.2 Neurobiology of PTSD

Many studies have attempted to understand the neurobiology of PTSD. Fear circuitry theory is the most prevalent and the most widely supported model of PTSD and is based on animal studies of fear conditioning (Pitman, Shalev, & Orr, 2000). Upon exposure to a fearful stimulus, the sensory cortices transmit information to the thalamus, which further connects to the amygdala, both directly and indirectly. This theory posits that PTSD is characterized by overly reactive amygdala and diminished

activation of the PFC. Amygdala belongs to the limbic system and is involved in fear processing (Heim & Nemeroff, 2009). Through its connection to the medial prefrontal cortex (mPFC), it regulates fear responses and extinction of fear memory (Heim & Nemeroff, 2009). The mPFC exerts inhibitory control over the emotional responses generated by the amygdala. In particular, it mediates fear extinction via direct inhibition of acquired fear memories (Heim & Nemeroff, 2009).

Evidence supporting this model comes from neuroimaging studies that have used both aversive but non-trauma related stimuli as well as trauma-related imagery (Britton, Phan, Taylor, Fig, & Liberzon, 2005; Bryant et al., 2008; Shin et al., 2001; Shin et al., 2004; Williams et al., 2006). Functional magnetic resonance imaging (fMRI) studies have observed reduced activation in the mPFC (in the anterior cingulate cortex (ACC) in particular) in response to fearful faces presented under overt conditions in PTSD patients compared to controls (Shin et al., 2005; Williams et al., 2006).

Changes in the activity of the amygdala in PTSD have also been demonstrated in a large number of fMRI studies using a variety of paradigms. In response to covertly presented fearful compared to happy faces, PTSD patients have displayed exaggerated amygdala response (Bryant et al., 2008; Rauch et al., 2000). Similar finding was observed in response to overtly presented fearful faces (Williams et al., 2006). Increased amygdala activation has also been associated with individual PTSD symptom clusters, such as avoidance symptoms, thus potentially indicating that avoidance may be a compensatory mechanism that helps to down regulate amygdala activity (Simmons et al., 2011). Some recent studies have also observed reduced volume in both left and right amygdalae (Morey et al., 2012). There is thus strong evidence from fMRI studies confirming the involvement of amygdala in mediating PTSD psychopathology.

Presentation of trauma-related imagery has been observed to produce similar results to negative stimuli presentation. Shin et al. (2004) asked combat veterans to recall personal traumatic experiences and observed increased regional cerebral blood

flow (rCBF) in the left amygdala which was inversely correlated with rCBF in the medial frontal gyrus. Britton et al. (2005) observed deactivation in the rostral ACC as demonstrated by increased activation to neutral autobiographical compared to traumatic autobiographical memories related to combat. These findings have generally been replicated across other provocation studies that have used a variety of stimuli to elicit emotional reactions in PTSD participants (Shin & Liberzon, 2010).

Another structure that has been implicated in PTSD is the hippocampus and has been associated with reduced volume (Bremner et al., 1997; Gurvits et al., 1996; Kasai et al.; 2008; Morey et al., 2012; Villarreal et al., 2002) and decreased activation in response to trauma-related images (Hayes et al., 2011). This area is known to be involved in regulating stress responses and contextual aspects of fear conditioning (Heim & Nemeroff, 2009). Some studies in chronic PTSD, however, have reported no changes in hippocampal volume suggesting that these changes are not PTSD specific (Jatzko et al., 2006). Furthermore, findings from twin studies indicate that reduction in hippocampal volume is a risk factor for stress related psychopathology rather than a consequence of PTSD symptomatology (Gilbertson et al., 2002; Pitman et al., 2006).

1.3 Overlap Between PTSD and mTBI

PTSD and mTBI very frequently co-occur in situations that are both psychologically traumatic and confer risk of brain injury (Vasterling, Bryant, & Keane, 2012). Hoge and colleagues found that the presence of PTSD seemed to increase the risk of post-concussive symptoms in Army personnel who have experienced mTBI with or without loss of consciousness (Hoge, Thomas, Cox, Engel, & Castro, 2008). Similarly, King (1996) showed that within one week of mild to moderate TBI, depression, anxiety and stress were highly predictive of PCS three months post- injury. Comparable findings have been observed in civilian survivors of traumatic injury, where impairment was increased by psychiatric disorder and not mTBI (Bryant, Creamer, O'Donnell, Silove, Clark, & McFarlane, 2010). When Vanderploeg, Belanger and

Curtiss (2009) measured the contribution of the two conditions to individual PCS symptom clusters, they found that PTSD and mTBI had independent contributions to the somatic, cognitive and emotional symptoms of PCS, with PTSD having a considerably larger effect. The authors concluded that the two conditions are likely to have additive and independent effects on the severity of PCS.

Some researchers have argued, however, that if the traumatic injury is followed by a loss of consciousness, PTSD is unlikely to develop since the memories of the event did not have a chance to consolidate (for a review, see Vasterling, 2009). This theory has been questioned by a number of studies indicating that only if the injury is moderate to severe does it reduce the risk of PTSD (McMillan, 2001; Sbordone & Liter, 1995; Zatzick, 2010). Nevertheless, regardless of loss of consciousness, it has been found that those with mTBI (11.8%) are more likely to develop PTSD than those without (7.5%) (Bryant, O'Donnell, Silove, Clark, & McFarlane, 2009). A longer post-concussive amnesia was found to be a protective factor thus emphasising the importance of memory encoding and consolidation in development of the disorder (Bryant et al., 2009).

Although, several studies have suggested that both PTSD and mTBI can result from a traumatic event, symptoms that characterise PTSD could also be a resulting manifestation of a brain injury (Schneiderman, 2008). For this reason, the relationship between these two conditions is sometimes explained in terms of their shared neural basis. As mentioned previously, areas that are frequently implicated in PTSD are those involved in fear conditioning and include the amygdala, mPFC and hippocampus (Shin & Liberzon, 2010). Damage to these areas of the brain has been found to reduce the occurrence of PTSD (Koenigs et al., 2008), thus further emphasizing their involvement in generating symptoms associated with this condition.

On the basis of the findings that prefrontal/limbic/amygdala networks are implicated in PTSD, it has been posited that compromise of these networks in the course

of sustaining mTBI may elevate the risk of PTSD (Bryant, 2008). Due to acceleration/deceleration and contre-coup injuries, areas that are frequently affected in traumatic events are those involved in emotional regulation, memory and judgement. Hence, these symptoms can sometimes mimic psychopathology or even perpetuate it (Vasterling et al., 2012). That is, mTBI is likely to result in a loss of inhibitory control over the limbic system through damage to the PFCs and further exacerbate PTSD symptoms.

1.4 Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a structural imaging technique that is able to provide insight into the microstructural organization of the living tissue. This technique has been applied in a large number of neuroscientific studies including traumatic brain injury, schizophrenia, depression, stroke and ageing (O'Donnell & Westin, 2011). In the context of DTI, diffusion (also known as Brownian motion) refers to the apparently random motion of water molecules within living tissue caused by thermal interactions between the molecules (Mori & Zhang, 2006). DTI relies on the idea that the shape of the ellipsoid that best describes the 3-dimensional shape of diffusion differs between different types of brain tissue due to the presence of microstructures such as axon membranes and intracellular organelles (O'Donnell & Westin, 2011). Specifically, in tissues where there are relatively few microstructures to obstruct diffusion (such as in the ventricles of the brain), water molecules tend to diffuse equally in all directions, which corresponds to an approximately spherical diffusion ellipsoid (isotropic diffusion). In contrast, tissues with a defined and ordered microstructure (such as white matter fasciculi) can provide significant obstacles to diffusion; for example, water molecules are more readily able to diffuse parallel to the tightly aligned, myelinated axons of white matter fasciculi as opposed to perpendicular to them. Hence the shape of the diffusion ellipsoid used to model the shape of diffusion is not spherical, but is instead elongated along its longitudinal axis (Figure 1.1). This

is known as anisotropic diffusion (Mori & Zhang, 2006). It is important to note that although conventionally the 3D shape of diffusion has been modelled in the shape of an ellipsoid, it is not a strict requirement.

In order to measure water diffusion within the brain, MRI relies on a gradient system (Mori, 2007). The magnet produces the magnetic field called *B0* along the magnet bore, defined as the *z* axis (Mori & Zhang, 2006). Apart from the main *z* axis, two additional axes exist that describe the right-left and up-down orientations referred to as *x* and *y* axes, respectively (Mori, 2007). A magnetic field gradient can be introduced along any of these axes, which in turn changes the strength of the *B0* linearly (Mori, 2007). By combining *x, y* and *z* gradients, a magnetic field gradient can be created. A gradient here refers to the idea that the strength of the magnetic field progressively decreases as it moves along the gradient axis. Gradients can be switched on and off and are therefore termed pulsed field gradients (Mori, 2007). It is this property of gradients that makes diffusion visualization possible.

At first, after radio frequency (RF) pulse excitation, protons at different locations produce MR signals of the same frequency (Mori, 2007). Upon presentation of the first gradient, water molecules undergo a phase shift depending on their position along the axis, with some molecules experiencing a greater shift than others (Mori, 2007). When the gradient pulse is switched off, phases of the molecules are no longer identical (Mori, 2007). As a result, loss of signal is observed (dephasing) (Mori, 2007). When the second gradient pulse is introduced (rephasing), the molecules that have remained stationery will return to their original alignment whereas molecules that have moved as a result of diffusion will no longer be in the same phase thereby creating a signal loss which in turn allows for inferences about the nature of diffusion to be made (Mori, 2007). Importantly, fibres are, of course, not always oriented along one of the specified axes and therefore in order to accurately measure axon orientation without having to measure diffusion along an impractically large number of axes, the concept of a diffusion tensor (or ellipsoid) has been introduced (Mori, 2007).

Construction of a diffusion tensor relies on a Gaussian model to describe the movement of water molecules (Jones, 2008). Based on this model, the diffusion tensor can be thought of as an ellipsoid with three eigenvectors that are perpendicular to each other and have three positive eigenvalues (λ_1, λ_2 and λ_3) associated with them (Jones, 2008). The physical length of the longest axis of the diffusion ellipsoid is determined by the eigenvalue λ_1 (O'Donnell & Westin, 2011). The eigenvalues λ_2 and λ_3 represent the physical lengths of the middle and shortest axes, respectively (Figure 1.1). The lengths of the axes (i.e. the eigenvalues) and their orientations (i.e. the eigenvectors) can be estimated according to six parameters. Using these six parameters, the diffusion ellipsoid can be calculated (Mori & Zhang, 2006). These six measurements are sufficient to create an ellipsoid using a 3×3 symmetric matrix of numbers termed the diffusion tensor (Basser, 1995) (Figure 1.2).

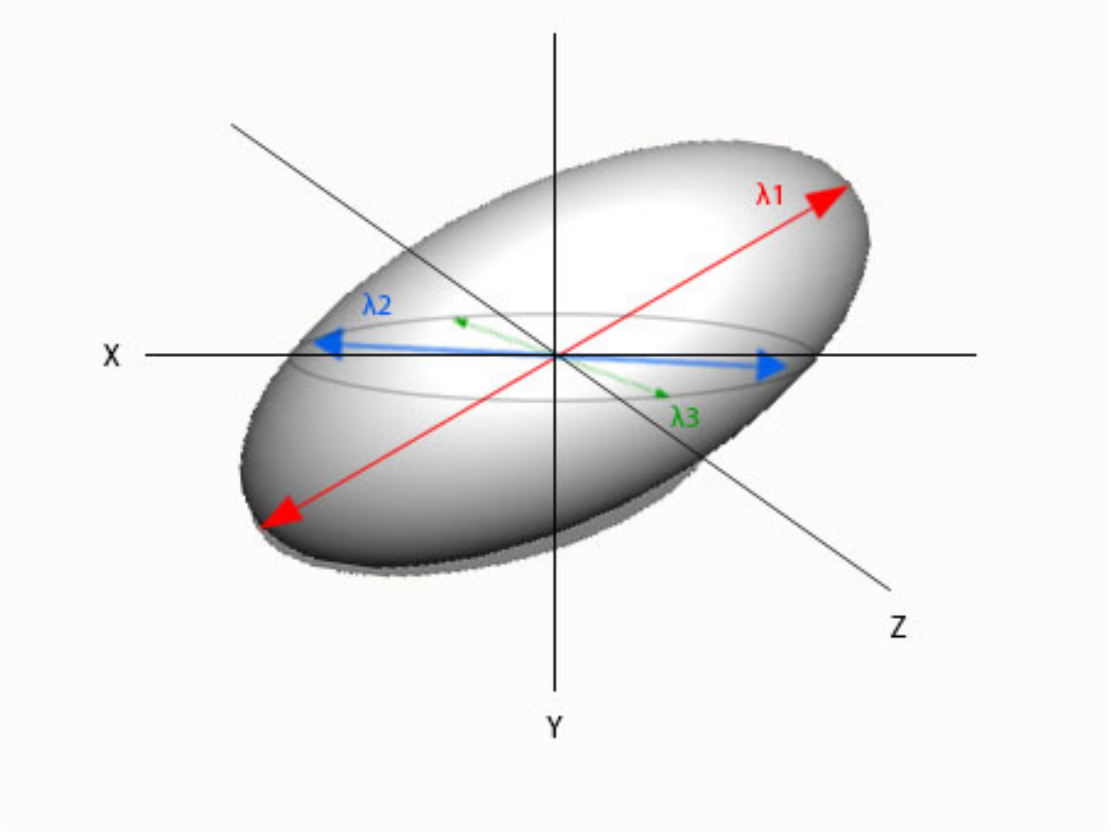

Figure 1.1. Schematic representation of the diffusion ellipsoid, with the lengths λ_1, λ_2 and λ_3 indicated (adapted from Mori and Zhang (2006))

$$\mathbf{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix}$$

Figure 1.2. Diffusion tensor matrix (adapted from Basser (1995))

A number of metrics have been developed that are used to quantify different aspects of the shape of the diffusion ellipsoid. Fractional Anisotropy (FA), Mean Diffusivity (MD), Perpendicular Diffusivity and Parallel Diffusivity are among the most frequently used metrics (Mori & Zhang, 2006). FA is one the most commonly used measures which estimates the level of anisotropy of the diffusion ellipsoid (i.e. the extent to which the diffusion ellipsoid is non-spherical), and is defined according to the following equation (where λ_1, λ_2 and λ_3 refer to the three eigenvalues of the diffusion tensor, as previously described):

$$FA = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \tag{1.1}$$

(Mori & Zhang, 2006).

FA values range from 0 to 1, with higher values indicating higher anisotropy (i.e., a less spherical diffusion ellipsoid). Clinical studies most frequently use FA as a marker of WM integrity with lower values reflecting more isotropic (i.e., spherical) diffusion, which could potentially reflect axonal membrane injury, demyelination, axonal damage and/or decreased axonal packing density (Kubicki, McCarley, Westin et al., 2007; Thomason & Thompson, 2011). A number of studies have provided a direct link between FA decrease and myelin damage (e.g. Concha, Gross, Wheatley, and Beaulieu (2006) and Klawiter et al. (2011)). Similar observation has been made for axonal membrane injury where reduction in FA has been shown to be associated with axonal fragmentation (e.g. Concha et al. (2006) and (Werring et al., 2000)). An association between decreased axonal packing density and decrease in FA has also been demonstrated (e.g. Cader et al. (2007)).

MD refers to the average of the three eigenvalues, and hence is dependent on the overall size of the diffusion ellipsoid (Thomason & Thompson, 2011). MD is defined according to the following equation:

$$MD = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3} \tag{1.2}$$

(Whitford, Kubicki, & Shenton, 2011)

Another measure that is closely related to MD is Trace and represents the sum of eigenvalues: $(\lambda_1 + \lambda_2 + \lambda_3)$ (Basser, 1995; Kubicki et al., 2007). Similar to MD, this measure has also been used to describe the overall displacement of water molecules (Kubicki et al., 2007).

MD and Trace describe the overall movement of water molecules whereas FA is a measure of the level of anisotropy (Choi et al., 2011). In healthy brain WM, diffusion within the axon is restricted due to the presence of myelin and various cellular organelles. When some part of the axon is damaged, however, water diffusion becomes less restricted, thereby increasing both Trace and MD. For this reason, increases in MD and Trace in WM have been associated with neuropathology (Thomason & Thompson, 2011).

Radial Diffusivity (also referred to as Perpendicular Diffusivity) refers to the magnitude of diffusion perpendicular to the principal eigenvector (Mori & Zhang, 2006; Song et al., 2002). Radial Diffusivity is defined in the following way:

$$\lambda \perp = \frac{(\lambda_2 + \lambda_3)}{2} \tag{1.3}$$

(Song et al., 2002).

Axonal Diffusivity (also referred to as Parallel Diffusivity) is represented by $\lambda \parallel = \lambda_1$ (Song et al., 2002). Increase in Radial Diffusivity has been interpreted to signal demyelination (Mori & Zhang, 2006; Song et al., 2002; Song et al., 2003; Song

et al., 2005). In their pioneering study, Song et al. (2002) damaged the myelin sheath in the optic nerve of a rat brain and using DTI demonstrated that dysmyelination was associated with increased Radial Diffusivity whereas there was no difference in Axonal Diffusivity between the experimental and control groups of animals. Later, Song et al. (2003) used a mouse model of optic ischemia to investigate whether axon and myelin degeneration could be predicted by Axonal Diffusivity and Radial Diffusivity, respectively. The authors observed that on the third day following the induced injury, there was a marked decrease in Axonal Diffusivity which corresponded to axonal loss reflected in histological findings. Moreover, on the fifth day, there was a marked increase in Radial Diffusivity which was associated with histological findings of myelin damage (Song et al., 2003). These DTI metrics, therefore, provide valuable information regarding the underlying WM microstructure that drives changes in FA. Even in the absence of changes in the global anisotropy measures, such as FA, alterations in Perpendicular Diffusivity and Parallel Diffusivity still provide valuable information regarding white matter microstructure. Unlike FA, these two metrics are capable of describing the exact nature of structural alterations.

Another metric that has recently gained interest is Mode which is used to describe the 3D shape of the diffusion ellipsoid and is characterized as being either tubular (cigar-shaped) or planar (coin-shaped) (Figure 1.3) with increased values proposed to reflect neuropathology of WM (Ennis & Kindlmann, 2006; Westin et al., 2002). Although both tubular and planar anisotropies are non-spherical, they describe very different shapes which in turn imply radically different underlying microstructure.

Mode is estimated using the following formula:

$$Mode = \frac{(2\lambda_1 - \lambda_2 - \lambda_3)(\lambda_1 - 2\lambda_2 - \lambda_3)(\lambda_1 - \lambda_2 - 2\lambda_3)}{2(\sqrt{\lambda_1\lambda_1 + \lambda_2\lambda_2 + \lambda_3\lambda_3 - \lambda_1 2\lambda_2 - \lambda_2\lambda_3 - \lambda_1\lambda_3})^3} \tag{1.4}$$

(Whitford et al., 2010).

FA, Mode and MD are (almost) mathematically independent and can be studied simultaneously (Whitford et al., 2011). Concurrent changes within these measures

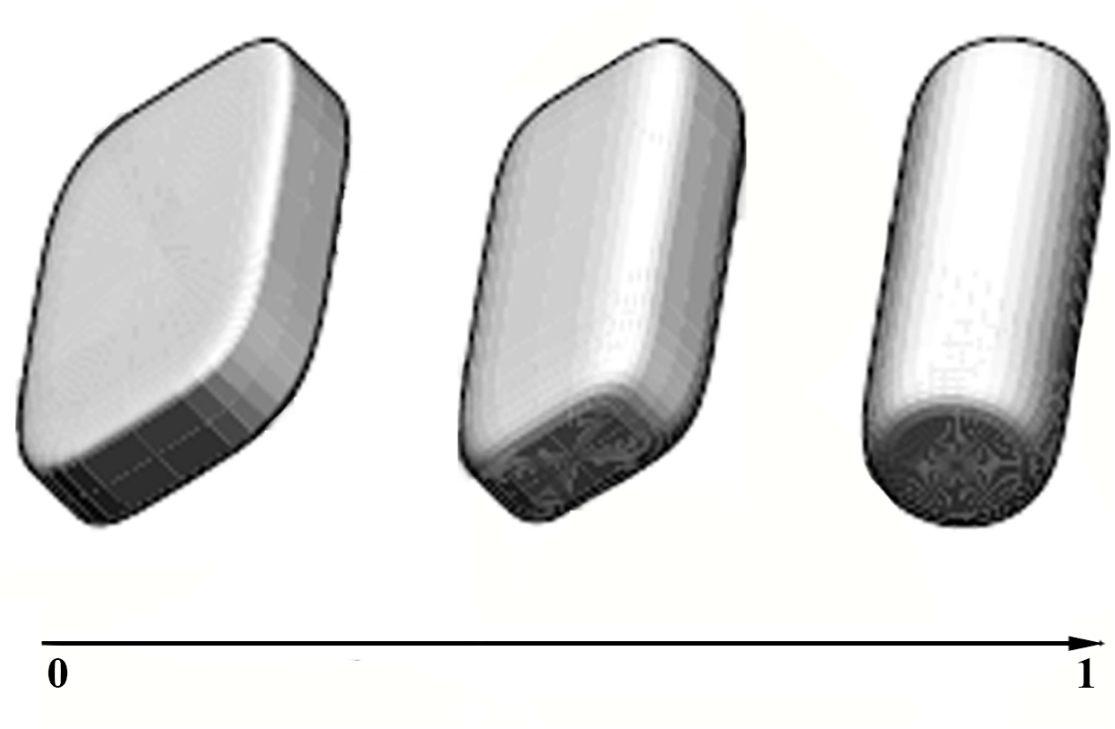

Figure 1.3. An anisotropic diffusion ellipsoid can either be planar (i.e. shaped like a coin) or tubular (i.e. shaped like a cigar). In this example, only 3D shapes of Mode in the positive value range are presented, with the leftmost representing a more planar ellipsoid and the rightmost displaying tubular anisotropy (Kindlmann, Ennis, Whitaker, & Westin, 2007).

may signal dysfunction as well as neural advantage (Thomason & Thompson, 2011.

1.5 Diffusion Tensor Tractography

Information obtained from DTI data can be used in tractography analysis for WM tracts visualization. Tractography allows one to select and identify WM fasciculi in vivo, and to hence visualize connections between different parts of the brain. Rather than visualizing axons directly, DTI tractography recreates these trajectories by measuring water diffusivity along different directions (Figure 1.4). In other words, tractography relies on the direction of the diffusion ellipsoid which is in turn determined by the eigenvectors (Catani, 2006).

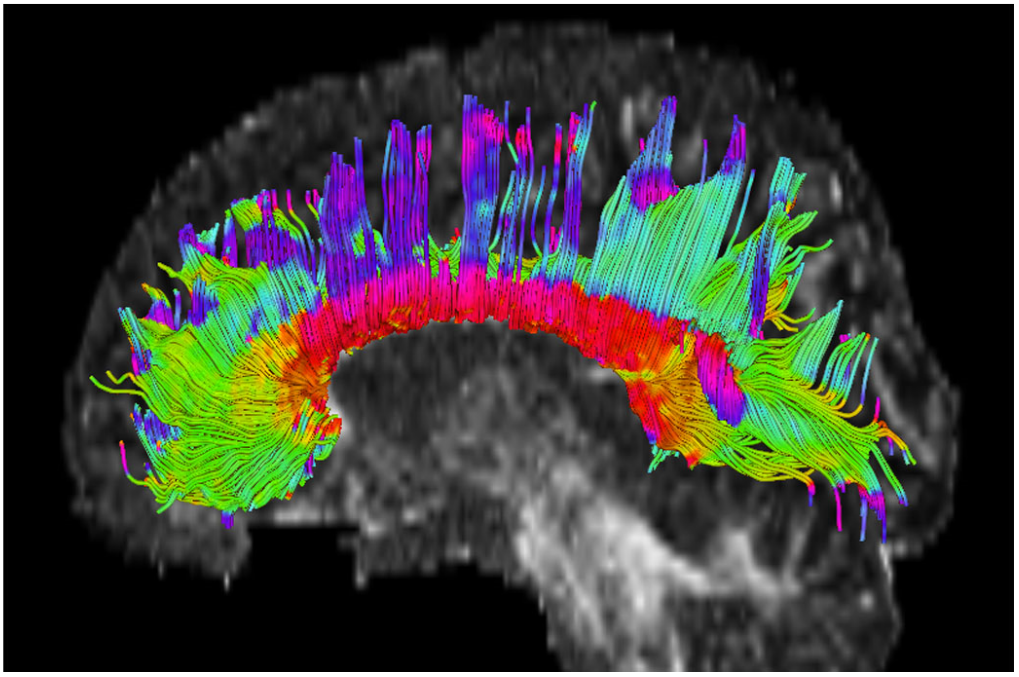

Figure 1.4. Example of a white matter tract, namely the corpus callosum, reconstructed using streamline tractography approach. Different colours are used to represent fibre orientations: red represents left to right orientation, green represents anterior- posterior orientation and blue shows inferior- superior connections. DTI is overlaid on FA map.

One of the commonly used approaches in tractography is referred to as one tensor streamline tractography or tract propagation (Mori, 2007; Mori & van Zijl, 2002). This approach was originally successfully used on a fixed rat brain and showed to be highly consistent with histological knowledge, such that the shape of the fibres visualised with tractography was consistent with the real shape of fibres that were surgically extracted (Mori, Crain, Chacko, & Van Zijl, 1999).

Streamline tractography follows three steps (Mori & van Zijl, 2002). The first step in this approach is to estimate the fibre orientation information provided by the principal eigenvector of the diffusion ellipsoid. As discussed earlier, since the principal direction of the diffusion ellipsoid is determined by its principal eigenvector, this information can then be used in 3D tract reconstruction by propagating a line (known as a streamline) from voxel to voxel through the principal eigenvectors. Finally, based on orientations of the principal eigenvectors, streamlines can propagate

until they reach a region of low anisotropy (where the orientation of the diffusion ellipsoid becomes ambiguous due to its spherical nature) at which point tractography is terminated. (Mori & Zhang, 2006) (Figure 1.5). Another termination approach relies on information about the angle change between voxels where an angle threshold is set that prohibits sharp turns during streamline propagation (Mori & van Zijl, 2002).

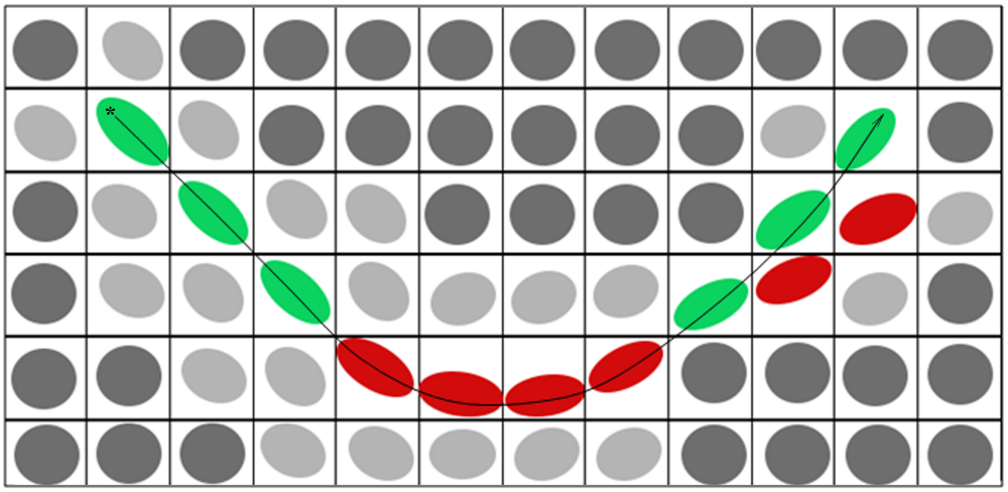

Figure 1.5. Schematic representation of streamline tractography approach. All circular shapes represent diffusion ellipsoids that are colour-coded according to their orientation such that green represents inferior to superior orientation and red is indicative of left to right orientation. Grey circles represent diffusion ellipsoids that have low anisotropy and hence are predominantly round in shape. Arrow connects the neighbouring voxels through their principal axes (Adapted from Mori and Zhang (2006)).

Although DTI provides information about static anatomy and not about physiology, cortical projections derived via tractography can be used in functional connectivity analysis by providing information on the directions of connections, or how the different regions interact within a specified behavioural network (Catani, 2006; Mori & Zhang, 2006). Additionally, tractography can be used in region-of-interest based analyses where the MR properties of segmented regions can be quantified (Mori, 2007). Finally, this technique has proved useful in estimating tract trajectories which can then be used to identify abnormalities of WM due to developmental pathologies or tumours (Mori, 2007).

1.6 White Matter Changes in PTSD and mTBI

Researchers have investigated WM changes in a range of neuropsychiatric conditions including head injury, PTSD, schizophrenia, major depressive disorder, obsessive- compulsive disorder, bipolar illness, Alzheimer's disease, Parkinson's disease and autism (Ayling, Aghajani, Fouche, & Wee, 2012; Shenton, Dickey, Frumin, & McCarley, 2001; Whitford et al., 2011). Findings in PTSD have largely been limited to the fibres that project to the frontal brain regions, in particular the uncinate fasciculus (UF) and cingulum, and interhemispheric fibres, such as the corpus callosum (CC). The anatomical architecture and function of these bundles as well as PTSD and mTBI findings pertaining to these are discussed below.

1.6.1 Corpus Callosum

The CC is the largest WM structure that connects right and left cerebral hemispheres (Catani & Thiebaut de Schotten, 2008). Originating in the cortex of all the hemispheric lobes, fibres of this tract join together at the midline to form a dense bundle that sits on top of the lateral ventricle and extends to the contralateral hemisphere (Catani, Howard, Pajevic, & Jones, 2002). Traditionally, this fibre bundle has been subdivided into an anterior portion (rostrum and genu), a central section (body) and a posterior part (splenium) (Crosby, Humphrey, & Lauer, 1962). The rostrum and genu connect the prefrontal and orbitofrontal regions, with the fibres projecting anteriorly and forming the anterior forcepts minor (Catani & Thiebaut de Schotten, 2008; Nieuwenhuys, Voogd, & Van Huijzen, 2007). The fibres of the splenium, on the other hand, form the posterior forcepts major and contain fibres from the occipital and temporal lobes (tapetum) (Catani & Thiebaut de Schotten, 2008). The body of the CC includes fibres that connect the precentral frontal areas and parietal lobes (Nieuwenhuys et al., 2007). Fibres of the body of the CC converge at the posterior horn of the lateral

ventricle and curve around it before bending upwards through the midline (Catani et al., 2002).

The involvement of the CC in interhemispheric transfer of sensory and cognitive information has long been known following lesion studies in both animals and humans. In a study of callosotomized cats, Myers (1956) demonstrated that lesioned animals showed deficit on a simple discrimination task when stimuli were presented to the contralateral hemisphere from that on which the animal received training but were able to learn two conflicting tasks without interhemispheric interference, thus suggesting a detrimental effect of callosal ablation on the transfer of somatosensory information.

Glickstein and Sperry (1960) were interested to see whether this deficit would also apply to transfer of a motor response. They first trained the animals on a simple discrimination task using one hand and then reversed the value of the response forcing the animals to use the contralateral hand which diminished the performance at first in both groups but slowly increased after a number of training trials. For the final stage of the experiment, the original hand and response stimulus were re- introduced in order to test the effect of callosotomy (Glickstein & Sperry, 1960). Lesioned animals were readily able to perform the discrimination task with little to no impairment whereas control animals showed clear interhemispheric interference where their performance dropped to the baseline level thus highlighting the importance of the CC in motor information transfer (Glickstein & Sperry, 1960).

Although animal disconnection studies are highly informative, the higher cognitive functions and ability to produce language emphasize the importance of understanding implications of hemispheric disconnection in humans (Gazzaniga, 2005; van der Knaap & van der Ham, 2011). Split brain surgeries used to treat intractable epilepsy have made a major contribution to the understanding of the function of this structure in humans. Through studying the effect of this surgery on performance of a range of behaviors, researchers have been able to differentiate various processes into

being controlled by either one dominant hemisphere or both (Gazzaniga, 2005). It has been demonstrated that somatosensory, stereognostic and visual information are largely lateralized such that perception of the stimulus is dependent on the contralateral hemisphere (Gazzaniga, 2000; Gazzaniga, Bogen, & Sperry, 1963). Muscular movements, however, have been shown to be under both ipsilateral and contralateral control, with proximal responses generated by ipsilateral hemisphere and distal responses influenced by both (Gazzaniga, 2000; Geffen, Jones, & Geffen, 1994).

Apart from improving the understanding of interhemispheric transfer of motor, sensory and cognitive information between relevant cortices, studies of split-brain patients have also shed light on the hemispheric dominance and specialization. It is now well accepted, for instance, that the left hemisphere is specialized in language whereas the right hemisphere dominates in processing of visuo-spatial information - although there is a small functional overlap with the left hemisphere capable of representing crude perceptional information and right hemisphere possessing lexicon (Gazzaniga, 2000; van der Knaap & van der Ham, 2011).

1.6.1.1 Corpus Callosum Findings in Psychiatric Conditions

Changes within the CC have been observed in some neurodegenerative conditions such as Alzheimer's and Multiple Sclerosis (MS), and to a lesser extent in certain psychiatric conditions, and PTSD in particular. A number of studies have demonstrated reduced total volume of the CC, as well as within its subregions, in adult-onset PTSD (Saar- Ashkenazy et al., 2014; Villareal et al., 2004). Saar-Ashkenazy et al. (2014) have also shown that reduction in the total volume of the CC was correlated with poorer performance on associative picture task. They proposed that the observed impairment is due to inadequate hemispheric lateralization based on task requirements as a result of impaired inhibitory control from the CC (Saar-Ashkenazy et al., 2014). Contrary to the previously mentioned studies, Landr et al. (2010) failed to observe any changes in the white or gray matter volume in females with sexual abuse- related

PTSD- a finding that has been attributed to potential sex-related differences as well as nature of trauma and its severity.

Some studies have also identified reduced CC volume and decrease in FA following maltreatment in children (De Bellis et al., 1999; De Bellis et al., 2002; Jackowski et al., 2008; Teicher et al., 2004). Two of these studies have also observed sex-dependent volumetric changes within the CC. De Bellis et al. (1999) demonstrated that girls displayed greater volume decrease in the CC than boys. Teicher et al. (2004) showed that after controlling for PTSD symptoms, neglect was the biggest predictor of volumetric changes in maltreated boys whereas in girls these changes were largely predicted by the history of sexual abuse. Taken together, these findings suggest a potential interaction between the CC changes and sex in a traumatized population.

1.6.1.2 Corpus Callosum Findings in mTBI

The CC is one of the commonly affected sites of traumatic axonal injury and has consequently been investigated by a large number of studies. Zhu et al. (2014) noted reduced FA in the CC, limbic system (anterior cingulate, parahippocampal gyrus and posterior cingulate) and insula in mTBI patients. In comparison, other studies have partitioned this structure into posterior, central and anterior regions based on their functionality (Inglese et al., 2005; Kumar et al., 2009; Rutgers et al., 2008). Rutgers et al. (2008) compared mTBI patients who were either less than three months post-injury or more than three months post-injury and observed reduced FA and increased MD in the genu of the CC in the group who had undergone MRI less than three months after the injury but not in the other mTBI group. Likewise, Kumar et al. (2009) also detected reduced FA and increased Radial Diffusivity in the genu and splenium of the CC in mild and moderate mTBI groups. The genu of the CC connects frontal and orbitofrontal regions and is therefore of particular interest as a potential mediator of the effect that mTBI has on the likelihood of PTSD development. Inglese et al. (2005) studied patients with mTBI 4.05 days after the injury and 5.7 years after the injury.

Both mTBI groups showed reduced FA and increased MD in the splenium of the CC compared to controls, both individually and combined. Similar to Inglese et al. (2005), Matsushita, Hosoda, Naitoh, Yamashita, and Kohmura's (2011) study found reduced FA in the splenium of the CC in the acute stages of injury, which further predicted cognitive functioning in the chronic stages of the disease.

1.6.2 Cingulum

The cingulum is an associative fibre bundle which is located within the cingulate gyrus and sits directly on top of the corpus callosum along its entire length (Catani & Thiebaut de Schotten, 2008). It is comprised of short and long fibres, with the longest fibre extending from the uncus in the anterior temporal gyrus, passing closely around the splenium of the CC, curving around the genu and terminating near the subcallosal gyrus and the paraolfactory area of Broca (Crosby et al., 1962). Short fibres are found along the tracts length and connect medial frontal, parietal, occipital and temporal lobes, as well as portions of the cingulate cortex (Catani & Thiebaut de Schotten, 2008; Nieuwenhuys et al., 2007).

This neural tract belongs to the limbic system and has therefore been implicated in emotional processes, memory and executive functioning (Nezamzadeh et al., 2010). First proposed by Papez (1937) and later modified by MacLean (1952), the limbic system is thought to encompass both cortical and subcortical areas including the amygdala, hippocampus, hypothalamus, fornix, cingulate and parrahippocampal gyri, septal region, olfactory bulb, mammillary bodies and cingulum (Concha, Gross, & Beaulieu, 2005). Since the original description of the limbic system, findings from both animal and human studies have been used to characterize these structures based on their function, the cingulum in particular.

A number of animal lesion studies have investigated contribution of this structure to animal learning. Using conditioned avoidance response, Thomas and Slotnick (1962) compared lesioned animals to controls and observed impairment in acquisition

of avoidance behavior and concurrent increase in freezing in response to a shock. A study conducted by Blanchard and Fial (1968) used a passive avoidance test to assess the effect of the cingulum ablation and showed that lesioned animals performed worse than controls, as demonstrated by decreased latency to escape the shock- free compartment. Taken together, these findings indicate that the cingulum plays an important role in fear conditioning.

Apart from animal lesion studies, some research has also looked at the effects of surgical removal of the cingulum in humans. Fedio and Ommaya (1970) examined patients who underwent bilateral cingulotomy for pain relief and showed that prior to surgery, stimulation of the left, but not the right, cingulum produced short-term memory impairment. Following the surgery, however, no memory deficits were observed, thus suggesting that memory processes potentially rely on more distal limbic mechanism (Fedio & Ommaya, 1970). Other bilateral cingulotomy studies have suggested that this tract is primarily involved in emotional processes, demonstrated by reduction in emotional states such as anxiety and aggressiveness following the surgery (Ballantine Jr, Cassidy, Flanagan, & Marino Jr, 1967; Brown & Lighthill, 1968; Foltz & White Jr, 1962). These early findings seem to suggest that the cingulum is directly involved in the emotive behavior whereas its contribution towards the memory processes potentially occurs via an alternative limbic pathway.

Support for the involvement of the cingulum in both emotion and memory processes comes from fMRI studies of the cingulate gyrus (Lane et al., 1998). Based on task-dependent activation findings, it has been proposed that anterior and posterior regions of the cingulate gyrus are functionally different (Bush, Luu, & Posner, 2000). Anterior portion of this region has been shown to be involved in emotional processing whereas posterior region has been more frequently implicated in memory related functions, thus suggesting functional heterogeneity within this region (Bush et al., 2000).

Originally proposed by Vogt, Finch, and Olson (1992) and later supported by fMRI findings, this traditional view of the cingulate gyrus was challenged when

the ACC was further subdivided into caudal-dorsal midline portion, thought to be involved in cognitive function, and rostral-ventral midline region that was proposed to be primarily responsible for emotional processing (Bush et al., 2000). This distinction is largely based on the anatomical connections that these regions have such that the caudal-rostral region has reciprocal connections with the PFC, parietal cortex, and premotor and supplementary motor areas; in contrast, the caudal-dorsal portion is connected to the amygdala, periaqueductal grey, nucleus accumbens, hypothalamus, anterior insula, hippocampus and orbitofrontal cortex (Devinsky, Morrell, & Vogt, 1995). Apart from the anatomical basis for the different functions performed by these subregions, findings from fMRI studies have provided further credibility to this hypothesis.

To directly evaluate the degree of involvement of these subregions in cognitive and emotional processes, Mohanty et al. (2007) compared activation during the performance of emotion-word Stroop task to colour-word Stroop task and demonstrated differential activation of these two regions. In response to negative compared to neutral words, a higher activation was observed in the rostral ACC whereas stronger activation in the dorsal ACC accompanied presentation of incongruent compared to congruent words (Mohanty et al., 2007). Similarly, Etkin, Egner, Peraza, Kandel, and Hirsch (2006) studied emotional conflict resolution where participants were presented with incongruent face/word combinations and showed increased activation in the rostral portion of the ACC with concurrently diminished activation in the amygdala which was in turn modulated by the level of incongruency in the previous trial. Similarly, using the emotional Stroop task, Whalen et al. (1998) observed increased activation in the rostral-ventral subdivision in response to negative compared to neutral words. In further support of the heterogeneity of the ACC, Bush et al. (2002) demonstrated recruitment of the dorsal part of the ACC during the completion of a reward based decision making task. As per above research, the rostral ACC appears to be involved in emotion recognition whereas the dorsal ACCs main function is more evaluative in nature.

Since the cingulum is the largest WM tract within the cingulate cortex that

connects it to the entorhinal cortex, it is likely that this neural tract also possesses a degree of functional heterogeneity within its subregions. Delano-Wood et al. (2012), for instance, have demonstrated that mild cognitive impairment was associated with reduction in FA in the posterior cingulum whereas no changes were observed in the anterior subregion. Providing further support for the involvement of the cingulum in memory processes, Delano-Wood et al. (2012) have also reported a positive association between FA in the posterior cingulum and verbal task performance. Other DTI studies of neuropsychiatric disorders, such as schizophrenia and bipolar disorder, have also reported functional heterogeneity within this fibre bundle, in particular within its anterior subregion (Fujiwara et al., 2007; Wang et al., 2008). Thus, these findings seem to indicate that similar to the ACC, the cingulum is also characterized by functionally distinct subregions.

The idea of functionally distinct regions of the ACC, however, has been challenged by an alternative theory suggesting that both of these subregions could be contributing to emotional processing (Etkin, Egner, & Kalisch, 2011). For instance, during fear conditioning task, Milad et al. (2007) observed increased activation in the dorsal ACC thus implicating this region in regulating or mediating fear expression. Using electrophysiological single cell level measures in patients undergoing cingulotomy for obsessive-compulsive disorder (OCD), Davis et al. (2005) compared their performance on a range of cognitively demanding tasks and observed involvement of the dorsal ACC not only in emotionally neutral tasks, but also in those with an emotional overlay. Etkin et al. (2011) proposed that although the two subregions perform distinct functions, they both aid emotional processing such that the dorsal ACC is responsible for emotional expression and appraisal whereas the ventral ACC is involved in emotional response generation.

Since the ACC is part of the limbic system which in turn is thought to be involved in fear processing, it has often been implicated in PTSD symptomatology. In

the context of combat, Shin et al. (2001) demonstrated that veterans with PTSD displayed no change in the activation of the rostral ACC compared to increased activation in controls in response to combat-related words. Likewise, Liberzon, Britton, and Phan (2003) observed deactivation in the rostral ACC in PTSD patients when viewing personally traumatic compared to neutral images as evidenced by reduced rCBF to this area. In a recent study by Offringa et al. (2013), however, the PTSD group displayed decrease in the rostral ACC in response to emotional stimuli that were unrelated to trauma, hence suggesting a more general abnormality in processing of emotional stimuli. Additionally, voxel based morphometry studies have found reduced volume in the rostral ACC in PTSD patients (Woodward et al., 2006) while increased volume has been associated with positive response to CBT (Bryant et al., 2008) and recovery (Dickie, Brunet, Akerib, & Armony, 2013).

1.6.2.1 Cingulum Findings in Psychiatric Conditions

Apart from the altered activation within the ACC, it has also been hypothesised that there may be reduced connectivity of the cingulum in PTSD patients which is, as mentioned earlier, the largest WM bundle found in the cingulate cortex. Kim et al. (2005) conducted one of the first studies using DTI investigating microstructural changes within this region in PTSD and observed decreased FA in the left ACC WM, which also negatively correlated with re-experiencing and avoidance subscales of Clinician Administered PTSD Scale (CAPS). In their follow-up study, Kim et al. (2007) subdivided the cingulum bundle into the rostral anterior, subgenual anterior, dorsal anterior and upper subregions and observed significant decrease in all but the upper subregion, hence suggesting consistent decrease in FA along almost the entire tract. Taken together, these studies suggest that PTSD is associated with reduction in FA in the left cingulum.

Contrary to these findings, more recent studies have shown reduction in FA in the right, rather than left, WM ACC, the cingulum in particular (Schuff et al., 2011;

Sekiguchi et al., 2014; Sun et al., 2013; Wang et al., 2010; Zhang et al., 2011). Sekiguchi et al. (2014) studied earthquake survivors prior to earthquake and three to four months after and indicated that state anxiety level was negatively associated with FA in the right cingulum whereas the same measure was positively correlated with the increased FA changes in the left cingulum from before to after the earthquake. The authors proposed that the decrease in FA within the right cingulum was a vulnerability factor whereas the increase in the left cingulum was acquired in relation to state anxiety. The left cingulum FA increase has also been reported in survivors of domestic terrorism with PTSD in a study by Abe et al. (2006). This finding accords with Sekiguchi et al.'s (2014) findings that have linked FA increase in the left cingulum to high levels of anxiety immediately following the traumatic event. It was theorized that exposure to a traumatic event would have led to an increased access to areas involved in providing cognitive resources for emotion regulation. This proposition is yet to be verified as some studies have reported decrease in both left and right cingulum in PTSD (Fani et al., 2012; Sanjuan, Thoma, Claus, Mays, & Caprihan, 2013).

1.6.2.2 Cingulum Findings in mTBI

Since the cingulum plays a critical role in emotion regulation circuitry, emotional difficulties experienced following mTBI could potentially be related to changes within this WM structure. In a study conducted by Costanzo et al. (2014), combat-related mTBI has been shown to be associated with reduced FA in the left posterior cingulum adjacent to the left precuneus/ posterior cingulate cortex compared to age matched controls, which in turn correlated positively with functional connectivity between the left posterior cingulate cortex (PCC) and medial frontal cortex (MFC). Connectivity between the PCC and MFC has also been linked to re-experiencing symptoms in this group, suggesting a potential mechanism via which mTBI affects the development of PTSD (Costanzo et al., 2014). Further support for the potential contribution of the cingulate gyrus to emotional dysregulation observed in mTBI comes from

an ERP study of emotional appraisal conducted by Shu et al. (2014), who demonstrated greater emotional processing ERPs, such as N300, in military personnel with comorbid PTSD and mTBI compared to veterans with mTBI alone - an effect largely mediated by the PCC. Increased ERPs also negatively correlated with the overall symptom severity, as well as with avoidance and hyperarousal clusters (Shu et al., 2014). In the context of combat, Sorg et al. (2014) studied WM changes in soldiers with mTBI within four years post-injury and proposed a link between diffuse axonal injuries and impaired executive function. Specifically, the following regions were identified to have reduced FA: dorsal prefrontal WM, the genu and splenium of the CC and the posterior cingulum. In addition, increased Radial Diffusivity in the posterior cingulum was associated with reduced executive functioning. Overall, these findings suggest that the cingulum is likely to belong to the network of structures that increase the likelihood of development of PTSD following mTBI.

1.6.3 Uncinate Fasciculus

The UF is an associative fibre bundle that connects the anterior part of the temporal lobe to the medial and lateral orbitofrontal cortex (Catani et al., 2002; Catani & Thiebaut de Schotten, 2008). This hook-like fibre bundle is described as consisting of two subdivisions: ventral and dorsal (Catani et al., 2002). Both of these subdivisions run posteriorly from the frontal pole passing beneath the fronto-occipital fasciculus and enter the temporal lobe as a single compact fibre (Catani et al., 2002). The UF then curves anteriorly and terminates in the temporal pole, hippocampal gyrus, uncus and amygdala (Klingler & Gloor, 1960).

Although the precise function of this fibre bundle remains unknown, a number of animal and human studies have proposed its involvement in memory functions. Graffan, Easton and Parker (2002) observed severe impairment in associative learning in a group of monkeys who received bilateral transection of the temporal stem, amygdala and fornix. In these animals, the UF was cut as part of the temporal stem

transection and hence this bundle was hypothesized to be among several tracts to play an important role in memory formation.

Papagno et al. (2010) have also proposed the involvement of this fibre bundle in memory processes by demonstrating that patients who had the UF surgically removed performed poorly on tasks that involved naming of famous faces and objects. They concluded that the UF is part of a neural system responsible for proper name retrieval. Lu et al. (2002) also observed retrieval difficulties in patients with left anterior temporal lobectomy that involved removal of the UF, with a particular impairment in retrieval of names of tools or implements (nouns) and human actions (verbs).

Further support for the involvement of the UF in memory processes comes from a study by Levine and colleagues, who demonstrated a link between isolated retrograde amnesia and the UF (Levine et al., 1998). It was proposed that lesions to the right ventral frontal cortical and subcortical areas that involve damage to the UF are associated with episodic memory dysfunction. Specifically, since activation in the right prefrontal area is associated with episodic retrieval (Tulving, Kapur, Craik, Moscovitch, & Houle, 1994) and isolated retrograde amnesia has been observed following right fronto-temporal lesion, the right UF damage has been linked to retrieval difficulties of episodic autobiographical information (Levine et al., 1998).

When this neural bundle was examined in healthy populations, studies have consistently observed left/right asymmetry in terms of both fibre density and anisotropy. A post-mortem histological study found that the right UF was 27% larger and had 33% more fibres than the left UF (Highley, Walker, Esiri, Crow, & Harrison, 2002). Furthermore, Rodrigo et al. (2007) demonstrated right-greater-than-left asymmetry in FA of the UF, a finding that contradicts previous research suggesting left-greater-than-right asymmetry (Park et al., 2004). This study has also found that FA was not uniform along the length of this tract, indicating that while the extrainsular portion of the UF showed right-greater-than-left pattern of anisotropy, a reverse pattern was identified in the subinsular segments of the UF (Rodrigo et al., 2007).

1.6.3.1 Uncinate Fasciculus Findings in Psychiatric Conditions

Changes in the microstructure of the UF have been linked to certain trait characteristics in healthy populations. Kim and Whalen (2009) studied the relationship between trait anxiety and degree of anisotropy and observed a negative correlation between mean FA and trait anxiety scores, suggesting that reduced anxiety is associated with stronger communication between the amygdala and ventromedial prefrontal cortex (vmPFC). A large number of studies have also looked at microstructural changes in the UF in relation to a number of anxiety disorders. Tromp et al. (2012) showed reduced FA in bilateral UF in patients with generalized anxiety disorder (GAD). This finding provides further explanation for the fMRI observations suggesting that GAD is characterized by abnormal functional coupling between the PFC and ACC with the amygdala (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010). In the study by Tromp et al. (2012), lower FA was observed in bilateral UF in GAD patients, hence providing a structural explanation for the emotional regulation disturbances observed in this condition.

Another anxiety disorder that is characterized by overactive amygdala and diminished activation in the PFC in response to threat stimuli is Social Anxiety Disorder (SAD) (Evans et al., 2008; Stein, Goldin, Sareen, Zorrilla, & Brown, 2002). This functional abnormality has been linked to anisotropic changes in the UF, with some variation in laterality of the findings (Baur et al., 2011; Phan et al., 2009). Phan et al. (2009) observed reduced FA in the right UF in SAD patients compared to healthy controls, whereas Baur et al. (2011) observed reduced FA in the left UF. Similar to Kim and Whallen (2009), Baur et al. (2011) identified a negative correlation between FA in bilateral UF and trait anxiety. This association, however, was only detected in the SAD group which was attributed by the authors to either a dimensional nature of the association between structural changes and pathological mechanisms or compensatory mechanisms that are present in clinical anxiety but are absent in a healthy population (Baur et al., 2011).

Similar to the anxiety disorders mentioned above, a large number of fMRI studies have provided evidence for the neurobiological model of PTSD which is characterized by hyperactive amygdala that is concurrently under-regulated by the vmPFC (Armony, Corbo, Clment, & Brunet, 2005; Hayes et al., 2011; Rauch, Shin, & Phelps, 2006; Rauch, Shin, Whalen, & Pitman, 1998; Shin et al., 2005; Shin et al., 2006). Considering the anatomical position and function of the UF, this structure could potentially be implicated in mediating the functional alterations associated with this condition. Only one DTI study to date has observed microstructural changes in the UF in a trauma-exposed population. In their study of Romanian orphans who were exposed to socio-emotional deprivation, Eluvathingal et al. (2006) observed reduction in FA in the left UF.

1.6.3.2 Uncinate Fasciculus Findings in mTBI

In contrast to PTSD, more DTI studies have observed anisotropic changes in the UF in mTBI. One recent study identified reduced FA and increased Mean Diffusivity in patients with mTBI following a motor vehicle accident (Xiong et al., 2014). Elevated Mean Diffusivity also negatively correlated with working memory indices, thus providing further evidence towards the involvement of this tract in memory processes (Xiong et al., 2014). Similarly, Levin (2010) observed a negative correlation between FA values in bilateral UF and verbal memory in blast-related TBI. Other studies have also identified reduction in FA and MD bilaterally (Bendlin et al., 2008; Brandstack, Kurki, & Tenovuo, 2013; Kinnunen et al., 2010; Niogi et al., 2008). Contrary to the majority of studies, one study observed increased FA that was also accompanied by reduced Radial Diffusivity which was attributed to cytoxic oedema (Mayer et al., 2010).

1.7 Implications for Research

The primary aim of this project was to describe neural disruptions in both PTSD and mTBI by examining WM structures that have been implicated in these conditions. The probability of developing PTSD at one year after the head injury is double the probability of developing PTSD following a traumatic event without a history of brain injury (Vasterling et al., 2012). It is therefore crucial to try to disentangle the contribution of the physical injury and psychological stress to cognitive and emotional disturbances observed in mTBI.

1.8 Methodological Issues

In order to evaluate the effect that PTSD has on WM alterations, four experimental groups were studied. Of primary interest, we examined WM integrity in participants with mTBI and those who met criteria for PTSD. Past research has predominantly used healthy individuals as a comparison group to infer the impact of mTBI, however, this precludes the ability to control for the role that PTSD symptoms might play in mediating the observed neural changes. Further, the reliance on healthy controls in previous studies does not allow to control for trauma-exposure as a potential explanation for WM disturbances. Accordingly, this project included two control groups (healthy controls and trauma-exposed healthy controls) in order to control for the exposure to a traumatic event as a potential confounding variable.

1.9 Overview of Current Project

Chapter 2 presents the overall methodology used in the present project, providing detailed information regarding participants, image acquisition, data processing and statistical analyses. Chapters 3, 4 and 5 examined WM changes in the CC, cingulum

and UF across the four groups, respectively. Based on the outcomes of the analyses performed in chapters 3, 4 and 5, the individual contributions of PTSD and mTBI to WM alterations were evaluated in Chapter 6. Finally, Chapter 7 provides a synthesis of the findings and discusses them in the context of previous studies and prevailing theories of mTBI and PTSD.

Chapter 2

Methodology

2.1 Participants

2.1.1 Mild Traumatic Brain Injury (mTBI)

Mild traumatic brain injury (mTBI) participants were recruited through three sources. Nineteen participants responded to an advertisement in local newspapers that invited volunteers to participate in a research study, 18 were recruited from outpatient records of the Brain Injury Rehabilitation Unit (BIRU), Westmead Hospital, Sydney, Australia and three from the Traumatic Stress Clinic (TSC), Westmead Hospital, Sydney, Australia. Patients from the BIRU were invited to participate if an examination of their medical records revealed a documented knock to the head, a Glasgow Coma Scale (GCS) score greater than or equal to 13, post-traumatic amnesia (PTA) no longer than 24 hours, loss of consciousness of no longer than 30 minutes and no indications of abnormalities on CT or MRI scans. Eligibility of the remaining participants recruited through advertising and TSC was determined based on the length of unconsciousness and need for hospitalisation following the incident. If hospitalisation was required, absence of CT or MRI abnormalities (based on medical records) also formed

part of the inclusion criteria. Information on the head injury site was not available via hospital records due to the mild nature of the sustained trauma. Additionally, participants who were recruited from the Traumatic Stress Clinic and general public were unable to provide such information regarding their injury.

2.1.2 Post-Traumatic Stress Disorder (PTSD)

PTSD participants were recruited from the TSC, Westmead Hospital, Sydney, Australia. All participants were treatment-seeking and were attending the clinic for cognitive-behavioural therapy (CBT). For the purpose of the present study, only participants who have experienced the following life events were included in the study: car accidents, physical assaults, natural disasters and/or industrial accidents. Events such as childhood abuse and sexual abuse were excluded from the study due to the complexity of psychological trauma associated with these experiences. Following clinical assessment, participants were informed about the research study by their treating clinicians and, if they expressed interest, their contact details were passed onto the research staff. PTSD was assessed on the basis of the *Diagnostic Statistical Manual of Mental Disorders, Version 4* (*DSM-4*, American Psychiatric Association, 1993) criteria using the *Clinician Administered PTSD Scale, Version 4* (CAPS-IV) (Blake et al., 1995). The CAPS-IV is a structured clinical interview that possesses good sensitivity (.84) and specificity (.95) relative to the Structured Clinical Interview for DSM Disorders (SCID) PTSD diagnosis, and also possesses sound test-retest reliability (.90) (George & Mallery, 2003).

2.1.3 Non- Trauma Exposed Healthy Controls (NTEC)

Non-trauma exposed healthy controls (NTEC) were recruited from the general public through local media and online advertising.

2.1.4 Trauma Exposed Healthy Controls (TEC)

Trauma exposed healthy controls (TEC) were recruited from the general public through advertising in local media and online advertising. Participants in this group have experienced a psychologically traumatic event but have never been diagnosed with a psychiatric disorder or had a history of head injury. Psychologically traumatic events experienced by participants in this experimental group were matched to those experienced by participants in the PTSD and mTBI groups. In order to determine whether participants in this group have experienced a psychologically traumatic event, research staff completed a thorough pre- screening interview identifying the presence of a history of psychological trauma and its nature. If the participant was deemed eligible for study participation, they were then asked to complete a series of standardized assessments, such as Traumatic Experiences Questionnaire and CAPS- IV, to further validate information that they have provided during the pre- screening stage of the study.

2.1.5 Inclusion and Exclusion Criteria

The following general exclusion and inclusion criteria were used for all participants: 1) age between 18 and 65 years; 2) no previously diagnosed neurological conditions; 3) no history of alcohol or substance abuse; 4) no active suicidality; 5) no pregnancy or breastfeeding; 6) no history of medium or severe head injury based on participants self- report of their trauma history and medical records (if these were available), and 7) absence of bipolar disorder, psychosis or primary eating disorders, as defined by the DSM- 4 (*DSM-4*, American Psychiatric Association, 1994). Participants first completed a preliminary phone interview which was then followed by a standardized clinical assessment to confirm their initial responses during pre- screening.

Table 2.1
Mean Time since Trauma as a Function of Group

	Time since Trauma		
	M	Min	Max
TEC	151.30 (111.09)	12	408
PTSD	155.06 (178.65)	5	672
mTBI	147.76 (132.40)	7	696

Note. Standard deviations appear in parentheses. Time measured in months. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury.

2.1.6 Participant Demographic and Clinical Characteristics

A total of 130 participants took part in the current project: mTBI (n = 40), PTSD (n = 35), NTEC (n = 29) and TEC (n = 26). Table 2.1 and Table 2.2 present mean age and time since trauma, respectively, for each group. Oneway analyses of variance (ANOVA) indicated that participants did not differ significantly in terms of time since trauma (F (2, 89) =.021, p = .979) but displayed a significant difference based on age (F (3, 126) = 4.84, p = .003). There were no significant differences between groups in terms of sex (χ^2 (3, N= 130) = 3.652, p = .302). The sex ratio in each group was as follows: the NTEC group consisted of 15 females and 14 males, the TEC group consisted of 12 females and 14 males, the PTSD group consisted of 18 females and 17 males, and the mTBI group was comprised of 13 females and 27 males. Information regarding participants IQ, years of education and socioeconomic status was not collected as part of this study.

To index depression and anxiety, all participants were administered the Beck Depression Inventory (BDI) (Beck & Steer, 1987) and Beck Anxiety Inventory (BAI) (Beck & Steer, 1990), respectively. Table 2.3 displays mean BAI and BDI scores. There were statistically significant differences between groups on the BDI (F (3, 114)=

Table 2.2
Mean Age as a Function of Group

	Mean Age		
	M	Min	Max
NTEC	33.86 (12.97)	18	65
TEC	37.96 (11.12)	23	58
PTSD	40.62 (11.01)	18	62
mTBI	44.55 (11.75)	18	62

Note. Standard deviations appear in parentheses. Age measured in years. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury.

Table 2.3
Mean BAI and BDI Scores as a Function of Group

	BAI			BDI		
	M	Min	Max	M	Min	Max
NTEC	3.74 (4.11)	0	14	4.74 (4.41)	0	17
TEC	5.71 (10.05)	0	45	7.08 (10.91)	0	50
PTSD	26.64 (12.63)	6	47	30.39 (11.09)	4	50
mTBI	7.73 (8.99)	0	31	10.17 (7.85)	0	31

Note. Standard deviations appear in parentheses. BAI= Beck Anxiety Inventory. BDI= Beck Depression Inventory. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury.

Table 2.4
Mean CAPS- IV Scores as a Function of Group

	CAPS- IV		
	M	Min	Max
TEC	6.92 (9.76)	0	33
PTSD	72.35 (20.22)	25	110
mTBI	9.13 (9.85)	0	42

Note. Standard deviations appear in parentheses. CAPS- IV= Clinician Administered PTSD Scale- IV. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury.

51.42 , p = .000), and BAI (F (3, 115)= 36.89 , p = .000) measures. Participants in the PTSD group had significantly higher BAI and BDI scores than those in the mTBI, NTEC and TEC groups.

To index post-traumatic stress severity, participants in the three trauma-exposed groups were administered the CAPS- IV (Blake et al., 1995). Table 2.4 displays mean CAPS-IV scores for each group. A oneway ANOVA indicated that participants in the PTSD group had significantly higher CAPS- IV scores compared to the mTBI and TEC groups (F (2.91)= 213.94 , p = .000).

2.2 Procedure

The study was approved by the Human Research Ethics Committee, Westmead Hospital, Sydney. All participants signed informed consent prior to the commencement of their testing session in the presence of an independent witness. During the first stage of the study, participants completed a clinical interview during which they were asked a range of questions related to their personal and medical history (a sample of the clinical interview is provided in Appendix A). All participants completed

the Mini International Neuropsychiatric Interview (M.I.N.I.), which is a structured clinical interview that provides diagnostic criteria for 17 disorders (Lecrubier et al., 1997). The M.I.N.I. possesses good sensitivity (.70), specificity (.85) and test- retest reliability (.76- .93 depending on the disorder) (Lecrubier et al., 1997; Sheehan et al., 1997). The M.I.N.I. was used to confirm that participants in the mTBI, NTEC and TEC groups did not have any psychiatric conditions. This clinical interview was also used to identify any comorbid conditions in the PTSD group. Participants with a history of a traumatic event (i.e. participants in the mTBI, PTSD, and TEC groups) also completed the CAPS- IV (Blake et al., 1995). Apart from the CAPS- IV, no further clinical measure was administered to confirm PTSD diagnosis in the PTSD group. Both the M.I.N.I. and CAPS- IV were administered either by a clinical psychologist or a trained research assistant. Following the clinical interview, all participants underwent an MRI scan which included a diffusion-weighted imaging sequence (described below) as part of the structural imaging protocol.

2.2.1 Image Acquisition

All Magnetic Resonance (MR) imaging was performed on a 3.0 Tesla GE Signa HDx scanner (GE Healthcare, Milwaukee, Wisconsin) using an 8 channel head coil.

A three dimensional SPGR sequence was used to acquire T1-weighted images in the sagittal plane (TR=8.3 ms; TE=3.2 ms; Flip Angle=11°; TI=500 ms; NEX=1; ASSET=1.5; Frequency direction: S/I). A 256 x 256 matrix with an in-plane resolution of 1 mm x 1 mm was used to obtain a total of 180 slices of 1 mm thickness, resulting in isotropic 1 mm^3 voxels.

A spin-echo DTI-Echo Planar Imaging sequence was used to acquire diffusion-weighted images (DWIs). Seventy contiguous, axial, 2.5 mm-thick slices (providing whole brain coverage) were acquired in 42 gradient directions with a b-value of 1250

s/mm^2. The imaging parameters were as follows: TR: 17000 ms; TE: 95 ms; Fat Saturation: ON; NEX: 1; frequency direction: R/L, in-plane resolution 1.72 mm x 1.72 mm, 128 x 128 matrix. Four baseline (b= 0) images were acquired at the start of the sequence and were used in the DTI tensor fit.

2.2.2 Image Processing and Analysis

Slicer 3D software was used to analyse the DWIs to identify and measure tracts of interest. DWIs were first converted to diffusion tensor images (DTIs) on the basis of a Least-Squares Estimation. The following diffusion metrics were calculated from the DTIs: Fractional Anisotropy (FA) (Mori, 2007; Whitford et al., 2011), Mode (Kindlmann et al., 2007), Trace (Whitford et al., 2011), Parallel diffusivity (Song et al., 2002) and Perpendicular diffusivity (Song et al., 2002). Fiducial-based tractography approach was used to identify and extract the UF and cingulum. Colour-by-orientation images were used in order to position fiducials within the UF and cingulum, which were identified using previously described anatomical references (Catani & Thiebaut de Schotten, 2008; Oishi, Faria, van Zijl, & Mori, 2010). Region- of- interest (ROI) approach was used to identify and measure the CC. Cronbach's alphas for the inter- and intra-rater reliabilities were both excellent, measuring at .928 and .922, respectively.

2.2.3 Statistical Analyses

A two- way mixed ANOVA was performed with group as the between-subjects factor (four levels: PTSD, mTBI, TEC and NTEC) and hemisphere as the within-subjects factor (two levels: left and right) for the UF and cingulum, whereas between group differences in the CC were analysed using one-way between-subjects ANOVA with group as the between-subjects factor (four levels: PTSD, mTBI, TEC and NTEC). Separate analyses were carried out for each metric: FA, Trace, Mode, Perpendicular

Diffusivity and Parallel Diffusivity. In the case of a significant main effect or interaction effect, post-hoc contrasts using Sidak adjustment to correct for multiple comparisons were carried out in order to tease out the underlying simple effects. To determine the potential influences of PTSD severity and mTBI on WM integrity, linear multiple regression analyses were used. Predictor variables, namely PTSD severity and mTBI, were entered using the simultaneous method.

Chapter 3

Study 1: Corpus Callosum

The CC is the largest WM bundle in the brain (Catani, Howard, Pajevic, & Jones, 2002). Fibres of the CC originate in the cortex of all the hemispheric lobes and join at the midline (Catani et al., 2002). The fundamental role of this tract in inter-hemispheric transfer has been thoroughly investigated in both human and animal studies (Gazzaniga, 2000; Gazzaniga et al., 1963; Glickstein & Sperry, 1960; Myers, 1956; van der Knaap & van der Ham, 2011). It has been proposed that in humans, the CC is responsible for integrating somatosensory, stereognostic and visual information, which is otherwise largely lateralized (Gazzaniga, 2000). This primary function of the CC has also been implicated in cognitive processes. For instance, since episodic encoding is achieved by the left hemisphere and retrieval processes are performed by the right hemisphere (Gazzaniga, 2000), this neural tract would play a critical role in any task that requires implementation of these memory processes.

Using a variety of neuroimaging techniques, studies have consistently demonstrated aberrant changes within the CC in PTSD. In both adult- and child- onset PTSD, studies have identified reduced volume and FA within this tract (De Bellis et al., 1999; De Bellis et al., 2002; Jackowski et al., 2008; Saar-Ashkenazy et al., 2014; Teicher et

al., 2004; Villarreal et al., 2004). In adults, volumetric reduction has also been associated with poor performance on memory tasks (Saar-Ashkenazy et al., 2014; Villarreal et al., 2004). Some studies have observed sex-dependent differences in the CC volume in maltreated children, such that girls demonstrated substantially larger decrease than boys (De Bellis et al., 1999). In contrast, using an all-female sample Landr et al. (2010) did not observe any changes in the CC volume, thus emphasizing the importance of further research into the nature of contribution of alterations within the CC to PTSD symptomatology.

Changes in the CC integrity have also been observed in mTBI with some studies showing reduced FA within the entire tract while others indicating reductions within the genu or splenium of the CC, with a concurrent increase in the Mean Diffusivity and Perpendicular Diffusivity (Inglese et al., 2005; Kumar et al., 2009; Matsushita et al., 2011; Rutgers et al., 2008; Zhu et al., 2014). These studies, however, have shown discordant results in relation to the mTBI chronicity with some studies reporting changes only in acute stages of the disease whereas others have proposed similar changes regardless of chronicity.

Consistent with prior research, in the present study it was predicted that compared to NTEC and TEC, the PTSD and mTBI groups would show compromised integrity of the CC that would be manifested by lower FA, higher Trace, higher Perpendicular Diffusivity, lower Parallel Diffusivity and higher Mode.

3.1 Results

3.1.1 Tractography

In order to identify and measure the CC, ROI approach was used. The CC is a neural bundle that is readily visible on the mid-sagittal slice (and nearby slices) and hence the use of manual ROI selection approach is the most appropriate. Figures

3.1, 3.2, 3.3 and 3.4 show examples of streamline tractography performed based on DTI data from three participants for each of the four groups: NTEC, TEC, PTSD and mTBI, respectively.

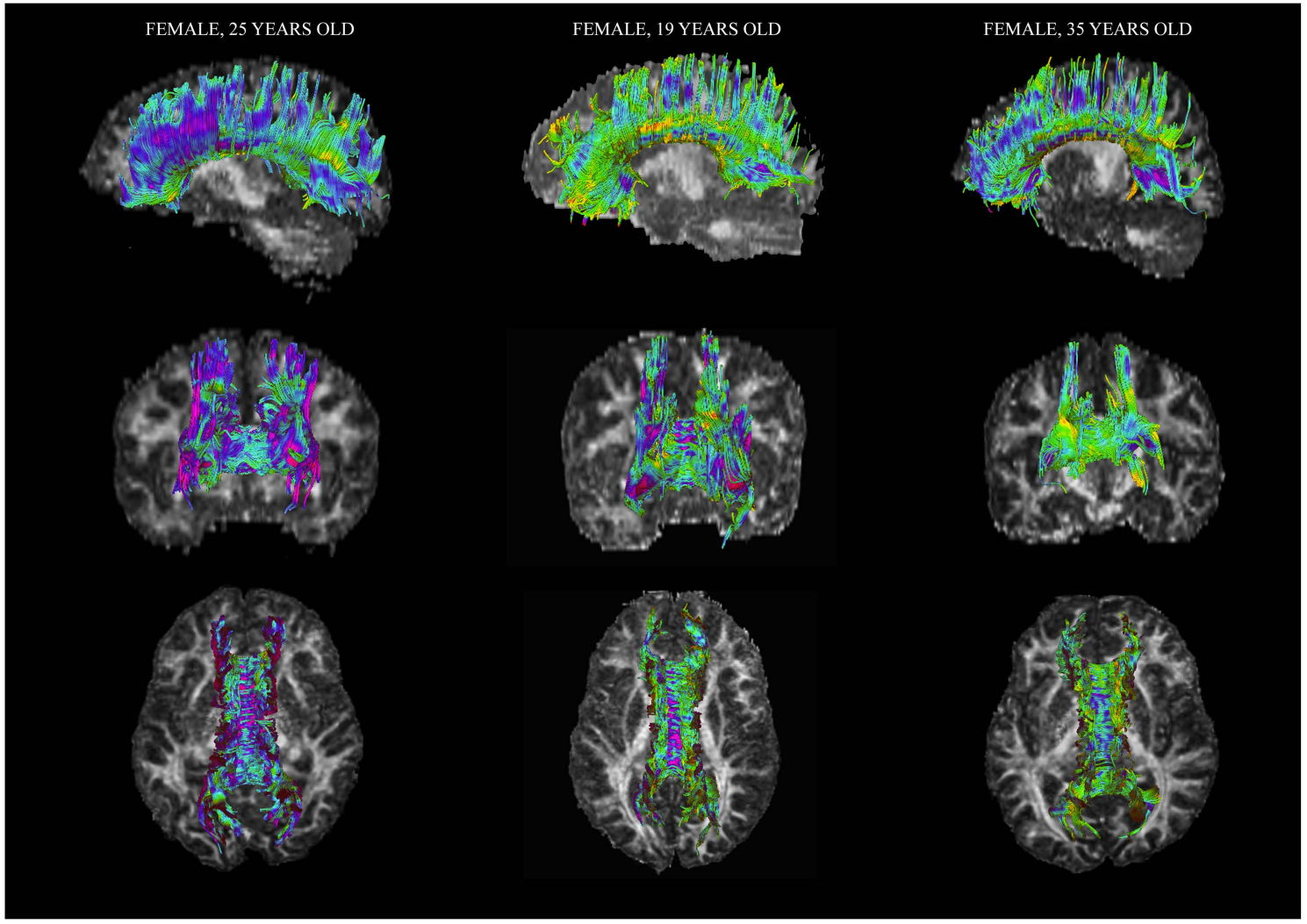

Figure 3.1. Examples of streamline tractography performed using DTI data from three participants from the NTEC group. Sex and age of each participant are indicated.

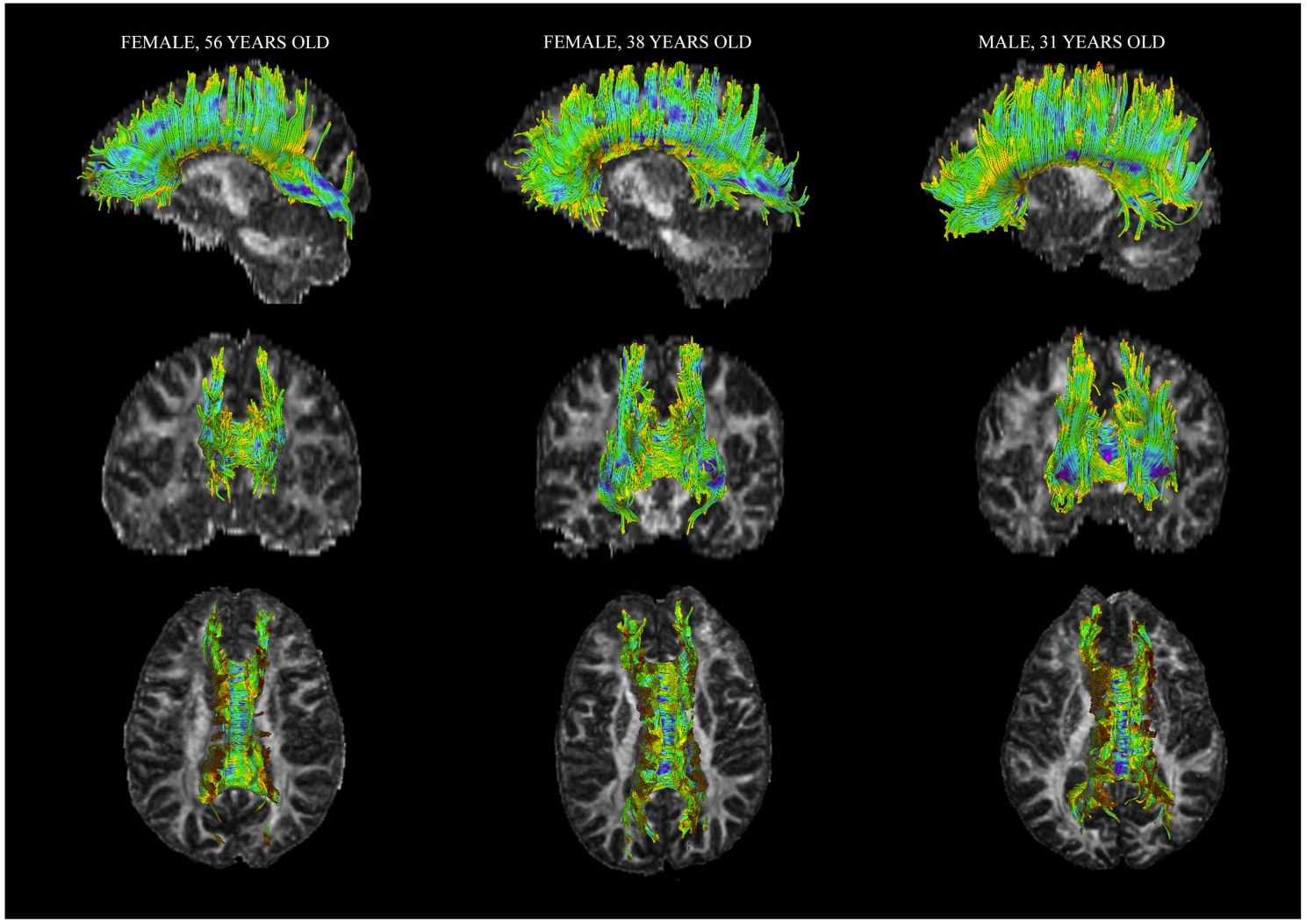

Figure 3.2. Examples of streamline tractography performed using DTI data from three participants from the TEC group. Sex and age of each participant are indicated.

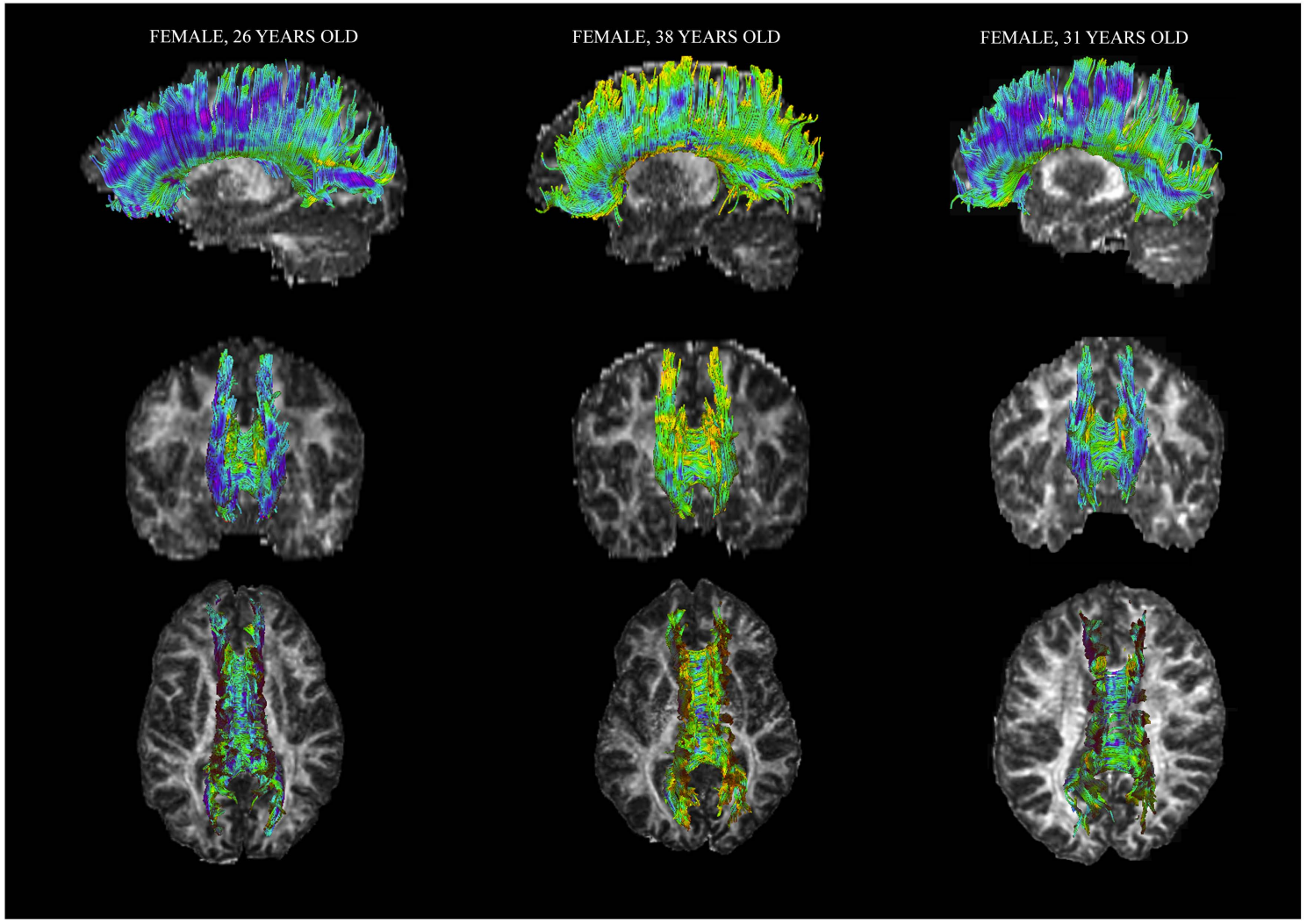

Figure 3.3. Examples of streamline tractography performed using DTI data from three participants from the PTSD group. Sex and age of each participant are indicated.

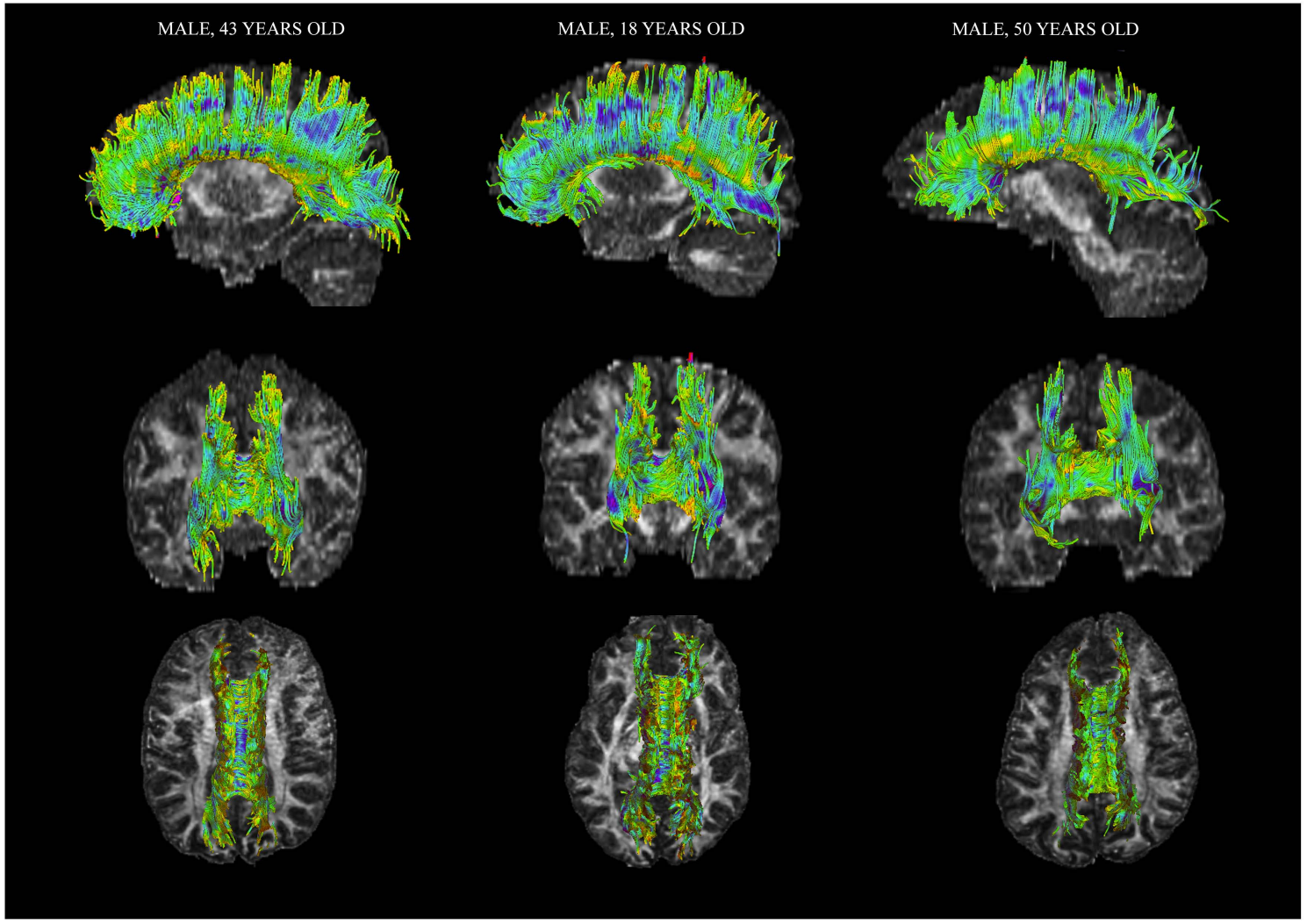

Figure 3.4. Examples of streamline tractography performed using DTI data from three participants from the mTBI group. Sex and age of each participant are indicated.

3.1.2 Group Comparisons

A one- way between- subjects ANOVA was performed on FA, Trace, Mode, Perpendicular Diffusivity and Parallel Diffusivity, with a follow-up post-hoc analyses using Sidak adjustment to control for multiple comparisons. The analyses revealed a statistically significant effect of group for FA (F (3,123) = 24.067, p = .000), Trace (F (3,124) =16.283, p = .000), Mode (F (3,121) =14.457, p = .000), Perpendicular Diffusivity (F (3,123) =25.300, p = .000) and Parallel Diffusivity (F (3,123) =3.693, p = .014).

Since there was a significant effect of age, the same analyses were repeated with age introduced as a covariate. Following these analyses, all group differences remained significant.

3.1.3 Pairwise Comparisons

Post-hoc tests showed that the PTSD group displayed significantly lower FA compared to NTEC (p = .042). The mTBI group had a significantly lower FA compared NTEC (p = .000), TEC (p = .000) and individuals with PTSD (p = .000). These results are presented in Figure 3.5.

Analysis also revealed that mTBI was associated with increased Trace compared to the PTSD, NTEC and TEC groups (p = .000, p = .000, and p = .000, respectively). These results are presented in Figure 3.6.

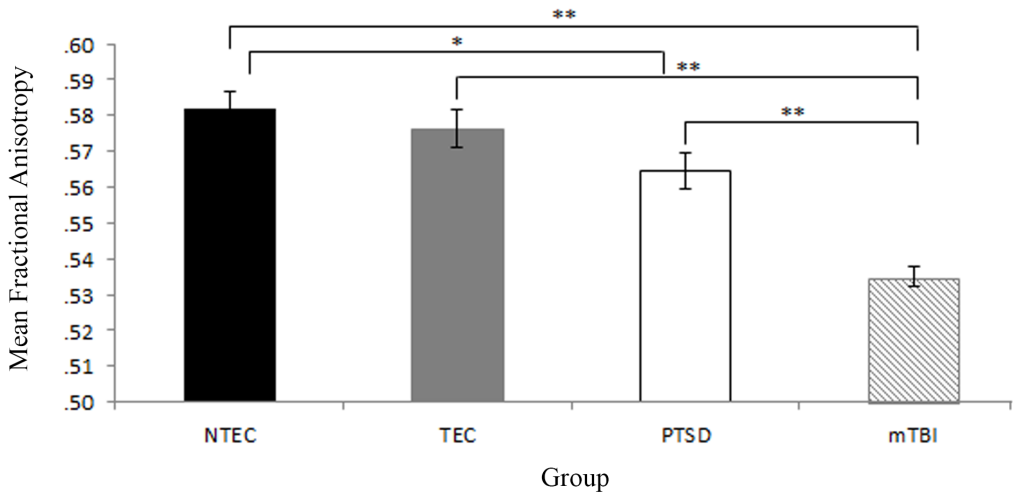

Figure 3.5. Fractional anisotropy group means. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. *Note. Significance of $< .05$ and $< .01$ indicated with * and **, respectively.*

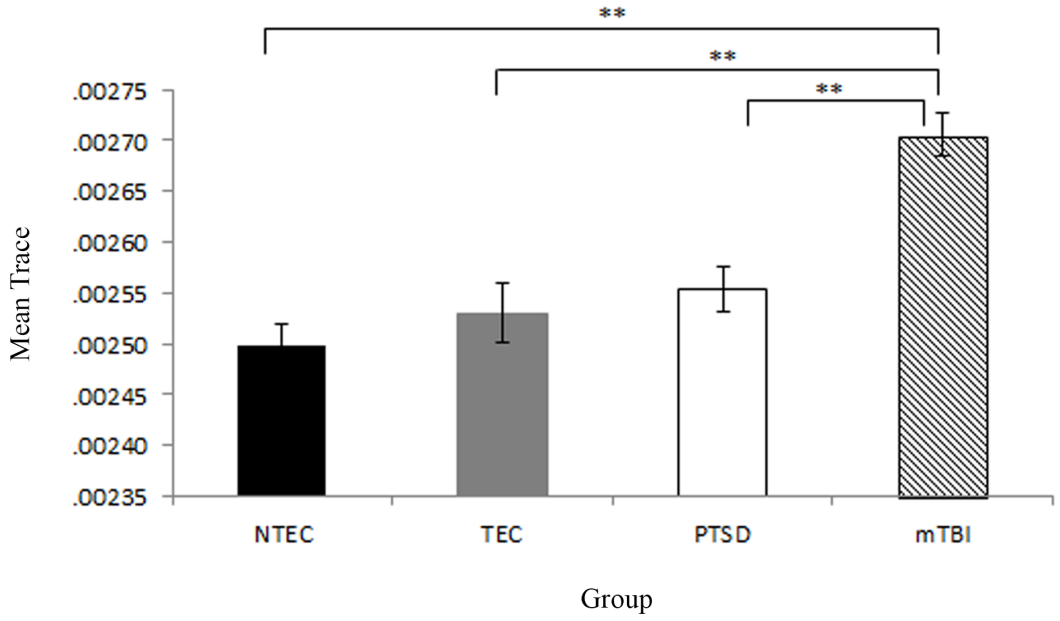

Figure 3.6. Trace group means. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. *Note. Significance of $< .01$ indicated with **.*

Similar patterns were observed for Perpendicular Diffusivity where mTBI showed an increase compared to the PTSD, NTEC and TEC groups (p = .000, p = .000, and p = .000, respectively). Additionally, there was a trend of significant difference between the PTSD group and NTEC, where the clinical group showed an increase compared to the control group (p = .075). These results are presented in Figure 3.7.

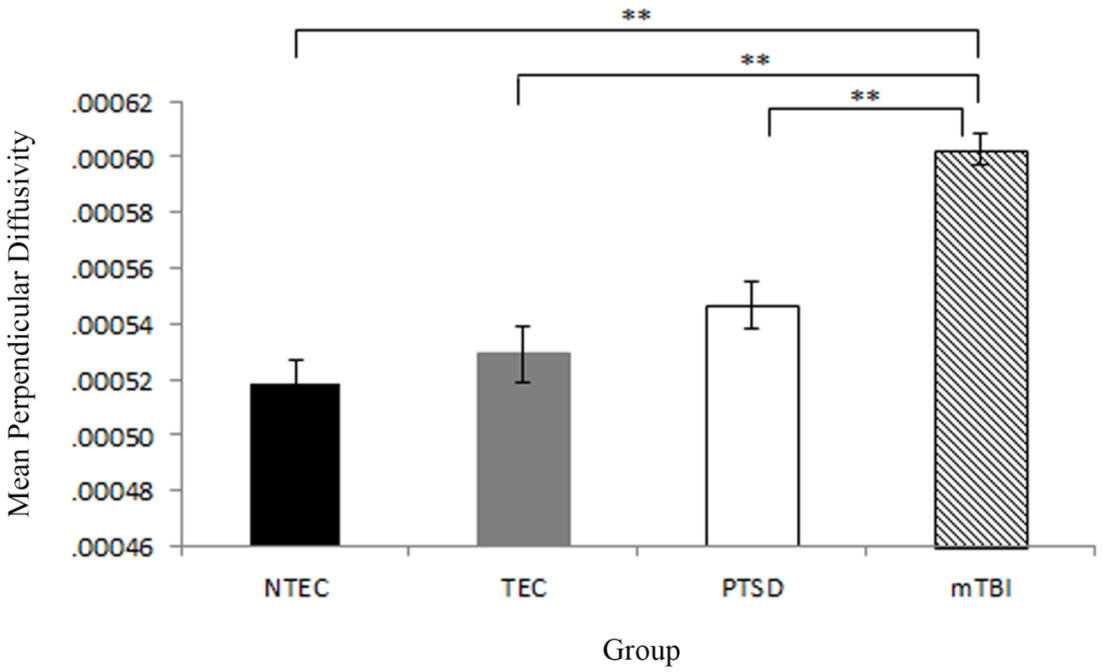

Figure 3.7. Perpendicular Diffusivity group means. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. *Note. Significance of* $< .01$ *indicated with* **.

Significant differences were also observed in Mode. The PTSD group showed reduced Mode compared to TEC (p = .001) and increased Mode compared to the mTBI group (p = .035). The mTBI group also showed decreased Mode compared to the NTEC and TEC groups (p = .011 and p = .000, respectively). The TEC group showed higher Mode compared to the NTEC group (p = .009). These results are presented in Figure 3.8.

Finally, the mTBI group had significantly higher Parallel Diffusivity compared to the PTSD group (p = .007). These results are displayed in Figure 3.9.

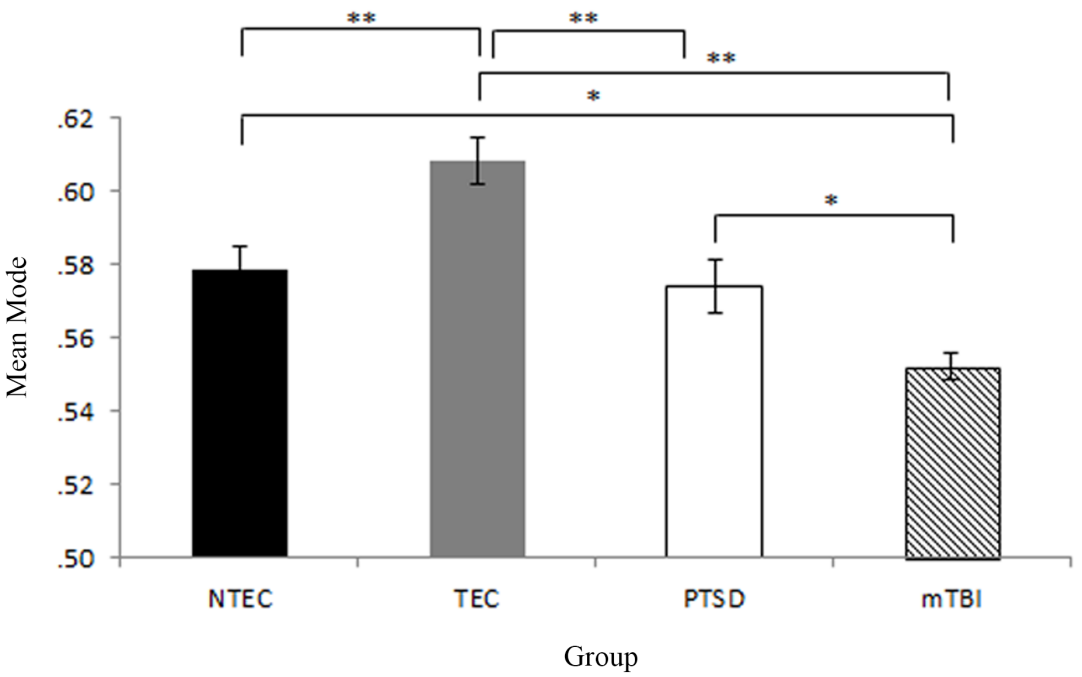

Figure 3.8. Mode group means. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. *Note. Significance of* $< .05$ *and* $< .01$ *indicated with * and **, respectively.*

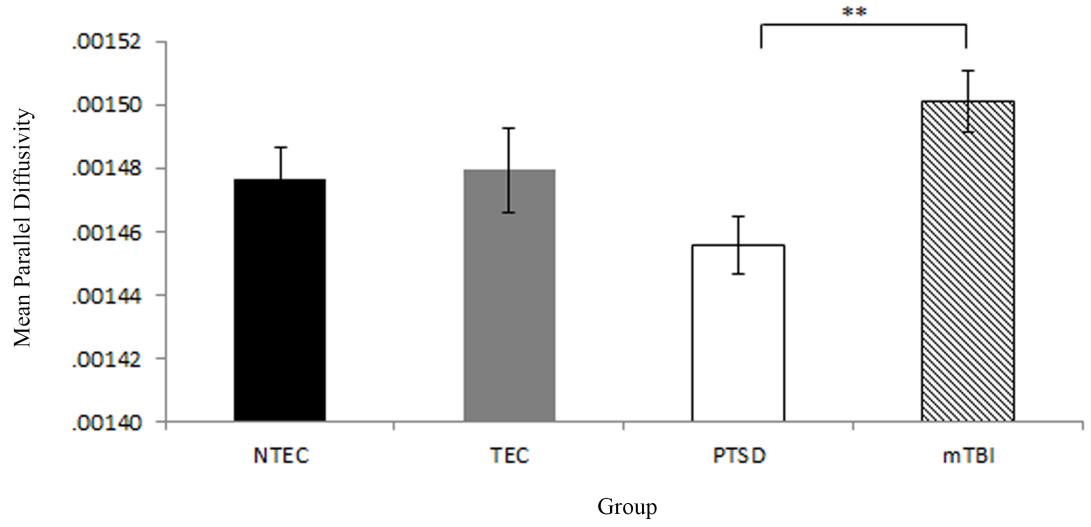

Figure 3.9. Parallel Diffusivity group means. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. *Note. Significance of* $< .01$ *indicated with* **.

3.2 Discussion

Results of the present study indicated that both PTSD and mTBI groups showed WM damage within the CC, with mTBI being associated with the worst outcome. Reduction in FA in the mTBI group was coupled by myelin damage.

Diffusion tensor data analysis provided insight into the diffusion properties of the CC. When the diffusion tensor data was averaged across all the voxels in the CC, the FA results revealed that, on average, NTEC had more anisotropic diffusion ellipsoids compared to the mTBI and PTSD groups. Compared to all groups, mTBI was associated with the least anisotropic diffusion ellipsoids. Additionally, based on the Trace data, it was demonstrated that the mTBI group had significantly larger diffusion ellipsoids compared to the rest of the groups. As outlined in Chapter 1, Parallel Diffusivity is defined in the following way: $\lambda \parallel = \lambda_1$, where λ_1 describes the length of the principal axis of the diffusion ellipsoid (Song et al., 2002). Therefore, since the mTBI group displayed increased Parallel Diffusivity, the diffusion ellipsoids in this group possessed the longest λ_1 compared to the other three groups. As described in Chapter 1, Perpendicular Diffusivity is the average of λ_2 and λ_3 - the lengths of the middle and shortest axes of the diffusion ellipsoid, respectively. Significantly increased Perpendicular Diffusivity in the mTBI group compared to the other three groups was thus indicative of a higher average of lengths λ_2 and λ_3. Finally, an increase in Mode in the mTBI group compared to the NTEC, TEC and PTSD groups suggested that the diffusion ellipsoids in this group were slightly more planar, or coin-shaped (Figure 1.3). TEC, on the other hand, possessed diffusion ellipsoids that were slightly more tubular in shape, or cigar-like, compared to the PTSD and NTEC groups (Figure 1.3).

Consistent with predictions, the mTBI group showed reduced FA and increased Trace compared to both control groups. This reduction in FA and increase in Trace were primarily driven by concurrent increase in Perpendicular Diffusivity. This finding is consistent with previous research that has observed decrease in FA with concurrent

increase in Trace within the CC in mTBI that was mediated by increase in Perpendicular Diffusivity (Inglese et al., 2005; Kumar et al., 2009). Studies have observed this pattern of anisotropic changes in both subregions of the CC, as well as throughout the entire tract (Inglese et al., 2005; Kumar et al., 2009; Rutgers et al., 2008; Zhu et al., 2014). Following from findings by Song et al. (2002) and Song et al. (2003) that provided evidence for increase in Perpendicular Diffusivity following myelin damage, these results indicate that WM damage in mTBI is associated with demyelination or other structural changes to the myelin.

As predicted, the PTSD group showed decreased FA compared to NTEC thus showing microstructural damage within the CC. This finding is consistent with past research that showed decreased FA in the CC of maltreated children with PTSD (Jackowski et al., 2008). The present finding is also consistent with macrostructural changes observed within this tract in PTSD, such as volume reduction (De Bellis et al., 1999; De Bellis et al., 2002; Saar-Ashkenazy et al., 2014; Teicher et al., 2004; Villarreal et al., 2004). One of the main distinctions from past research showing reduction in FA within the CC is the age of onset of the disease, with the present findings identified in adult-onset PTSD. As such, this study provides initial evidence of microstructural WM damage in the CC in adult-onset PTSD.

A recent study by Saar-Ashkenazy et al. (2014) has linked structural changes within the CC to poor associative memory in PTSD, thereby emphasizing the importance of interhemispheric transfer in performance of this function. Since encoding and retrieval functions are lateralized, with encoding predominantly achieved by the left hemisphere and retrieval being the right hemisphere function (Gazzaniga, 2000), it is possible that reduction in FA would result in a weaker connectivity between the hemispheres which in turn would lead to impaired inhibitory control required for lateralization. Memory disturbances observed in PTSD could therefore be attributed to disrupted interhemispheric communication.

FA reduction in PTSD did not appear to be mediated by increase in Perpendicular Diffusivity and therefore cannot be attributed to demyelination. Other possible contributing factors to aberrant changes in FA are axonal membrane injury and/or decreased axonal packing density (Kubicki et al., 2007; Thomason & Thompson, 2011). As there were no significant changes in Parallel Diffusivity between this group and controls, axonal damage is not likely to be the driving force behind the observed pathology.

Compared to previous studies that found FA reduction in PTSD compared to healthy controls, the present project aimed to extend on past research by including the TEC group in order to control for exposure to psychological stress as a potential covariate. When the PTSD group was compared to TEC, no significant differences were observed in FA. This observation raises the possibility that trauma exposure, rather than PTSD itself, may be linked to WM damage. On the other hand, there were no significant differences in FA between TEC and NTEC, suggesting that trauma exposure is not associated with WM abnormalities. Taken together, these findings potentially indicate that PTSD symptoms contribute to WM alterations to a degree substantial enough to differentiate them from those with no past exposure to a traumatic event but are at the same time indistinguishable from those with a prior exposure to a traumatic event.

As per past research, exposure to traumatic events has been shown to induce changes within the CC, even after controlling for PTSD symptoms (Teicher et al., 2004). A study by Paul et al. (2008) showed that reduction in FA in the CC was negatively correlated with the number of early life traumatic events in the absence of clinically significant psychiatric symptoms (Paul et al., 2008). Paul et al.'s (2008) study has also failed to establish a relationship between the CC volume and reduction in FA. Although the current study did not observe a significant difference in FA between the PTSD and TEC, potentially providing further support to Paul et al.'s (2008) findings, the results also indicated that when compared to NTEC, PTSD was associated with microstructural damage within the CC. It is unclear from the present findings to what

extent exposure to a psychologically traumatic event per se affects WM microstructure.

The mTBI group showed decreased FA compared to the PTSD group. Similar to the comparison with the two control groups, this decrease was associated with a concurrent increase in Trace and was mediated by increased Perpendicular Diffusivity. It appears that apart from PTSD-driven WM neuropathology, there are also factors that are unique to mTBI that have an individual effect on WM integrity. Therefore, in light of the present findings, PTSD and mTBI could potentially have independent and additive effects on WM integrity following mTBI. This possibility is explored in Chapter 6.

This study observed mixed results for Mode. Contrary to the predictions, TEC displayed higher Mode than the rest of the groups. As discussed in Chapter 1, diffusion can be characterized as being either tubular (cigar-shaped) or planar (coin-shaped), with tubular diffusivity associated with higher Mode, which in turn has been observed in regions of parallel fibres (Davoodi-Bojd & Soltanian-Zadeh, 2011; Westin et al., 2002). Decrease in Mode, on the other hand, has been detected in regions of crossing fibres and increase in this metric has been linked to decrease in fibre density (Whitford et al., 2010; Wiegell, Larsson, & Wedeen, 2000). Since TEC have also displayed similar FA to the PTSD group but higher Mode, it could be argued that it is through this unique combination of microstructural features of the CC that TEC are able to show resilience when confronted with stressful life events. Importantly, this is only a speculation and further research into the significance of Mode in its ability to describe WM abnormality is needed.

This study also observed decreased Mode in the mTBI group compared to the other three groups. As mentioned earlier, decreased Mode has been previously observed in regions of fibre crossings, suggesting higher fibre density (Kindlmann et al., 2007). The significance of this finding is, however, unclear.

Contrary to the original predictions, this study observed increased Parallel Diffusivity in the mTBI group compared to the PTSD group. Although it is possible that this finding is related to WM pathology, its underlying nature is unclear. As proposed by Wheeler-Kingshott and Cercignani (2009), the presence of crossing fibres can lead to misalignment of the primary axes, potentially causing arbitrary changes in Parallel Diffusivity that are unrelated to structure of the underlying biological tissue.

One limitation of this study is that the CC was only investigated along its entire length. Previous research has observed FA changes not only throughout the entire length of the CC but also within different subregions of this tract, such as the genu and splenium (Inglese et al., 2005; Jackowski et al., 2008; Kumar et al., 2009). Since different subregions of the CC connect functionally different parts of the left and right cerebral hemispheres, some subregions could be more important than others in explaining PTSD symptomatology and effects of mTBI. Specifically, since the genu connects frontal and orbitofrontal cortices, this subregion could potentially play a critical role in symptomatology of PTSD and mTBI. At the same time, reduction in FA in the splenium in the acute stages of mTBI has been linked to cognitive functioning in the chronic stages of the injury (Matsushita et al., 2011). Therefore, the observed WM damage could be primarily driven by changes in one of these subregions of the CC rather than being due to alterations along the entire tract.

The next step of this project was to investigate whether previously implicated in these disorders associative fibre bundles moderate the intersection of PTSD and mTBI. Chapter 4 will explore the contribution of the cingulum bundle.

Chapter 4

Study 2: Cingulum

As outlined in Chapter 1, the cingulum is an associative fibre bundle that belongs to the limbic system and is thought to be involved in emotional and cognitive processes, such as memory and executive functioning. In light of the functions performed by this tract, the cingulum has often been implicated in psychopathology.

The involvement of the cingulum bundle in emotion processing was first proposed by human lesion studies indicating reduced levels of anxiety and aggressiveness upon the surgical removal of this tract (Ballantine Jr et al., 1967; Brown & Lighthill, 1968; Foltz & White Jr, 1962). More recently, however, fMRI studies have proposed functional heterogeneity of the cingulum bundle such that the anterior region has been thought to be involved in emotional processing while the posterior region has been implicated in cognition, memory in particular (Bush, Luu, & Posner, 2000). Vogt et al. (1992) have further subdivided the ACC into caudal-dorsal midline, assumed to be primarily involved in cognitive processing, and rostral-ventral midline region that has been mainly associated with emotion. This proposed functional heterogeneity of distinct regions of the ACC has been confirmed using an emotional Stroop task, where

activation in the rostral ACC was increased in response to negative compared to neutral words (Etkin et al., 2006; Mohanty et al., 2007; Whalen et al., 1998). When a traditional Stroop task was used, however, increased activation was observed in the dorsal ACC in response to incongruent compared to congruent coloured words (Mohanty et al., 2007).

The idea of the existence of functionally distinct subregions of the ACC was challenged by the observation of increased activation in the dorsal ACC in response to cognitively demanding tasks that were also emotionally laden (Davis et al., 2005). Based on findings of this nature, Etkin et al. (2011) speculated that rather than being functionally distinct, the rostral and dorsal subregions of the ACC are likely involved in different aspects of emotional processing.

The ACC has often been implicated in PTSD symptomatology, with studies showing deactivation in the rostral ACC in response to personally traumatic words (Liberzon et al., 2003; Shin et al., 2001). Some research has also indicated reduction in activation within this region in response to emotional stimuli unrelated to trauma, thus suggesting a more general deactivation in the rostral ACC in PTSD (Offringa et al., 2013).

Microstructural changes have also been observed in the main WM tract of the cingulate cortex, namely the cingulum. Although studies have consistently observed decrease in FA within this bundle in PTSD, results have varied in regards to laterality, with changes observed within the left cingulum, right cingulum or bilaterally (Fani et al., 2012; Kim et al., 2005; Kim et al., 2006; Sanjuan et al., 2013; Schuff et al. 2011; Sekiguchi et al., 2014; Sun et al. 2013; Wang et al., 2010; Zhang et al., 2011).

Similarly, since emotional disturbances are commonly observed in the aftermath of mTBI, they have often been attributed to alterations within the cingulum. Reduced connectivity has been commonly observed in the posterior cingulum which in turn has been linked to symptoms of re-experiencing (Costanzo et al., 2014; Sorg et al., 2014). Consequently, this association has been used to describe a mechanism via

which mTBI increases the likelihood of PTSD (Costanzo et al., 2014). It is important to note, however, that unlike mTBI, anisotropic changes in PTSD have predominantly been observed in the anterior rather than posterior cingulum.

In light of the past research (Costanzo et al., 2014; Fani et al., 2012; Kim et al., 2005; Kim et al., 2006; Schuff et al., 2011; Sekiguchi et al., 2014; Sun et al., 2013; Wang et al., 2010; Zhang et al., 2011), it was hypothesised that the PTSD and mTBI groups would show aberrant anisotropy within bilateral cingulum compared to NTEC and TEC as would be evidenced by reduced FA, increased Perpendicular Diffusivity, increased Mode, increased Trace and reduced Parallel Diffusivity.

4.1 Results

4.1.1 Tractography

The cingulum is a WM tract that is characterized by a very distinctive anatomical shape and as such can be located using fiducial-based approach with a high level of precision and accuracy. Due to the presence of long and short fibres and in order to increase accuracy, the cingulum was seeded using multiple fiducials (min= 3, max= 4). Examples of streamline tractography performed for three participants from each of the four groups are depicted in Figure 4.1, 4.2, 4.3 and 4.4 for NTEC, TEC, PTSD and mTBI, respectively.

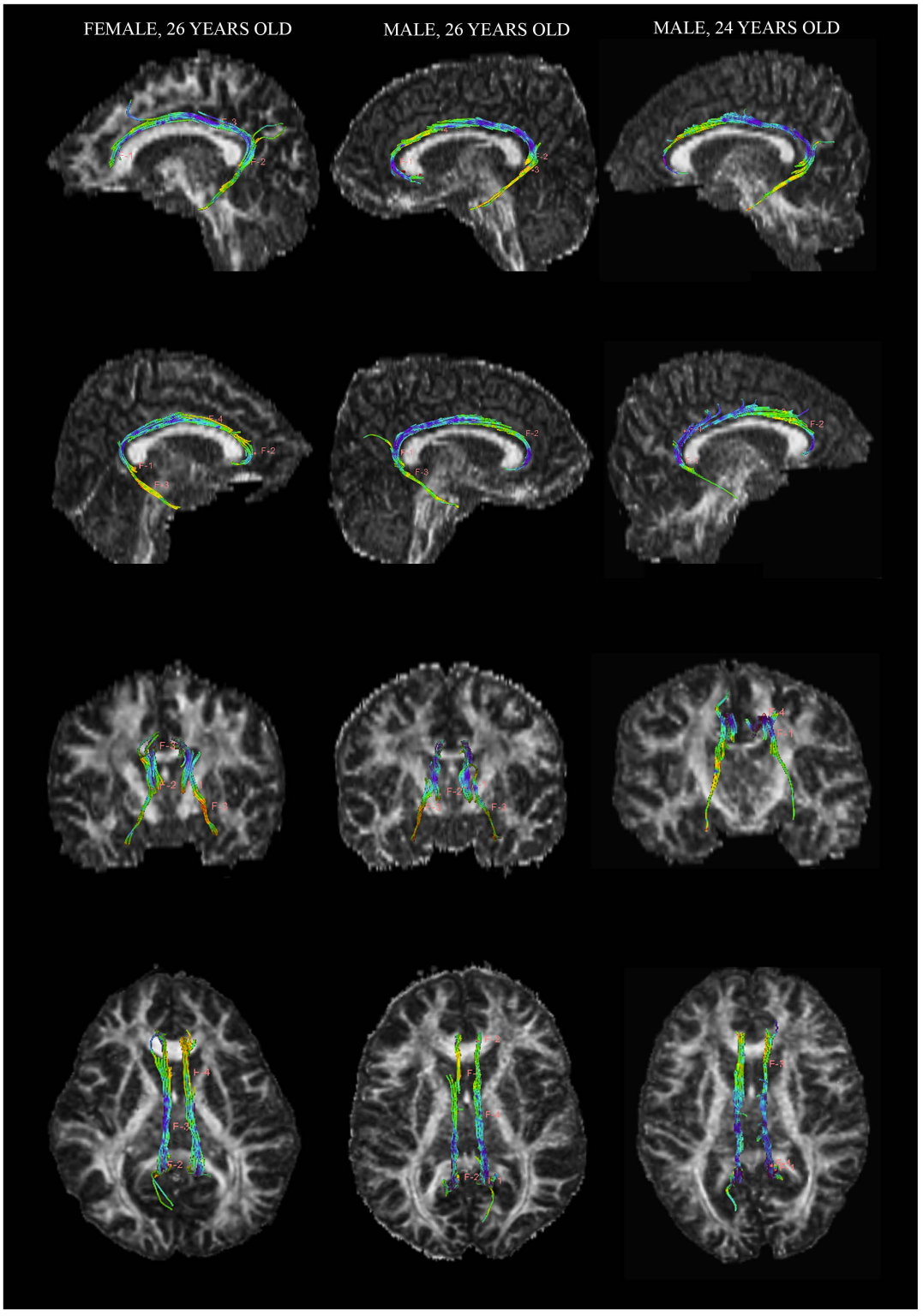

Figure 4.1. Examples of streamline tractography performed for three participants from the NTEC group. Sex and age of each participant are indicated. Locations of fiducials from which the cingulum was seeded are marked F1, F2, F3 and F4.

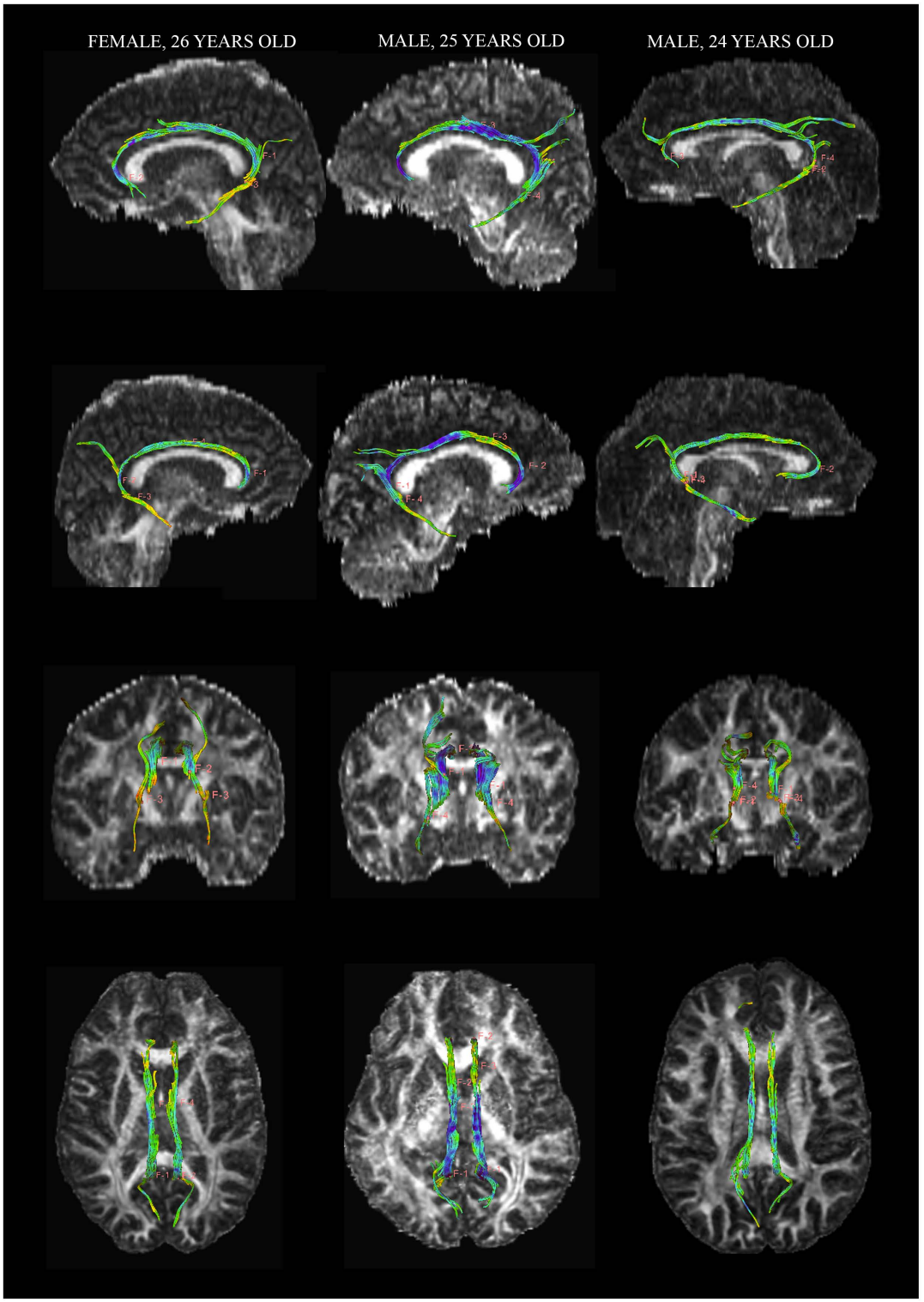

Figure 4.2. Examples of streamline tractography performed for three participants from the TEC group. Sex and age of each participant are indicated. Locations of fiducials from which the cingulum was seeded are marked F1, F2, F3 and F4.

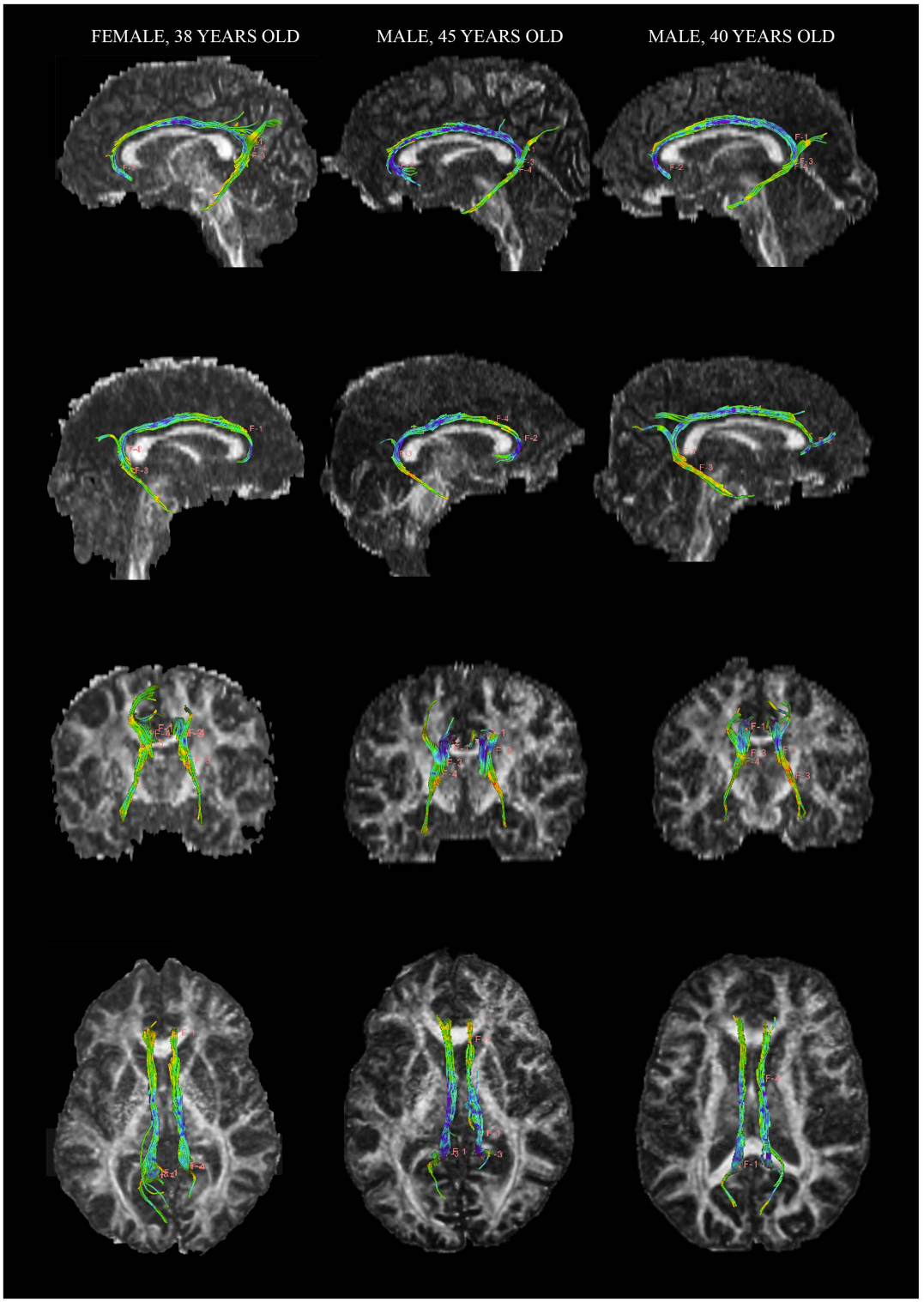

Figure 4.3. Examples of streamline tractography performed for three participants from the PTSD group. Sex and age of each participants are indicated. Locations of fiducials from which the cingulum was seeded are marked F1, F2, F3 and F4.

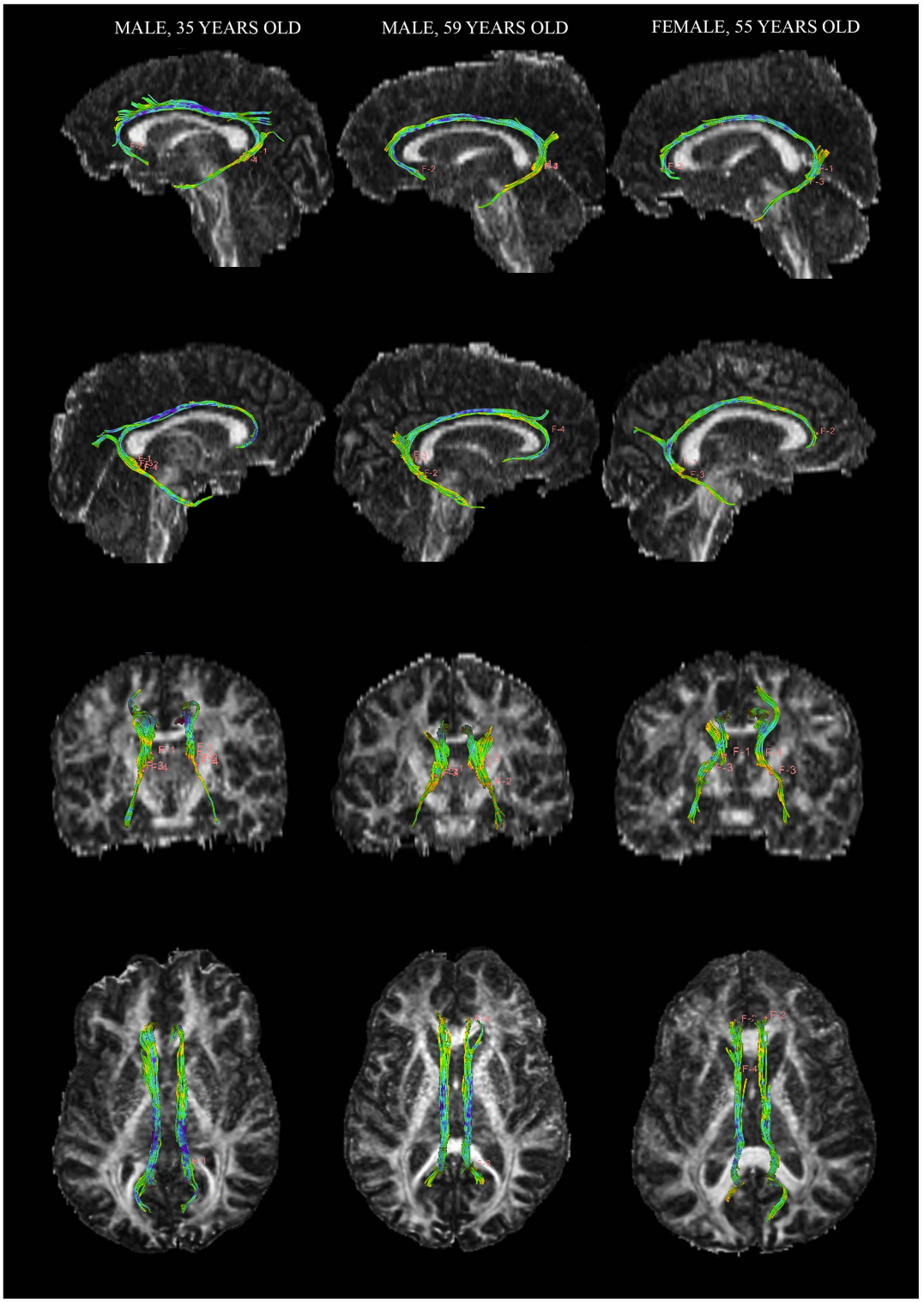

Figure 4.4. Examples of streamline tractography performed for three participants from the mTBI group. Sex and age of each participant are indicated. Locations of fiducials from which the cingulum was seeded are marked F1, F2, F3 and F4.

4.1.2 Group Comparisons

Two-way mixed ANOVAs were performed for FA, Trace, Perpendicular Diffusivity, Parallel Diffusivity and Mode, with hemisphere as a within-subjects factor (two levels: left and right) and group as a between-subjects variable (four levels: NTEC, TEC, PTSD and mTBI).

For FA, the main effect of the within-subjects factor hemisphere was significant: F (3, 121) = 22.458, p = .000, partial η^2 = .157 (Figure 4.5). The main effect of group was not significant: F (3, 121) = 2.175, p = .094, partial η^2 = .051, nor was the two-way interaction: hemisphere by group: F (3, 121) = .465, p = .707, partial η^2 = .011.

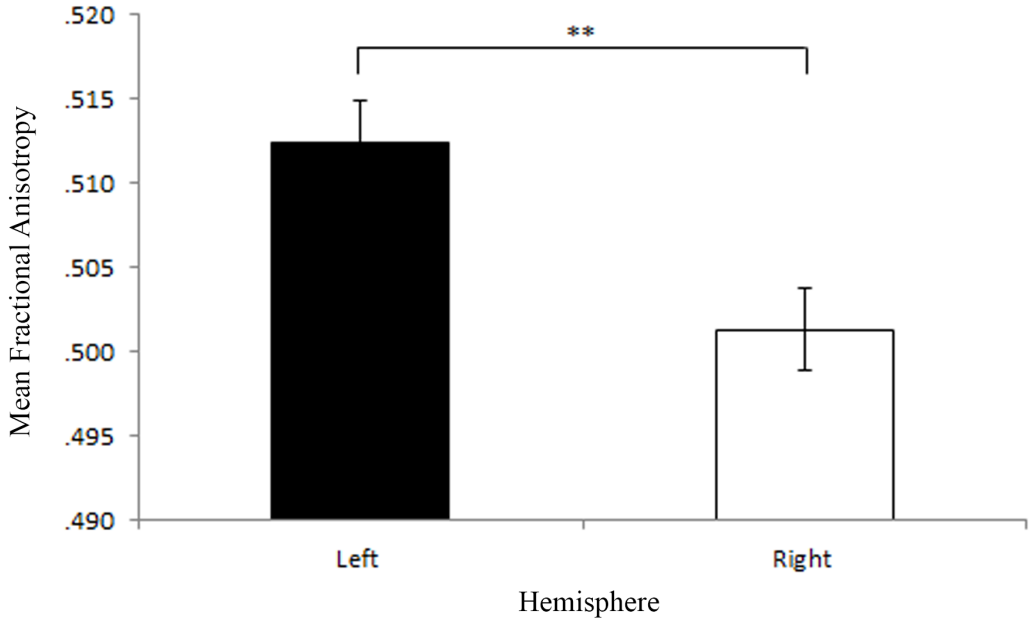

Figure 4.5. Mean FA as a function of hemisphere across all groups. *Note. Significance of <.01 indicated with* **.

For Trace, the main effect of the within-subjects factor hemisphere was significant: F (3, 122) = 8.110, p = .005, partial η^2 = .062 (Figure 4.6). The main effect of group was also significant: F (3, 122) = 5.346, p = .002, partial η^2 = .116. The group

by hemisphere two-way interaction was not significant: F (3, 122) = 1.591, p = .195, partial η^2 = .038.

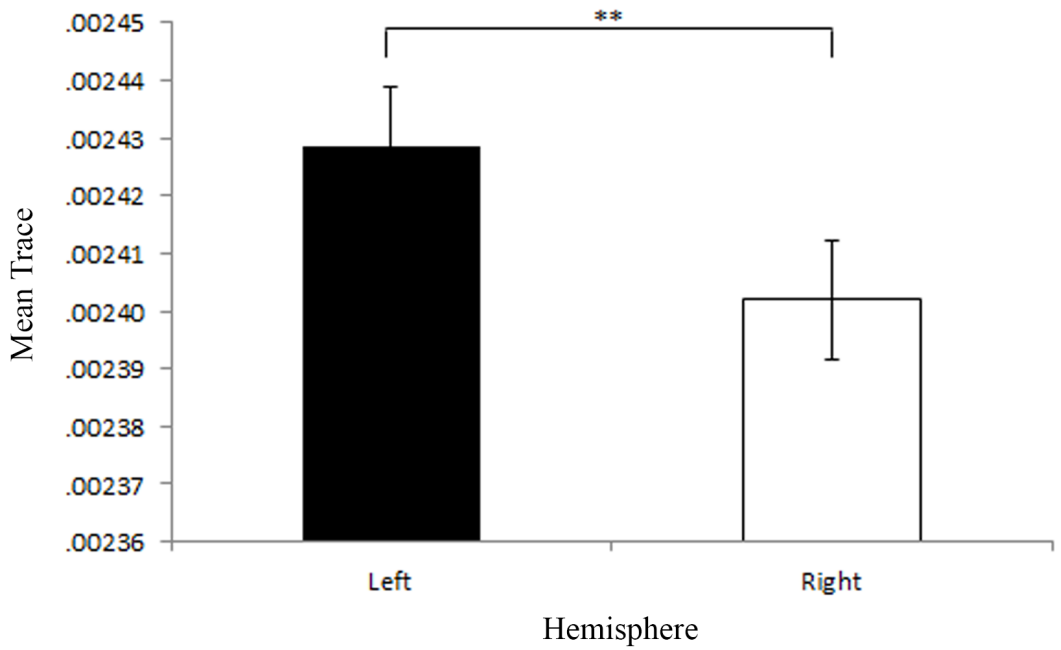

Figure 4.6. Mean Trace as a function of hemisphere across all groups. *Note. Significance of <.01 indicated with **.*

For Mode, the main effect of the within-subjects factor hemisphere was significant: F (3, 122) = 33.511, p = .000, partial η^2 = .215 (Figure 4.7). The main effect of group was also significant: F (3, 122) = 6.049, p = .001, partial η^2 = .129. The group by hemisphere two-way interaction was not significant: F (3, 122) = .486, p = .693, partial η^2 = .012.

For Perpendicular Diffusivity, the main effect of the within-subjects factor hemisphere was not significant: F (3, 120) = 1.821, p = .180, partial η^2 = .015, nor was the group by hemisphere interaction effect: F (3, 120) = .585, p = .626, partial η^2 = .129. The main effect of group was significant: F (3, 120) = 5.541, p = .001, partial η^2 = .122.

For Parallel Diffusivity, the main effect of the within- subjects factor hemisphere was significant: F (3, 120) = 63.540, p = .000, partial η^2 = .346 (Figure 4.8).

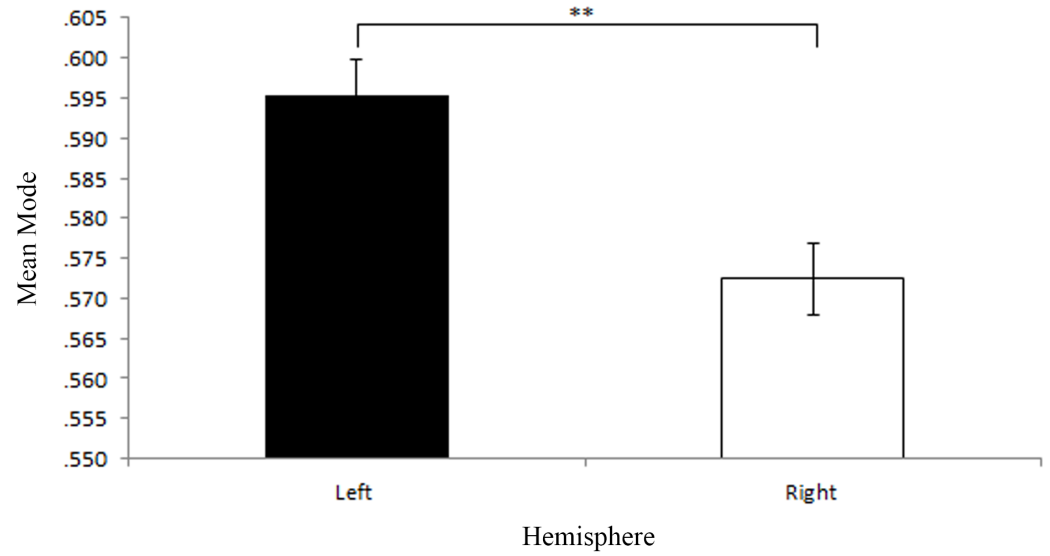

Figure 4.7. Mean Mode as a function of hemisphere across all groups. *Note. Significance of <.01 indicated with **.*

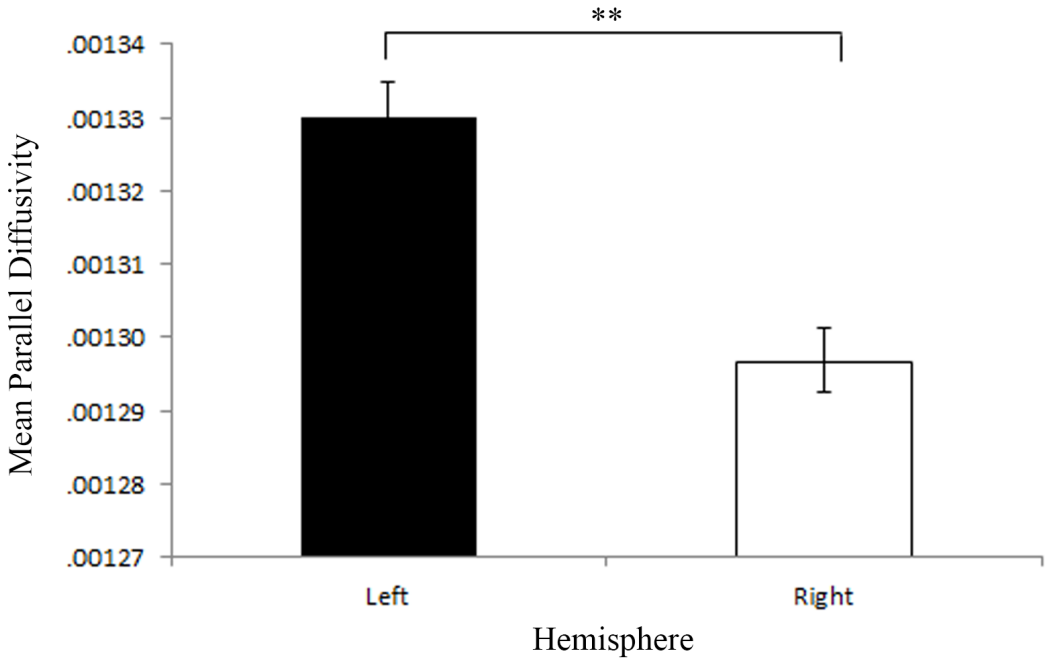

Figure 4.8. Mean Parallel Diffusivity as a function of hemisphere across all groups. *Note. Significance of < .01 indicated with **.*

The main effect of group was also significant: F (3, 120) = 4.688, p = .004, partial η^2 = .105. The group by hemisphere interaction effect was not significant: F (3, 120) = 2.066, p = .108, partial η^2 = .049.

Since there was a significant difference between groups in terms of age, all analyses were repeated with age introduced as a covariate. All significant results remained unchanged.

4.1.3 Pairwise Comparisons

Using Sidak adjustment to control for multiple testing, pairwise comparisons were conducted on statistically significant main and interaction effects. The mTBI group displayed increased Trace compared to the NTEC (p = .021) and PTSD groups (p = .002) (Figure 4.9).

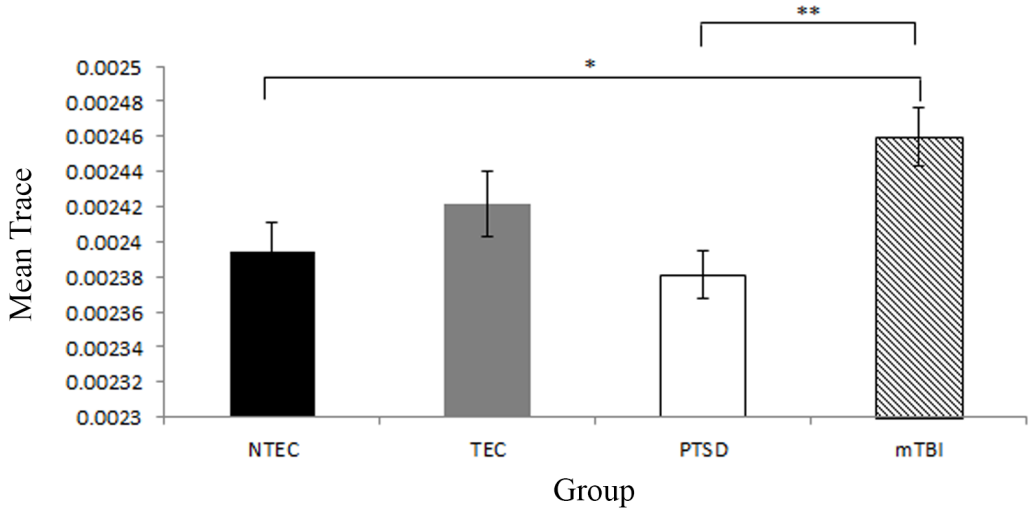

Figure 4.9. Mean Trace as a function of group. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury.*Note. Significance of* $< .05$ *and* $< .01$ *indicated with * and **, respectively.*

The mTBI group displayed increased Mode compared to NTEC (p = .000). TEC had higher Mode than NTEC (p = .025) (Figure 4.10).

The mTBI group displayed significantly higher Perpendicular Diffusivity than the PTSD group (p = .0001), and approached significance when compared to NTEC (p = .056) and TEC (p =.068) (Figure 4.11).

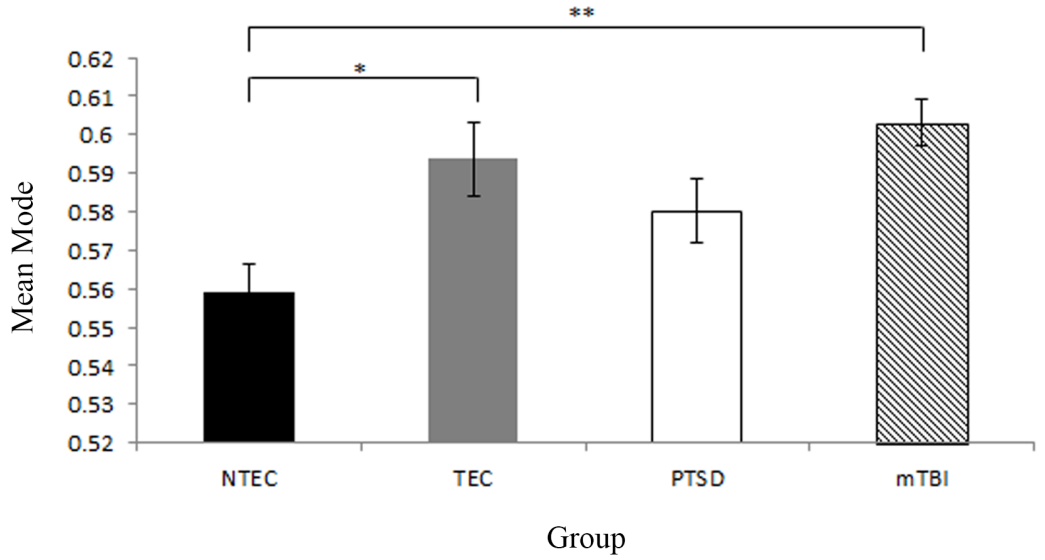

Figure 4.10. Mean Mode as a function of group. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. *Note. Significance of $< .05$ and $< .01$ indicated with * and **, respectively.*

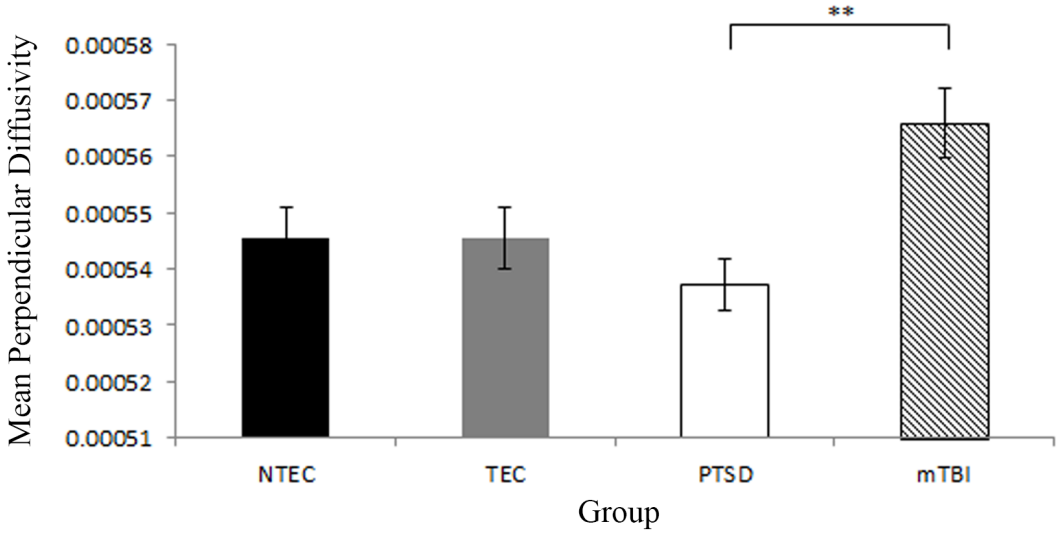

Figure 4.11. Mean Perpendicular Diffusivity as a function of group. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. Significance of $< .01$ indicated with **. *Note. Significance of $< .01$ indicated with **.*

Finally, the mTBI group showed increased Parallel Diffusivity compared to NTEC (p = .024) and PTSD (p = .006) (Figure 4.12).

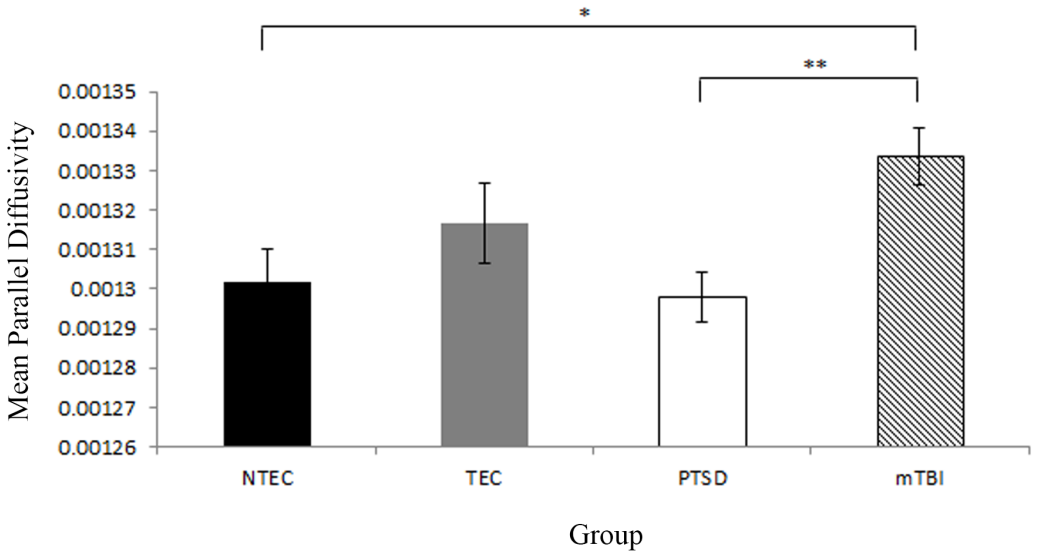

Figure 4.12. Mean Parallel Diffusivity as a function of group. NTEC= Non- Trauma Exposed Controls. TEC= Trauma Exposed Controls. PTSD= Post- Traumatic Stress Disorder. mTBI= mild Traumatic Brain Injury. *Note. Significance of* $< .05$ *and* $< .01$ *indicated with * and **, respectively.*

4.2 Discussion

In the present study, mTBI was associated with microstructural changes within the cingulum bundle. Specifically, the mTBI group showed increased Trace and Perpendicular Diffusivity compared to the PTSD group. Compared to the NTEC group, both the mTBI and TEC groups showed increased Mode. Contrary to hypotheses, the mTBI group displayed increased Parallel Diffusivity compared to PTSD and NTEC. Also, contrary to predictions, PTSD participants showed no significant changes within this tract compared to neither NTEC nor TEC.

Using diffusion tensor imaging data, the diffusion properties of the cingulum bundle were examined. Across all groups, there was an anisotropic asymmetry such that the diffusion ellipsoids (averaged across all the voxels in the cingulum) in the left

hemisphere were larger and more anisotropic than in the right hemisphere. Additionally, the diffusion ellipsoids in the left hemisphere possessed longer λ_1 and were characterized by a slightly more tubular, or cigar shaped, anisotropy (Figure 1.3). Based on the findings related to Trace, Parallel Diffusivity and Mode it appeared that, on average, the mTBI group was characterized by overall more voluminous diffusion ellipsoids that had both longer λ_1 and possessed a slightly more tubular, cigar-like shape (Figure 1.3) compared to the NTEC group. Compared to the PTSD group, mTBI was associated with larger diffusion ellipsoids that were also characterized by longer λ_1 and a higher average of λ_2 and λ_3- lengths of the middle and shortest axes of the diffusion ellipsoid, respectively. Also, TEC displayed diffusion ellipsoids that were slighly more cigar- like than the diffusion ellipsoids observed for the NTEC group that were characterized by more planar, or coin-shaped, anisotropy (Figure 1.3).

mTBI was characterized by increased Trace which in literature has been associated with unrestricted diffusion - a pattern that has been observed in regions of WM damage. This increase appeared to be mediated by concurrent rise in Perpendicular Diffusivity which has been previously linked to demyelination (Klawiter et al., 2011; Song et al., 2002; Song et al., 2003). Animal studies have shown that while increase in Perpendicular Diffusivity is associated with demyelination, decrease is associated with remyelination (Song et al., 2002; Song et al., 2005). Likewise, human studies of MS have provided a positive link between the severity of myelin loss and Perpendicular Diffusivity (Klawiter et al., 2011). Taken together, these findings indicate that mTBI is associated with loss of coherence within the cingulum, which is characterized by an overall increased diffusivity, potentially due to demyelination. This observation is consistent with past research that has identified reduced connectivity within this fibre bundle in mTBI (Sorg et al., 2014).

The observed increase in Trace is of a particular importance in light of Costanzon et al.'s (2014) proposed model of neural mechanisms that mediate the effect that mTBI has on the development of PTSD, purportedly involving aberrant connections between the PCC and MFC. Based on this mechanism, it is plausible to assume that

changes within this limbic system tract contribute to the cognitive and emotional disturbances observed in mTBI. However, since no significant changes were observed in the PTSD group compared to NTEC or TEC in relation to Perpendicular Diffusivity or Trace, and since the mTBI group was significantly worse than the PTSD group on these diffusivity measures, it is likely that the observed results are attributable to mTBI rather than PTSD. However, this question is yet to be thoroughly investigated.

Contrary to prediction, the mTBI group displayed increase in Parallel Diffusivity compared to NTEC. Since Parallel Diffusivity is thought to describe diffusion along the axon, reduction in this metric has been associated with axonal injury (Song et al., 2003). Song et al. (2003) has observed reduction in Parallel Diffusivity as a result of axonal damage within the optic nerve following retinal ischemia in mice. The link between reduction in Parallel Diffusivity and axonal damage has been further confirmed through a strong association of this DTI metric with histological markers of axonal damage (Budde, Xie, Cross, & Song, 2009). There are two possible explanations for the observed inconsistency between the present findings and proposed significance of changes in Parallel Diffusivity. Firstly, increase in Parallel Diffusivity could be attributed to factors secondary to the WM changes. For instance, Della Nave et al. (2011) have proposed that increase in extracellular water content could potentially affect diffusion along the axon by restricting the directionality of diffusion and hence increasing Parallel Diffusivity. Another contributing secondary factor that has been proposed is the flux associated with accumulation of the constituents of cytoskeleton - a process potentially driven by the changes in glial cells (Basser & Pierpaoli, 1996; Beaulieu, 2002; Della Nave et al., 2011). Secondly, changes in Parallel Diffusivity have been attributed to factors other than underlying biophysical properties of WM, such as the direction of the principal vector. Through evaluation of numerical simulations and DTI data, Wheeler-Kingshott and Cercignani (2009) proposed that the presence of crossing fibres in the unhealthy brain could result in misalignment of the principal vectors causing arbitrary changes to both Parallel and Perpendicular diffusivities that are unrelated to the underlying tissue architecture.

Another unexpected finding was observed in the TEC group, who showed increased Mode compared to NTEC. It has been proposed that increase in Mode is associated with decrease in fibre density since reduction in this metric has been observed in regions of fibre crossings (Kindlmann et al., 2007; Whitford et al., 2011). It is possible that differences in Mode between the two control conditions could be attributed to (a) unintended sampling bias, or (b) WM integrity contributing to behavioural factors that may contribute to the likelihood of being exposed to trauma. Considerable research has shown that trauma exposure is not necessarily a random event, and that prior trauma exposure or stress response can impact on the probability of being exposed to subsequent trauma (Zatzick et al., 2004). Importantly, the significance of Mode in relation to WM microstructure is yet to be clarified and hence the proposed interpretations of this finding are only speculative in nature.

Contrary to the past research (e.g. Kim et al., 2005; Sun et al., 2013; Costanzo et al., 2014), this study did not observe FA changes within the cingulum in the PTSD or mTBI groups. Two factors may potentially have contributed to the lack of findings. Firstly, PTSD participants in the present study underwent MRI scans on average 155 months after the traumatic experience compared to a maximum of 48 months in the majority of studies that reported decrease in FA within this tract. It is plausible that after a certain period of time, any changes within the cingulum that may have originally been present subsided and became undetectable through DTI or disappeared altogether. Similarly, mTBI may be characterized by certain aberrant changes within the cingulum that improve over time whereas other changes may be more permanent and persist into chronic stages of the condition. Secondly, past research suggests that the anterior and posterior regions of the cingulum are affected differently in PTSD and mTBI. In the present study, this bundle was measured and analysed in its entirety as the main focus of this project was to assess its integrity with reference to overall PTSD severity rather than specific symptoms. As a result, this may have masked real differences in this bundle between PTSD, mTBI and control groups.

Across all groups, this study observed hemispheric asymmetry within the cingulum such that the left hemisphere was characterized by stronger connectivity within this bundle compared to the right hemisphere, as evidenced by higher FA. This finding is consistent with previous research showing left-greater-than right anisotropy within the cingulum (Park et al., 2004). Similar pattern of asymmetry was observed for Trace, Parallel Diffusivity and Mode. Although increase in Parallel Diffusivity is consistent with the FA findings, the nature of laterality observed for Trace and Mode is unclear.

One clear limitation of the present study is the lack of between group comparisons between the anterior and posterior subregions of the cingulum. The posterior cingulum has recently been identified as a potential neural candidate contributing to the mTBI/PTSD symptom overlap (Costanzo et al., 2014). Additionally, previously observed cingulum changes in PTSD have been limited to the anterior region (e.g. Sun et al., 2013; Scuff et al., 2011; Sekiguchi et al., 2014). Therefore, in order to disentangle individual effects of changes within the anterior and posterior subregions on these conditions, further analysis is required. It could also be informative to link structural changes within the subsections of this tract to functional MRI in order to gain a better understanding of their individual contributions to PTSD symptoms.

This thesis now turns to Chapter 5, which focuses on the UF - a fronto- temporal fibre that has been implicated in memory function and was therefore deemed of particular importance in PTSD symptomatology.

Chapter 5

Study 3: Uncinate Fasciculus

As discussed in Chapter 1, the UF is a fronto-temporal fibre bundle that originates in the frontal pole, passes through the temporal lobe and terminates in the temporal pole, hippocampal gyrus, uncus and amygdala. Although generally this fibre bundle has been primarily implicated in memory processes (e.g. Gaffan & Eascott, 1995; Levine et al., 1998; Lu et al., 2002; Papagano et al., 2010), due to its anatomical position, it has also been studied in relation to a number of anxiety disorders.

Changes within the UF have been observed in GAD and SAD, where studies have reported reduced FA, although with variable laterality (Baur et al., 2011; Phan et al., 2009; Tromp et al., 2012). These observations are consistent with fMRI findings in both GAD and SAD that have observed overactive amygdala with a concurrently diminished activation in the PFC in response to aversive stimuli (Evans et al., 2008; Stein et al., 2002; Tromp et al., 2012).

Although the neurobiological model of PTSD described in Chapter 1 also implies involvement of the PFC and amygdala in mediating symptoms associated with this condition, there have been limited findings to date of alterations within the UF - the WM tract that connects sections of these regions (Eluvathingal et al., 2006; Heim & Nemeroff, 2009). Due to the lack of consistent findings establishing a clear link

between anxiety and the UF, with variance observed in laterality and nature of correlations between different indices of anxiety and FA, Von Der Heide, Skipper, Klobusicky, and Olson (2013) proposed that the contribution of the UF to anxiety is possibly small to none. Therefore, further research is needed to establish the precise role of this tract in mediating symptoms of anxiety, at both normal and clinical levels.

Findings in mTBI, on the other hand, have consistently shown reduced FA within the UF, with some studies additionally indicating increase in Mean Diffusivity (Bendlin et al., 2008; Brandstack, Kurki, & Tenovuo, 2013; Kinnunen et al., 2010; Levin, 2010; Niogi et al., 2008; Xiong et al., 2014). Increased Mean Diffusivity in mTBI has been linked to impaired working memory thus further supporting the importance of this tract in memory function (Xiong et al., 2014).

Following prior research (Eluvathingal et al., 2006; Heim & Nemeroff, 2009), it was hypothesised that the PTSD and mTBI groups would show weaker communication between frontal and temporal regions compared to both NTEC and TEC, which would be evidenced by reduced FA, increased Trace, increased Perpendicular Diffusivity, increased Mode and reduced Parallel Diffusivity within bilateral UF.

5.1 Results

5.1.1 Tractography

The UF possesses a very distinctive anatomical shape meaning that it can be located using fiducial-based approach with a high precision and accuracy. In the present study, in order to locate the UF, only one fiducial was seeded. Figures 5.1, 5.2, 5.3 and 5.4 illustrate examples of streamline tractography obtained for three participants from each of the four groups: NTEC, TEC, PTSD and mTBI, respectively.

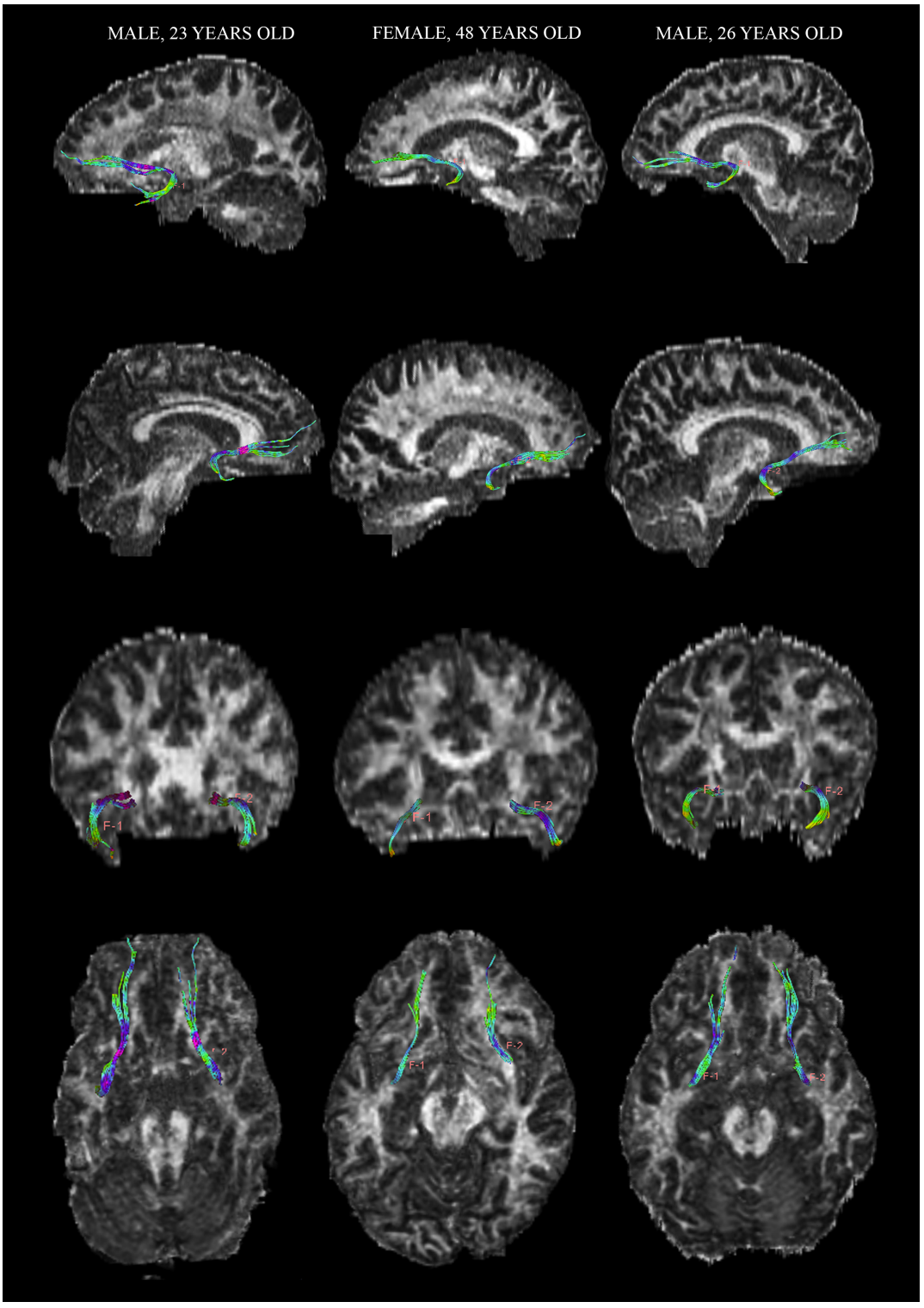

Figure 5.1. Examples of streamline tractography performed for three participants from the NTEC group. Sex and age of each participant are indicated. Locations of fiducials from which the UF was seeded are marked as F1 and F2 for the left and right UF, respectively.

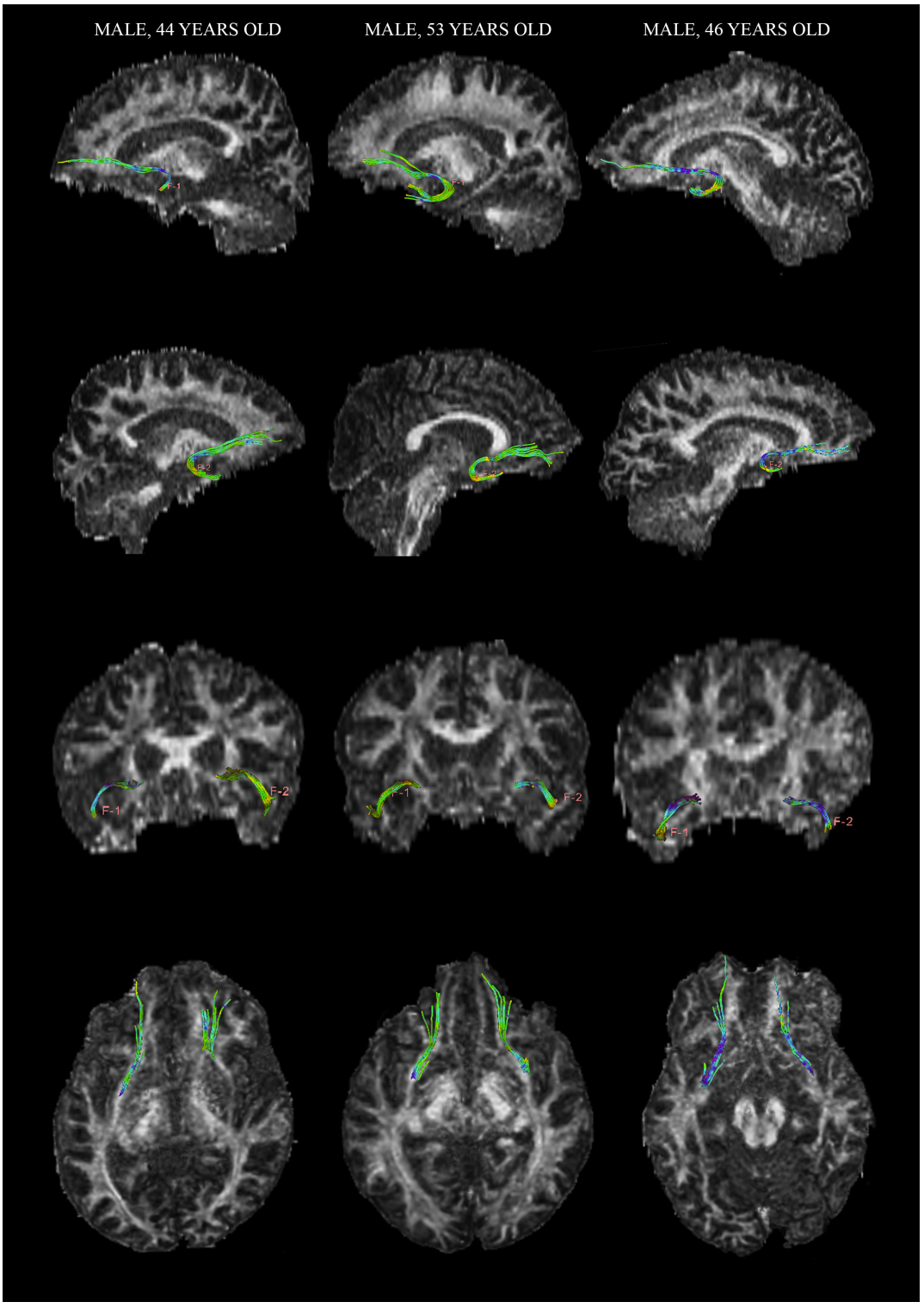

Figure 5.2. Examples of streamline tractography performed for three participants from the TEC group. Sex and age of each participant are indicated. Locations of fiducials from which the UF was seeded are marked as F1 and F2 for the left and right UF, respectively.

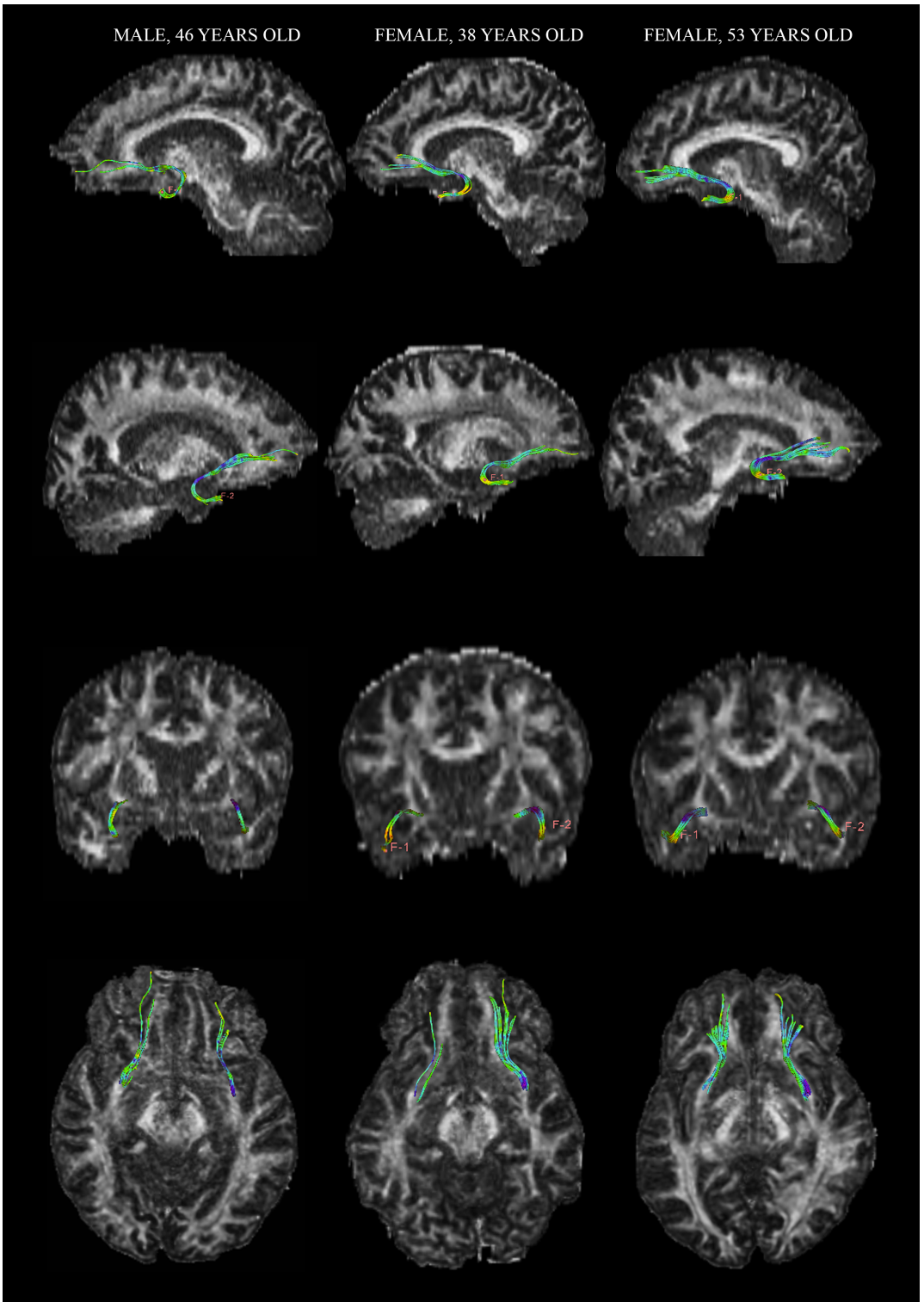

Figure 5.3. Examples of streamline tractography performed for three participants from the PTSD group. Sex and age of each participant are indicated. Locations of fiducials from which the UF was seeded are marked as F1 and F2 for the left and right UF, respectively.

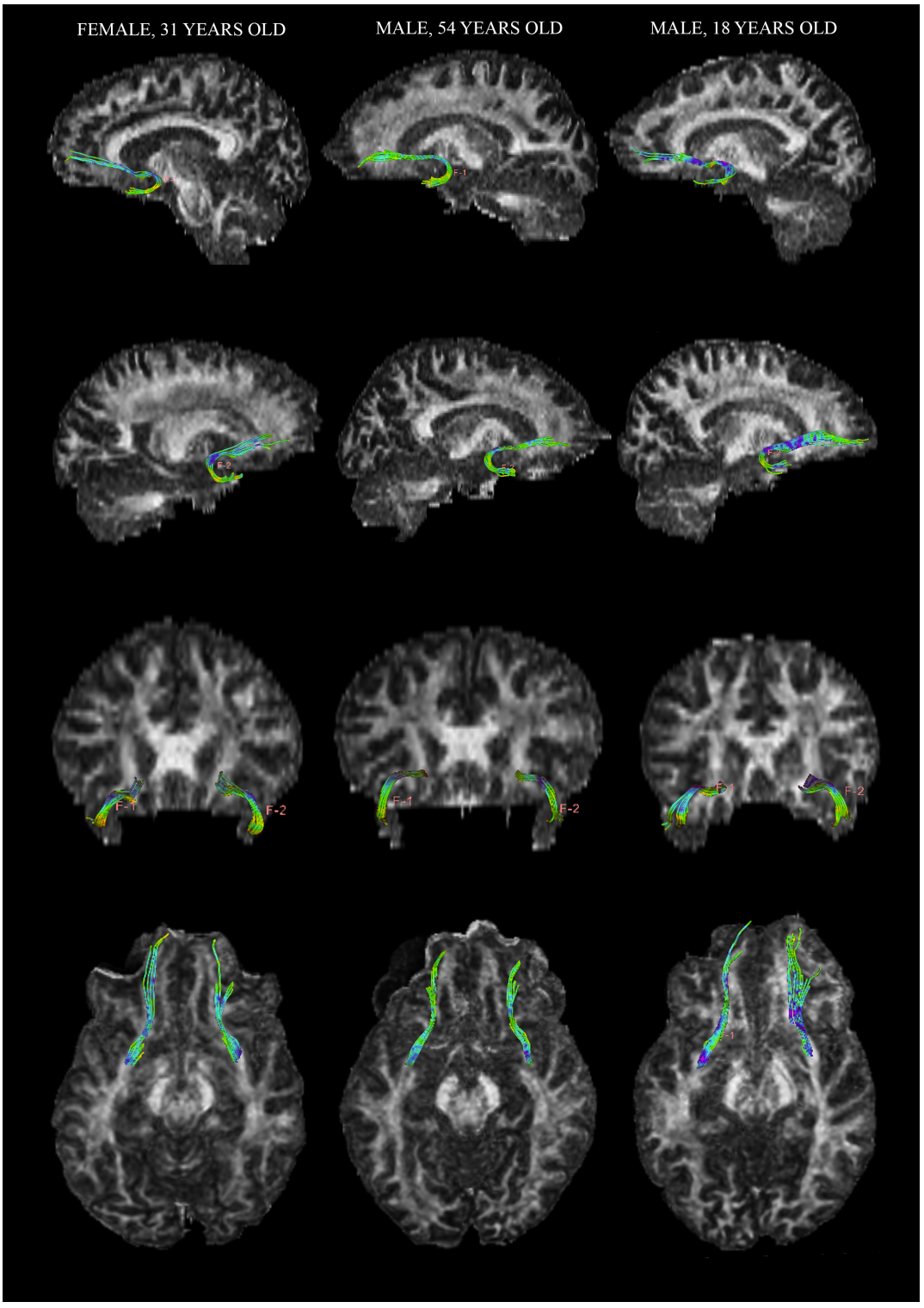

Figure 5.4. Examples of streamline tractography performed for three participants from the mTBI group. Sex and age of each participant are indicated. Locations of fiducials from which the UF was seeded are marked as F1 and F2 for the left and right UF, respectively.

5.1.2 Group Comparisons

A two-way mixed design ANOVA was conducted on FA, Trace, Mode, Parallel Diffusivity and Perpendicular Diffusivity with hemisphere as a within-subjects variable (two levels: left, right) and group as a between-subjects variable (four levels: NTEC, TEC, PTSD and mTBI).

For FA, the main effect of hemisphere was not significant: F (1, 110) = 2.934, p = .090, partial η^2 = .026, nor were the main effect of group or interaction effect: F (3, 110) = 1.884, p = .136, partial η^2 = .049 and F (3, 110) = 1.338, p = .266, partial η^2 = .035, respectively.

For Mode, the main effect of hemisphere was not significant: F (1, 111) = 1.158, p = .284, partial η^2 = .010, nor was the main effect of group: F (3, 111) = .273, p = .845, partial η^2 = .007. The group by hemisphere interaction was significant: F (3, 111) = 4.728, p = .004, partial η^2 = .113.

For Trace, the main effect of hemisphere was significant: F (1, 109) = 87.602, p = .000, partial η^2 = .446. This result is presented in Figure 5.5. The main effect of group was also significant: F (3, 109) = 3.650, p = .015, partial η^2 = .091. The group by hemisphere interaction was not significant: F (3, 109) = .452, p = .717, partial η^2 = .012.

For Perpendicular Diffusivity, the main effect of hemisphere was significant: F (1, 109) = 13.175, p = .000, partial η^2 = .108. This result is presented in Figure 5.6. The main effect of group was not significant, F (3, 109) = 2.306, p = .081, partial η^2 = .060, nor was the group by hemisphere interaction effect: F (3, 109) = .900, p = .444, partial η^2 = .024.

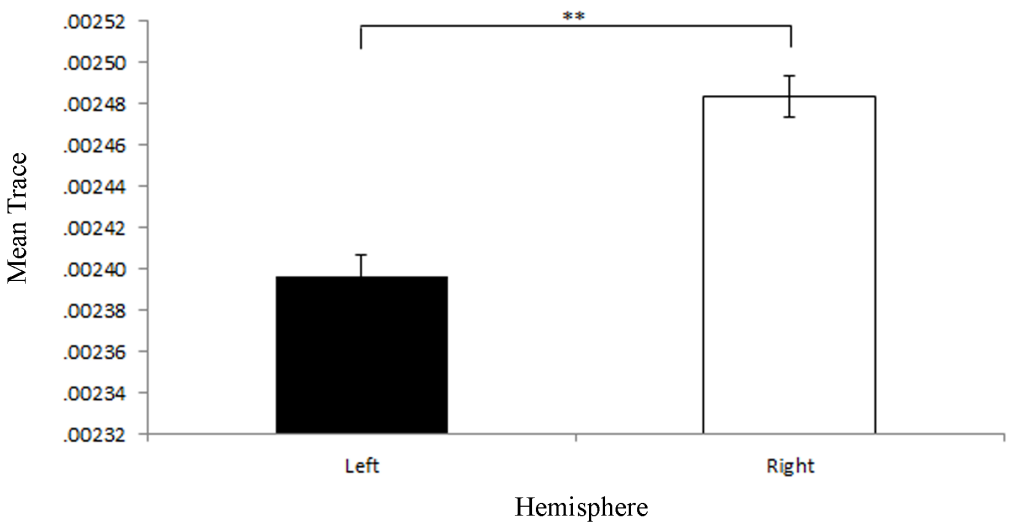

Figure 5.5. Mean Trace as a function of hemisphere. *Note. Significance of* $< .01$ *indicated with* **.

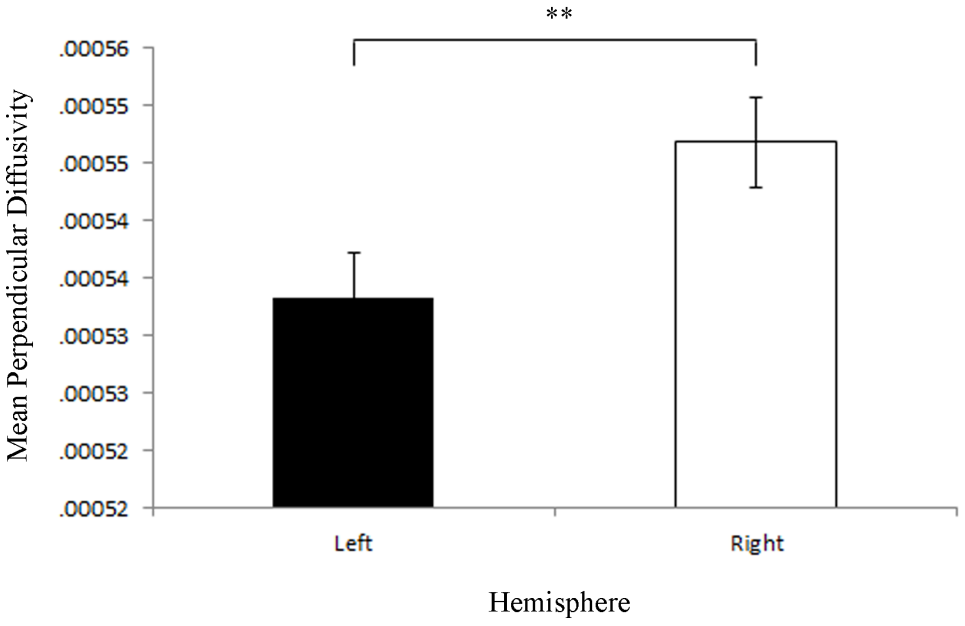

Figure 5.6. Mean Perpendicular Diffusivity as a function of hemisphere. *Note. Significance of* $< .01$ *indicated with* **.

For Parallel Diffusivity, the main effect of hemisphere was significant: F (1, 111) = 91.673, p = .000, partial η^2 = .452. This result is presented in Figure 5.7. The main effect of group was not significant: F (3, 111) = .628, p = .598, partial η^2 = .017,

nor was the interaction effect between group and hemisphere: F (3, 111) = .1.217, p = .307, partial η^2 = .032.

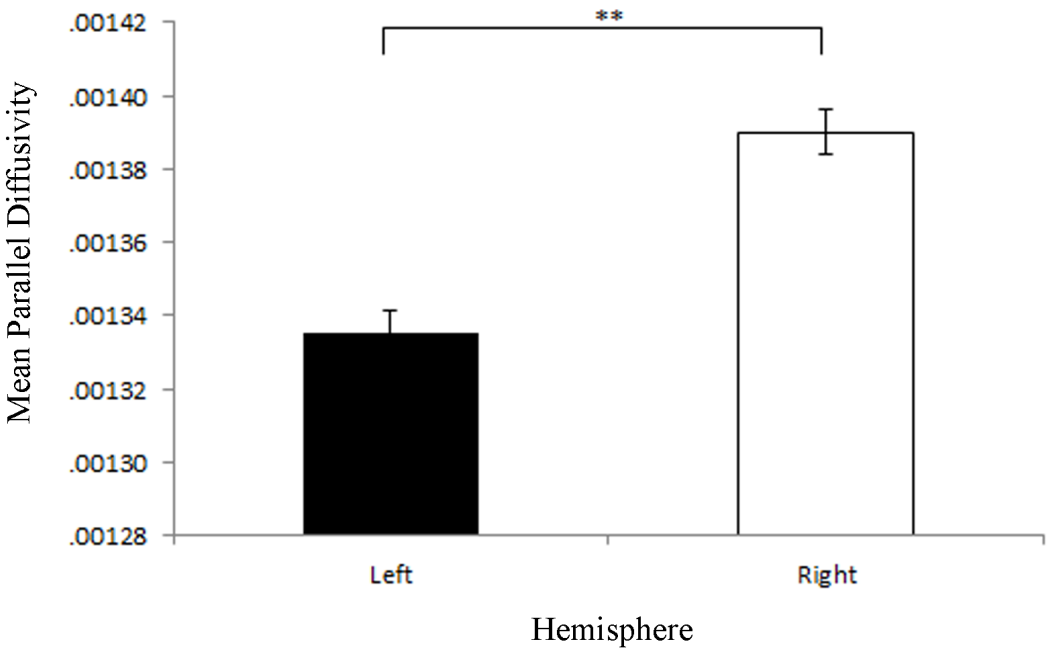

Figure 5.7. Mean Parallel Diffusivity as a function of hemisphere. *Note. Significance of* $< .01$ *indicated with* **.

Since there was a significant difference between groups in terms of age, these analyses were re-run with age as a covariate. After controlling for age, all significant effects remained unchanged.

5.1.3 Pairwise Comparisons

The mTBI group showed significant difference in Mode between hemispheres, with higher Mode observed in the left hemisphere compared to the right (p = .009). A near significant difference was also observed in the left hemisphere for TEC showing a higher Mode in the left hemisphere compared to the right (p = .054). Means for the left and right hemispheres observed in mTBI and TEC are presented in Figure 5.8 and Figure 5.9, respectively.

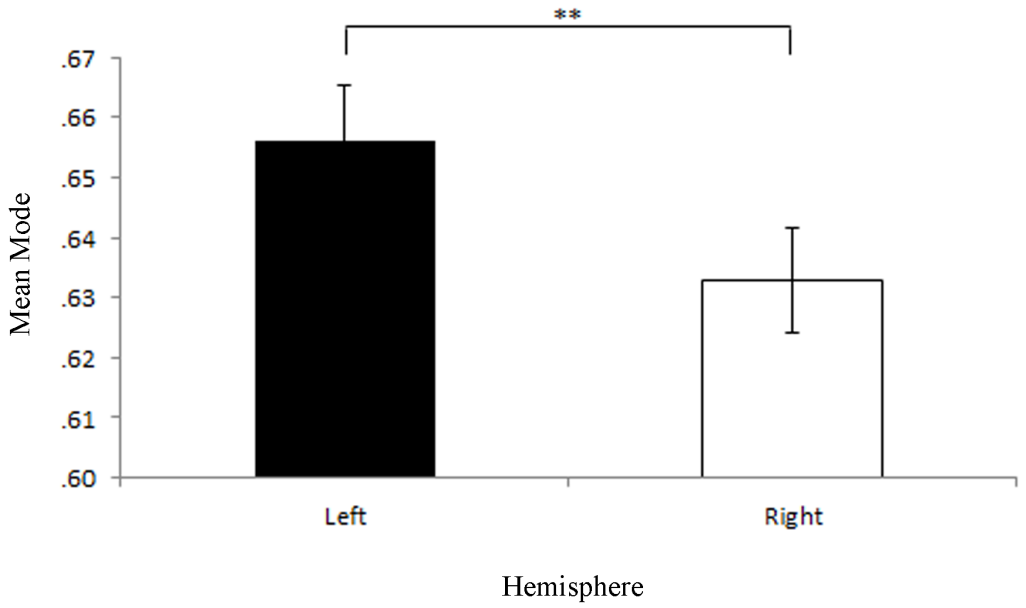

Figure 5.8. Mean Mode as a function of hemisphere in the mTBI group. *Note. Significance of* $< .01$ *indicated with* **.

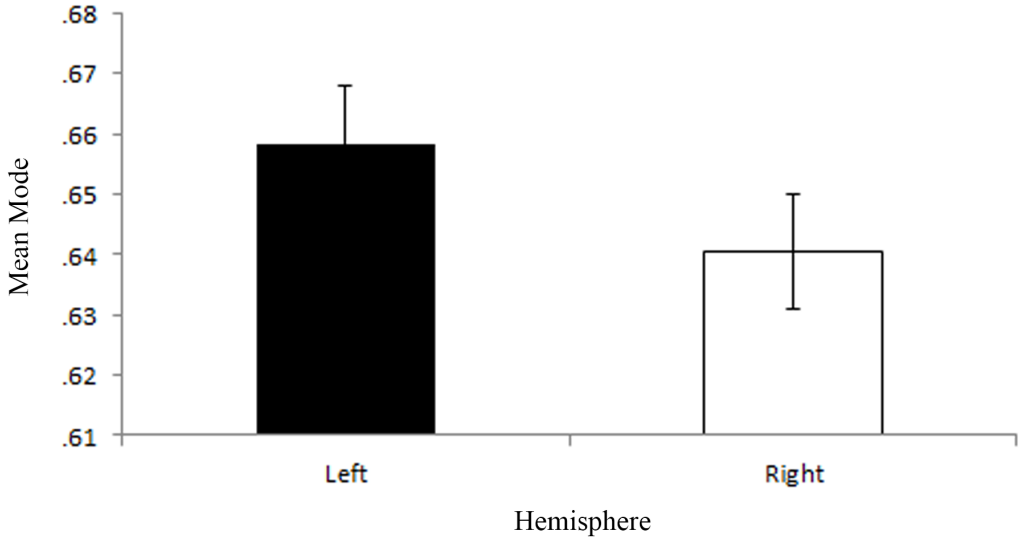

Figure 5.9. Mean Mode as a function of hemisphere in the TEC group.

There was a significant difference between TEC and NTEC in Trace, with the former displaying higher Trace than the latter ($p = .020$). There was also a near significant difference between the mTBI group and NTEC, with the mTBI group showing

higher Trace than NTEC (p = .066). These results are presented in Figure 5.10.

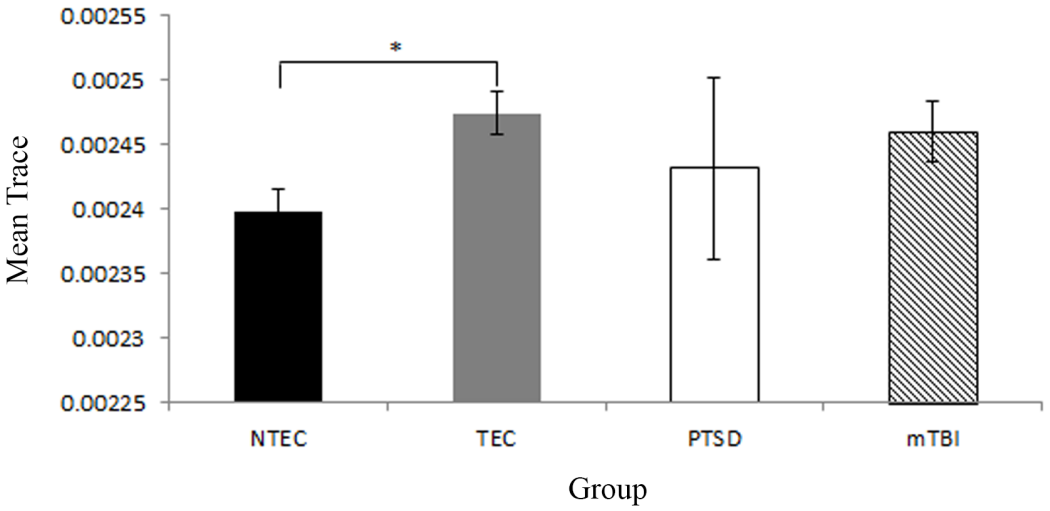

Figure 5.10. Mean Trace as a function of group membership. *Note. Significance of* $< .05$ *indicated with *.*

5.2 Discussion

Overall, in terms of the diffusion ellipsoid characteristics, all groups displayed larger diffusion ellipsoids (averaged across all the voxels in the UF) in the right hemisphere compared to the left hemisphere. The diffusion ellipsoids in the left hemisphere, on average, also had a longer λ_1 and a higher average of the lengths of the middle and shortest axes i.e. λ_2 and λ_3, respectively. The mTBI group was observed to have somewhat more tubular, or cigar- shaped, ellipsoids in the left hemisphere compared to the right hemisphere (Figure 1.3). Also, TEC had an overall larger diffusion ellipsoids than NTEC.

Contrary to predictions, this study did not observe any changes in the UF in the mTBI or PTSD groups when compared to the two control groups on any of the metrics measured. Unexpectedly, TEC were observed to have higher Trace than NTEC. This

study also showed hemispheric asymmetry within the UF microstructutre across all groups.

Only one study to date has observed changes within the UF in PTSD (Eluvathingal et al., 2006). This study, however, is not directly comparable to the current one due to the differences in sample characteristics. Eluvathingal et al. (2006) studied orphaned children who have experienced socio-emotional deprivation. In children, certain WM structures do not fully develop until after adolescence. Specifically, a number of developmental studies have proposed that the UF continues to develop substantially after adolescence with concurrent increase in FA (Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007; Hasan et al., 2009; Lebel & Beaulieu, 2011; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Since the participants in the Eluvathingal et al.'s (2006) study were of pre-adolescent age and the study used a very small sample, it is possible that the obtained findings could be attributed to natural variation in FA within this age range. Therefore, the unique contribution of psychological trauma to the observed changes within the UF reported by Eluvathingal et al. (2006) cannot be readily established from this study. If the findings from the study by Eluvathingal et al. (2006) were to be attributed to psychological trauma, only limited conclusions could be drawn regarding generalizability of the results to adult population since the developing brain is more susceptible to the effects of stress (e.g. Teicher et al. (2003)), and thus would be differentially affected compared to a fully matured brain. Considering past research and present findings, the exact role of the UF in PTSD symptomatology remains unclear.

One possible explanation for the lack of findings in the present study is the idea that memory disturbances observed in PTSD and mTBI may be mediated via WM tracts other than the UF. As discussed in Chapter 4, the cingulum is thought to be involved in regulating emotive behavior and memory processes and a considerably large number of studies have observed changes within this tract in PTSD (e.g. Kim et al. (2006) and Sanjuan et al. (2013)). Similar to the UF, the cingulum also has fibres that connect frontal regions with structures in the temporal lobes, including the

amygdala (Jones, Christiansen, Chapman, & Aggleton, 2013). Memory disturbances observed in PTSD could thus be a result of weakened connection with this tract. Although the study described in Chapter 4 did not observe changes within the cingulum in the PTSD group, the lack of findings in this group could be attributed to secondary factors, such as the chronicity of PTSD.

As discussed in Chapter 4, the chronicity of trauma might have a considerable effect on WM changes. Some studies (e.g. Zhang et al. (2012)) have shown that aberrant changes in anisotropy measures, such as in FA, that are observed in acute PTSD may improve over time. Considering the average time since trauma in the PTSD and mTBI groups in this study was 12 years, it is plausible that the microstructural composition of the UF may have undergone significant improvement. Even if this tract is implicated in disturbances observed in PTSD and mTBI with changes in anisotropy apparent in the early stages of these conditions, it is possible that they are not long lasting.

Although some studies have identified changes in the UF in mTBI (e.g. Brandstack, Kurki, & Tenovuo, 2013; Xiong et al., 2014), this condition is characterized by a heterogeneity of regions that may be affected. If the disturbances observed following mTBI are primarily explained by the physical trauma to the brain, then the experienced difficulties could be dependent on the function of the region most affected in the course of sustaining head injury. The lack of anisotropic changes in the mTBI group could thus be attributed to the intact microstructure of this tract.

Similar to the cingulum findings in Chapter 4, TEC displayed altered structural integrity in the UF, as evidenced by increased Trace in this group compared to NTEC. Unlike the PTSD group, TEC were asymptomatic while at the same time having a history of psychological trauma. Individuals in this group may have developed adaptive strategies in order to deal with stress in effective ways that the PTSD group potentially lacks. Alternately, there may be pre-existing factors that differentiate trauma-exposed

participants who do and do not develop PTSD, and these factors may have affected WM changes observed in this study.

Consistent with previous findings of right-greater-than-left fibre density asymmetry (e.g. Highley et al., 2002), the mTBI group showed greater Mode in the left compared to the right UF. Since decrease in Mode has been observed in regions of fibre crossings (a finding that has been used to suggest a higher fibre density) (Kindlmann et al., 2007), the present finding suggests that the UF in mTBI is characterized by higher fibre density in the right compared to the left hemisphere. It is unclear why none of the other groups showed this pattern of asymmetry.

Finally, this study observed hemispheric asymmetry across all groups where the right UF was associated with higher Trace, Perpendicular Diffusivity and Parallel Diffusivity compared to the left UF. These findings are consistent with past research showing anisotropic asymmetry within the UF, although some studies have reported right-greater-than left pattern of asymmetry, whereas others have observed the reverse (Park et al., 2004; Rodrigo et al., 2007).

In Chapter 6, the unique effects of mTBI and PTSD symptom severity on WM coherence in the CC and cingulum were evaluated.

Chapter 6

Study 4: The Effects of mTBI and PTSD on White Matter Integrity

As discussed in Chapter 1, PTSD and mTBI frequently occur in situations that are both psychologically traumatic and pose a risk of brain injury (Vasterling et al., 2012). Symptoms that are associated with these conditions substantially overlap. This observation has led to a debate over the underlying neural basis of this overlap.

One side of the debate argues that memory and emotional disturbances observed following mTBI are primarily driven by the organic damage to the brain. Proponents of this view have argued that since similar areas are affected when sustaining mTBI as the ones implicated in PTSD symptomatology, it is through damage to these regions that mTBI may increase the risk of PTSD (Bryant, 2008). Specifically, since these areas are involved in emotional processing and memory, such as the frontotemporal regions, disruption of their functions as a result of injury may further exacerbate stress reactions (Vasterling et al., 2012).

On the other hand, it has been argued that the presence or absence of mTBI-related problems (including PCS) is determined largely by the degree of psychiatric symptoms present. It has been observed that impairment following mTBI was largely

determined by psychiatric disorders rather than mTBI (Bryant, Creamer, O'Donnell, Silove, Clark, & Mcfarlane, 2009). Specifically, anxiety, stress, depression and PTSD have all been shown to be strongly associated with PCS (Hoge et al., 2008; King, 1996). Based on these observations, the important contribution of psychiatric symptoms to disease prognosis has often been emphasized in mTBI literature.

A third view maintains that rather than being mutually exclusive, both mTBI and psychiatric symptoms may contribute to the after-effects of mTBI. Indeed, Vanderploeg et al. (2009) observed that mTBI and PTSD had independent contributions to PCS symptoms and hence proposed that these conditions could co-exist and produce additive effects on emotional and cognitive impairments associated with mTBI. In light of this view, it has been proposed that both physiological injury and disturbed psychological reactions to trauma may significantly affect recovery following mTBI.

From the review above, it is evident that despite the existent support highlighting the importance of both physical injury and psychiatric symptoms in evaluating mTBI etiology, no neural mechanism explaining the observed comorbidity has been identified. Thus, the primary aim of the current study was to examine whether any of the WM changes observed in the previous chapters could be explained by PTSD severity, mTBI or both. Based on the between- group results from Chapters 3, 4 and 5, only the CC and cingulum were selected for analyses since significant differences between the experimental and control groups were only detected in these tracts. As per research reviewed in Chapter 1 pertaining to the CC and cingulum findings in PTSD and mTBI, it was hypothesized that both mTBI and PTSD severity would be significant predictors of WM changes within these tracts.

6.1 Results

In order to assess the amount of variance in WM that could be attributed to the effects of PTSD symptom severity and history of mTBI, linear regression analyses

were performed. As mentioned earlier, only the CC and cingulum were selected for regression analyses since these structures showed between group differences using one- way between-subjects and two-way mixed ANOVAs, respectively, as described in chapters 3 and 4. Since no changes were observed for the mTBI or PTSD groups within the UF, this tract was not selected for further analysis.

6.1.1 Corpus Callosum

mTBI and PTSD severity were entered into a multiple regression using the simultaneous method. A significant model emerged for FA: F (2, 88) = 27.680, p =.000. This model explained 37% of the variance in FA (Adjusted R^2 = .372). Both PTSD severity and mTBI were significant predictors. A significant model was also obtained for Trace: F (2, 88) = 16.658, p = .000. Only mTBI was found to be a significant predictor, explaining 26% of the variance in this metric (Adjusted R^2 = .258). For Mode, both PTSD severity and mTBI emerged as statistically significant predictors: F (2, 86) = 23.122, p =.000. This model explained 33% of the variance in Mode (Adjusted R^2 = .335). A significant model was observed for Perpendicular Diffusivity with only mTBI emerging as a significant predictor of the variance in this metric: F (2, 87) = 27.826, p =.000. This model accounted for 38% of the variance in Perpendicular Diffusivity (Adjusted R^2 = .376). Finally, a significant model emerged for Parallel Diffusivity but neither of the predictors were significant: F (2, 88) = 4.854, p =.01. Summary of the simultaneous regression analyses performed for the CC are presented in Table 6.1.

6.1.2 Cingulum

To evaluate the contribution of PTSD severity and mTBI to WM damage observed in the cingulum, linear regression was constructed using the simultaneous method. A significant model emerged for Trace: F (2, 88) = 9.009, p =.000. Only mTBI was a significant predictor of the variance in this metric. This model explained 15% of the

Table 6.1
Summary of the Corpus Callosum Simultaneous Regression Models for FA, Trace, Mode, Perpendicular Diffusivity and Parallel Diffusivity

	B	SE*B*	*β*	*p*
	FA			
Model 1: PTSD severity	.000	.000	-.206	.036*
mTBI	.043	.006	.699	.000**
	Trace			
Model 1: PTSD severity	.000	.000	.128	.227
mTBI	.000	.000	-.577	.000**
	Mode			
Model 1: PTSD severity	-.001	.000	-.414	.000**
mTBI	.055	.008	.687	.000**
	Perpendicular Diffusivity			
Model 1: PTSD severity	.000	.000	.178	.072
mTBI	.000	.000	-.697	.000**

Note. SE*B*= Standard Error of *B*.FA. Model 1: R^2 = .386. Trace. Model 1: R^2 = .275. Mode. Model 1: R^2 = .35. Perpendicular Diffusivity. Model 1: R^2 = .39. Parallel Diffusivity. Model 1: R^2 = .099. Significant *p* values < .05 and <.01 are indicated with * and **, respectively.

variability in this measure (Adjusted R^2 = .151). A significant model was obtained for Perpendicular Diffusivity with only mTBI being a significant predictor: *F* (2, 89) = 8.559, *p* =.000. This model explained 14 % of the variance (Adjusted R^2 = .142). A significant model was also observed for Parallel Diffusivity: *F* (2, 88) = 6.834, *p* =.002, where only PTSD severity was a significant predictor explaining 11.5 % of the variance (Adjusted R^2 = .115). Finally, when FA and Mode were entered as criterion variables, regression models were not significant: *F* (2, 89) = 2.675, *p* =.074 and *F* (2,

89) = 2.511, p =.087, respectively. Table 6.2 displays summary of the regression analyses performed for the cingulum.

Table 6.2

Summary of the Cingulum Simultaneous Regression Models for FA, Trace, Mode, Perpendicular Diffusivity and Parallel Diffusivity

	B	SE*B*	*β*	*p*
	Trace			
Model 1: PTSD severity	.000	.000	-.168	.143
mTBI	.000	.000	-.299	.010*
	Perpendicular Diffusivity			
Model 1: PTSD severity	.000	.000	-.043	.706
mTBI	.000	.000	-.378	.001**
	Parallel Diffusivity			
Model 1: PTSD severity	.000	.000	-.268	.023*
mTBI	.000	.000	-.148	.206
	Mode			
Model 1: PTSD severity	.000	.000	-.182	.132
mTBI	-.007	.011	-.077	.524

Note. SE*B* = Standard Error of *B*. Trace. Model 1: R^2 = .17. Mode. Model 1: R^2 = .053. Perpendicular Diffusivity. Model 1: R^2 = .161. Parallel Diffusivity. Model 1: R^2 = .134. Significant *p* values < .05 and <.01 are indicated with * and **, respectively.

6.2 Discussion

Based on the findings from Chapters 3, 4 and 5, the present study aimed to evaluate the extent to which mTBI and PTSD severity contributed to the observed WM changes. Results of the present study indicated that both mTBI and PTSD symptoms were associated with WM damage. The amount of contribution of these variables to the variance in WM metrics depended on the region that showed microstructural abnormalities.

WM damage in the CC, as evidenced by decrease in FA, in the PTSD and mTBI groups compared to NTEC was predicted by both history of mTBI and PTSD severity. This is consistent with Vanderploeg et al.'s (2009) proposal that mTBI and PTSD have independent and additive contributions to the difficulties observed in the aftermath of TBI. While Vanderploeg et al. (2009) drew these conclusions based on the results obtained from the self-report measures assessing difficulties associated with PCS, this study provides initial evidence of the neural basis for their findings. Thus, due to the additive nature of these effects, upon exposure to a psychologically traumatic event coupled with mTBI, an individual is more likely to develop PTSD than those who do not have a history of mTBI as a result of microstructural damage to the CC. Since PCS symptoms were not measured as part of this study, the specificity of PCS symptoms that could be potentially reflected in the CC damage remains unclear.

Changes within the CC have frequently been observed in both PTSD and mTBI (Jackowski et al., 2008; Saar-Ashkenazy et al., 2014; Villarreal et al., 2004; Zhu et al., 2014). This fibre bundle connects many regions that perform emotional and memory functions and is critical for interhemispheric transfer of information. Aberrant changes in the CC have been linked to cognitive dysfunctions in PTSD and mTBI, such as associative memory impairment (Matsushita et al., 2011; Saar-Ashkenazy et al., 2014). It is thus proposed that memory disturbances observed in PCS could be due to the reduced connectivity in the CC which in turn is partially explained by both a psychiatric

disorder, namely PTSD, and mTBI.

The variance in Trace and Perpendicular Diffusivity in the CC were only predicted by history of mTBI. This observation is consistent with the findings described in Chapter 3 where changes in FA in the mTBI group were associated with concurrent increase in Trace and appeared to be mediated by demyelination as evidenced by increase in Perpendicular Diffusivity. Reduction in FA in the PTSD group, on the other hand, did not appear to be moderated by changes in the myelin. Changes in FA in the PTSD group could be related to secondary neural changes or microstructural anomalies other than myelin loss. The precise nature of these alterations is, however, unclear and its investigation is not within the scope of this thesis and hence requires further evaluation in the future.

Within the CC, both mTBI and PTSD severity were found to be significant predictors of the variance in Mode. In other words, it appeared that both psychological and physiological factors are important when three dimensional shape of the diffusion ellipsoid is concerned. One possibility is that these conditions produce changes within WM fibre bundles by affecting their density (Ennis & Kindlmann, 2006). As the exact nature of microstructural changes associated with the variation in Mode is yet to be clarified, it is unclear from the present results via what mechanism mTBI and PTSD severity contribute to this variation.

Changes in Perpendicular Diffusivity and Trace in the cingulum were predicted by mTBI even though only a small amount of the variance was explained by this predictor. Considering that a substantial amount of the variance remained unexplained, other factors affecting WM integrity within the cingulum in a traumatized population are yet to be identified and their importance evaluated.

PTSD severity was a significant predictor of the variance in Parallel Diffusivity within the cingulum thus suggesting that the significant decrease observed in Chapter 4 in the PTSD group compared to the mTBI group was primarily driven by the severity of PTSD. As there were no changes in FA or Trace within the cingulum of

the PTSD group compared to NTEC and TEC, the contribution of PTSD severity to the variation in this measure is unclear.

In summary, results of the present study showed that WM changes observed within the CC are predicted by both mTBI and PTSD severity whereas changes within the cingulum are largely mediated by history of mTBI alone. Thus, it appears that some regions, such as the CC, are more vulnerable to psychological stress than others such that when a traumatic event puts an individual at risk of both mTBI and PTSD, each factor will have an independent effect on WM integrity. Other WM regions, such as the cingulum, on the other hand, seem to be at risk of damage only in the presence of mechanical injury to the brain, regardless of the extent of PTSD.

Chapter 7

General Discussion

7.1 Summary of Findings

The overarching aim of this project was to identify and describe neural mechanisms that underlie both mTBI and PTSD. Firstly, this project attempted to identify WM structures that would show abnormality in PTSD, mTBI or both. Secondly, the main predictors of the observed WM changes in these conditions were also evaluated, with a particular emphasis on PTSD severity and a history of mTBI. Importantly, in order to control for the effects of exposure to a traumatic event, this project included two control groups where one group had never been exposed to a traumatic event while the other group was comprised of individuals who had prior traumatic experiences. In this chapter, the main findings are summarized, implications discussed and directions for future research are proposed.

In the first study (Chapter 3), microstructure of the largest WM tract, namely the CC, was investigated. Reduced FA was observed in both PTSD and mTBI groups compared to the NTEC group. Moreover, participants with mTBI showed further reduction in FA compared to the PTSD and TEC groups. There were no significant differences between the PTSD and TEC groups. There were also no differences in FA

between the two control groups. Consistent with the FA findings, the mTBI group showed significantly increased Trace compared to the PTSD, NTEC and TEC groups. Increased Perpendicular Diffusivity was observed in the mTBI group compared to the PTSD, NTEC and TEC groups. Results also showed reduced Mode in the mTBI group compared to the PTSD, NTEC and TEC groups. TEC displayed higher Mode than NTEC. Finally, the mTBI group showed significantly higher Parallel Diffusivity compared to the PTSD group.

In the second study (Chapter 4), microstructure of the cingulum bundle was investigated. Across all groups, there was left-greater-than-right anisotropic asymmetry within this neural bundle. It was also observed that mTBI was associated with higher Trace compared to the PTSD and NTEC groups. Additionally, the mTBI group showed increased Perpendicular Diffusivity compared to the PTSD group. mTBI was also associated with increased Parallel Diffusivity compared to the PTSD and NTEC groups. Finally, reduced Mode was observed in the NTEC group compared to the TEC and mTBI groups.

In the third study (Chapter 5), microstructure of the UF was investigated. Across all groups, there was right-greater-than left anisotropic asymmetry within this tract. Increased Trace was observed in TEC compared to NTEC. Mode asymmetry was observed in the mTBI group with the right hemisphere showing lower Mode than the left hemisphere.

Based on the significant findings from Studies 1, 2 and 3, the unique contributions of PTSD severity and mTBI to WM integrity were evaluated in Study 4. Both mTBI and PTSD symptom severity were significant predictors of the FA and Mode changes within the CC. Only mTBI was a significant predictor of the variance in Perpendicular Diffusivity and Trace within this tract. Neither PTSD severity nor mTBI were significant predictors of the variance in Parallel Diffusivity within the CC.

Changes in Trace and Perpendicular Diffusivity within the cingulum were only significantly predicted by a history of mTBI. On the other hand, changes in Parallel Diffusivity within the cingulum were only associated with PTSD severity. The variance in Mode was not predicted by either of the two factors. Since there were no significant group differences in microstructure of the UF, regression analyses were not performed on the predictor variables for this fibre bundle.

7.2 Evidence of WM Damage in mTBI

Structural neuroimaging data indicated that mTBI was associated with WM damage in the cingulum and CC. These findings are in line with past DTI research that has suggested that mTBI is most frequently associated with compromised integrity within fronto-limbic projection pathways and interhemispheric connections (for a review, see Niogi and Mukherjee (2010)). Since these structures perform unique functions, their damage in mTBI could be expected to be associated with distinct behavioral outcomes. The importance of these neural bundles in mediating emotional and cognitive disturbances observed in mTBI will thus be discussed individually.

Previous literature has indicated that mTBI is associated with cognitive and emotional problems, as well as physiological complaints (McMillan, 2001; Vasterling et al., 2009). If these difficulties have physiogenic causes, then damage to the areas that are thought to perform these functions could be hypothesized to be part of the neural network that mediates these symptoms (Bryant, 2008). The cingulum is part of the limbic system and has been often associated with emotional processing and certain cognitive functions, such as memory (Concha et al., 2005; MacLean, 1952). It is therefore not surprising that damage to this WM tract has long been linked to emotional and cognitive disturbances (Ballantine Jr et al., 1967; Brown & Lighthill, 1968). In line with this functional observation, mTBI studies that have revealed diffuse axonal injury, including microstructural damage to the cingulum, have also proposed an association between PCS symptoms and microstructural damage within specific WM

regions (Niogi et al., 2008; Yeh et al., 2014). For instance, Niogi et al. (2008) have reported a positive correlation between the number of damaged WM structures, such as the cingulum, and PCS severity. Specifically, Niogi et al. (2008) proposed that this association was specific to cognitive disturbances. The study by Niogi et al. (2008), however, did not evaluate individual contribution of changes within specific structures to the PCS symptoms. Yeh et al. (2014), on the other hand, indicated that the severity of PCS negatively correlated with FA values within both anterior and posterior regions of the dorsal cingulum. Taken together, these studies highlight a possible contribution of changes within the cingulum to cognitive (and other) difficulties observed following mTBI.

Although the above studies have shed light on a potential contribution of the cingulum to cognitive disturbances observed in the aftermath of mTBI, none of them explained whether these changes are related to *specific* symptoms. Sorg et al. (2014), in contrast, observed that individuals with chronic mTBI (2-4 years) displayed reduced FA and increased Perpendicular Diffusivity in the posterior cingulum, where the latter was associated with impaired executive functioning. Taken together, these studies indicate that damage to the cingulum bundle as a result of mTBI is associated with increased severity of PCS, characterized by a particular impairment in cognition, with executive functioning being one of the affected functions.

A number of earlier human lesion studies have argued that the cingulum is primarily involved in regulation of emotive behavior, with cognitive processes achieved via an alternative route (Ballantine Jr et al., 1967; Brown & Lighthill, 1968; Foltz & White Jr, 1962). Recent fMRI studies, however, have proposed a direct contribution of the cingulum to cognitive processes (Delano-Wood et al., 2012; Schermuly et al., 2010; Wilde et al., 2010). For instance, Schermuly et al. (2010) showed a negative

correlation between the middle-anterior and middle-posterior cingulum FA and performance on tests of executive functioning and divided attention in patients with major depressive disorder (MDD). Delano-Wood et al. (2012) reported a positive correlation between FA values within the posterior cingulum and verbal memory performance. Hence, these findings further confirm the likely association between cognitive impairment and loss of coherence within the cingulum. Studies in mTBI are yet to demonstrate the contribution of changes within the cingulum bundle to emotional disturbances associated with PCS.

Apart from the cingulum, the current project also observed WM damage within the CC in the mTBI group. This finding is in line with a large number of previous studies that have observed changes within this tract, either through its entirety or within its subregions (Inglese et al., 2005; Kumar et al., 2009; Matsushita et al., 2011; Rutgers et al., 2008; Zhu et al., 2014). Moreover, in their recent review of MRI and DTI findings in mTBI, Shenton et al. (2012) revealed that the CC appears to be one of the most frequently affected WM tracts in this clinical population. Taken together, present results and past literature suggest that this WM fibre bundle could be particularly vulnerable to axonal damage following mTBI (Shenton et al., 2012).

As outlined in Chapter 1, the CC is primarily involved in interhemispheric transfer of cognitive, sensory and motor information (Gazzaniga, 2000). Theories that have attempted to explain how this transfer of information is achieved have been generally subdivided into two categories: inhibitory and excitatory (van der Knaap & van der Ham, 2011). The excitatory model proposes that the CC allows integration and transfer of information by activating the unstimulated hemisphere (van der Knaap & van der Ham, 2011). The inhibitory model argues, on the other hand, that the CC provides inhibitory connections between the two hemispheres, allowing efficient task completion via hemispheric lateralization (van der Knaap & van der Ham, 2011). Due to the existing evidence supporting both theories, it is not yet clear whether one of them is a stronger candidate than the other or whether they are both equally valid (van der Knaap & van der Ham, 2011). Damage to the CC could therefore lead to impaired

transfer and integration of information via one of these mechanisms. Saar-Ashkenazy et al. (2014) proposed that inability to effectively lateralize task components and integrate information, as a result of the CC injury, may lead to ineffective cognitive resource allocation during task performance. This impairment, in turn, might be one of the underlying, contributing factors that mediate ongoing cognitive disturbances observed in mTBI. In fact, impaired cognitive functioning in mTBI has previously been linked to reduced anisotropy in this tract, where decrease in FA in the splenium of the CC in the acute stages of mTBI predicted overall cognitive functioning in chronic mTBI (Matsushita et al., 2011). In summary, reduced connectivity within both cingulum and CC appears to be related to cognitive disturbances observed in the aftermath of mTBI, albeit via different mechanism.

7.3 Evidence of WM Damage in PTSD

The integrity of three distinct WM structures was studied in individuals with PTSD and only one of these structures showed evidence of microstructural damage. Specifically, there was evidence of compromised microstructure within the CC but not within either of the associative fibres studied, namely the UF and cingulum. These results appeared to be driven by clinically significant PTSD symptoms.

The CC results are in line with a number of morphometric studies that showed reduced volume within this neural bundle in relation to PTSD and psychological trauma, in both adult and child clinical populations (De Bellis et al., 1999; De Bellis et al., 2002; Saar-Ashkenazy et al., 2014; Teicher et al., 2004; Villarreal et al., 2004). Using DTI, however, previous studies have observed reduced FA within this tract in a traumatized population in the absence of clinically significant psychiatric symptoms, which was also negatively associated with the number of traumatic life events (Paul et al., 2008). Importantly, Paul et al. (2008) failed to observe any association between reduction in FA and volume of the CC. They consequently argued that volume reduction within this tract is PTSD-specific, whereas WM changes are largely explained

by a history of prior traumatic experiences. The present findings, however, provide initial evidence that aberrant changes within the CC in PTSD occur not only on a macrostructural level but may also be observed in a form of more subtle neural alterations. Since the volume of the CC was not measured as part of this project, it cannot be concluded with certainty to what extent the volume of the CC and reduction in FA are related to each other. Nonetheless, in individuals with PTSD, the CC is characterized by microstructural injury that is substantial enough to allow them to be differentiated from a healthy, non-trauma exposed population. As there were no significant differences between the PTSD and TEC groups, it is unclear to what extent stressful life events alter WM within this tract and if they do, whether they have an accumulative effect.

As discussed earlier, the CC plays a crucial role in interhemispheric transfer of information and compromised integrity of this tract has been linked to inadequate hemispheric lateralization during performance of associative memory tasks (Saar-Ashkenazy et al., 2014). One of the criteria for PTSD diagnosis is re-experiencing of the traumatic event. Reduced connectivity between opposite sides of the same cortices that are involved in memory processes could at least partially mediate these symptoms. Since the CC connects distinct cortical regions that perform unique sets of functions, this hypothesis would need to be verified in the future by partitioning the CC into its subregions.

7.4 Impact of PTSD on mTBI

One of the main debates in the mTBI literature centers around the nature of the underlying causes of disturbances experienced by individuals following mTBI. Some have argued that these causes are primarily physiogenic whereas others have emphasized the importance of psychogenic underpinnings (Bryant, 2008; Hoge, Thomas, Cox, Engel, & Castro, 2008). A major goal of the present project was to investigate

these causes by studying WM regions that have been frequently implicated in PTSD, mTBI or both.

The CC was found to be the only structure among the studied neural tracts that showed particular vulnerability to the effects of PTSD. This structure was also affected by a history of mTBI. From these results it appears that the effects of mTBI could be attributed to both organic injury and traumatic stress. Since mTBI occurs in the context of a psychologically traumatic event, stress reactions are likely to form in response to such an event. It has long been known that stress can produce functional and structural alterations within a variety of structures including the PFC, hippocampus and hypothalamus (McEwen, 2007). Specific to PTSD, neural atrophy, as evidenced by changes in the volumetric composition of the neural structure, has been frequently observed in a variety of structures, including the CC (Kitayama et al., 2007; Saar-Ashkenazy et al., 2014; Villarreal et al., 2004). Based on the results of the present study, it is proposed that apart from the macrostructural changes in the CC, intense psychological stress may also be associated with axonal damage. This damage may already be present in those who have experienced a traumatic event (e.g. Paul et al. (2008)), with PTSD symptoms further exacerbating this effect. Reverse causation, however, is also possible. That is, rather than PTSD symptomatology leading to WM damage, it is possible that changes within the CC are present before a person experiences a traumatic event and could thus be considered as potential risk factors for the development of PTSD. Previous research has indeed indicated that the presence of microstructural changes prior to the traumatic event predicted future level of anxiety (e.g. Sekiguchi et al. (2014)), thus highlighting the importance of differentiating between changes that are present prior to the onset of the disorder and those that are caused by reactions in response to traumatic stress.

Animal models of fear conditioning have demonstrated that prolonged stress produces neurochemical changes within the mPFC, which are in turn associated with

impaired fear extinction (Miracle, Brace, Huyck, Singler, & Wellman, 2006). As outlined in Chapter 1, the PFC is thought to play a crucial role in explaining PTSD symptomatology and has been implicated in fear circuitry models of this condition. It is thus proposed that reduced connectivity between the left and right prefrontal cortices could lead to aberrant control over the amygdala and consequently lead to under regulation of this structure. This proposition is only speculative in nature and the exact mechanism of this potential effect is unclear.

At the same time, since PTSD presents a range of symptoms that encompass a variety of emotional and cognitive problems, such as memory disturbances with an emotional undertone in the form of flashbacks and intrusive memories, reduced connectivity throughout the entirety of the CC could potentially lead to an overall compromised information processing ability. This is likely to be associated with inadequate resource allocation during cognitive reappraisal of emotional experiences and consequently decrease efficacy of cognitive behavioral treatment (CBT).

Although PTSD has been primarily associated with emotional dysregulation, and fear conditioning in particular, it has also been well-documented that PTSD is characterized by mild to moderate cognitive impairment as revealed through neuropsychological assessment (Dolan et al., 2012). PTSD has been most frequently associated with impairment of overall intelligence, attention, memory and executive functioning (Brewin, 2005; Brewin, Kleiner, Vasterling, & Field, 2007; Bryant & Harvey, 1997; Buckley, Blanchard, & Neill, 2000; Dolan et al., 2012; Johnsen & Asbjrnsen, 2008; Macklin et al., 1998; McNally, Lasko, Macklin, & Pitman, 1995; McNally & Shin, 1995; Constans, 2005; Vasterling & Verfaellie, 2009). Based on these past observations and present findings, changes within the CC could potentially play a critical role in mediating certain cognitive disturbances.

Outcomes of this research project showed that PTSD severity only predicted WM changes in the CC, an interhemispheric projection fibre, and failed to obtain evidence of PTSD contribution to microstructural changes within associative neural

tracts, namely the UF and cingulum. Lack of findings in the UF is in line with one of the recent observations. After a thorough examination of a large number of studies, a recent review by Von Der Heide, Skipper, Klobusicky, and Olson (2013) concluded that the UF plays little to no role in mediating symptomatology of anxiety disorders. Based on this proposition, it could be hypothesized that although the UF is one of the most likely candidates due to its fronto-temporal orientation, memory disturbances observed in PTSD are potentially mediated via an alternative WM route. Even though changes within this WM tract have been implicated in both clinically significant anxiety levels, such as in GAD and SAD, and trait anxiety in healthy populations (e.g. Kim and Whalen (2009) and Tromp et al. (2012)), PTSD is characterized by a unique clinical profile that differentiates it from other anxiety disorders. It is probable that despite the observed similarity in the PFC and amygdala activation patterns between the aforementioned anxiety disorders and PTSD, the latter develops via repeatedly elevated fear responses in reaction to intrusive memories, thereby activating the prefrontal-amygdala network. The presence of distressing memories in PTSD could result in fronto-temporal dysregulation via aberrant connectivity within an alternative WM neural fibre. This possibility could be further tested through studies that compare WM integrity of PTSD with other anxiety disorders, and specifically in relation to memory disturbances.

Previous studies have often observed compromised integrity within the cingulum in adult-onset PTSD. These studies, however, are characterized by a great degree of heterogeneity in terms of populations studied and methodology employed. For instance, some studies have looked exclusively at either females (Fani et al., 2012) or males (Sanjuan, et al., 2013; Schuff et al., 2011; Wang et al., 2010), combat-related PTSD (Sanjuan et al., 2013; Schuff et al., 2011), sexual abuse survivors (Fani et al., 2012), as well as using different magnet strengths and image processing software. Additionally, while some studies attempted to control for a history of prior trauma exposure by including participants who had previously experienced a traumatic event as a control group, others relied on healthy populations for comparison. Consequently, this

heterogeneity led to mixed results, with studies showing both decrease and increase in FA in the left, right or bilateral cingulum (Abe et al., 2006; Fani et al., 2012; Sanjuan et al., 2013). The discrepancy between the current findings and these prior studies could be attributed to sample characteristics since none of the current participants in the PTSD group had combat experience or been a victim of sexual abuse. The type of trauma could arguably play an important role in the outcomes of the present and past studies. Since different types of trauma vary in intensity of emotional stress that they produce, the magnitude of potential WM injury associated with them would likely increase or decrease accordingly. It is possible that the type of traumas included in this project, such as car accidents and physical assaults, may not have been sufficiently prolonged to produce alterations within the cingulum bundle.

7.5 Overlap between PTSD and mTBI: Evidence from DTI

A large body of research has been conducted in the area of TBI looking at various levels of severity and evaluating different aspects of these conditions ranging from behavioral presentations to neural abnormalities. Nonetheless, mTBI remains the least well understood of all TBI severities (Vasterling et al., 2012). This is complicated by a great degree of heterogeneity in the domain of DTI research relating to changes within WM regions that are thought to be implicated in mTBI and the nature of these changes (for a review, see Shenton et al. (2012)). This lack of consistency is partly due to the anatomical positon of regions selected, image processing approaches used, magnet strength, as well as the poorly specified site of injury (for a review, see Shenton et al. (2012)). This further emphasizes the complex, multilayered nature of mTBI.

This thesis has shown that both associative fibres and interhemispheric connections may be damaged as a result of mTBI. This adds to the existing literature showing

alterations in a range of associative fibres, such as the cingulum and superior longitudinal fasciculus (e.g. Sorg et al. (2014) and Kraus et al. (2007)), as well as in interhemispheric connections, such as within the CC (e.g. (Sorg et al., 2014)). Present findings and past research potentially point to the non-specificity of this disorder, meaning that there might not be a single neural tract neuropathology of which could explain difficulties observed following mTBI. This hypothesis could also potentially help explain the relatively high degree of variability in theoretical and operational definitions of mTBI.

Traumatic stress research has previously identified neural substrates that are thought to mediate the emotional and cognitive difficulties associated with PTSD. Both functional and structural contributions of these regions, including the PFC, amygdala and hippocampus, have been described. These neural findings have been mapped onto the PTSD symptoms, providing concrete foundation to the conceptual models of this condition that have previously been only hypothetical in nature. Results of the current project potentially provide further evidence that regions implicated in PTSD are unique to this disorder and alterations within the same regions could be expected across different studies. Thus, PTSD severity appears to be associated with specific neural regions via which this disorder develops and persists. Specifically, the CC seems to show a particular vulnerability to the effects of PTSD. On the other hand, the observed damage within the CC could be a risk factor for development of PTSD, similar to the findings relating to hippocampal volume (Gilbertson et al., 2002). The two associative fibre bundles, namely the UF and cingulum, do not appear to be associated with this condition. The fact that previous studies observed changes within these associative tracts, the cingulum in particular, may be attributed to the study specific sample characteristics such as trauma type, trauma chronicity and treatment exposure.

In summary, both mTBI and PTSD severity were shown to produce microstructural damage within WM, with the CC being particularly vulnerable to both of these effects. Associative neural bundles, on the other hand, seemed to be more prone to damage as a result of physical injury to the brain that characterizes mTBI.

7.6 Methodological Issues

7.6.1 Nature of Study Groups

DTI studies investigating the effects of traumatic stress on WM microstructure have examined these in the context of a wide range of traumatic experiences. In the context of combat, a number of studies have primarily focused on the incidence of PTSD and mTBI in military personnel (e.g. Bazarian et al. (2013) and Yeh et al. (2014)) This interest is primarily driven by epidemiological studies that have reported a higher rate of one or both of these conditions following deployment compared to the general population (Dohrenwend et al., 2006; Hoge et al., 2008; Vasterling, Bryant, & Keane, 2012). Other studies have studied WM alterations in those affected by sexual abuse and natural disasters (e.g. Fani et al. (2012) and Chen et al. (2013)).

In this study, the mTBI and PTSD groups were comprised of participants who have experienced a discrete psychological trauma where their own or someone else's life was in danger and included events such as car accidents, physical assaults and natural disasters. Individuals with a history of sexual assault were excluded from the study due to the complicated and dissimilar nature of this event compared to other traumas. Traumatic experiences of the TEC group were matched to those of the two experimental groups (i.e. PTSD and mTBI). Since none of the studied participants had previous experience in the military or had experienced sexual/childhood abuse, this project is limited in its ability to draw conclusions about the generalizability of the findings to effects of other forms of traumatic stress. It is important to note that frequent mechanisms of injury in combat-related TBI involve improvised explosive devices (IED), with blast or explosion and fragment or shrapnel being the primary causes of injury (Hoge et al., 2008). Due to the nature of these injuries, they are likely to produce a more profound damage (even on a microstructural level) compared to injuries resulting from falls and car accidents. Thus, it may not be appropriate to compare

PTSD and mTBI acquired in military versus civil contexts. Similarly, effects of discrete trauma are markedly different from prolonged childhood trauma that can impact neural development (for a review, see Daniels, Lamke, Gaebler, Walter, and Scheel (2013)). Future research is needed to determine whether the neural profiles of PTSD and mTBI acquired under different circumstances show any degree of overlap.

Another important sample characteristic that needs to be considered when interpreting DTI findings is the trauma chronicity. Some of the previous studies in both mTBI and PTSD have investigated WM changes in participants who have experienced a psychologically traumatic event within 24 hours of scanning whereas others studied patients who have experienced a trauma close to ten years prior to scanning (e.g. Arfanakis et al. (2002), Rutgers et al. (2008) and Sekiguchi et al. (2014)). In the context of PTSD, the intensity and frequency of symptoms associated with this disorder are likely to shift over time. Moreover, it is probable that microstructural changes present in the early stages of the disorder may be absent or have progressed in the opposite direction in the chronic stages of the condition. In fact, studies have indicated that increased chronicity is associated with changes in FA (e.g. Yeh et al. (2014)). Thus, it is essential to take time post-trauma into account when interpreting alterations within brain WM.

One final factor that is worth mentioning in relation to clinical populations that have been used to study the effects of psychological stress on WM integrity is the division of PTSD into two main subtypes that are characterized by either prominent hyperarousal or dissociative symptoms (*DSM- 5*, American Psychiatric Association, 2013). DSM-5 has introduced the dissociative subtype of PTSD partly because of neural evidence that people with these dissociative symptoms have a distinct neural response to affective stimuli (Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012). Subtypes of the same disorder with distinct clinical and neurofunctional profiles may also have different WM architecture. Hence, accurate clinical assessment and subsequent classification of study participants according to the disorder subtypes is recommended in order to allow for firmer conclusions and between study comparisons.

7.6.2 Sample Size

Another limitation of the present project is the relatively small sample size. Although it was sufficiently large to allow for between group comparisons based on clinical diagnosis, further comparisons between subgroups based on sex of the participants could not be carried out due to the lack of statistical power. Thus, the effect of sex on WM microstructure that has been previously demonstrated in the cingulum and CC, for instance by Menzler et al. (2011), could not be presently investigated in the context of traumatic stress. Future studies could look at the effect of sex on WM microstructure within the context of PTSD and mTBI.

7.6.3 Definition of mTBI

Despite the fact that both epidemiological and empirical findings have lent strong support to the debilitating effects of mTBI, there is still an ongoing debate over the precise diagnostic criteria for this condition. In the present study, mTBI was defined according to the classification recommended by the World Health Organization (WHO) (Cassidy et al., 2004). A number of other multi-agency bodies, such as the Centres for Disease Controls and Prevention (National Centre for Injury Prevention Control , 2003) and the American Congress of Rehabilitation Medicine Head Injury Interdisciplinary Special Interest Group (1993), however, have also proposed definitions that include both overlapping and distinct characteristics of mTBI compared to the definition proposed by the WHO. The main criterion that has been commonly proposed by the majority of public health consortia is that the injury must result from an external force being applied to the brain with brief disruption of neural functions (Vasterling et al., 2012). To further classify this condition in terms of severity, the following operational definitions have been proposed: loss of consciousness should be no

longer than 30 minutes and post- traumatic amnesia must not exceed 24 hours (Vasterling et al., 2012). Additionally, GCS of 13-15 has also been recommended for diagnosis (Teasdale & Jennett, 1974). These operational definitions, as well as absence of abnormalities on CT or MRI scans, were applied in the present project as the selection criteria for the mTBI group.

The ambiguity surrounding the precise definition of mTBI is partly driven by the fact that mTBI is currently the least understood TBI, with a heterogeneous array of injury features and outcomes (Vasterling et al., 2012). For instance, mTBI can be classified into complicated and non- complicated subtypes, with the former characterized by abnormal CT or MRI scans (Vasterling et al., 2012). Complicated mTBI could be expected to have more profound effects on post-injury functional outcomes than non-complicated mTBI. Indeed, studies have indicated that PCS is diagnosed in the majority of patients (82%) in the presence of acute hemorrhages, contusions or edemas, which is considerably higher compared to the prevalence of PCS (less than 50%) in those showing no abnormalities using conventional imaging techniques (Rickels, von Wild, & Wenzlaff, 2010; Smits et al., 2008). Thus, direct comparison of non-complicated mTBI to the studies that have included patients with visible neural abnormalities may lead to false conclusions in regard to the nature of the commonly observed symptoms, as well as the underlying neural mechanisms of these symptoms. When a more sensitive imaging technique, such as DTI, is used, additional caution should be taken when defining mTBI.

Another issue pertaining to the lack of a universally accepted definition of mTBI is a common confusion of this condition with its possible sequelae, namely PCS (Vasterling et al., 2012). While the term mTBI has been used to describe the initial injury, PCS refers to ongoing subjective difficulties observed in the aftermath of TBI. In light of this, some have argued that TBI should be studied as a chronic condition, with symptoms persisting beyond the isolated incident of head trauma (Masel & DeWitt, 2010). The present study aimed to investigate whether history of mTBI per se had a significant effect on WM integrity after controlling for PTSD symptoms. We did not

measure PCS symptoms since they were not the primary focus of this research project, and so the present findings are limited in terms of how they shed light on the utility of placing emphasis on the injury (mTBI) or the subsequent symptoms (PCS) as an operational definition.

This lack of standardized definition has led to inconsistent conceptualization of mTBI among clinicians and researchers alike, consequently making a comparison between different research studies difficult. It is thus important to bear in mind that since the definition used here may differ from those used in other studies, extra caution should be taken when interpreting present results and drawing conclusions in relation to a wider mTBI population.

7.6.4 Post- Concussive Syndrome

As mentioned in the previous section, PCS is a constellation of emotional, cognitive and physical problems that are frequently observed following mTBI (Ruff, Camenzuli, & Mueller, 1996). The presence of these symptoms has been previously used to inform disease prognosis and define potential neural abnormalities that may not be readily visualized using MRI or CT (Masel & DeWitt, 2010; Smits et al., 2011). In the context of DTI research, individual symptoms of PCS following mTBI (e.g. cognitive deficits) have been previously linked to abnormalities in WM brain regions such as the corona radiata, UF, cingulum, CC and inferior longitudinal fasciculus (Niogi et al., 2008). Although these findings do not allow one to make causal inferences, they highlight the importance of measuring PCS in order to establish a link between clinical presentation of mTBI and underlying neural alterations.

One of the main criticisms of assigning PCS diagnosis following TBI is the lack of specificity of PCS symptoms. In particular, some of the symptoms that comprise PCS have also been observed in non-brain related conditions such as chronic pain and orthopedic injury (Bazarian et al., 1999; Smith-Seemiller, Fow, Kant, & Franzen, 2003). Moreover, after controlling for psychological factors such as PTSD,

mTBI does not appear to contribute to the severity of PCS (Meares et al., 2008; Meares et al., 2011). Additionally, similar to the debate surrounding the definition of mTBI, several diagnostic manuals, such as the DSM-5 and International Classification of Disease (ICD), have specified criteria for the diagnosis of PCS (Masel & DeWitt, 2010). These variable definitions of PCS have hindered the capacity for standardized research into the specific microstructural underpinnings of PCS.

Despite the diagnostic issues outlined above, severity of PCS provides a wealth of information that can be used to interpret WM findings in terms of their functional significance. As mentioned earlier, one of the limitations of the present study is the lack of data on the level of PCS symptoms in the mTBI group. As a result, it is impossible to determine whether the WM changes observed in the CC and cingulum are also related to PCS symptoms. Future research is needed in order to draw firm conclusions regarding the association between the observed WM damage within the CC and cingulum, and symptoms of PCS.

7.6.5 Measures of WM Integrity

FA and Trace are global measures of WM microstructure that have been used to investigate brain morphological changes with respect to a variety of psychiatric and neurological conditions such as mTBI, schizophrenia, depression, MS and anxiety disorders (Ayling, Aghajani, Fouche, & Wee, 2012; Klawiter et al., 2011; Korgaonkar et al., 2011; Kubicki et al., 2002; Lipton et al., 2009). Decrease in FA and increase in Trace (or its closely related measure, MD) have traditionally been linked to compromise of WM integrity. Some studies, however, have also shown increase in FA in a diseased brain thus suggesting that both increase and decrease in FA may be indicative of pathology (e.g. Abe et al. (2006) and Sekiguchi et al. (2014)). Additionally, changes in FA have been observed in both normal ageing and as a consequence of disease progression (e.g. Moseley (2002), Sexton et al. (2014) and Gregory et al. (2014)). It is therefore yet to be validated with certainty under what circumstances FA changes

are suggestive of aberrant microstructure and when they are reflective of healthy processes within brain WM.

Perpendicular Diffusivity and Parallel Diffusivity are two DTI metrics that have often been used to explain changes in the two global anisotropy measures, namely FA and Trace. In their pioneering study, Song et al. (2002) demonstrated that increase in Perpendicular Diffusivity was associated with demyelination and was unrelated to axonal damage. This finding was later confirmed in their later study as well as in human research with patients with MS - a neurodegenerative condition characterized by myelin loss (Klawiter et al., 2011; Song et al., 2003; Song et al., 2005). In contrast, decrease in Parallel Diffusivity has been linked to axonal damage (Budde, Xie, Cross, & Song, 2009). These findings, however, have been challenged by Wheeler-Kingshott and Cercignani (2009) who argued that in the regions of crossing fibres, changes in Perpendicular Diffusivity can produce changes in Parallel Diffusivity that are fictitious in nature and vice versa. Thus, further research is needed to further verify the extent to which changes within these measures, namely Perpendicular Diffusivity and Parallel Diffusivity, are reflective of the underlying neural microstructure.

Mode is a DTI measure that has been used to describe three dimensional shape of the diffusion ellipsoid (Kindlmann et al., 2007). The anatomical significance of this metric, however, is unclear. Some studies have observed variation in mode in regions of crossing fibres (Kindlmann et al., 2007). Apart from Kindlmann et al.'s (2007) study, however, no other studies to date have proposed alternative explanation for the variance within this metric and hence its relevance to psychopathology is yet to be clarified.

One of the main flaws of DTI is its simplification of neural architecture. DTI relies on the Gaussian model to describe water movement within the brain which is based on the assumption that fibre orientation is represented by one long axis of the diffusion ellipsoid (Mori, 2007). However, this is only true in the absence of crossing fibres (Mori, 2007). Presence of crossing fibres may lead to the same DTI result

despite the presence of differently oriented fibres (Mori, 2007). This information degeneration leads to decrease in FA and hence may result in incorrect tract estimation (Mori, 2007). This limitation should be taken into consideration when drawing conclusions regarding changes within microstructure of WM.

7.7 Future Directions

7.7.1 Subregions of WM Tracts

The present study investigated microstructure of selected WM tracts with an emphasis on the entirety of these tracts. This approach has been commonly applied in studies of WM in neuropsychiatric disorders (e.g. Wilde et al. (2010)). Another approach that has been previously utilized is based on the idea that subregions of certain WM structures are functionally heterogeneous. For instance, Sorg et al. (2014) subdivided the cingulum into anterior and posterior regions and observed decrease in FA in the posterior region which was in turn associated with reduced executive functioning in mTBI. Similarly, Rutgers et al. (2008) studied integrity of subregions of the CC in mTBI and observed reduced FA in the genu, a section of the CC that connects frontal and orbitofrontal regions. These and many other studies have based their choice of analysis on the rationale that anatomically distinct regions must also have unique sets of functions. For instance, the CC has traditionally been subdivided into three sections, each of which connects functionally different cortices (Catani & Thiebaut de Schotten, 2008). Presence of functional heterogeneity within subsections of WM fibre bundles may lead to variable degree of contribution of different subregions to psychopathology. This variance is likely to be dependent on the clinical presentation of the disorder. For instance, since functional alterations within the PFC have been frequently reported in PTSD (e.g. Gold et al. (2011)), the genu of the CC is a plausible candidate subregion as it connects the prefrontal and orbitofrontal cortices of opposite hemispheres and is hence likely to be implicated in symptomatology of this disorder.

Therefore, to increase the specificity of findings, future researchers looking to describe the relationship between WM damage and symptoms of PTSD and/ or mTBI are urged to subdivide structures of interest based on their previously documented anatomical and functional properties.

7.7.2 WM Microstructure and Functionality

As outlined in Chapter 1, the fear circuitry model of PTSD emphasizes the involvement of roughly three main regions in symptomatology of this disorder. In particular, it has proposed that PTSD is characterized by an overly active amygdala with concurrently diminished activation in the prefrontal cortices (Heim & Nemeroff, 2009). Additionally, the hippocampus has also been implicated in this disorder and has been thought to process contextual cues of fear conditioning (Heim & Nemeroff, 2009). Although functions of the above structures have been well described and their aberrant alterations have been linked to clinical symptoms of a number of disorders, including PTSD, the underlying structural connections that mediate functional coupling between these regions are yet to be fully described. Some studies have already utilized functional connectivity analysis in individuals with mTBI, which has proved to be highly informative in describing a potential pathway via which PTSD and mTBI complicate each other (Costanzo et al., 2014). Thus, future research could immensely benefit from working towards integrating functional and structural information gained from ever advancing imaging techniques.

7.7.3 Causality

Finally, another important factor that needs to be addressed is the nature of the casual relationship between WM microstructure and PTSD. It has previously been demonstrated that the likelihood of developing PTSD- related symptoms is at least partially determined by pre-existing macrostructural (e.g. Gilbertson et al. (2002)) and

microstructural (e.g. Sekiguchi et al. (2014)) changes. Since no DTI data was collected prior to PTSD onset, the results of the present study cannot establish causal links between WM damage and PTSD severity. Thus, future research is advised to conduct longitudinal twin studies in order to assess WM composition in individuals with PTSD and their genetically identical siblings who do not have a history of previous psychological problems.

7.8 Conclusions

In summary, the studies discussed in this research project provide new evidence regarding the underlying neural causes of disturbances observed following mTBI, showing that WM damage that has been frequently reported in the mTBI literature is predicted by both physiogenic and psychogenic causes. The present findings offer concrete support for previously tentative propositions based on self-report measures suggesting that psychiatric symptoms may be important in mediating and potentially exacerbating difficulties observed in the aftermath of mTBI. Importantly, the current findings lent support not only for neural overlap between PTSD and mTBI but also highlight the important distinctions between these conditions in terms of microstructural vulnerability of their WM.

The observation of reduced connectivity within the interhemispheric projection fibres in PTSD and mTBI could potentially inform existing therapies. There is now a growing body of evidence supporting the idea of plasticity of WM, with studies demonstrating increase in WM connectivity following memory and visuo-motor skills training (e.g. Lövdén et al. (2010), Scholz, Klein, Behrens, and Johansen-Berg (2009), Takeuchi et al. (2010) and Tang et al. (2010)). Specific to the CC, using a large sample of adult participants, Lövdén et al. (2010) observed increase in FA and decrease in Mean Diffusivity in the genu of the CC, as well as an increase in volume of this subregion, following cognitive training on tasks that are thought to rely on the PFC and require attentional control that is achieved via interhemispheric communication. We thus

speculate that introducing tasks that engage the CC by relying on interhemispheric transfer and integration of information as part of psychological treatment, for instance CBT, could be beneficial for increasing connectivity within the genu of the CC - a subregion which due to its anatomical position is likely to be implicated in some of PTSD and mTBI related symptomatology.

Although much further research is needed, these preliminary findings provide new insight into microstructural alterations in the context of psychological trauma and offer a novel approach to treatment following traumatic stress that encompasses not only traditional evidence-based therapy but also emphasizes the importance of cognitive training in order to improve WM connectivity and thereby potentially increase treatment efficacy.

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APPENDICES

Appendix A

Participant Information and Consent Forms

Participant Information and Consent Form for Patients: Clinical trial excluding genetic testing and collection/ storage of human tissue ……163

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PARTICIPANT INFORMATION
(For Patients)

CLINICAL TRIAL

(EXCLUDING GENETIC TESTING AND COLLECTION/STORAGE OF HUMAN TISSUE)

Study Title: Biomarkers of Anxiety Disorders and Treatment Response (CCRE)

Chief Investigator:

Dr Anthony Harris Department: Psychiatry

Associate Investigators:

Prof Richard Bryant Department: Brain Dynamics Centre

Prof Lea Williams Department: Brain Dynamics Centre

Dr Kim Felmingham Department: Brain Dynamics Centre

Ms Dharani Karthikeyan Department: Brain Dynamics Centre

Ms. Aleksandra Klimova Department: Brain Dynamics Centre

Ms. Srishti Yadav Department: Brain Dynamics Centre

Ms. Adele Stavropoulos Department: Brain Dynamics Centre

What is the purpose of the study?

The purpose of this study is to bring together measures of brain and body function to predict response to cognitive behavioural therapy in four distinct anxiety disorders (Panic Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder and Posttraumatic Stress Disorder) and Major Depressive Disorder. Cognitive behavioural treatments are effective treatments for anxiety disorders and Major Depressive Disorder, but not everyone responds equally. There is an urgent need to identify valid predictors of treatment response. Currently there are no accurate predictors of how patients will respond to cognitive behaviour therapy. By combining brain, body arousal, and cognitive measures we can obtain a comprehensive profile of biological responses that may relate to different anxiety disorders and Major Depressive Disorder, and predict response to cognitive behavioural treatment.

Who will be invited to enter the study?

You have been invited to participate in the study because you have been diagnosed with an anxiety disorder (i.e. Panic Disorder, Social Anxiety Disorder, Posttraumatic Stress Disorder or Generalized

Anxiety Disorder) or Major Depressive Disorder, and your clinician has recommended that you begin cognitive behavior therapy for your symptoms.

What will happen on the study?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. If you agree to participate in the study, you will then be asked to undergo the following procedures (described in more detail below):

- Clinical Assessment
- Electroencephalogram (EEG) recording
- Magnetic Resonance Imaging (MRI) recording
- Psychological Testing
- Psychophysiological Recording

You will be asked to attend the testing facility on two separate occasions, for baseline testing and again 10 weeks later. We would also like to contact you three months following the second testing session to assess how you are. This would be done by asking you a number of questions over the phone as well as completing questionnaires that would be mailed out to you after.

Clinical Assessment

You will undergo a clinical assessment with a clinical psychologist to examine your psychological wellbeing and you will be asked to fill in several questionnaires regarding your mood. You will then be asked to answer questions about demographics (such as age, gender, personality, current physical health, family history and life experiences) using a computer touch screen. You will also be asked to describe a memory of a fearful experience that you have had to the psychologist which will be used in a later task in the study. It is up to you which experience you choose to describe. The duration of the clinical assessment in total will take approximately 90 minutes.

The Encephalogram (EEG) Recording

The EEG recording measures brain function. A skull cap containing recording discs will be placed on your head. Water-based gel will be inserted into each recording disc so that your brain's activity may be recorded. The gel will not harm the scalp or hair in any way, and can be washed off with water after the procedure. Before the gel is administered at each disc site, your skin may be prepared with a mild abrasive cream and cleaned off with a gauze swab, this will not cause any harm and serves to clean the skin from any oils or residues that can contaminate the recordings. Recording devices will also be placed on your fore and middle fingers (to measure sweat rate), wrist (ECG to assess heart rate), face (eye and jaw muscle activity) and neck (referencing). Also you will wear a respiration belt around the chest – armpit line (above clothing) to measure breathing rates. Headphones will be worn over the EEG cap to aid in auditory stimulation and automated task instructions. Once the set-up is completed you will undergo a brief hearing test so as to ascertain whether or not you can clearly hear task instructions through the headphones. During the EEG recording, you will conduct tests on a computer program, which assess the brain's response to specific tasks. These tasks include a resting state (resting with your eyes open), cognitive tests (attention, memory), and emotion processing tests (looking at faces with different emotional expressions). You will be monitored via closed circuit TV and communication between technician and participant will be via an intercom during the procedure. This will take approximately 65 minutes to complete.

The Magnetic Resonance Imaging (MRI) Recording

The MRI recording is a procedure that allows us to take detailed pictures of your brain in action. Firstly, you will undergo an MRI safety check with the MRI specialist. You will be asked to remove all metallic items that you are wearing and be asked to change into a hospital gown. Sweat rate recording discs will be placed on your fore and middle fingers. Your pulse rate is measured by a toe

clamp, and breathing rate is measured through a nose piece. All of these methods are MR compatible and have passed the required safety tests for use. You will then be guided into the scanner room and asked to lie on the scanner bed with the assistance of the MR specialist. You will be fitted with headphones which allow you to hear the task instructions and other noises which are part of the tasks. The scanner bed will then be slowly moved into Machine. A small number of people may feel claustrophobic inside the MRI machine since the procedure involves being scanned inside a lighted plastic tunnel, where there is a little room for movement and the machine makes a lot of loud noises. But you will be monitored by an MRI specialist during the entire procedure through a video camera, observation window, and a sound system. You can stop scanning at any time at the MR Specialist's discretion or at your request. You will be given a 'squeeze ball' which you may use at any time that you feel uncomfortable, and scanning will be stopped.

During the MRI recording you will be asked to look at a mirror on the plastic head coil above you. This mirror can be adjusted until you can best see the screen to which the computer tasks are projected. You will then be given a button press box, which you will use in certain tasks. You will have an initial brief hearing test to ascertain whether or not you can clearly hear and understand task instructions. You are able both see as well as hear task instructions. You will be scanned while conducting tasks on four tasks, which will assess visual-motor skills, memory, attention, emotion perception (viewing faces of different emotional expressions) and emotion regulation (viewing scenes of injury or assault). The entire procedure takes about 45 minutes. Following these tasks a structural MRI will be conducted for which you will simply be asked to stay still while your brain is being scanned. This procedure takes about 15 minutes. The total MRI testing will take approximately 1 hour. After finishing, you will be asked to change back into your clothes and asked a few final questions, taking approximately 10 minutes.

Psychological Testing

The psychological (cognitive) testing component: is conducted in front of a touchscreen computer screen and includes questionnaires asking about demographics (such as age, gender), personality, current physical health, family history and life experiences as well as tasks which assess sensory-motor skills, memory, language and verbal executive skills, attention and learning. The duration of the psychological testing component is approximately 60 minutes depending on whether your answers lead to more detailed questions.

Psychophysiological Recording

Recording devices will be placed on your fore and middle fingers (to measure sweat rate), wrist (ECG to assess heart rate), face (eye and jaw muscle activity) and neck (referencing). Also you will wear a respiration belt around the chest – armpit line (above clothing) to measure breathing rates. Once set up, you will listen to a 30 second audiotape of a script that describes a fearful or anxiety-provoking experience. This script will be developed by yourself and the clinical psychologist during the clinical assessment. You will listen to this script three times. This procedure takes approximately 5 minutes. Each assessment will take a total duration of approximately 4 and a half hours to 5 hours including a short break.

Are there any risks?

All medical procedures involve some potential risk of injury. In spite of all reasonable precautions, there is a small risk that you may develop complications from participating in this study. The known risks of this study are:

- You may feel a small amount of arousal or distress to the emotion-inducing stimuli (fearful or

angry facial expressions, viewing scenes of injury or assault, listening to a script of your most frightening experience), but these stimuli have been employed in many studies with minimal negative consequences for participants. If you do feel uncomfortable, you can opt out of this section of the study or discontinue the study at any time without penalty. You will be able to communicate with the researchers throughout the entire testing procedure via intercom.

- The EEG caps used in this procedure are designed for non-invasive measurement of the brain's electrical activity. The caps record naturally occurring electrical activity and do not produce any electricity themselves.
- MRI uses strong magnetic fields and radiowaves to produce images of the body to detect the flow of oxygenated blood to areas of your brain that you are using. This allows very high detailed images to be produced safely and painlessly. MRI is well validated and there are no short- or long-term side-effects. No X-rays are used and therefore there is no exposure to radiations.

Are there any benefits?

This study will not directly benefit the participants involved. This study aims to improve our knowledge of anxiety disorders and Major Depressive Disorder, and of how to predict treatment. This may result in benefits for individuals with anxiety disorders and Major Depressive Disorder in future.

Confidentiality / Privacy

All aspects of this study, including results will be strictly confidential and only the researchers will have access to your personal information. Any publication of results will only use de-identified information. Confidentiality will be maintained at all times and information about genetic analysis will not be made available to participants or others outside the study. Original data will be stored in a locked office and entered into a Registry database that will be password protected. The information will be stored for an indefinite period. All persons who are to have access to name-identified data from the Registry shall complete a signed declaration binding them to respect the confidentiality of the information contained therein. We note that the genetic analyses we conduct explore polymorphisms that contribute to normal individual variation as well as susceptibility to anxiety disorders and Major Depressive Disorder. We cannot determine paternity or maternity from our analyses, and genetic information will not be accessible to participants under any circumstances.

Compensation

Every reasonable precaution will be taken to ensure your safety during the course of this study. If you suffer any serious injuries or complications as a result of your participation in this study, you should, as soon as possible, contact the study doctor who will arrange appropriate medical treatment free of charge in any Australian public hospital.

Your participation in this study will not affect any right to compensation that you might have under statute or common law for any serious injuries or complications resulting from this study, caused by unsafe drugs or equipment or by negligence.'

What will happen at the conclusion of this study?

At the conclusion of the study, the data will be analysed and presented at scientific meetings and in publications so that other scientists around the world will be informed of our findings. No individual will be able to be identified in these publications. A brief report summarizing the group findings of the study will be sent to each participant following the finalization of data analysis (often several months after the final participant has been collected). Data will be kept in a secured location for seven years (in line with national guidelines for research) and then destroyed.

Do you have a choice?

Your participation in this study is entirely voluntary. If you choose not to join the study, or you wish to withdraw from it at any time, your medical care will not be affected.

Complaints

If you have any concerns about the conduct of the study, or your rights as a study participant, you may contact Westmead Hospital Patient Representative, on Telephone No 9845 7014

Contact details

If you have any problems while on the study, please contact

Prof Richard Bryant

Working hours Telephone No – (02) 9385 3640

After hours Telephone No – 0405 375 874

CONSENT TO PARTICIPATE IN RESEARCH

Study Title: Biomarkers of Anxiety Disorders and Treatment Response

Chief Investigator: Dr Anthony Harris Department: Psychiatry

Name of Researcher:

1. I understand that the researcher will conduct this study in a manner conforming with ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.
2. I acknowledge that I have read, or have had read to me the Participant Information Sheet relating to this study. I acknowledge that I understand the Participant Information Sheet. I acknowledge that the general purposes, methods, demands and possible risks and inconveniences which may occur to me during the study have been explained to me by _____ ("the researcher") and I, being over the age of 16 years, acknowledge that I understand the general purposes, methods, demands and possible risks and inconveniences which may occur during the study.
3. I acknowledge that I have been given time to consider the information and to seek other advice.
4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.
6. I acknowledge that this research has been approved by the Sydney West Area Health Service Human Research Ethics Committee.
7. I acknowledge that I have received a copy of this form and the Participant Information Sheet, which I have signed.
8. I acknowledge any regulatory authorities may have access to my medical records to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Before signing, please read 'IMPORTANT NOTE' following.

Name of participant _____Date of Birth _____

Address of participant _____

Name of parent or person responsible(where applicable) _____

Address of parent or person responsible (where applicable) _____

Signature of participant _____ Date: _____

Signature of parent or person responsible (where applicable) _____Date: _____

Signature of researcher _____ Date: _____

Signature of witness _____ Date: _____

IMPORTANT NOTE
This consent should only be signed as follows:

1. *Where a participant is over the age of 16 years, then by the participant personally.*
2. *Where a participant is between the age of 14 and 16 years, it should be signed by the participant and by a parent or person responsible.*
3. *Where a participant is under the age of 14 years, then the parent or person responsible only should sign the consent form.*
4. *Where a participant has impaired capacity, intellectual disability or is unconscious, then specific approval for the process for obtaining consent must be sought from the Human Research Ethics Committee.*

WITNESS:

I, _____ (name of witness) hereby certify as follows:

1. I was present when _____ (the 'participant') appeared to read or had read to him/her a Participant Information Sheet comprising (pages); **or** was told by _____ the participant that he/she had read the Participant Information Sheet (*delete as applicable*).

2. I was present when _____ (the 'researcher') explained the general purposes, methods, demands and the possible risks and inconveniences of participating in the study to the participant. I asked the participant whether he/she had understood the Participant Information Sheet and understood what he/she had been told and he/she told me that he/she did understand.
3. I observed the participant sign the consent to participate in research and he/she appeared to me to be signing the document freely and without duress.
4. The participant showed me a form of identification which satisfied me as to his/her identity.
5. I am not involved in any way as a researcher in this project.
6. (*Delete this clause if not applicable*) I was present when _____ (the 'interpreter') read the Participant Information Sheet to the participant in the _____ (*insert appropriate language*) language. I certify that when the researcher explained the general purposes, methods, demands and possible risks and inconveniences of participating in the study that what was said by both the researcher and the participant was translated by the interpreter from the English language into the above language and vice versa. When I spoke to the participant, what I said and what the participant said was translated by the interpreter from the English language into the above language and vice versa.

Name of witness _____Relationship to participant _____

Address of witness _____

Signature of witness _____ Date: _____

Name of interpreter (if applicable) _____

Signature of Interpreter (if applicable) _____ Date: _____

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(For Controls)

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Dr Kim Felmingham Department: Brain Dynamics Centre

Ms Dharani Karthikeyan Department: Brain Dynamics Centre

Ms. Srishti Yadav Department: Brain Dynamics Centre

Ms. Adele Stavropoulos Department Brain Dynamics Centre

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Who will be invited to enter the study?

You have been invited to participate in this study because you do not currently suffer from a psychiatric illness (including anxiety and Major Depressive Disorder) – we need to include people without psychiatric illnesses to act as a control group for comparison to the anxiety and Major Depressive Disorder groups.

What will happen on the study?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. If you agree to participate in the study, you will then be asked to undergo the following procedures (described in more detail below):

- Clinical Assessment
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- Magnetic Resonance Imaging (MRI) recording
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You will undergo a clinical assessment with a clinical psychologist to examine your psychological wellbeing and you will be asked to fill in several questionnaires regarding your mood. You will then be asked to answer questions about demographics (such as age, gender, personality, current physical health, family history and life experiences) using a computer touch screen. You will also be asked to describe a memory of a fearful experience that you have had to the psychologist which will be used in a later task in the study. It is up to you which experience you choose to describe. The duration of the clinical assessment in total will take approximately 90 minutes.

The Encephalogram (EEG) Recording

The EEG recording measures brain function. A skull cap containing recording discs will be placed on your head. Water-based gel will be inserted into each recording disc so that your brain's activity may be recorded. The gel will not harm the scalp or hair in any way, and can be washed off with water after the procedure. Before the gel is administered at each disc site, your skin may be prepared with a mild abrasive cream and cleaned off with a gauze swab, this will not cause any harm and serves to clean the skin from any oils or residues that can contaminate the recordings. Recording devices will also be placed on your fore and middle fingers (to measure sweat rate), wrist (ECG to assess heart rate), face (eye and jaw muscle activity) and neck (referencing). Also you will wear a respiration belt around the chest – armpit line (above clothing) to measure breathing rates. Headphones will be worn over the EEG cap to aid in auditory stimulation and automated task instructions. Once the set-up is completed you will undergo a brief hearing test so as to ascertain whether or not you can clearly hear task instructions through the headphones. During the EEG recording, you will conduct tests on a computer program, which assess the brain's response to specific tasks. These tasks include a resting state (resting with your eyes open), cognitive tests (attention, memory), and emotion processing tests (looking at faces with different emotional expressions). You will be monitored via closed circuit TV and communication between technician and participant will be via an intercom during the procedure. This will take approximately 65 minutes to complete.

The Magnetic Resonance Imaging (MRI) Recording

The MRI recording is a procedure that allows us to take detailed pictures of your brain in action. Firstly, you will undergo an MRI safety check with the MRI specialist. You will be asked to remove all metallic items that you are wearing and be asked to change into a hospital gown. Sweat rate recording discs will be placed on your fore and middle fingers. Your pulse rate is measured by a toe clamp, and breathing rate is measured through a nose piece. All of these methods are MR compatible and have passed the required safety tests for use. You will then be guided into the scanner room and

asked to lie on the scanner bed with the assistance of the MR specialist. You will be fitted with headphones which allow you to hear the task instructions and other noises which are part of the tasks. The scanner bed will then be slowly moved into Machine. A small number of people may feel claustrophobic inside the MRI machine since the procedure involves being scanned inside a lighted plastic tunnel, where there is a little room for movement and the machine makes a lot of loud noises. But you will be monitored by an MRI specialist during the entire procedure through a video camera, observation window, and a sound system. You can stop scanning at any time at the MR Specialist's discretion or at your request. You will be given a 'squeeze ball' which you may use at any time that you feel uncomfortable, and scanning will be stopped.

During the MRI recording you will be asked to look at a mirror on the plastic head coil above you. This mirror can be adjusted until you can best see the screen to which the computer tasks are projected. You will then be given a button press box, which you will use in certain tasks. You will have an initial brief hearing test to ascertain whether or not you can clearly hear and understand task instructions. You are able both see as well as hear task instructions. You will be scanned while conducting tasks on four tasks, which will assess visual-motor skills, memory, attention, emotion perception (viewing faces of different emotional expressions) and emotion regulation (viewing scenes of injury or assault). The entire procedure takes about 45 minutes. Following these tasks a structural MRI will be conducted for which you will simply be asked to stay still while your brain is being scanned. This procedure takes about 15 minutes. The total MRI testing will take approximately 1 hour. After finishing, you will be asked to change back into your clothes and asked a few final questions, taking approximately 10 minutes.

Psychological Testing
The psychological (cognitive) testing component: is conducted in front of a touchscreen computer screen and includes questionnaires asking about demographics (such as age, gender), personality, current physical health, family history and life experiences as well as tasks which assess sensory-motor skills, memory, language and verbal executive skills, attention and learning. The duration of the psychological testing component is approximately 60 minutes depending on whether your answers lead to more detailed questions.

Psychophysiological Recording
Recording devices will be placed on your fore and middle fingers (to measure sweat rate), wrist (ECG to assess heart rate), face (eye and jaw muscle activity) and neck (referencing). Also you will wear a respiration belt around the chest – armpit line (above clothing) to measure breathing rates. Once set up, you will listen to a 30 second audiotape of a script that describes a fearful or anxiety-provoking experience. This script will be developed by yourself and the clinical psychologist during the clinical assessment. You will listen to this script three times. This procedure takes approximately 5 minutes. Each assessment will take a total duration of approximately 4 and a half hours to 5 hours including a short break.

Are there any risks?

All medical procedures involve some potential risk of injury. In spite of all reasonable precautions, there is a small risk that you may develop complications from participating in this study. The known risks of this study are:

- You may feel a small amount of arousal or distress to the emotion-inducing stimuli (fearful or angry facial expressions, viewing scenes of injury or assault, listening to a script of your most frightening experience), but these stimuli have been employed in many studies with minimal negative consequences for participants. If you do feel uncomfortable, you can opt out of this

section of the study or discontinue the study at any time without penalty. You will be able to communicate with the researchers throughout the entire testing procedure via intercom.

- The EEG caps used in this procedure are designed for non-invasive measurement of the brain's electrical activity. The caps record naturally occurring electrical activity and do not produce any electricity themselves.
- MRI uses strong magnetic fields and radiowaves to produce images of the body to detect the flow of oxygenated blood to areas of your brain that you are using. This allows very high detailed images to be produced safely and painlessly. MRI is well validated and there are no short- or long-term side-effects. No X-rays are used and therefore there is no exposure to radiations.

Are there any benefits?

This study will not directly benefit the participants involved. This study aims to improve our knowledge of anxiety disorders and Major Depressive Disorder, and of how to predict treatment. This may result in benefits for individuals with anxiety disorders and Major Depressive Disorder in future.

Confidentiality / Privacy

All aspects of this study, including results will be strictly confidential and only the researchers will have access to your personal information. Any publication of results will only use de-identified information. Confidentiality will be maintained at all times and information about genetic analysis will not be made available to participants or others outside the study. Original data will be stored in a locked office and entered into a Registry database that will be password protected. The information will be stored for an indefinite period. All persons who are to have access to name-identified data from the Registry shall complete a signed declaration binding them to respect the confidentiality of the information contained therein. We note that the genetic analyses we conduct explore polymorphisms that contribute to normal individual variation as well as susceptibility to anxiety disorders and Major Depressive Disorder. We cannot determine paternity or maternity from our analyses, and genetic information will not be accessible to participants under any circumstances.

Compensation

Every reasonable precaution will be taken to ensure your safety during the course of this study. If you suffer any serious injuries or complications as a result of your participation in this study, you should, as soon as possible, contact the study doctor who will arrange appropriate medical treatment free of charge in any Australian public hospital.
Your participation in this study will not affect any right to compensation that you might have under statute or common law for any serious injuries or complications resulting from this study, caused by unsafe drugs or equipment or by negligence.'

What will happen at the conclusion of this study?

At the conclusion of the study, the data will be analysed and presented at scientific meetings and in publications so that other scientists around the world will be informed of our findings. No individual will be able to be identified in these publications. A brief report summarizing the group findings of the study will be sent to each participant following the finalization of data analysis (often several months after the final participant has been collected). Data will be kept in a secured location for seven years (in line with national guidelines for research) and then destroyed.

Do you have a choice?

Your participation in this study is entirely voluntary. If you choose not to join the study, or you wish to withdraw from it at any time, your medical care will not be affected.

Complaints

If you have any concerns about the conduct of the study, or your rights as a study participant, you may contact Westmead Hospital Patient Representative, on Telephone No 9845 7014

Contact details

If you have any problems while on the study, please contact

Prof Richard Bryant

Working hours Telephone No – (02) 93853640

After hours Telephone No – 0405375874

CONSENT TO PARTICIPATE IN RESEARCH

Study Title: Biomarkers of Anxiety Disorders and Treatment Response

Chief Investigator: Dr Anthony Harris Department: Psychiatry

Name of Researcher:

1. I understand that the researcher will conduct this study in a manner conforming with ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.
2. I acknowledge that I have read, or have had read to me the Participant Information Sheet relating to this study. I acknowledge that I understand the Participant Information Sheet. I acknowledge that the general purposes, methods, demands and possible risks and inconveniences which may occur to me during the study have been explained to me by _____ ("the researcher") and I, being over the age of 16 years, acknowledge that I understand the general purposes, methods, demands and possible risks and inconveniences which may occur during the study.
3. I acknowledge that I have been given time to consider the information and to seek other advice.
4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.
6. I acknowledge that this research has been approved by the Western Sydney Local Health District Human Research Ethics Committee.
7. I acknowledge that I have received a copy of this form and the Participant Information Sheet, which I have signed.
8. I acknowledge any regulatory authorities may have access to my medical records to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Before signing, please read 'IMPORTANT NOTE' following.

Name of participant _____Date of Birth _____

Address of participant _____

Name of parent or person responsible (where applicable) _____

Address of parent or person responsible (where applicable) _____

Signature of participant _____ Date: _____

Signature of parent or person responsible (where applicable) _____Date: _____

Signature of researcher _____Date: _____

Signature of witness _____Date:_____

IMPORTANT NOTE
This consent should only be signed as follows:

5. *Where a participant is over the age of 16 years, then by the participant personally.*
6. *Where a participant is between the age of 14 and 16 years, it should be signed by the participant and by a parent or person responsible.*
7. *Where a participant is under the age of 14 years, then the parent or person responsible only should sign the consent form.*
8. *Where a participant has impaired capacity, intellectual disability or is unconscious, then specific approval for the process for obtaining consent must be sought from the Human Research Ethics Committee.*

WITNESS:

I, _____ (name of witness) hereby certify as follows:

1. I was present when _____ (the 'participant') appeared to read or had read to him/her a Participant Information Sheet comprising (pages); **or** was told by _____ the participant that he/she had read the Participant Information Sheet (*delete as applicable*).

2. I was present when _____ (the 'researcher') explained the general purposes, methods, demands and the possible risks and inconveniences of participating in the study to the participant. I asked the participant whether he/she had understood the Participant Information Sheet and understood what he/she had been told and he/she told me that he/she did understand.
3. I observed the participant sign the consent to participate in research and he/she appeared to me to be signing the document freely and without duress.
4. The participant showed me a form of identification which satisfied me as to his/her identity.
5. I am not involved in any way as a researcher in this project.
6. (*Delete this clause if not applicable*) I was present when _____ (the 'interpreter') read the Participant Information Sheet to the participant in the _____ (*insert appropriate language*) language. I certify that when the researcher explained the general purposes, methods, demands and possible risks and inconveniences of participating in the study that what was said by both the researcher and the participant was translated by the interpreter from the English language into the above language and vice versa. When I spoke to the participant, what I said and what the participant said was translated by the interpreter from the English language into the above language and vice versa.

Name of witness _____ Relationship to participant _____

Address of witness _____

Signature of witness _____ Date: _____

Name of interpreter (if applicable) _____

Signature of Interpreter (if applicable) _____Date: _____

PARTICIPANT INFORMATION
(For Trauma Exposed Controls)

CLINICAL TRIAL

(EXCLUDING GENETIC TESTING AND COLLECTION/STORAGE OF HUMAN TISSUE)

Study Title: Biomarkers of Anxiety Disorders and Treatment Response (CCRE)

Co-ordinating Chief Investigator: Dr Anthony Harris Department: Psychiatry

Associate Investigators:

What is the purpose of the study?

The purpose of this study is to bring together measures of brain and body function to predict response to cognitive behavioural therapy in four distinct anxiety disorders (Panic Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder and Posttraumatic Stress Disorder) and Major Depressive Disorder. Cognitive behavioural treatments are effective treatments for anxiety disorders and Major Depressive Disorder, but not everyone responds equally. There is an urgent need to identify valid predictors of treatment response. Currently there are no accurate predictors of how patients will respond to cognitive behaviour therapy. By combining brain, body arousal, and cognitive measures we can obtain a comprehensive profile of biological responses that may relate to different anxiety disorders and Major Depressive Disorder, and predict response to cognitive behavioural treatment.

Who will be invited to enter the study?

You have been invited to participate in this study because you have experienced a traumatic event.

Where will the study be conducted?

The study will be conducted at . The date and time of the appointment will be arranged on the case by case basis depending on the participant's availability.

What will happen on the study?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. If you agree to participate in the study, you will then be asked to undergo the following procedures (described in more detail below):

- Clinical Assessment
- Electroencephalogram (EEG) recording
- Magnetic Resonance Imaging (MRI) recording
- Psychological Testing
- Psychophysiological Recording

You will be asked to attend the testing facility on two separate occasions, for baseline testing and again 10 weeks later. We would also like to contact you three months following the second testing session to assess how you are. This would be done by asking you a number of questions over the phone as well as completing questionnaires that would be mailed out to you after.

Clinical Assessment

You will undergo a clinical assessment with a clinical psychologist to examine your psychological wellbeing and you will be asked to fill in several questionnaires regarding your mood. You will then be asked to answer questions about demographics (such as age, gender, personality, current physical health, family history and life experiences) using a computer touch screen. You will also be asked to describe a memory of a fearful experience that you have had to the psychologist which will be used in a later task in the study. It is up to you which experience you choose to describe. The duration of the clinical assessment in total will take approximately 90 minutes.

The Encephalogram (EEG) Recording

The EEG recording measures brain function. A skull cap containing recording discs will be placed on your head. Water-based gel will be inserted into each recording disc so that your brain's activity may be recorded. The gel will not harm the scalp or hair in any way, and can be washed off with water after the procedure. Before the gel is administered at each disc site, your skin may be prepared with a mild abrasive cream and cleaned off with a gauze swab, this will not cause any harm and serves to clean the skin from any oils or residues that can contaminate the recordings. Recording devices will also be placed on your fore and middle fingers (to measure sweat rate), wrist (ECG to assess heart rate), face (eye and jaw muscle activity) and neck (referencing). Also you will wear a respiration belt around the chest – armpit line (above clothing) to measure breathing rates. Headphones will be worn over the EEG cap to aid in auditory stimulation and automated task instructions. Once the set-up is completed you will undergo a brief hearing test so as to ascertain whether or not you can clearly hear task instructions through the headphones. During the EEG recording, you will conduct tests on a computer program, which assess the brain's response to specific tasks. These tasks include a resting state (resting with your eyes open), cognitive tests (attention, memory), and emotion processing tests (looking at faces with different emotional expressions). You will be monitored via closed circuit TV and communication between technician and participant will be via an intercom during the procedure. This will take approximately 65 minutes to complete.

The Magnetic Resonance Imaging (MRI) Recording

The MRI recording is a procedure that allows us to take detailed pictures of your brain in action. Firstly, you will undergo an MRI safety check with the MRI specialist. You will be asked to remove all metallic items that you are wearing and be asked to change into a hospital gown. Sweat rate recording discs will be placed on your fore and middle fingers. Your pulse rate is measured by a toe clamp, and breathing rate is measured through a nose piece. All of these methods are MR compatible and have passed the required safety tests for use. You will then be guided into the scanner room and asked to lie on the scanner bed with the assistance of the MR specialist. You will be fitted with headphones which allow you to hear the task instructions and other noises which are part of the tasks. The scanner bed will then be slowly moved into Machine. A small number of people (1 in 20) may feel claustrophobic inside the MRI machine since the procedure involves being scanned inside a lighted plastic tunnel, where there is a little room for movement and the machine makes a lot of loud noises. But you will be monitored by an MRI specialist during the entire procedure through a video camera, observation window, and a sound system. You can stop scanning at any time at the MR Specialist's discretion or at your request. You will be given a 'squeeze ball' which you may use at any time that you feel uncomfortable, and scanning will be stopped.

During the MRI recording you will be asked to look through goggles, through which you will see the computer tasks. You will then be given a button press box, which you will use in certain tasks. You

will have an initial brief hearing test to ascertain whether or not you can clearly hear and understand task instructions. You are able both see as well as hear task instructions. You will be scanned while conducting tasks on four tasks, which will assess visual-motor skills, memory, attention, emotion perception (viewing faces of different emotional expressions) and emotion regulation (viewing scenes of injury or assault). The entire procedure takes about 45 minutes. Following these tasks a structural MRI will be conducted for which you will simply be asked to stay still while your brain is being scanned. This procedure takes about 15 minutes. The total MRI testing will take approximately 1 hour. After finishing, you will be asked to change back into your clothes and asked a few final questions, taking approximately 10 minutes.

Psychological Testing

The psychological (cognitive) testing component: is conducted in front of a touchscreen computer screen and includes questionnaires asking about demographics (such as age, gender), personality, current physical health, family history and life experiences as well as tasks which assess sensory-motor skills, memory, language and verbal executive skills, attention and learning. The duration of the psychological testing component is approximately 60 minutes depending on whether your answers lead to more detailed questions.

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Are there any risks?

All medical procedures involve some potential risk of injury. In spite of all reasonable precautions, there is a small risk that you may develop complications from participating in this study. The known risks of this study are:

- You may feel a small amount of arousal or distress to the emotion-inducing stimuli (fearful or angry facial expressions, viewing scenes of injury or assault, listening to a script of your most frightening experience), but these stimuli have been employed in many studies with minimal negative consequences for participants. If you do feel uncomfortable, you can opt out of this section of the study or discontinue the study at any time without penalty. You will be able to communicate with the researchers throughout the entire testing procedure via intercom.
- The EEG caps used in this procedure are designed for non-invasive measurement of the brain's electrical activity. The caps record naturally occurring electrical activity and do not produce any electricity themselves.
- MRI uses strong magnetic fields and radiowaves to produce images of the body to detect the flow of oxygenated blood to areas of your brain that you are using. This allows very high detailed images to be produced safely and painlessly. MRI is well validated and there are no short- or long-term side-effects. No X-rays are used and therefore there is no exposure to radiations.

Are there any benefits?

This study will not directly benefit the participants involved. This study aims to improve our knowledge of anxiety disorders and Major Depressive Disorder, and of how to predict treatment. This may result in benefits for individuals with anxiety disorders and Major Depressive Disorder in future.

Confidentiality / Privacy

All aspects of this study, including results will be strictly confidential and only the researchers will have access to your personal information. Any publication of results will only use de-identified information. Confidentiality will be maintained at all times and information about genetic analysis will not be made available to participants or others outside the study. Original data will be stored in a locked office and entered into a Registry database that will be password protected. The information will be stored for an indefinite period. All persons who are to have access to name-identified data from the Registry shall complete a signed declaration binding them to respect the confidentiality of the information contained therein. We note that the genetic analyses we conduct explore polymorphisms that contribute to normal individual variation as well as susceptibility to anxiety disorders and Major Depressive Disorder. We cannot determine paternity or maternity from our analyses, and genetic information will not be accessible to participants under any circumstances.

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Every reasonable precaution will be taken to ensure your safety during the course of this study. If you suffer any serious injuries or complications as a result of your participation in this study, you should, as soon as possible, contact the study doctor who will arrange appropriate medical treatment free of charge in any Australian public hospital.

Your participation in this study will not affect any right to compensation that you might have under statute or common law for any serious injuries or complications resulting from this study, caused by unsafe drugs or equipment or by negligence.'

What will happen at the conclusion of this study?

At the conclusion of the study, the data will be analysed and presented at scientific meetings and in publications so that other scientists around the world will be informed of our findings. No individual will be able to be identified in these publications. A brief report summarizing the group findings of the study will be sent to each participant following the finalization of data analysis (often several months after the final participant has been collected). Data will be kept in a secured location for seven years (in line with national guidelines for research) and then destroyed.

Do you have a choice?

Your participation in this study is entirely voluntary. If you choose not to join the study, or you wish to withdraw from it at any time, your medical care will not be affected.

Complaints

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name	*[Name]*
Position	*[Position]*
Telephone	*[Phone number]*
Email	*[Email address]*

Contact details

If you have any problems while on the study, please contact

CONSENT TO PARTICIPATE IN RESEARCH

Study Title: Biomarkers of Anxiety Disorders and Treatment Response

Co-ordinating Chief Investigator: Dr Anthony Harris Department: Psychiatry

Name of Researcher:

1. I understand that the researcher will conduct this study in a manner conforming with ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.
2. I acknowledge that I have read, or have had read to me the Participant Information Sheet relating to this study. I acknowledge that I understand the Participant Information Sheet. I acknowledge that the general purposes, methods, demands and possible risks and inconveniences which may occur to me during the study have been explained to me by _____ ("the researcher") and I, being over the age of 16 years, acknowledge that I understand the general purposes, methods, demands and possible risks and inconveniences which may occur during the study.
3. I acknowledge that I have been given time to consider the information and to seek other advice.
4. I acknowledge that refusal to take part in this study will not affect the usual treatment of my condition.
5. I acknowledge that I am volunteering to take part in this study and I may withdraw at any time.
6. I acknowledge that this research has been approved by the Western Sydney Local Health District Human Research Ethics Committee.
7. I acknowledge that I have received a copy of this form and the Participant Information Sheet, which I have signed.

8. I acknowledge any regulatory authorities may have access to my medical records to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

Before signing, please read 'IMPORTANT NOTE' following.

Name of participant _____Date of Birth _____

Address of participant _____

Name of parent or person responsible (where applicable) _____

Address of parent or person responsible (where applicable) _____

Signature of participant _____ Date: _____

Signature of parent or person responsible (where applicable) _____Date: _____

Signature of researcher _____Date: _____

Signature of witness _____Date:_____

IMPORTANT NOTE
This consent should only be signed as follows:

9. *Where a participant is over the age of 16 years, then by the participant personally.*
10. *Where a participant is between the age of 14 and 16 years, it should be signed by the participant and by a parent or person responsible.*
11. *Where a participant is under the age of 14 years, then the parent or person responsible only should sign the consent form.*
12. *Where a participant has impaired capacity, intellectual disability or is unconscious, then specific approval for the process for obtaining consent must be sought from the Human Research Ethics Committee.*

WITNESS:

I, _____ (name of witness) hereby certify as follows:

1. I was present when _____ (the 'participant') appeared to read or had read to him/her a Participant Information Sheet comprising (pages); **or** was told by _____ the participant that he/she had read the Participant Information Sheet (*delete as applicable*).

2. I was present when _____ (the 'researcher') explained the general purposes, methods, demands and the possible risks and inconveniences of participating in the study to the participant. I asked the participant whether he/she had understood the Participant Information Sheet and understood what he/she had been told and he/she told me that he/she did understand.
3. I observed the participant sign the consent to participate in research and he/she appeared to me to be signing the document freely and without duress.
4. The participant showed me a form of identification which satisfied me as to his/her identity.
5. I am not involved in any way as a researcher in this project.
6. (*Delete this clause if not applicable*) I was present when _____ (the 'interpreter') read the Participant Information Sheet to the participant in the _____ (*insert appropriate language*) language. I certify that when the researcher explained the general purposes, methods, demands and possible risks and inconveniences of participating in the study that what was said by both the researcher and the participant was translated by the interpreter from the English language into the above language and vice versa. When I spoke to the participant, what I said and what the participant said was translated by the interpreter from the English language into the above language and vice versa.

Name of witness _____Relationship to participant _____

Address of witness _____

Signature of witness _____Date: _____

Name of interpreter (if applicable) _____

Signature of Interpreter (if applicable) _____ Date: _____

Appendix B

Clinical Assessment

Clinical Interview ……185

Beck Depression Inventory (BDI)……...189

Beck Anxiety Inventory (BAI)……191

Mini- International Neuropsychiatric Interview (M.I.N.I.)……..……...192

Clinician Administered PTSD Scale- IV (CAPS- IV)……216

Clinical Interview

CCRE Clinical interview

Medical History:

Do you have any ongoing medical conditions that require treatment?

➔ *If yes,* When? What was the treatment? Did you suffer any permanent damage from these?
(*Prompt:* Have you ever been hospitalized/had surgery? When was the last time you took any medications?)

Condition	Dates/duration	Treatment/s	Outcome

Neurological History *(if said 'YES' to this question in BRC questionnaire, get more detail)*

- Do you have a history of brain injury?
- Have you ever been knocked unconscious for longer than 5 minutes? Did you ever become confused about who or where you were after a knock to the head?

- *If yes,* did you need to go to hospital? For how long?

- How long ago did this event occur?
- Do you suffer from any neurological disorders, such as epilepsy, Parkinson's disease, or have you suffered from a stroke?

Previous/Current Psychological Treatments:

Counselling, CBT, medications, hospitalisations – when, and length of treatment.

If report counselling or CBT, ask what they actually did in session. If they report "just talking", ask if any specific strategies were used (e.g. exposure to feared situations, exposure to feared memories, identifying and challenging thoughts).

Treatment:	Dates:	No of sessions:	Content type:

Clinical Interview *(continued)*

Psychiatric History:

Have you experienced any other psychological problems in the past? When and for how long? How was this treated? Were you given a diagnosis?

Disorder: Dates/ duration: Treatment:

Family Psychiatric History:

Has anyone in your immediate family (Mum, dad, siblings, grandparents) suffered from significant psychological problems? *Prompt:* Any depression? Substance abuse? Anxiety?

Relationship to ppt: Disorder: Duration: Treatment:

Complicated Grief/Bereavement:

Have you ever had an experience where someone very close to you has died?

Relationship to pt: Date of death:

➔ If criterion A met, administer PG-13. (If difficult to contain, move to PG-13 now).

Clinical Interview *(continued)*

Trauma History:

I'm not going to need many details here, but have you experienced any traumatic events in your life, such as assault, sexual assault, car accidents or natural disasters?

➔ *Check:* Were you concerned for your safety *[/physical integrity]* or that of someone else? Did you experience intense fear, helplessness or horror?

Did you experience any traumatic events in your childhood?

Event: Age of onset: Duration:

➔ If criterion A met, administer CAPS. (If difficult to contain, move to CAPS now).

Drugs and Alcohol - Current and Past Use:

Now I'd like to ask a few questions about your drug and alcohol use. We need to ask about this because at certain levels some of these things can interfere with our brain scans. This information will be kept strictly confidential.

- Do you drink alcohol? How many standard drinks a week?
  (*Exclude if >15 for women, or >25 for men – discontinue but still reimburse*)

- Have you ever had a period of time where you drank more heavily than this?
  - When, how much, for how long, etc?

  - Have you ever passed out from drinking?
  - Do you think you have a drinking problem?

- Do you use any street drugs such as marijuana, speed/meth, ecstasy, LSD, cocaine, or heroin?
  How often, how much, for how long?

  ➔ *For illicit drugs:* ***If more frequently than monthly then exclude.***
  ➔ *Marijuana:* ***7 joints/week or less – still run; 10+ definitely exclude****.*

- Have you ever had a period of time where you used _____ more heavily than this?
- [*Or, if answered no to street drugs*] Have you ever used these substances in the past? When? for how long?

Clinical Interview *(continued)*

- Do you use prescription medications or over the counter medications?
  How often, how much, for how long?

Current Mood and Suicidality

Mood: How would you describe your mood over the past week or two?

What about today?

➔ *Ideation:* In the past month, have you ever thought about harming yourself or ending your life?
- *If yes,* how frequent are these thoughts? Can you give me an example of these actual thoughts?

➔ *[If ideation present] Plan:* Some people have these thoughts but would never act on them; others may feel an impulse to act on them or to carry out a plan to end their life. Do you have a plan of how to end your life? *Get a description....*

➔ *[If plan] Means:* Do you have access to xxxx? What would stop you?

Prior attempts: Have you tried to end your life or harm yourself before?

When? What did you do? What happened?

➔ *[If ideation present] Intent:* On a scale from 1 to 10, where 1 means you would never harm yourself and 10 means nothing would stop you from killing yourself, where is your current risk? _____/10
What has been your highest level of risk in the past month? _____/10

7+/10 – exclude. *If there is a high risk (~5/10), ask them to contract with you that they will not harm themselves for the duration of the study, provide them with lifeline number and ask for their permission to inform the treating clinician. Consider support, mood, lethality of any prior attempts.*

- *Use above info to complete MINI suicidality module*

Administer MINI, CAPS/Ham-D if required, and Questionnaires (with genetics). Thank them.

Beck Depression Inventory (BDI)

BDI-II Date:

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

Beck Depression Inventory (BDI) *(continued)*

11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.
1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.
2a I sleep a lot more than usual.
2b I sleep a lot less than usual.
3a I sleep most of the day.
3b I wake up 1–2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.
1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.
2a My appetite is much less than before.
2b My appetite is much greater than usual.
3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Beck Anxiety Inventory (BAI)

BAI

Name_____ **Date**_____

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by each symptom during the PAST WEEK, INCLUDING TODAY, by placing an X in the corresponding space in the column next to each symptom.

	NOT AT ALL	**MILDLY** It did not bother me much.	**MODERATELY** It was very unpleasant but I could stand it.	**SEVERELY** I could barely stand it.
1. Numbness or tingling.				
2. Feeling hot.				
3. Wobbliness in legs.				
4. Unable to relax.				
5. Fear of the worst happening.				
6. Dizzy or lightheaded.				
7. Heart pounding or racing.				
8. Unsteady.				
9. Terrified.				
10. Nervous.				
11. Feelings of choking.				
12. Hands trembling.				
13. Shaky.				
14. Fear of losing control.				
15. Difficulty breathing.				
16. Fear of dying.				
17. Scared.				
18. Indigestion or discomfort in abdomen.				
19. Faint.				
20. Face flushed.				
21. Sweating (not due to heat).				

Mini- International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I.

MINI INTERNATIONAL NEUROPSYCHIATRIC INTERVIEW

English Version 5.0.0

DSM-IV

USA: **D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan**
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Hôpital de la Salpétrière - Paris

M.I.N.I. 5.0.0 (January 1, 2004)

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

Patient Name:		*Patient Number:*	
Date of Birth:		*Time Interview Began:*	
Interviewer's Name:		*Time Interview Ended:*	
Date of Interview:		*Total Time:*	

	MODULES	TIME FRAME	MEETS CRITERIA	DSM-IV	ICD-10
A	MAJOR DEPRESSIVE EPISODE	Current (2 weeks) Recurrent	☐ ☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x
	MDE WITH MELANCHOLIC FEATURES Optional	Current (2 weeks)	☐	296.20-296.26 Single 296.30-296.36 Recurrent	F32.x F33.x
B	DYSTHYMIA	Current (Past 2 years)	☐	300.4	F34.1
C	SUICIDALITY	Current (Past Month) Risk: ☐ Low ☐ Medium ☐ High	☐		
D	MANIC EPISODE	Current Past	☐ ☐	296.00-296.06	F30.x-F31.9
	HYPOMANIC EPISODE	Current Past	☐ ☐	296.80-296.89	F31.8-F31.9/F34.0
E	PANIC DISORDER	Current (Past Month) Lifetime	☐ ☐	300.01/300.21	F40.01-F41.0
F	AGORAPHOBIA	Current	☐	300.22	F40.00
G	SOCIAL PHOBIA (Social Anxiety Disorder)	Current (Past Month)	☐	300.23	F40.1
H	OBSESSIVE-COMPULSIVE DISORDER	Current (Past Month)	☐	300.3	F42.8
I	POSTTRAUMATIC STRESS DISORDER Optional	Current (Past Month)	☐	309.81	F43.1
J	ALCOHOL DEPENDENCE ALCOHOL ABUSE	Past 12 Months Past 12 Months	☐ ☐	303.9 305.00	F10.2x F10.1
K	SUBSTANCE DEPENDENCE (Non-alcohol) SUBSTANCE ABUSE (Non-alcohol)	Past 12 Months Past 12 Months	☐ ☐	304.00-.90/305.20-.90 304.00-.90/305.20-.90	F11.1-F19.1 F11.1-F19.1
L	PSYCHOTIC DISORDERS	Lifetime Current	☐ ☐	295.10-295.90/297.1/ 297.3/293.81/293.82/ 293.89/298.8/298.9	F20.xx-F29
	MOOD DISORDER WITH PSYCHOTIC FEATURES	Current	☐	296.24	F32.3/F33.3
M	ANOREXIA NERVOSA	Current (Past 3 Months)	☐	307.1	F50.0
N	BULIMIA NERVOSA	Current (Past 3 Months)	☐	307.51	F50.2
	ANOREXIA NERVOSA, BINGE EATING/PURGING TYPE	Current	☐	307.1	F50.0
O	GENERALIZED ANXIETY DISORDER	Current (Past 6 Months)	☐	300.02	F41.1
P	ANTISOCIAL PERSONALITY DISORDER Optional	Lifetime	☐	301.7	F60.2

DISCLAIMER

Our aim is to assist in the assessment and tracking of patients with greater efficiency and accuracy. Before action is taken on any data collected and processed by this program, it should be reviewed and interpreted by a licensed clinician. This program is not designed or intended to be used in the place of a full medical and psychiatric evaluation by a qualified licensed physician – psychiatrist. It is intended only as a tool to facilitate accurate data collection and processing of symptoms elicited by trained personnel.

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

GENERAL INSTRUCTIONS

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization for lay interviewers for ICD-10). The results of these studies show that the M.I.N.I. has acceptably high validation and reliability scores, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

INTERVIEW:

In order to keep the interview as brief as possible, inform the patient that you will conduct a clinical interview that is more structured than usual, with very precise questions about psychological problems which require a yes or no answer.

GENERAL FORMAT:

The M.I.N.I. is divided into **modules** identified by letters, each corresponding to a diagnostic category.
•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a **gray box**.
•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

CONVENTIONS:

Sentences written in « normal font » should be read exactly as written to the patient in order to standardize the assessment of diagnostic criteria.

Sentences written in « CAPITALS » should not be read to the patient. They are instructions for the interviewer to assist in the scoring of the diagnostic algorithms.

Sentences written in « **bold** » indicate the time frame being investigated. The interviewer should read them as often as necessary. Only symptoms occurring during the time frame indicated should be considered in scoring the responses.

Answers with an arrow above them (➡) indicate that one of the criteria necessary for the diagnosis(es) is not met. In this case, the interviewer should go to the end of the module, circle « **NO** » in all the diagnostic boxes and move to the next module.

When terms are separated by a *slash (/)* the interviewer should read only those symptoms known to be present in the patient (for example, question H6).

Phrases in (parentheses) are clinical examples of the symptom. These may be read to the patient to clarify the question.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).
Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I. The M.I.N.I. Plus has questions that investigate these issues.

For any questions, suggestions, need for a training session, or information about updates of the M.I.N.I., please contact :

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Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

A. MAJOR DEPRESSIVE EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

A1	Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?	NO	YES
A2	In the past two weeks, have you been much less interested in most things or much less able to enjoy the things you used to enjoy most of the time?	NO	YES
	IS **A1** OR **A2** CODED **YES?** ➡	NO	YES

A3 **Over the past two weeks, when you felt depressed or uninterested:**

a	Was your appetite decreased or increased nearly every day? Did your weight decrease or increase without trying intentionally (i.e., by ±5% of body weight or ±8 lbs. or ±3.5 kgs., for a 160 lb./70 kg. person in a month)? IF YES TO EITHER, CODE YES.	NO	YES *
b	Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES
c	Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?	NO	YES *
d	Did you feel tired or without energy almost every day?	NO	YES
e	Did you feel worthless or guilty almost every day?	NO	YES
f	Did you have difficulty concentrating or making decisions almost every day?	NO	YES
g	Did you repeatedly consider hurting yourself, feel suicidal, or wish that you were dead?	NO	YES

ARE **5** OR MORE ANSWERS (**A1-A3**) CODED **YES**?

NO **YES ***

MAJOR DEPRESSIVE EPISODE, CURRENT

IF PATIENT HAS CURRENT MAJOR DEPRESSIVE EPISODE CONTINUE TO A4, OTHERWISE MOVE TO MODULE B:

A4	a	During your lifetime, did you have other periods of two weeks or more when you felt depressed or uninterested in most things, and had most of the problems we just talked about? ➡	NO	YES
	b	Did you ever have an interval of at least 2 months without any depression and any loss of interest between 2 episodes of depression?		

NO **YES**

MAJOR DEPRESSIVE EPISODE, RECURRENT

* If patient has Major Depressive Episode, Current, code **YES** in corresponding questions on page 5

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

MAJOR DEPRESSIVE EPISODE WITH MELANCHOLIC FEATURES (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF THE PATIENT CODES POSITIVE FOR A CURRENT MAJOR DEPRESSIVE EPISODE (**A3** = **YES**), EXPLORE THE FOLLOWING:

A5	a	During the most severe period of the current depressive episode, did you lose almost completely your ability to enjoy nearly everything?	NO	YES
	b	During the most severe period of the current depressive episode, did you lose your ability to respond to things that previously gave you pleasure, or cheered you up? **IF NO:** When something good happens does it fail to make you feel better, even temporarily?	NO	YES
		IS EITHER **A5a** OR **A5b** CODED **YES**?	➡ NO	YES
A6		**Over the past two week period, when you felt depressed and uninterested:**		
	a	Did you feel depressed in a way that is different from the kind of feeling you experience when someone close to you dies?	NO	YES
	b	Did you feel regularly worse in the morning, almost every day?	NO	YES
	c	Did you wake up at least 2 hours before the usual time of awakening and have difficulty getting back to sleep, almost every day?	NO	YES
	d	IS **A3c** CODED **YES** (PSYCHOMOTOR RETARDATION OR AGITATION)?	NO	YES
	e	IS **A3a** CODED **YES** FOR ANOREXIA OR WEIGHT LOSS?	NO	YES
	f	Did you feel excessive guilt or guilt out of proportion to the reality of the situation?	NO	YES

ARE **3** OR MORE **A6** ANSWERS CODED **YES**?

NO	**YES**
	Major Depressive Episode **with** ***Melancholic Features Current***

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

B. DYSTHYMIA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

IF PATIENT'S SYMPTOMS CURRENTLY MEET CRITERIA FOR MAJOR DEPRESSIVE EPISODE, DO NOT EXPLORE THIS MODULE.

B1		Have you felt sad, low or depressed most of the time for the last two years?	➡ NO	YES
B2		Was this period interrupted by your feeling OK for two months or more?	NO	➡ YES
B3		**During this period of feeling depressed most of the time:**		
	a	Did your appetite change significantly?	NO	YES
	b	Did you have trouble sleeping or sleep excessively?	NO	YES
	c	Did you feel tired or without energy?	NO	YES
	d	Did you lose your self-confidence?	NO	YES
	e	Did you have trouble concentrating or making decisions?	NO	YES
	f	Did you feel hopeless?	NO	YES
		ARE **2** OR MORE **B3** ANSWERS CODED **YES**?	➡ NO	YES
B4		Did the symptoms of depression cause you significant distress or impair your ability to function at work, socially, or in some other important way?	➡ NO	YES
		IS **B4** CODED **YES**?		

NO	YES
DYSTHYMIA **CURRENT**	

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

C. SUICIDALITY

	In the past month did you:			Points
C1	Think that you would be better off dead or wish you were dead?	NO	YES	1
C2	Want to harm yourself?	NO	YES	2
C3	Think about suicide?	NO	YES	6
C4	Have a suicide plan?	NO	YES	10
C5	Attempt suicide?	NO	YES	10
	In your lifetime:			
C6	Did you ever make a suicide attempt?	NO	YES	4

IS AT LEAST **1** OF THE ABOVE CODED **YES**?

IF YES, ADD THE TOTAL NUMBER OF POINTS FOR THE ANSWERS (C1-C6) CHECKED 'YES' AND SPECIFY THE LEVEL OF SUICIDE RISK AS FOLLOWS:

NO	**YES**

SUICIDE RISK CURRENT

1-5 points	Low	☐
6-9 points	Moderate	☐
≥ 10 points	High	☐

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

D. (HYPO) MANIC EPISODE

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

D1	a	Have you **ever** had a period of time when you were feeling 'up' or 'high' or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? (Do not consider times when you were intoxicated on drugs or alcohol.) IF PATIENT IS PUZZLED OR UNCLEAR ABOUT WHAT YOU MEAN BY 'UP' OR 'HIGH', CLARIFY AS FOLLOWS: By 'up' or 'high' I mean: having elated mood; increased energy; needing less sleep; having rapid thoughts; being full of ideas; having an increase in productivity, motivation, creativity, or impulsive behavior. IF NO, CODE NO TO **D1b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling 'up' or 'high' or full of energy?	NO	YES
D2	a	Have you **ever** been persistently irritable, for several days, so that you had arguments or verbal or physical fights, or shouted at people outside your family? Have you or others noticed that you have been more irritable or over reacted, compared to other people, even in situations that you felt were justified? IF NO, CODE NO TO **D2b**: IF **YES** ASK:	NO	YES
	b	Are you currently feeling persistently irritable?	NO	YES
			➡	
		IS **D1a** OR **D2a** CODED **YES**?	NO	YES

D3		IF **D1b** OR **D2b** = **YES**: EXPLORE ONLY **CURRENT** EPISODE, OTHERWISE IF **D1b** AND **D2b** = **NO**: EXPLORE THE MOST SYMPTOMATIC **PAST** EPISODE **During the times when you felt high, full of energy, or irritable did you:**		
	a	Feel that you could do things others couldn't do, or that you were an especially important person?	NO	YES
	b	Need less sleep (for example, feel rested after only a few hours sleep)?	NO	YES
	c	Talk too much without stopping, or so fast that people had difficulty understanding?	NO	YES
	d	Have racing thoughts?	NO	YES
	e	Become easily distracted so that any little interruption could distract you?	NO	YES
	f	Become so active or physically restless that others were worried about you?	NO	YES
	g	Want so much to engage in pleasurable activities that you ignored the risks or consequences (for example, spending sprees, reckless driving, or sexual indiscretions)?	NO	YES
			➡	
		ARE **3** OR MORE **D3** ANSWERS CODED **YES** (OR **4** OR MORE IF **D1a** IS **NO** (IN RATING PAST EPISODE) OR IF **D1b** IS **NO** (IN RATING CURRENT EPISODE)) ?	NO	YES

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

D4 Did these symptoms last at least a week **and** cause significant problems at home, at work, socially, or at school, **or** were you hospitalized for these problems?

NO ↓ ❒ YES ↓ ❒

THE EPISODE EXPLORED WAS A: ***HYPOMANIC EPISODE*** ***MANIC EPISODE***

IS **D4** CODED **NO**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
HYPOMANIC EPISODE	
CURRENT	❒
PAST	❒

IS **D4** CODED **YES**?

SPECIFY IF THE EPISODE IS CURRENT OR PAST.

NO	**YES**
MANIC EPISODE	
CURRENT	❒
PAST	❒

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

E. PANIC DISORDER

(➡ MEANS : CIRCLE NO IN E5, E6 AND E7 AND SKIP TO F1)

E1	a	Have you, on more than one occasion, had spells or attacks when you **suddenly** felt anxious, frightened, uncomfortable or uneasy, even in situations where most people would not feel that way?	➡ NO	YES
	b	Did the spells peak within 10 minutes?	➡ NO	YES
E2		At any time in the past, did any of those spells or attacks come on unexpectedly or occur in an unpredictable or unprovoked manner?	➡ NO	YES
E3		Have you ever had one such attack followed by a month or more of persistent concern about having another attack, or worries about the consequences of the attack?	NO	YES
E4		**During the worst spell that you can remember:**		
	a	Did you have skipping, racing or pounding of your heart?	NO	YES
	b	Did you have sweating or clammy hands?	NO	YES
	c	Were you trembling or shaking?	NO	YES
	d	Did you have shortness of breath or difficulty breathing?	NO	YES
	e	Did you have a choking sensation or a lump in your throat?	NO	YES
	f	Did you have chest pain, pressure or discomfort?	NO	YES
	g	Did you have nausea, stomach problems or sudden diarrhea?	NO	YES
	h	Did you feel dizzy, unsteady, lightheaded or faint?	NO	YES
	i	Did things around you feel strange, unreal, detached or unfamiliar, or did you feel outside of or detached from part or all of your body?	NO	YES
	j	Did you fear that you were losing control or going crazy?	NO	YES
	k	Did you fear that you were dying?	NO	YES
	l	Did you have tingling or numbness in parts of your body?	NO	YES
	m	Did you have hot flushes or chills?	NO	YES
E5		ARE BOTH **E3,** AND **4** OR MORE **E4** ANSWERS, CODED **YES**? IF YES TO E5, SKIP TO E7.	NO	YES *PANIC DISORDER LIFETIME*
E6		IF **E5** = **NO,** ARE ANY E4 ANSWERS CODED **YES**? THEN SKIP TO **F1.**	NO	YES *LIMITED SYMPTOM ATTACKS LIFETIME*
E7		In the past month, did you have such attacks repeatedly (2 or more) followed by persistent concern about having another attack?	NO	YES *PANIC DISORDER CURRENT*

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

F. AGORAPHOBIA

F1	Do you feel anxious or uneasy in places or situations where you might have a panic attack or the panic-like symptoms we just spoke about, or where help might not be available or escape might be difficult: like being in a crowd, standing in a line (queue), when you are alone away from home or alone at home, or when crossing a bridge, traveling in a bus, train or car?	NO YES

IF **F1** = **NO**, CIRCLE **NO** IN **F2**.

F2	Do you fear these situations so much that you avoid them, or suffer through them, or need a companion to face them?	NO YES *AGORAPHOBIA CURRENT*

IS **F2** (CURRENT AGORAPHOBIA) CODED **NO**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER without Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E7** (CURRENT PANIC DISORDER) CODED **YES**?

NO **YES**

PANIC DISORDER with Agoraphobia CURRENT

IS **F2** (CURRENT AGORAPHOBIA) CODED **YES**

and

IS **E5** (PANIC DISORDER LIFETIME) CODED **NO**?

NO **YES**

AGORAPHOBIA, CURRENT ***without history of Panic Disorder***

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

G. SOCIAL PHOBIA (Social Anxiety Disorder)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO AND MOVE TO THE NEXT MODULE)

G1	In the past month, were you fearful or embarrassed being watched, being the focus of attention, or fearful of being humiliated? This includes things like speaking in public, eating in public or with others, writing while someone watches, or being in social situations.	➡ NO	YES
G2	Is this fear excessive or unreasonable?	➡ NO	YES
G3	Do you fear these situations so much that you avoid them or suffer through them?	➡ NO	YES
G4	Does this fear disrupt your normal work or social functioning or cause you significant distress?		

NO **YES**

SOCIAL PHOBIA
(Social Anxiety Disorder)
CURRENT

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

H. OBSESSIVE-COMPULSIVE DISORDER

(➡ ABOVE A **NO** MEANS: GO TO THE DIAGNOSTIC BOX, CIRCLE **NO** AND MOVE TO THE NEXT MODULE)

H1	In the past month, have you been bothered by recurrent thoughts, impulses, or images that were unwanted, distasteful, inappropriate, intrusive, or distressing? (For example, the idea that you were dirty, contaminated or had germs, **or** fear of contaminating others, **or** fear of harming someone even though you didn't want to, **or** fearing you would act on some impulse, **or** fear or superstitions that you would be responsible for things going wrong, **or** obsessions with sexual thoughts, images or impulses, **or** hoarding, collecting, **or** religious obsessions.) (DO NOT INCLUDE SIMPLY EXCESSIVE WORRIES ABOUT REAL LIFE PROBLEMS. DO NOT INCLUDE OBSESSIONS DIRECTLY RELATED TO EATING DISORDERS, SEXUAL DEVIATIONS, PATHOLOGICAL GAMBLING, OR ALCOHOL OR DRUG ABUSE BECAUSE THE PATIENT MAY DERIVE PLEASURE FROM THE ACTIVITY AND MAY WANT TO RESIST IT ONLY BECAUSE OF ITS NEGATIVE CONSEQUENCES.)	NO YES ➡ to **H4**
H2	Did they keep coming back into your mind even when you tried to ignore or get rid of them?	NO YES ➡ to **H4**
H3	Do you think that these obsessions are the product of your own mind and that they are not imposed from the outside?	NO YES **obsessions**
H4	In the past month, did you do something repeatedly without being able to resist doing it, like washing or cleaning excessively, counting or checking things over and over, or repeating, collecting, arranging things, or other superstitious rituals?	NO YES **compulsions**
	IS **H3** OR **H4** CODED **YES**?	➡ NO YES
H5	Did you recognize that either these obsessive thoughts or these compulsive behaviors were excessive or unreasonable?	➡ NO YES
H6	Did these obsessive thoughts and/or compulsive behaviors significantly interfere with your normal routine, occupational functioning, usual social activities, or relationships, or did they take more than one hour a day?	**NO** **YES** ***O.C.D. CURRENT***

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

I. POSTTRAUMATIC STRESS DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

I1	Have you ever experienced or witnessed or had to deal with an extremely traumatic event that included actual or threatened death or serious injury to you or someone else? EXAMPLES OF TRAUMATIC EVENTS INCLUDE: SERIOUS ACCIDENTS, SEXUAL OR PHYSICAL ASSAULT, A TERRORIST ATTACK, BEING HELD HOSTAGE, KIDNAPPING, FIRE, DISCOVERING A BODY, SUDDEN DEATH OF SOMEONE CLOSE TO YOU, WAR, OR NATURAL DISASTER.		➡ NO	YES
I2	Did you respond with intense fear, helplessness or horror?		➡ NO	YES
I3	During the past month, have you re-experienced the event in a distressing way (such as, dreams, intense recollections, flashbacks or physical reactions)?		➡ NO	YES
I4	**In the past month:**			
	a	Have you avoided thinking about or talking about the event ?	NO	YES
	b	Have you avoided activities, places or people that remind you of the event?	NO	YES
	c	Have you had trouble recalling some important part of what happened?	NO	YES
	d	Have you become much less interested in hobbies or social activities?	NO	YES
	e	Have you felt detached or estranged from others?	NO	YES
	f	Have you noticed that your feelings are numbed?	NO	YES
	g	Have you felt that your life will be shortened or that you will die sooner than other people?	NO	YES
		ARE **3** OR MORE **I4** ANSWERS CODED **YES**?	➡ NO	YES
I5	**In the past month:**			
	a	Have you had difficulty sleeping?	NO	YES
	b	Were you especially irritable or did you have outbursts of anger?	NO	YES
	c	Have you had difficulty concentrating?	NO	YES
	d	Were you nervous or constantly on your guard?	NO	YES
	e	Were you easily startled?	NO	YES
		ARE **2** OR MORE **I5** ANSWERS CODED **YES**?	➡ NO	YES

I6	During the past month, have these problems significantly interfered with your work or social activities, or caused significant distress?	**NO** **YES** ***POSTTRAUMATIC STRESS DISORDER CURRENT***

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

J. ALCOHOL ABUSE AND DEPENDENCE

(➡ MEANS: GO TO DIAGNOSTIC BOXES, CIRCLE **NO** IN BOTH AND MOVE TO THE NEXT MODULE)

		➡ NO	YES
J1	**In the past 12 months**, have you had 3 or more alcoholic drinks within a 3 hour period on 3 or more occasions?		
J2	**In the past 12 months**:		
a	Did you need to drink more in order to get the same effect that you got when you first started drinking?	NO	YES
b	When you cut down on drinking did your hands shake, did you sweat or feel agitated? Did you drink to avoid these symptoms or to avoid being hungover, for example, "the shakes", sweating or agitation? IF YES TO EITHER, CODE **YES**.	NO	YES
c	During the times when you drank alcohol, did you end up drinking more than you planned when you started?	NO	YES
d	Have you tried to reduce or stop drinking alcohol but failed?	NO	YES
e	On the days that you drank, did you spend substantial time in obtaining alcohol, drinking, or in recovering from the effects of alcohol?	NO	YES
f	Did you spend less time working, enjoying hobbies, or being with others because of your drinking?	NO	YES
g	Have you continued to drink even though you knew that the drinking caused you health or mental problems?	NO	YES

ARE **3** OR MORE **J2** ANSWERS CODED **YES**?

NO **YES***

* IF YES, SKIP J3 QUESTIONS, CIRCLE N/A IN ABUSE BOX AND MOVE TO THE NEXT DISORDER. DEPENDENCE PREEMPTS ABUSE.

ALCOHOL DEPENDENCE
CURRENT

J3	**In the past 12 months:**		
a	Have you been intoxicated, high, or hungover more than once when you had other responsibilities at school, at work, or at home? Did this cause any problems? (CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)	NO	YES
b	Were you intoxicated more than once in any situation where you were physically at risk, for example, driving a car, riding a motorbike, using machinery, boating, etc.?	NO	YES
c	Did you have legal problems more than once because of your drinking, for example, an arrest or disorderly conduct?	NO	YES
d	Did you continue to drink even though your drinking caused problems with your family or other people?	NO	YES

ARE **1** OR MORE **J3** ANSWERS CODED **YES**?

NO **N/A** **YES**

ALCOHOL ABUSE
CURRENT

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

K. NON-ALCOHOL PSYCHOACTIVE SUBSTANCE USE DISORDERS

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE NO IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

Now I am going to show you / read to you a list of street drugs or medicines.

			➡	
K1	a	**In the past 12 months**, did you take any of these drugs more than once, to get high, to feel better, or to change your mood?	NO	YES

CIRCLE EACH DRUG TAKEN:

Stimulants: amphetamines, "speed", crystal meth, "rush", Dexedrine, Ritalin, diet pills.

Cocaine: snorting, IV, freebase, crack, "speedball".

Narcotics: heroin, morphine, Dilaudid, opium, Demerol, methadone, codeine, Percodan, Darvon, OxyContin.

Hallucinogens: LSD ("acid"), mescaline, peyote, PCP ("Angel Dust", "peace pill"), psilocybin, STP, "mushrooms", ecstasy, MDA, or MDMA.

Inhalants: "glue", ethyl chloride, nitrous oxide ("laughing gas"), amyl or butyl nitrate ("poppers").

Marijuana: hashish ("hash"), THC, "pot", "grass", "weed", "reefer".

Tranquilizers: quaalude, Seconal ("reds"), Valium, Xanax, Librium, Ativan, Dalmane, Halcion, barbiturates, Miltown.

Miscellaneous: steroids, nonprescription sleep or diet pills, GHB. Any others?

SPECIFY MOST USED DRUG(S): _____

CHECK ONE BOX

ONLY ONE DRUG / DRUG CLASS HAS BEEN USED ☐

ONLY THE MOST USED DRUG CLASS IS INVESTIGATED. ☐

EACH DRUG CLASS USED IS EXAMINED SEPARATELY (PHOTOCOPY K2 AND K3 AS NEEDED) ☐

b SPECIFY WHICH DRUG/DRUG CLASS WILL BE EXPLORED IN THE INTERVIEW BELOW IF THERE IS CONCURRENT OR SEQUENTIAL POLYSUBSTANCE USE: _____

K2 **Considering your use of (NAME THE DRUG / DRUG CLASS SELECTED), in the past 12 months:**

	a	Have you found that you needed to use more (NAME OF DRUG / DRUG CLASS SELECTED) to get the same effect that you did when you first started taking it?	NO	YES
	b	When you reduced or stopped using (NAME OF DRUG / DRUG CLASS SELECTED), did you have withdrawal symptoms (aches, shaking, fever, weakness, diarrhea, nausea, sweating, heart pounding, difficulty sleeping, or feeling agitated, anxious, irritable, or depressed)? Did you use any drug(s) to keep yourself from getting sick (withdrawal symptoms) or so that you would feel better?	NO	YES
		IF **YES** TO EITHER, CODE **YES**.		
	c	Have you often found that when you used (NAME OF DRUG / DRUG CLASS SELECTED), you ended up taking more than you thought you would?	NO	YES
	d	Have you tried to reduce or stop taking (NAME OF DRUG / DRUG CLASS SELECTED) but failed?	NO	YES
	e	On the days that you used (NAME OF DRUG / DRUG CLASS SELECTED), did you spend substantial time (>2 HOURS), obtaining, using or in recovering from the drug, or thinking about the drug?	NO	YES

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

f Did you spend less time working, enjoying hobbies, or being with family or friends because of your drug use? NO YES

g Have you continued to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused you health or mental problems? NO YES

ARE **3** OR MORE **K2** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO ➡ **YES** *

SUBSTANCE DEPENDENCE
CURRENT

* IF YES, SKIP K3 QUESTIONS, CIRCLE N/A IN ABUSE BOX FOR THIS SUBSTANCE AND MOVE TO THE NEXT DISORDER.
DEPENDENCE PREEMPTS ABUSE.

Considering your use of (NAME THE DRUG CLASS SELECTED), in the past 12 months:

K3 a Have you been intoxicated, high, or hungover from (NAME OF DRUG / DRUG CLASS SELECTED) more than once, when you had other responsibilities at school, at work, or at home? Did this cause any problem? NO YES

(CODE **YES** ONLY IF THIS CAUSED PROBLEMS.)

b Have you been high or intoxicated from (NAME OF DRUG / DRUG CLASS SELECTED) more than once in any situation where you were physically at risk (for example, driving a car, riding a motorbike, using machinery, boating, etc.)? NO YES

c Did you have legal problems more than once because of your drug use, for example, an arrest or disorderly conduct? NO YES

d Did you continue to use (NAME OF DRUG / DRUG CLASS SELECTED), even though it caused problems with your family or other people? NO YES

ARE **1** OR MORE **K3** ANSWERS CODED **YES**?

SPECIFY DRUG(S): _____

NO **N/A** **YES**

SUBSTANCE ABUSE
CURRENT

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

L. PSYCHOTIC DISORDERS

ASK FOR AN EXAMPLE OF EACH QUESTION ANSWERED POSITIVELY. CODE **YES** ONLY IF THE EXAMPLES CLEARLY SHOW A DISTORTION OF THOUGHT OR OF PERCEPTION OR IF THEY ARE NOT CULTURALLY APPROPRIATE. BEFORE CODING, INVESTIGATE WHETHER DELUSIONS QUALIFY AS "BIZARRE".

DELUSIONS ARE "BIZARRE" IF: CLEARLY IMPLAUSIBLE, ABSURD, NOT UNDERSTANDABLE, AND CANNOT DERIVE FROM ORDINARY LIFE EXPERIENCE.

HALLUCINATIONS ARE SCORED "BIZARRE" IF: A VOICE COMMENTS ON THE PERSON'S THOUGHTS OR BEHAVIOR, OR WHEN TWO OR MORE VOICES ARE CONVERSING WITH EACH OTHER.

		Now I am going to ask you about unusual experiences that some people have.			BIZARRE
L1	a	Have you ever believed that people were spying on you, or that someone was plotting against you, or trying to hurt you? **NOTE**: ASK FOR EXAMPLES TO RULE OUT ACTUAL STALKING.	NO	YES	YES
	b	**IF YES:** do you currently believe these things?	NO	YES	YES ➡**L6**
L2	a	Have you ever believed that someone was reading your mind or could hear your thoughts, or that you could actually read someone's mind or hear what another person was thinking?	NO	YES	YES
	b	**IF YES:** do you currently believe these things?	NO	YES	YES ➡**L6**
L3	a	Have you ever believed that someone or some force outside of yourself put thoughts in your mind that were not your own, or made you act in a way that was not your usual self? Have you ever felt that you were possessed? CLINICIAN: ASK FOR EXAMPLES AND DISCOUNT ANY THAT ARE NOT PSYCHOTIC.	NO	YES	YES
	b	**IF YES:** do you currently believe these things?	NO	YES	YES ➡**L6**
L4	a	Have you ever believed that you were being sent special messages through the TV, radio, or newspaper, or that a person you did not personally know was particularly interested in you?	NO	YES	YES
	b	**IF YES:** do you currently believe these things?	NO	YES	YES ➡**L6**
L5	a	Have your relatives or friends ever considered any of your beliefs strange or unusual? INTERVIEWER: ASK FOR EXAMPLES. ONLY CODE **YES** IF THE EXAMPLES ARE **CLEARLY** DELUSIONAL IDEAS NOT EXPLORED IN QUESTIONS L1 TO L4, FOR EXAMPLE, SOMATIC OR RELIGIOUS DELUSIONS OR DELUSIONS OF GRANDIOSITY, JEALOUSY, GUILT, RUIN OR DESTITIUTION, ETC.	NO	YES	YES
	b	**IF YES:** do they currently consider your beliefs strange?	NO	YES	YES
L6	a	Have you ever heard things other people couldn't hear, such as voices? HALLUCINATIONS ARE SCORED "BIZARRE" ONLY IF PATIENT ANSWERS **YES** TO THE FOLLOWING:	NO	YES	
		IF YES: Did you hear a voice commenting on your thoughts or behavior or did you hear two or more voices talking to each other?			YES
	b	**IF YES:** have you heard these things in the past month?	NO	YES	YES ➡**L8b**

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

L7 a Have you ever had visions when you were awake or have you ever seen things other people couldn't see? NO YES
CLINICIAN: CHECK TO SEE IF THESE ARE CULTURALLY INAPPROPRIATE.

b **IF YES:** have you seen these things in the past month? NO YES

CLINICIAN'S JUDGMENT

L8 b IS THE PATIENT CURRENTLY EXHIBITING INCOHERENCE, DISORGANIZED SPEECH, OR MARKED LOOSENING OF ASSOCIATIONS? NO YES

L9 b IS THE PATIENT CURRENTLY EXHIBITING DISORGANIZED OR CATATONIC BEHAVIOR? NO YES

L10 b ARE NEGATIVE SYMPTOMS OF SCHIZOPHRENIA, E.G. SIGNIFICANT AFFECTIVE FLATTENING, POVERTY OF SPEECH (ALOGIA) OR AN INABILITY TO INITIATE OR PERSIST IN GOAL-DIRECTED ACTIVITIES (AVOLITION), PROMINENT DURING THE INTERVIEW? NO YES

L11 ARE 1 OR MORE « b » QUESTIONS CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « b » QUESTIONS CODED **YES** (RATHER THAN **YES BIZARRE**)?

NO **YES**

PSYCHOTIC DISORDER
CURRENT

L12 ARE 1 OR MORE « a » QUESTIONS CODED **YES BIZARRE**?

OR

ARE 2 OR MORE « a » QUESTIONS CODED **YES** (RATHER THAN **YES BIZARRE**)?

CHECK THAT AT LEAST TWO SYMPTOMS OCCURRED DURING THE SAME TIME PERIOD.

OR IS **L11** CODED **YES**?

NO **YES**

PSYCHOTIC DISORDER
LIFETIME

L13 a ARE 1 OR MORE « b » QUESTIONS FROM L1b TO L7b CODED **YES** AND IS EITHER:

MAJOR DEPRESSIVE EPISODE, (CURRENT)
OR
MANIC EPISODE, (CURRENT OR PAST) CODED **YES**? ➡ NO YES

b You told me earlier that you had period(s) when you felt (depressed/high/persistently irritable).
Were the beliefs and experiences you just described (SYMPTOMS CODED YES FROM **L1**b TO **L7**b) restricted exclusively to times when you were feeling depressed/high/irritable?

NO **YES**

MOOD DISORDER WITH
PSYCHOTIC FEATURES
CURRENT

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

M. ANOREXIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE NO, AND MOVE TO THE NEXT MODULE)

M1	a	How tall are you?	❑ ft ❑❑ in. ❑ ❑ ❑ cm.
	b.	What was your lowest weight in the past 3 months?	❑ ❑ ❑ lbs. ❑ ❑ ❑ kgs.
	c	IS PATIENT'S WEIGHT LOWER THAN THE THRESHOLD CORRESPONDING TO HIS / HER HEIGHT? (SEE TABLE BELOW)	NO ➡ YES

In the past 3 months:

M2		In spite of this low weight, have you tried not to gain weight?	NO ➡ YES
M3		Have you feared gaining weight or becoming fat, even though you were underweight?	NO ➡ YES
M4	a	Have you considered yourself fat or that part of your body was too fat?	NO YES
	b	Has your body weight or shape greatly influenced how you felt about yourself?	NO YES
	c	Have you thought that your current low body weight was normal or excessive?	NO ➡ YES
M5		ARE 1 OR MORE ITEMS FROM **M4** CODED **YES**?	NO ➡ YES
M6		FOR WOMEN ONLY: During the last 3 months, did you miss all your menstrual periods when they were expected to occur (when you were not pregnant)?	NO ➡ YES

FOR WOMEN: ARE **M5 AND M6** CODED **YES**?

FOR MEN: IS **M5** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
CURRENT

TABLE HEIGHT / WEIGHT THRESHOLD (height-without shoes; weight-without clothing)

Female Height/Weight														
ft/in	4'9	4'10	4'11	5'0	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10
lbs.	84	85	86	87	89	92	94	97	99	102	104	107	110	112
cm	145	147	150	152	155	158	160	163	165	168	170	173	175	178
kgs	38	39	39	40	41	42	43	44	45	46	47	49	50	51

Male Height/Weight															
ft/in	5'1	5'2	5'3	5'4	5'5	5'6	5'7	5'8	5'9	5'10	5'11	6'0	6'1	6'2	6'3
lbs.	105	106	108	110	111	113	115	116	118	120	122	125	127	130	133
cm	155	156	160	163	165	168	170	173	175	178	180	183	185	188	191
kgs	47	48	49	50	51	51	52	53	54	55	56	57	58	59	61

The weight thresholds above are calculated as a 15% reduction below the normal range for the patient's height and gender as required by DSM-IV. This table reflects weights that are 15% lower than the low end of the normal distribution range in the Metropolitan Life Insurance Table of Weights.

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

N. BULIMIA NERVOSA

(➡ MEANS : GO TO THE DIAGNOSTIC BOXES, CIRCLE **NO** IN ALL DIAGNOSTIC BOXES, AND MOVE TO THE NEXT MODULE)

N1	In the past three months, did you have eating binges or times when you ate a very large amount of food within a 2-hour period?	NO ➡	YES
N2	In the last 3 months, did you have eating binges as often as twice a week?	NO ➡	YES
N3	During these binges, did you feel that your eating was out of control?	NO ➡	YES
N4	Did you do anything to compensate for, or to prevent a weight gain from these binges, like vomiting, fasting, exercising or taking laxatives, enemas, diuretics (fluid pills), or other medications?	NO ➡	YES
N5	Does your body weight or shape greatly influence how you feel about yourself?	NO ➡	YES
N6	DO THE PATIENT'S SYMPTOMS MEET CRITERIA FOR ANOREXIA NERVOSA?	NO ↓ Skip to N8	YES
N7	Do these binges occur only when you are under (____lbs./kgs.)? INTERVIEWER: WRITE IN THE ABOVE PARENTHESIS THE THRESHOLD WEIGHT FOR THIS PATIENT'S HEIGHT FROM THE HEIGHT / WEIGHT TABLE IN THE ANOREXIA NERVOSA MODULE.	NO	YES

N8 IS **N5** CODED **YES** AND **N7** CODED **NO** OR SKIPPED?

NO **YES**

BULIMIA NERVOSA
CURRENT

IS **N7** CODED **YES**?

NO **YES**

ANOREXIA NERVOSA
Binge Eating/Purging Type
CURRENT

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

O. GENERALIZED ANXIETY DISORDER

(➡ MEANS : GO TO THE DIAGNOSTIC BOX, CIRCLE **NO**, AND MOVE TO THE NEXT MODULE)

O1	a	Have you worried excessively or been anxious about several things over the past 6 months?	➡ NO	YES
	b	Are these worries present most days?	➡ NO	YES
		IS THE PATIENT'S ANXIETY RESTRICTED EXCLUSIVELY TO, OR BETTER EXPLAINED BY, ANY DISORDER PRIOR TO THIS POINT?	NO	➡ YES
O2		Do you find it difficult to control the worries or do they interfere with your ability to focus on what you are doing?	➡ NO	YES
O3		FOR THE FOLLOWING, CODE **NO** IF THE SYMPTOMS ARE CONFINED TO FEATURES OF ANY DISORDER EXPLORED PRIOR TO THIS POINT.		
		When you were anxious over the past 6 months, did you, most of the time:		
	a	Feel restless, keyed up or on edge?	NO	YES
	b	Feel tense?	NO	YES
	c	Feel tired, weak or exhausted easily?	NO	YES
	d	Have difficulty concentrating or find your mind going blank?	NO	YES
	e	Feel irritable?	NO	YES
	f	Have difficulty sleeping (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?	NO	YES

ARE **3** OR MORE **O3** ANSWERS CODED **YES**?

NO	**YES**
GENERALIZED ANXIETY DISORDER **CURRENT**	

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

P. ANTISOCIAL PERSONALITY DISORDER (optional)

(➡ MEANS : GO TO THE DIAGNOSTIC BOX AND CIRCLE NO.)

P1 **Before you were 15 years old, did you:**

a	repeatedly skip school or run away from home overnight?	NO	YES
b	repeatedly lie, cheat, "con" others, or steal?	NO	YES
c	start fights or bully, threaten, or intimidate others?	NO	YES
d	deliberately destroy things or start fires?	NO	YES
e	deliberately hurt animals or people?	NO	YES
f	force someone to have sex with you?	NO ➡	YES
	ARE **2** OR MORE **P1** ANSWERS CODED **YES**?	NO	YES

DO NOT CODE **YES** TO THE BEHAVIORS BELOW IF THEY ARE EXCLUSIVELY POLITICALLY OR RELIGIOUSLY MOTIVATED.

P2 **Since you were 15 years old, have you:**

a	repeatedly behaved in a way that others would consider irresponsible, like failing to pay for things you owed, deliberately being impulsive or deliberately not working to support yourself?	NO	YES
b	done things that are illegal even if you didn't get caught (for example, destroying property, shoplifting, stealing, selling drugs, or committing a felony)?	NO	YES
c	been in physical fights repeatedly (including physical fights with your spouse or children)?	NO	YES
d	often lied or "conned" other people to get money or pleasure, or lied just for fun?	NO	YES
e	exposed others to danger without caring?	NO	YES
f	felt no guilt after hurting, mistreating, lying to, or stealing from others, or after damaging property?	NO	YES

ARE **3** OR MORE **P2** QUESTIONS CODED **YES**?

NO	YES
	ANTISOCIAL PERSONALITY DISORDER **LIFETIME**

THIS CONCLUDES THE INTERVIEW

Mini- International Neuropsychiatric Interview (M.I.N.I.) *(continued)*

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Translations	**M.I.N.I. 4.4 or earlier versions**	**M.I.N.I. 4.6/5.0, M.I.N.I. Plus 4.6/5.0 and M.I.N.I. Screen 5.0:**
Afrikaans	R. Emsley	W. Maartens
Arabic		O. Osman, E. Al-Radi
Bengali		H. Banerjee, A. Banerjee
Brazilian Portuguese	P. Amorim	P. Amorim
Bulgarian	L.G.. Hranov	
Chinese		L. Carroll, Y-J. Lee, Y-S. Chen, C-C. Chen, C-Y. Liu, C-K. Wu, H-S. Tang, K-D. Juang, Yan-Ping Zheng.
Croatian		In preparation
Czech		P. Zvlosky
Danish	P. Bech	P. Bech, T. Schütze
Dutch/Flemish	E. Griez, K. Shruers, T. Overbeek, K. Demyttenaere	I. Van Vliet, H. Leroy, H. van Megen
English	D. Sheehan, J. Janavs, R. Baker, K. Harnett-Sheehan, E. Knapp, M. Sheehan	D. Sheehan, R. Baker, J. Janavs, K. Harnett-Sheehan, M. Sheehan
Estonian		J. Shlik, A. Aluoja, E. Khil
Farsi/Persian		K. Khooshabi, A. Zomorodi
Finnish	M. Heikkinen, M. Lijeström, O. Tuominen	M. Heikkinen, M. Lijeström, O. Tuominen
French	Y. Lecrubier, E. Weiller, I. Bonora, P. Amorim, J.P. Lepine	Y. Lecrubier, E. Weiller, P. Amorim, T. Hergueta
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Greek	S. Beratis	T. Calligas, S. Beratis
Gujarati		M. Patel, B. Patel
Hebrew	J. Zohar, Y. Sasson	R. Barda, I. Levinson, A. Aviv
Hindi		C. Mittal, K. Batra, S. Gambhir
Hungarian	I. Bitter, J. Balazs	I. Bitter, J. Balazs
Icelandic		J.G. Stefansson
Italian	I. Bonora, L. Conti, M. Piccinelli, M. Tansella, G. Cassano, Y. Lecrubier, P. Donda, E. Weiller	L. Conti, A. Rossi, P. Donda
Japanese		T. Otsubo, H. Watanabe, H. Miyaoka, K. Kamijima, J.Shinoda, K.Tanaka, Y. Okajima
Korean		In preparation, Anxiety Disorder Association of Korea
Latvian	V. Janavs, J. Janavs, I. Nagobads	V. Janavs, J. Janavs
Lithuanian		A. Bacevicius
Norwegian	G. Pedersen, S. Blomhoff	K.A. Leiknes , U. Malt, E. Malt, S. Leganger
Polish	M. Masiak, E. Jasiak	M. Masiak, E. Jasiak
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Punjabi		A. Gahunia, S. Gambhir
Romanian		O. Driga
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Setswana		K. Ketlogetswe
Slovenian	M. Kocmur	M. Kocmur
Spanish	L. Ferrando, J. Bobes-Garcia, J. Gilbert-Rahola, Y. Lecrubier	L. Ferrando, L. Franco-Alfonso, M. Soto, J. Bobes-Garcia, O. Soto, L. Franco, G. Heinze
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Clinician Administered PTSD Scale- IV (CAPS- IV)

National Center for PTSD

CLINICIAN-ADMINISTERED PTSD SCALE (CAPS)

Form 1 - Current and Lifetime Diagnosis Version

Patient: **Pt #:** **Date:** **Clinician:**

Purpose: The CAPS-1 was developed to measure cardinal and hypothesized signs and symptoms of PTSD. This clinician-administered instrument provides a method to evaluate the frequency and intensity of individual symptoms, as well as the impact of the symptoms on social and occupational functioning, the degree of improvement since an earlier rating, the validity of the ratings obtained, and the overall intensity of the symptoms. Whenever possible, the CAPS-1 should be used in conjunction with self-report, behavioral, and physiological measures when assessing either baseline or post-treatment status.

Instructions: The time frame for each symptom is one month. Using the prompt questions or comparable alternatives, and appropriate follow-up questions, first assess the *frequency*, over the previous month, of the identified symptom. Next, using the same method, evaluate the *intensity* of symptom occurrence. The descriptors for the anchor points of both the frequency and intensity dimensions can be read to the patient in arriving at the most accurate rating. **A frequency rating of one (1) or greater and an intensity rating of two (2) or greater reflect significant problems with a particular symptom, and should be considered a symptom endorsement.** This symptom then can be counted toward the required total for a given criterion (i.e., one symptom for B, three for C, two for D). It is important to note that criteria C, D, and E require that the symptoms *not* be present before the trauma. The clinician should clarify with the patient that the onset of any of the symptoms for criteria C, D, or E occurred *after* the trauma. If the veracity or accuracy of the patient's report of a symptom is in doubt, the clinician should circle QV ("Questionable Validity") to the right of the corresponding item.

If the patient meets the PTSD diagnostic criteria for the past month, he or she automatically meets the criteria for a lifetime diagnosis. If not, use the "Lifetime Symptom Query" to establish a high-symptom one month period since the trauma for which to reassess the frequency and intensity of each symptom.

D. Blake, F. Weathers, L. Nagy, D. Kaloupek, G. Klauminzer, D. Charney & T. Keane
National Center for Posttraumatic Stress Disorder
Behavioral Science Division - Boston Neurosciences Division - West Haven
October, 1990

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

National Center for PTSD

CLINICIAN-ADMINISTERED PTSD SCALE (CAPS)

Form 1 - Current and Lifetime Diagnosis Version

A. *Traumatic event*

B. *The traumatic event is persistently reexperienced:*

(1) recurrent and intrusive distressing recollections of the event

Frequency

Have you ever experienced unwanted memories of the event(s) without being exposed to something that reminded you of the event? Did these memories occur while you were awake, or only in dreams? [Exclude if memories only occurred during dreams] How often in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Description/Examples:

Intensity

At their worst, how much distress or discomfort did these memories cause you? Did these memories cause you to stop what you were doing? Are you able to dismiss the memories if you try?

0 None
1 Mild, minimal distress
2 Moderate, distress clearly present but still manageable, some disruption of activities
3 Severe, considerable distress, marked disruption of activities and difficulty dismissing memories
4 Extreme, incapacitating distress, unable to continue activities and cannot dismiss memories

C	L
QV	QV
F	F
I	I

(2) intense psychological distress at exposure to events that symbolize or resemble an aspect of the traumatic event, including anniversaries of the trauma

Frequency

Have you ever gotten upset when you were exposed to things that reminded you of the event(s)? [For example, particular males for rape victims, tree lines or wooded areas for combat veterans] How often in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Description/Examples:

Intensity

At its worst, how much distress or discomfort did exposure to these reminders cause you?

0 None
1 Mild, minimal distress
2 Moderate, distress clearly present but still manageable
3 Severe, considerable distress
4 Extreme, incapacitating distress

C	L
QV	QV
F	F
I	I

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

3) sudden acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative [flashback] episodes, even those that occur upon awakening or when intoxicated)

Frequency

Have you ever suddenly acted or felt as if the event(s) was happening again? How often in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Description/Examples:

Intensity

At its worst, how much did it seem that the event(s) was happening again? How long did it last? What did you do while this was happening?

0 Not at all
1 Mild, slightly more realistic than just thinking about the event
2 Moderate, definite but transient dissociative quality; still very aware of surroundings; daydreaming quality
3 Severe, strongly dissociative (reports images, sounds, smells), but retained some awareness of surroundings
4 Extreme, complete dissociation (flashback), no awareness of surroundings, possible amnesia for the episode (blackout)

C	L
QV	QV
F	F
I	I

(4) recurrent distressing dreams of the event

Frequency

Have you ever had unpleasant dreams about the event(s)? How often in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Nightly or almost every night

Description/Examples:

Intensity

At their worst, how much distress or discomfort did these dreams cause you? Did these dreams wake you up? [If yes, ask:] What were you feeling or doing when you awoke? How long does it usually take to get back to sleep? [Listen for report of panic symptoms, yelling, posturing]

0 None
1 Mild, minimal distress, did not awaken
2 Moderate, awoke in distress but readily returned to sleep
3 Severe, considerable distress, difficulty returning to sleep
4 Extreme, overwhelming or incapacitating distress, could not return to sleep

C	L
QV	QV
F	F
I	I

Current Symptoms from Criterion B = _____

Lifetime Symptoms from Criterion B = _____

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

C. *Persistent avoidance of stimuli associated with the trauma or numbing of general responsiveness (not present before the trauma)*

(5) efforts to avoid thoughts or feelings associated with the trauma

Frequency

Have you ever tried to avoid thinking about the event(s)? Have you ever tried to avoid feelings related to the event(s) (e.g., rage, sadness, guilt)? How often in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Description/Examples:

Intensity

How much effort did you make to avoid thoughts or feelings related to the event(s)? [rate all attempts at cognitive avoidance, including distraction, suppression, and reducing awareness with alcohol or drugs]

0 No effort
1 Mild, minimal effort
2 Moderate, some effort, avoidance definitely present
3 Severe, considerable effort, marked avoidance
4 Extreme, drastic attempts at avoidance

C	L
QV	QV
F	F
I	I

(6) efforts to avoid activities or situations that arouse recollections of the trauma

Frequency

Have you ever tried to stay away from activities or situations that reminded you of the event(s)? How often in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Description/Examples:

Intensity

How much effort did you make to avoid activities or situations related to the event(s)? [rate all attempts at behavioral avoidance, e.g., combat veteran who avoids veteran activities, war movies, etc.]

0 No effort
1 Mild, minimal effort
2 Moderate, some effort, avoidance definitely present
3 Severe, considerable effort, marked avoidance
4 Extreme, drastic attempts at avoidance

C	L
QV	QV
F	F
I	I

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

(7) inability to recall an important aspect of the trauma (psychogenic amnesia)

Frequency

Have you been unable to remember important parts of the event(s) (e.g., names, faces, sequence of events)? How much of the event(s) have you had difficulty remembering in the past month?

- **0 None, clear memory of event(s)**
- **1 Few aspects of event(s) not remembered (less than 10%)**
- **2 Some aspects of the event(s) not remembered (approx 20-30%)**
- **3 Many aspects of the event(s) not remembered (approx 50-60%)**
- **4 Most of event(s) not remembered (more than 80%)**

Intensity

How much difficulty did you have recalling important parts of the event(s)?

- **0 No difficulty at recalling event(s)**
- **1 Mild, minimal difficulty recalling event(s)**
- **2 Moderate, some difficulty, could recall event(s) with concentration**
- **3 Severe, considerable difficulty recalling the event(s)**
- **4 Extreme, completely unable to recall the event(s)**

C	L
QV	QV
F	F
I	I

Description/Examples:

(8) markedly diminished interest in significant activities

Frequency

Have you been less interested in important activities that once gave you pleasure, such as sports, hobbies, or social activities? As compared to before the event(s), how many activities in the past month have you had less interest in?

- **0 No loss of interest**
- **1 Few activities (less than 10%)**
- **2 Several activities (approx 20-30%)**
- **3 Many activities (approx 50-60%)**
- **4 Most activities (more than 80%)**

Intensity

At its worst, how strong was your loss of interest in these activities?

- **0 No loss of interest**
- **1 Mild, only slight loss of interest, probably would enjoy after starting activities**
- **2 Moderate, definite loss of interest, but still has some enjoyment of activities**
- **3 Severe, marked loss of interest in activities**
- **4 Extreme, complete loss of interest, intentionally does not engage in activities**

C	L
QV	QV
F	F
I	I

Description/Examples:

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

(9) feelings of detachment or estrangement from others

Frequency

Have you felt distant or cut off from those around you? Is this different from how you felt before the event(s)? How much of the time have you felt this way in the past month?

0 None of the time
1 Very little of the time (less than 10%)
2 Some of the time (approx 20-30%)
3 Much of the time (approx 50-60%)
4 Most or all of the time (more than 80%)

Description/Examples:

Intensity

At their worst, how strong were your feelings of being distant or cut off from others? Who do you feel closest to?

0 No feelings of detachment or estrangement
1 Mild, occasionally feels "out of synch" with others
2 Moderate, feelings of detachment clearly present, but still feels some interpersonal connection or belonging with others
3 Severe, marked feelings of detachment or estrangement from most people; may confide in only one person
4 Extreme, feels completely detached or estranged from others; not close with anyone

C	L
QV	QV
F	F
I	I

(10) restricted range of affect, e.g., unable to have loving feelings

Frequency

Have you had periods where you felt emotionally numb, or had trouble experiencing feelings such as love or happiness? Is this different from how you felt before the event(s)? How much of the time have you felt this way in the past month?

0 None of the time
1 Very little of the time (less than 10%)
2 Some of the time (approx 20-30%)
3 Much of the time (approx 50-60%)
4 Most or all of the time (more than 80%)

Description/Examples:

Intensity

At their worst, how strong were your feelings of emotional numbness? [In rating this item include observations of range of affect displayed in interview]

0 No emotional numbing
1 Mild, slight emotional numbing
2 Moderate, emotional numbing clearly present, but still able to experience emotions
3 Severe, marked emotional numbing in at least two primary emotions (e.g., love, happiness)
4 Extreme, feels completely unemotional

C	L
QV	QV
F	F
I	I

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

(11) sense of a foreshortened future, e.g., does not expect to have a career, marriage, children, or a long life

Frequency

Have you had times when you felt that there is no need to plan for the future, that somehow your future will be cut short? [If yes, rule out realistic risks such as life-threatening medical conditions] Is this different from how you felt before the event(s)? How much of the time in the past month have you felt this way?

0 None of the time
1 Very little of the time (less than 10%)
2 Some of the time (approx 20-30%)
3 Much of the time (approx 50-60%)
4 Most or all of the time (more than 80%)

Description/Examples:

Intensity

At its worst, how strong was this feeling that your future will be cut short? How long do you think you will live? How convinced were you that you will die prematurely?

0 No sense of a foreshortened future
1 Mild, slight sense of a foreshortened future
2 Moderate, sense of a foreshortened future definitely present, but no specific prediction about longevity
3 Severe, marked sense of a foreshortened future; may make specific prediction about longevity
4 Extreme, overwhelming sense of a foreshortened future; completely convinced of premature death

C	L
QV	QV
F	F
I	I

 # Current Symptoms from Criterion C = _____

 # Lifetime Symptoms from Criterion C = _____

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

D. *Persistent symptoms of increased arousal (not present before the trauma)*

(12) difficulty falling or staying asleep

Frequency

Have you had any problems falling or staying asleep? Is this different from the way you were sleeping before the event(s)? How often have you had difficulty sleeping in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Nightly or almost every night

Sleep Onset Problems? Y N

Mid Sleep Awakening? Y N

Early AM Awakening? Y N

Total #hrs Sleep/Night ____

Desired #hrs Sleep/Night ____

Intensity

[Ask probe items and rate overall sleep disturbance] How long did it take you to fall asleep? How many times did you wake up in the night? How many hours total did you sleep each night?

0 No sleep problems
1 Mild, takes slightly longer to fall asleep, or minimal difficulty staying asleep (up to 30 minutes loss of sleep)
2 Moderate, definite sleep disturbance, with clearly longer latency to sleep or clear difficulty staying asleep (30 to 90 minutes loss of sleep)
3 Severe, much longer latency to sleep or marked difficulty staying asleep (90 minutes to 3 hours loss of sleep)
4 Extreme, very long latency to sleep or profound difficulty staying asleep (greater than 3 hours loss of sleep)

C	L
QV	QV
F	F
I	I

(13) irritability or outbursts of anger

Frequency

Have there been times when you felt unusually irritable, or expressed feelings of anger and acted aggressively? Is this different from how you felt or acted before the event(s)? How often have you felt or acted this way in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Description/Examples:

Intensity

How angry were you? In what ways did you express/show anger?

0 No irritability or anger
1 Mild, minimal irritability, raises voice when angry
2 Moderate, irritability clearly present, easily becomes argumentative when angry, but can recover quickly
3 Severe, marked irritability, becomes verbally or physically aggressive when angry
4 Extreme, pervasive anger, episodes of physical violence

C	L
QV	QV
F	F
I	I

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

(14) difficulty concentrating

Frequency

Have you found it difficult to concentrate on what you were doing or on things going on around you? Has your concentration changed since the event(s)? How much of the time have you had difficulty concentrating in the past month?

0 None of the time
1 Very little of the time (less than 10%)
2 Some of the time (approx 20-30%)
3 Much of the time (approx 50-60%)
4 Most or all of the time (more than 80%)

Intensity

How difficult was it for you to concentrate? [In rating this item include observations of concentration and attention in the interview]

0 No difficulty with concentration
1 Mild, only slight effort needed to concentrate
2 Moderate, definite loss of concentration, but could concentrate with effort
3 Severe, marked loss of concentration, even with effort
4 Extreme, complete inability to concentrate

C	L
QV	QV
F	F
I	I

Description/Examples:

(15) hypervigilance

Frequency

Have you been especially alert or watchful, even when there was no obvious need to be? is this different from how you felt or acted before the event(s)? How much of the time have you been alert or watchful in the past month?

0 None of the time
1 Very little of the time (less than 10%)
2 Some of the time (approx 20-30%)
3 Much of the time (approx 50-60%)
4 Most or all of the time (more than 80%)

Intensity

How much effort did you make to try to be aware of everything around you? [In rating this item include observations of hypervigilance during the interview]

0 No hypervigilance
1 Mild, minimal hypervigilance, slight heightening of awareness
2 Moderate, hypervigilance clearly present, watchful in public (e.g., chooses safe place to sit in a restaurant or movie theater)
3 Severe, marked hypervigilance, very alert, scans environment for danger, exaggerated concern for safety of self (and home and family)
4 Extreme, excessive hypervigilance, efforts to ensure safety consume significant time and energy, and may involve extensive safety-checking behaviors, marked guarded behavior during interview

C	L
QV	QV
F	F
I	I

Description/Examples:

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

(16) exaggerated startle response

Frequency

Have you experienced strong startle reactions to loud, unexpected noises (e.g., car backfires, fireworks, doorslams, etc.) or things that you saw (e.g., movement in the corner of your eye)? Is this different from how you were before the event(s)? How often has this happened in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Intensity

At their worst, how strong were these startle reactions?

0 No startle reaction
1 Mild, minimal reaction
2 Moderate, definite startle response, feels "jumpy"
3 Severe, marked startle response, sustained arousal following initial reaction
4 Extreme, excessive startle response, overt coping behavior (e.g., combat veteran who "hits the dirt")

C	L
QV	QV
F	F
I	I

Description/Examples:

(17) physiologic reactivity upon exposure to events that symbolize or resemble an aspect of the traumatic event

Frequency

Have you experienced any physical reactions when you were faced with situations that reminded you of the event(s)? [Listen for report of symptoms such as heart racing, tremulousness, sweating, or muscle tension, but do not suggest symptoms to patient] How often in the past month?

0 Never
1 Once or twice
2 Once or twice a week
3 Several times a week
4 Daily or almost every day

Intensity

At their worst, how strong were these physical reactions?

0 No physical reaction
1 Mild, minimal reaction
2 Moderate, physical reaction clearly present, reports some discomfort
3 Severe, marked physical reaction, reports strong discomfort
4 Extreme, dramatic physical reaction, sustained arousal

C	L
QV	QV
F	F
I	I

Description/Examples:

Current Symptoms from Criterion D = _____

Lifetime Symptoms from Criterion D = _____

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

CAPS Global Ratings

(18) **Impact on Social Functioning: Have the symptoms you've told me about affected your social life?** Rate the overall impact that the PTSD symptoms have had on the patient's social functioning, taking into consideration impressions of the patient's behavior as well as his/her report provided at other times during the interview.

0 = No adverse impact on social functioning
1 = Slight/mild impact on social functioning, some impairment
2 = Moderate impact on social functioning
3 = Severe impact on social functioning
4 = Extreme impact on social functioning

(19) **Impact on Occupational Functioning: Are you working now ? Have the symptoms you've told me about affected your work or your ability to work?** Rate the overall impact that the PTSD symptoms have had on the patient's ability to obtain and maintain employment. Take into consideration the patient's reported work history, including the number and duration of jobs, as well as the quality of work relationships. Also consider work functioning problems due to reasons other than PTSD symptoms.

0 = No adverse impact on occupational functioning
1 = Slight/mild impact on occupational functioning, some impairment
2 = Moderate impact on occupational functioning, significant impairment, intermittent employment
3 = Severe impact on occupational functioning, chronically unemployed
4 = Extreme impact on occupational functioning, not employed since event

(20) **Global Improvement:** Rate total overall improvement present since the initial rating. If no earlier rating, ask how the symptoms endorsed have changed over the past 6 months. Rate the degree of change, whether or not, in your judgment, it is due to treatment.

0 = Asymptomatic
1 = Very much improvement
2 = Moderate improvement
3 = Slight improvement
4 = No improvement or not sufficient information

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

(21) **Rating Validity**: Total number of QV's circled on interview form: _____

Estimate the overall validity of the ratings obtained. Factors that may affect validity include the patient's cooperativeness and his/her attempts to appear more or less symptomatic than is actually the case. Furthermore, the type and intensity of PTSD symptoms present may interfere with the patient's concentration, attention, or ability to communicate in a coherent fashion.

0 = Excellent, no reason to suspect invalid responses
1 = Good, factor(s) present that may adversely affect validity
2 = Fair, factor(s) present that definitely reduce validity
3 = Poor, very low validity
4 = Invalid responses, suspect deliberate "faking bad" or "faking good"

(22) **Global Severity**: Interviewer's judgment of the overall intensity of the patient's PTSD symptoms. Consider the degree of distress reported by the patient, the symptoms observed, and the functional impairment reported. Your judgment is required with respect to the emphasis placed on particular information as well as the accuracy of patient reporting. This judgment should be based on information obtained during this interview only.

0 = Asymptomatic
1 = Slight/mild symptoms, little functional impairment
2 = Moderate symptoms, but functions satisfactorily with effort
3 = Severe symptoms, limited functioning even with effort
4 = Extreme symptoms, pervasive impairment

Current Symptoms

Cx A met? No Yes

_____ # current symptoms for Criterion B - Cx B met (≥ 1)? No Yes

_____ # current symptoms for Criterion C - Cx C met (≥ 3)? No Yes

_____ # current symptoms for Criterion D - Cx D met (≥ 2)? No Yes

PTSD (Criteria A-D met)? No Yes

[If PTSD Criteria are met, skip next section and go on to "Associated or hypothesized features" (p. 12). If Criteria are not met, assess for Lifetime Diagnostic Status.]

Clinician Administered PTSD Scale- IV (CAPS- IV) *(continued)*

CAPS-1 SUMMARY SHEET

Patient:_____ Pt#:___ Clinician:_____ Date:_____

PTSD Symptoms

A. Traumatic event:_____

B. The traumatic event is persistently reexperienced:		Current Sxs Freq	Current Sxs Ints	Lifetime Sxs Freq	Lifetime Sxs Ints
(1)	recurrent and intrusive recollections	___	___	___	___
(2)	distress when exposed to events	___	___	___	___
(3)	acting or feeling as if event recurring	___	___	___	___
(4)	recurrent distressing dreams of event	___	___	___	___

NUMBER OF CURRENT SYMPTOMS FOR CRITERION B (NEED 1): ___ **Cx met? Yes No**

NUMBER OF LIFETIME SYMPTOMS FOR CRITERION B (NEED 1): ___ **Cx met? Yes No**

C. Persistent avoidance of stimuli/numbing of responsiveness					
(5)	efforts to avoid thoughts or feelings	___	___	___	___
(6)	efforts to avoid activities or situations	___	___	___	___
(7)	inability to recall trauma aspects	___	___	___	___
(8)	markedly diminished interest in activities	___	___	___	___
(9)	Feelings of detachment or estrangement	___	___	___	___
(10)	restricted range of affect	___	___	___	___
(11)	sense of a foreshortened future	___	___	___	___

NUMBER OF CURRENT SYMPTOMS FOR CRITERION C (NEED 3): ___ **Cx met? Yes No**

NUMBER OF LIFETIME SYMPTOMS FOR CRITERION C (NEED 3): ___ **Cx met? Yes No**

D. Persistent symptoms of increased arousal					
(12)	difficulty falling or staying asleep	___	___	___	___
(13)	irritability or outbursts of anger	___	___	___	___
(14)	difficulty concentrating	___	___	___	___
(15)	hypervigilance	___	___	___	___
(16)	exaggerated startle response	___	___	___	___
(17)	physiologic reactivity	___	___	___	___

NUMBER OF CURRENT SYMPTOMS FOR CRITERION D (NEED 2): ___ Cx met? Yes No

NUMBER OF LIFETIME SYMPTOMS FOR CRITERION D (NEED 2): ___ Cx met? Yes No

PTSD Cx Met (Circle): Current: YES NO Lifetime: YES NO

Appendix C

Statistical Summaries

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Table C 1.1

One- way Between- Subjects ANOVA Summary Table for Group Differences in the Corpus Callosum Diffusion Metrics

DTI Metric	Source	SS	df	MS	F	Sig.
FA	Between	.045	3	.015	24.07	.000
	Within	.077	123	.001		
	Total	.122	126			
Trace	Between	.000	3	.000	16.28	.000
	Within	.000	124	.000		
	Total	.000	127			
Perpendicular Diffusivity	Between	.000	3	.000	25.30	.000
	Within	.000	123	.000		
	Total	.000	126			
Parallel Diffusivity	Between	.000	3	.000	3.69	.014
	Within	.000	123	.000		
	Total	.000	126			
Mode	Between	.048	3	.016	14.46	.000
	Within	.133	121	.001		
	Total	.181	124			

Table C 1.2

Two- way Mixed Design ANOVA Summary Table for Group Differences in the Cingulum Diffusion Metrics

DTI Metric	Source	SS	df	MS	F	Sig.	Partial Eta Squared
FA	Between	.007	3	.002	2.17	.094	.051
	Within	.008	1	.008	22.46	.000	.157
	Interaction	.000	3	.000	.46	.707	.011
	Total	.041	121	.000			
Trace	Between	2.58 E-7	3	8.62 E-8	5.35	.002	.116
	Within	3.62 E-8	1	3.62 E-8	8.11	.005	.062
	Interaction	2.13 E-8	3	7.10 E-9	1.59	.195	.038
	Total	5.44 E-7	122	4.47 E-9			
Perpendicular Diffusivity	Between	3.17 E-8	3	1.06 E-8	5.54	.001	.122
	Within	9.27 E-10	1	9.27 E-10	1.82	.180	.015
	Interaction	8.93 E-10	3	2.98 E-10	.58	.626	.014
	Total	6.11 E-8	120	5.09 E-10			
Parallel Diffusivity	Between	5.43 E-8	3	1.81 E-8	4.69	.004	.105
	Within	6.36 E-8	1	6.36 E-8	63.54	.000	.346
	Interaction	6.27 E-9	3	2.07 E-9	2.07	.108	.049
	Total	1.20 E-7	120	1.00 E-9			
Mode	Between	.069	3	.023	6.05	.001	.129
	Within	.032	1	.032	33.51	.000	.215
	Interaction	.001	3	.000	.486	.693	.012
	Total	.118	122	.001			

Table C 1.3

Two- way Mixed Design ANOVA Summary Table for Group Differences in the UF Diffusion Metrics

DTI Metric	Source	SS	df	MS	F	Sig.	Partial Eta Squared
FA	Between	.009	3	.003	1.884	.136	.049
	Within	.002	1	.002	2.934	.09	.026
	Interaction	.003	3	.001	1.338	.226	.035
	Total	.074	110	.001			
Trace	Between	1.81 E-7	3	6.03 E-8	3.650	.015	.091
	Within	4.13 E-7	1	4.13 E-7	87.602	.000	.446
	Interaction	6.39 E-9	3	2.13 E-9	.452	.717	.012
	Total	5.14 E-7	109	4.71 E-9			
Perpendicular Diffusivity	Between	1.68 E-8	3	5.60 E-9	2.306	.081	.060
	Within	9.52 E-9	1	9.52 E-9	13.175	.000	.108
	Interaction	1.95 E-9	3	6.50 E-10	.900	.444	.024
	Total	7.87 E-8	109	7.22 E-10			
Parallel Diffusivity	Between	1.04 E-8	3	3.46 E-9	.628	.598	.017
	Within	1.7 E-7	1	1.7 E-7	91.67	.000	.452
	Interaction	6.79 E-9	3	2.26 E-9	1.21	.307	.032
	Total	2.06 E-7	111	1.86 E-9			
Mode	Between	.003	3	.001	.273	.845	.007
	Within	.001	1	.001	1.158	.284	.010
	Interaction	.015	3	.005	4.728	.004	.113
	Total	.118	111	.001			

Table C 1.4

Simultaneous Linear Regression Summary Table for the Corpus Callosum

DTI Metric	Source	SS	df	MS	F	Sig.
FA	Regression	.033	2	.016	27.68	.000
	Residual	.052	88	.001		
	Total	.085	90			
Trace	Regression	.000	2	.000	16.66	.000
	Residual	.000	88	.000		
	Total	.000	90			
Perpendicular Diffusivity	Regression	.000	2	.000	27.83	.000
	Residual	.000	87	.000		
	Total	.000	89			
Parallel Diffusivity	Regression	.000	2	.000	4.85	.010
	Residual	.000	88	.000		
	Total	.000	90			
Mode	Regression	.049	2	.025	23.12	.000
	Residual	.091	86	.001		
	Total	.140	88			

Table C 1.5

Simultaneous Linear Regression Summary Table for the Cingulum

DTI Metric	Source	SS	df	MS	F	Sig.
FA	Regression	.003	2	.002	2.67	.074
	Residual	.051	89	.001		
	Total	0.54	91			
Trace	Regression	.000	2	.000	9.00	.000
	Residual	.000	88	.000		
	Total	.000	90			
Perpendicular Diffusivity	Regression	.000	2	.000	8.56	.000
	Residual	.000	89	.000		
	Total	.000	91			
Parallel Diffusivity	Regression	.000	2	.000	6.83	.002
	Residual	.000	88	.000		
	Total	.000	90			
Mode	Regression	.010	2	.005	2.51	.087
	Residual	.173	89	.002		
	Total	.183	91			

Table C 1.6

Participant Demographic and Clinical Characteristics Summary Table

Characteristic	Source	SS	df	MS	F	Sig.
Age	Between	2036.91	3	678.97	4.94	.003
	Within	17304.48	126	137.34		
	Total	19341.39	129			
CAPS	Between	85357.53	2	42678.76	213.94	.000
	Within	18153.29	91	199.49		
	Total	103510.82	93			
Time Since Trauma	Between	917.59	2	458.78	.021	.98
	Within	1935208.87	89	21743.92		
	Total	1936126.47	91			
BAI	Between	10064.37	3	3354.78	36.89	.000
	Within	10458.54	115	90.94		
	Total	20522.87	118			
BDI	Between	12298.69	3	4099.565	51.42	.000
	Within	9089.37	114	79.731		
	Total	21388.07	117			