MONASH University

# NEUROANATOMICAL CORRELATES OF ATTENTION AND WORKING MEMORY DEFICITS FOLLOWING TRAUMATIC BRAIN INJURY


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**BSc (Hons)**

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| | |
|---|---|
| **5HT** | Serotonin |
| **5HIAA** | HVA/5-Hydroxyindole-Acetic Acid |
| **ACh** | Acetylcholine |
| **ADC** | Apparent Diffusion Coefficient |
| **ADHD** | Attention Deficit Hyperactivity Disorder |
| **ASL** | Arterial Spin Labelling |
| **BOLD** | Blood-Oxygen-Level Dependent |
| **CASL** | Continuous Arterial Spin Labelling |
| **CBF** | Cerebral Blood Flow |
| **CDS** | Constrained Spherical Deconvolution |
| **COAT** | Ponsner' Covert Orienting Of Attention Task |
| **CSAT** | Complex Selective Attention Task |
| **CSF** | Cerebral Spinal Fluid |
| **CT** | Computerised Tomography |
| **CVLT-II** | California Verbal Learning Test, Second Edition |
| **DA** | Dopamine |
| **DAergic** | Dopaminergic |
| **DAI** | Diffuse Axonal Injury |
| **DAT** | Dopamine-Transporter |
| **DMN** | Default Mode Network |
| **DTI** | Diffusion Tensor Imaging |
| **EEG** | Electroencephalography |
| **FA** | Fractional Anisotropy |
| **fMRI** | Functional Magnetic Resonance Imaging |
| **FSIQ** | Full Scale IQ |
| **GCS** | Glasgow Coma Scale |
| **GREFEX** | Groupe De Réflexion Sur L'évaluation Des Fonctions Exécutives |
| **HVA** | Homovanillic Acid |

| | |
|---|---|
| **ICA** | Independent Component Analysis |
| **imMFB** | Inferio-Medial Medial Forebrain Bundle |
| **IQR** | Interquartile Range |
| **MD** | Mean Diffusivity |
| **MFB** | Medal Forebrain Bundle |
| **MHPG** | Methoxyhydroxyphenylglycol |
| **MNI** | Montreal Neurological Institute |
| **mPFC** | Medial Prefrontal Cortex |
| **MRI** | Magnetic Resonance Imaging |
| **MR** | Magnetic Resonance |
| **MVA** | Motor Vehicle Accident |
| **NART** | The National Adult Reading Test |
| **NE** | Norepinephrine |
| **PASAT** | Paced Auditory Serial Addition Test |
| **PCA** | Principal Components Analysis |
| **PET** | Positron Emission Tomography |
| **PFC** | Prefrontal Cortex |
| **PTA** | Post-Traumatic Amnesia |
| **PTE** | Post Traumatic Epilepsy |
| **QBI** | Q-Ball Imaging |
| **RD** | Radial Diffusivity |
| **ROI** | Region Of Interest |
| **rs-fMRI** | Resting-State Functional Magnetic Resonance Imaging |
| **RT** | Reaction Time |
| **SART** | The Sustained Attention To Response Task |
| **SAS** | Supervisory Attentional System |
| **SAT** | Selective Attention Task |
| **SDMT** | Symbol Digit Modalities Test |
| **SIRT** | Sternberg Item Recognition Task |
| **slMFB** | Superio-Lateral Medial Forebrain Bundle |

| | |
|---|---|
| **SN** | Salience Network |
| **SSAT** | Simple Selective Attention Task |
| **Super-CDS** | Super-Resolved Constrained Spherical Deconvolution |
| **TBI** | Traumatic Brain Injury |
| **TBSS** | Tact-Based Spatial Statistics |
| **TH** | Tyrosine Hydroxylase |
| **TMT** | Trail Making Task |
| **TMT-A** | Trail Making Task Part A |
| **TMT-B** | Trail Making Task Part B |
| **VBM** | Voxel Based Morphology |

## THESIS OVERVIEW

This thesis forms the major research component of Doctorate of Clinical Neuropsychology program at Monash University, in Melbourne Australia, a four year combined clinical training and research program.

The current thesis was designed to follow on from previous research conducted by my supervisors, Dr Catherine Willmott and Professor Jennie Ponsford and fellow student Dr Alicia Dymowski. Thus, prior to my commencing the thesis, the general aims of the study were established. However, in collaboration with my supervisors and with advice and guidance from Dr Jerome Maller, Associate Professor Alex Fornito, and Dr Gershon Spitz, I was involved in a large part of the development of the three studies and specific research questions that were addressed. Under the guidance of my supervisors, I was responsible for recruitment, assessment, and data entry. Given the current thesis was somewhat related to my fellow student, Dr Alicia Dymowski's project, some of the behavioural attention measures data collection was shared. Associate Professor Alex Fornito, Dr Orwa Dandash, and in particular Dr Gershon Spitz provided assistance and advice with regards to the imaging analysis, however, I completed the bulk of the analysis. Additionally, I prepared the manuscripts under the guidance of my supervisors.

In line with the Monash University guidelines, the experimental chapters are presented in a 'thesis by publication' format, whereby parts of the thesis have been written as manuscripts and submitted for publication instead of the more traditional thesis format. As such, there is some unavoidable repetition of introductory comments and methodologies across chapters.

The thesis starts with a comprehensive 'Introduction' which reviews the current literature on this topic, placing this study in context of the broader literature, and finally outlines the thesis aims and hypotheses. Chapters Two, Three, and Four contain three prepared manuscripts and address the three major aims of the study, respectively. With regard to

publications status; Chapter Two titled *"An investigation of white matter integrity and attention deficits following traumatic brain injury"* is currently under review with *The Journal of Neurotrauma* (submitted October 2016). Chapter Three titled "*White matter integrity of the medial forebrain bundle and attention and working memory deficits following traumatic brain injury"* has been accepted for publication in *Brain and Behavior* (Accepted 19th October 2016). Chapter Four titled "*The functional connectivity between the ventral tegmental area and default mode network and associated attentional deficits following traumatic brain injury"* is currently under review at *Brain and Cognition* (submitted November 2016). Finally, Chapter Five summarises study findings and presents some general discussion around their clinical implications, discusses limitations, and provides recommendations for future research in this area.

## ABSTRACT

Attention and working memory deficits are frequent following moderate to severe traumatic brain injury (TBI), and can greatly impact everyday functioning. The mechanisms underpinning these deficits, however, are poorly understood. Identification of potential neuroanatomical markers that are associated with attentional impairment may help to inform targeted treatments, such as pharmacological interventions.

The aims of the current studies were to investigate the association between attention and working memory deficits and TBI related brain changes, specially: (1) whole brain white matter microstructure; (2) white matter microstructure of the supero-lateral branch of the medial forebrain bundle (slMFB), a pathway rich in catecholamine; and (3) functional connectivity between the ventral tegmental area (VTA) (a brain region containing a large proportion of dopamine (DA) cell bodies) and the default mode network (DMN) – a resting-state network highly implicated in attention function.

Twenty participants with a history of moderate to severe TBI and 20 demographically matched control participants were included in the study. White matter microstructure and functional connectivity between the VTA and DMN nodes were investigated using diffusion tensor imaging (DTI), and resting state functional magnetic resonance imaging (rs-fMRI), respectively. Participants also underwent neuropsychological assessment of attention and working memory.

Participants with TBI demonstrated significantly slower performances on the Trail Making Task, Hayling, Selective Attention Task, *n*-back, and Symbol Digit Modalities Test ($p < 0.001$), when compared to controls. No impairments were identified in working memory or executive control of attention.

The majority of white matter tracts within the brain were found to be altered following TBI, as indicated by lower FA ($p < 0.001$) and higher MD ($p < 0.001$). Correlation analysis revealed slowed information processing speed post-TBI was associated with lower FA

values in the corpus callosum, superior longitudinal fasciculus, cingulum, inferior fronto-occipital fasciculi, corona radiata, and cerebral white matter, when controlling for age and estimated pre-morbid intelligence.

Alterations within the slMFB were also identified post-TBI. Participants with TBI demonstrated significantly lower FA (M = .32, SD = .03, $p < 0.001$) and higher MD (M = 7.43, SD = .46, $p < 0.001$) within the slMFB when compared to controls. No associations were found between slMFB white matter microstructure and attentional performance.

Finally, the VTA was found to be functionally connected to the angular gyrus and precuneus ($p < 0.05$) for the control group only. Between-group differences were, however, not statistically significant. Individual variability in damage caused by TBI likely accounted for the lack of significant findings in this cohort. Given no significant alterations were identified, the correlation analysis with attention tasks was not undertaken. Findings from the control group suggest the VTA may influence the DMN via dopaminergic input into key DMN nodes.

This thesis highlights the association between widespread white matter damage and slowed information processing speed following TBI. Additionally, it demonstrates both structural and functional changes to the DA system following TBI. Investigating dysfunction of catecholamine systems such as the DA system is promising as currently many therapeutic pharmacological agents are available. However, the current thesis did not provide substantial evidence for the role of DA disruption in attentional deficits following TBI.

## GENERAL DECLARATION

Monash University Declaration for thesis based or partially based on conjointly published or unpublished work
In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes an original paper accepted for publication in a peer reviewed journal and 2 unpublished publications. The core theme of the thesis is investigating neurological damaged associated with attention and working memory deficits following TBI. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Psychological Sciences (Medicine, Nursing and Health Sciences) under the supervision of Dr. Catherine Willmott and Professor Jennie Ponsford. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2 – 4 my contribution to the work involved the following:

| Thesis chapter | Publication title | Publication status* | Nature and extent (%) of students contribution | Co-author name(s) Nature and % of author contribution | Co-author(s) Monash Student (Y/N) |
|---|---|---|---|---|---|
| 2 | An investigation of white matter integrity and attention deficits following traumatic brain injury | Submitted | Literature review, data collection, data analysis (with consultation) and preparation of manuscript. (70% students contribution) | 1) Gershon Spitz, data analysis, input into manuscript (10%)<br>2) Jennie Ponsford, generation of research questions, input into manuscript (5%)<br>3) Alicia Dymowski, recruitment, data collection, input into manuscript (5%)<br>4) Catherine Willmott, generation of research questions, | 1) No<br>2) No<br>3) Yes<br>4) No |

| | | | | | |
|---|---|---|---|---|---|
| | | | | input into manuscript (10%) | |
| 3 | White matter integrity of the medial forebrain bundle and attention and working memory deficits following traumatic brain injury | Accepted for publication | Literature review, data collection, data analysis (with consultation) and preparation of manuscript. (65% students contribution) | 1) Gershon Spitz, data analysis, input into manuscript (10%)<br>2) Jennie Ponsford, generation of research questions, input into manuscript (5%)<br>3) Alicia Dymowski, recruitment, data collection, input into manuscript (5%)<br>4) Nicholas Ferris, data analysis consultation (5%)<br>5) Catherine Willmott, generation of research questions, input into manuscript (10%) | 1) No<br>2) No<br>3) Yes<br>4) No<br>5) No |
| 4 | The functional connectivity between the ventral tegmental area and default mode network and associated attentional deficits following traumatic brain injury | Submitted | Literature review, data collection, data analysis (with consultation) and preparation of manuscript. (70% students contribution) | 1) Orwa Dandash, data analysis, input into manuscript (10%)<br>2) Alex Fornito, generation of research questions, data analysis consultation, input into manuscript (5%) | 1) No<br>2) No<br>3) No<br>4) No<br>5) No |

| | | | | | |
|---|---|---|---|---|---|
| | | | | 3) Jennie Ponsford, generation of research questions, input into manuscript (5%)<br>4) Gershon Spitz, data analysis, input into manuscript (5%)<br>5) Catherine Willmott, generation of research questions, input into manuscript (5%) | |

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

**Student signature:**  Date: 17/11/2016

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors

**Main Supervisor signature:**  Date: 17/11/2016

## PUBLICATIONS DURING ENROLMENT

During my candidature, the following manuscripts were prepared and submitted from my doctoral data. I also presented doctoral research findings at a number of international conferences in the final year of my candidature. These are outlined below:

JOURNAL ARTICLES

**Owens, J.,** Spitz, G., Ponsford, J., Dymowski, A., & Willmott, C. (2016) An investigation of white matterintegrity and attention deficits following traumatic brain injury. *Journal of Neurotrauma (Submitted).*

**Owens, J.,** Spitz, G., Ponsford, J., Dymowski, A., Ferris, N., & Willmott, C. (2016). White matter integrity of the medial forebrain bundle and attention and working memory defcits following trauamtic brain injury. *Brain and Behavior* (accepted 16th October 2016).

**Owens, J.,** Dandash, O., Fornito, A., Ponsford, J., Spitz, G., & Willmott, C. (2016). The functioanl connectivity between the ventral tegmental area and default mode network and associated attentional defcits following traumatic brain injury. *Brain and Cognition (Submitted)*

CONFERENCE PRESENTATIONS

**Owens, J**., Spitz, G., Ponsford, J., Dymowski, A., Ferris, N., & Willmott, C. (2016). White matter integrity of the medial forebrain bundle and attention and working memory defcits following trauamtic brain injury. Poster presented at The 5th INS/ASSBI Pacific Rim Conference, Sydney, Australia, 1st-4th July 2015

**Owens, J**., Spitz, G., Ponsford, J., Dymowski, A., Ferris, N., & Willmott, C. (2016). White matter integrity of the medial forebrain bundle and attention and working memory defcits following trauamtic brain injury. Poster presented at The the 5th Scientific Meeting of the ESN and 12th Nordic Meeting in Neuropsychology, Tampere, Finland. 9-11 September 2015

## ACKNOWLEDGEMENTS

First and foremost, I wish to thank my supervisors Dr. Catherine Willmott and Professor Jennie Ponsford. I feel incredibly fortunate to have worked with such supportive and inspiring mentors. I am so grateful for your investments in my learning and development over the past 5 years. I cannot thank you enough for so generously providing your time, dedication, guidance and expertise over the course of my candidature.

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To my collaborators, Associate Professor Alex Fornito, Doctor Nicholas Ferris, Doctor Orwa Dandash and in particular Doctor Gershon Spitz, I am very grateful for your guidance and assistance with the imaging analysis. Thank you for generously giving your time and knowledge when you had no obligation.

I wish to thank Doctor Alicia Dymowski, for all your assistance and support with this project. I am grateful to have had someone to share the ups and downs of recruitment and data collection with. I appreciate all your advice and guidance you gave not just about the project but other aspects of the course as well.

To my family, my parents Niece and Steve, and my sisters Michelle, Amanda and Kristine, thank you for the much needed support throughout my candidature, I am very grateful for your enthusiasm, encouragement and understanding over the past 5 years. I could not have done it without you. Thank you to Amanda who came all the way to a conference in Tampere, Finland with me, it was fun to share that experience with you.

Last, but not least, I would like to thank my amazing group of friends. The fun times we have shared and your constant support has helped me through the stressful times and kept me smiling. In particular, I would like to thank my best friend Jo. You have been there every step of the way and I could not have asked for a more understanding or supportive friend.

## Funding

This research was funded by three sources; The Monash Biomedical Imaging- School of Psychological Sciences Grant, Monash University Faculty of Medicine, Nursing & Health Sciences Strategic Grant Scheme awarded to my two supervisors, and my Monash University Doctoral Research Fund.

## STUDY OVERVIEW

Twenty participants with complicated-mild to severe TBI and 20 healthy controls were included in the study. Diffusion tensor imaging (DTI) and resting-state functional magnetic imaging (rs-fMRI) were used to characterise neurological changes associated with TBI, with a specific focus on brain regions associated with the dopamine (DA) system. Specific alterations to DA neurotransmission following TBI, however, were not directly measured. Participants also underwent neuropsychological assessment of attention and working memory. The overall aim of the current study was to investigate the neurological and neurochemical (specifically dopamine) changes that are associated with attention deficits following TBI.

**STUDY 1: An investigation of white matter integrity and attention deficits following traumatic brain injury**

*AIM 1a:* To identify whole brain white matter changes using TBSS following TBI

*AIM 1b:* To investigate the association between these white matter alterations and attention deficits following TBI.

**STUDY 2: White matter integrity of the medial forebrain bundle and attention and working memory defcits following trauamtic brain injury**

*AIM 2a:* To explore white matter alterations to the superior-lateral medial forebrain bundle (slMFB) following TBI

*AIM 2b:* To examine the association between slMFB alterations and attentional impairment post-TBI

**STUDY 3: The functioanl connectivity between the ventral tegmental area and default mode network and associated attentional defcits following traumatic brain injury**

*AIM 3a:* To examine the changes to the functional connectivity between the VTA and DMN nodes in participants with TBI, when compared to controls.

*AIM 3b:* To investigate whether these alterations in functional connectivity were associated with attention deficits following TBI.

# CHAPTER ONE

# INTRODUCTION

## 1.1 TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a leading cause of death and long term disability in adults living in the developed world. Attention and working memory deficits are commonly seen in people who have suffered a moderate to severe TBI (Mathias & Wheaton, 2007; Ponsford & Willmott, 2004; Willmott, Ponsford, Hocking, & Schonberger, 2009), and can greatly impact on the ability to work, socialise and function in everyday life (Bercaw, Hanks, Millis, & Gola, 2010; Draper, Ponsford, & Schönberger, 2007). These deficits include difficulties sustaining attention, dividing attention over two or more tasks, slowed processing speed and reduced ability to hold and manipulate information in the mind.

Attention and working memory are complex cognitive abilities reliant on diffuse and integrated brain networks (De Simoni et al., 2016; Jilka et al., 2014; Pandit et al., 2013; Sharp et al., 2011), as well as multiple neurotransmitter systems (Clark & Noudoost, 2014). As the attention neural network is widespread throughout the brain it is vulnerable to damage caused by TBI, which can lead to attention and working memory deficits. Understanding the underlying neuropathology that leads to these deficits is crucial for understanding severity, selection of interventions and treatment planning.

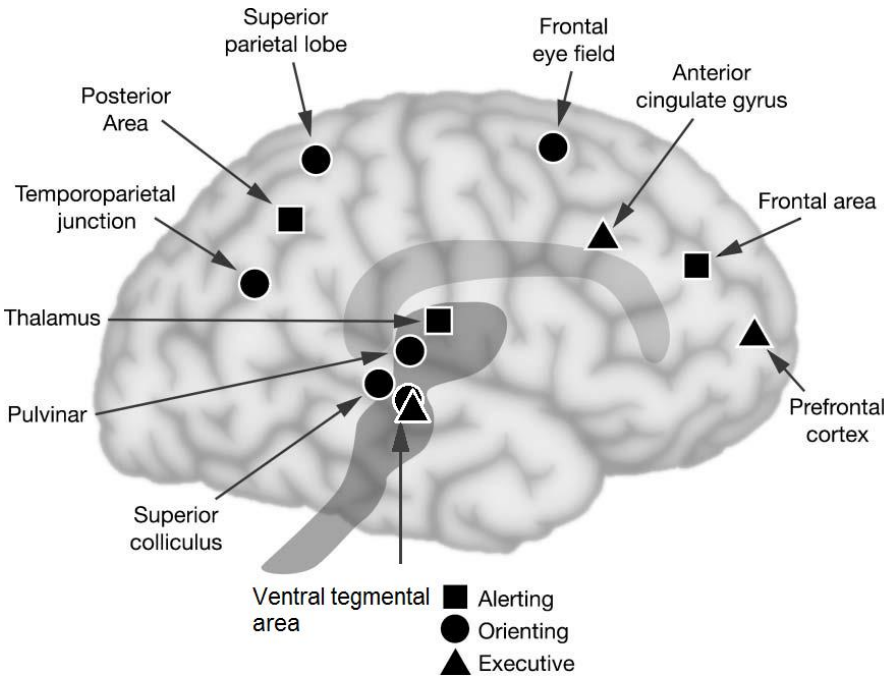


Figure 1.1 Key brain regions involved in different aspects of attention including alerting network, orienting network and executive control of attention network. *Note*. Figure adapted from (Posner & Rothbart, 2007).

Given the interconnectedness of the attention neural network, the association between white matter microstructure and attention deficits following TBI is a key area of research. Multiple studies have identified links between white matter pathology and attentional impairments (Little et al., 2010; Niogi et al., 2008; Spitz, Maller, O'Sullivan, & Ponsford, 2013), however, the majority of these studies have investigated individuals within the chronic phase of injury. Less is known regarding the more acute phase of injury (< 12months post injury) which is a critical time for recovery (Christensen et al., 2008). In addition, these studies have only focused on one or two aspects of attention. Given the potential impact of attention and working memory deficits on life roles, investigating the full extent of impairment and underlying neuropathology is crucial.

As with neuropathology, disruption to neurotransmitter and neuromodulator systems is also a common cause of persistent attention deficits. Dopamine (DA), in particular, has been found to be highly implicated in attention and working memory (Clark, Geffen, & Geffen, 1986b, 1987a, 1987b, 1989; Clark & Noudoost, 2014), and disruptions to the DA

system have been observed following TBI (Massucci, Kline, Ma, Zafonte, & Dixon, 2004). The damage associated with these changes in DA neurotransmission is, however, not well understood. Investigating the pathogenesis on DA disruption and related attention deficits is important as many medications are currently available that augment DA neurotransmission, providing a potential treatment option.

White matter damage to dopaminergic (DAergic) pathways is purported to have deleterious effects of DA signalling (Bales, Wagner, Kline, & Dixon, 2009; Chen et al., 2017; Donnemiller et al., 2000; Yan, Kline, Ma, Li, & Dixon, 2002). Little is known, however, regarding the association between DAergic white matter pathology and attention deficits following TBI. Furthermore, no study to date has investigated microstructural changes to the medial forebrain bundle, a key pathway in the DA system, and the associated attention deficits.

In addition, TBI may have implications for the interactions between the DA systems and other brain systems. The default mode network (DMN) is a prominent resting-state network that is highly implicated in attention (Gusnard & Raichle, 2001; Shulman et al., 1997). Efficient deactivation of the DMN is linked to better attentional performance (Weissman, Roberts, Visscher, & Woldorff, 2006), and extracellular DA concentrations influence DMN deactivation (Tomasi et al., 2009). Damage as a result of TBI may alter DA signalling within the brain resulting in inefficient DMN deactivation and subsequent attention deficits. The ventral tegmental area (VTA) contains a large proportion of DA cell bodies and has previous been found to be functionally connected to DMN nodes (Tomasi & Volkow, 2014). Studies in other clinical groups suggest that alterations in the functional connectivity of the VTA may underpin attention deficits (Tomasi & Volkow, 2012), however alterations to functional connectivity between the VTA and DMN nodes, and associated attention deficits is yet to be assessed in a TBI sample.

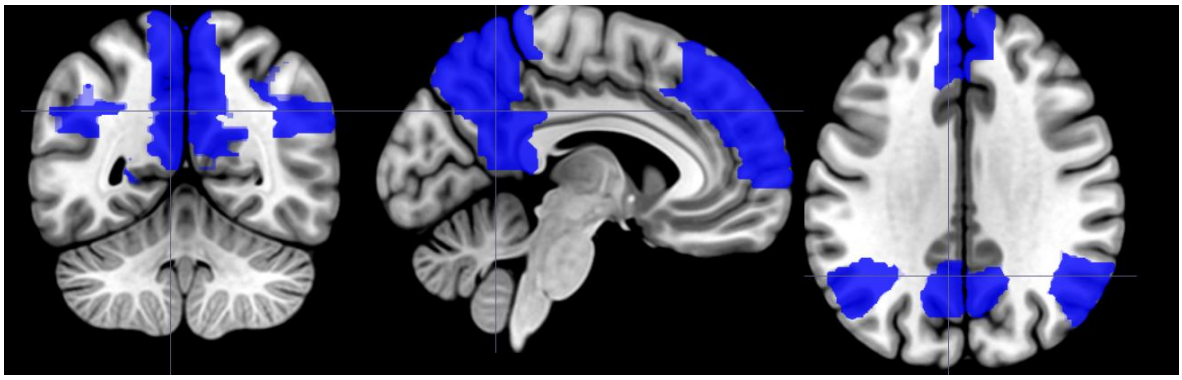

Figure 1.2 Key brain regions implicated in the default mode network including the medial frontal cortex, angular gyrus and posterior cingulate cortex.

Historically, it has been difficult to capture the brain injuries that underpinned specific cognitive changes. Older neuroimaging techniques such as computed tomography (CT) and traditional magnetic resonance imaging (MRI) can reliably capture large focal lesions, however, focal lesions do not always account for the severity or type of cognitive deficits seen following TBI (Bigler, 2001). Diffusion tensor imaging (DTI) is a relatively new imaging technique, that has been proven to be more sensitive than CT or conventional MRI to the diffuse microstructural white mater alterations caused by TBI (Arfanakis et al., 2002; Rugg-Gunn, Symms, Barker, Greenwood, & Duncan, 2001). Additionally, resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as a valuable method for assessing functional connectivity within the brain (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Fornito & Bullmore, 2010; Fox & Raichle, 2007). By correlating spontaneous activation patterns of anatomically separated brain regions during rest (i.e. not performing a task), rs-fMRI is able to provide information about how different regions in neuronal networks interact (Smith et al., 2009). With these relatively recent advances in neuroimaging, it is now possible to investigate previously undetectable white matter microstructural alterations and quantify the functional connectivity between brain regions.

This thesis has three major aims. Firstly, this thesis will determine the extent of white matter pathology following moderate to severe TBI and its association with performance

on attentional measures. A second focus will be to specifically explore microstructural alterations within the supero-lateral medial forebrain bundle (slMFB) and their association with attentional deficits. Finally, this thesis will explore alterations to the functional connectivity of the VTA and DMN nodes and their relationship with attentional performance.

### 1.1.1 Epidemiology

Traumatic brain injury is one of the most common causes of death and disability in adults with incidence estimated at 107 people per 100,000 population in Australia (*Australian Institute of Health and Welfare*, 2004; Fortune & Wen, 2000; O'Rance & Fortune, 2007). The most common cause of TBI is motor vehicle accident, accounting for approximately 50-70% of cases, followed by falls for 20-25% of cases, then assaults, sporting activities and other recreational activities accounting for 10-15% of cases (von Holst, 2007). There are peaks in the incidence of TBI in people over the age of 60 and children under the age of 10 (Bazarian et al., 2005; von Holst, 2007). Fall-related injuries are frequent in geriatrics and toddles (Keenan & Bratton, 2006), whereas sports-related injuries are common in school age children and, motor-vehicle accidents occur more frequently in older children (Keenan & Bratton, 2006; von Holst, 2007). The most frequently affected individuals are typically aged 15-24 years, male (Barker-Collo, Wilde, & Feigin, 2009), and have a lower socio-economic status (Valery, Suzanne, Rita, Alice, & Nicola, 2010). Pre-existing psychiatric and substance use disorders are also commonly seen in patients with TBI (Parry-Jones, Vaughan, & Miles Cox, 2006; Robinson & Jorge, 2002). Approximately 70-90% of head injuries result in a mild TBI, with 5-20% of cases being moderate to severe and resulting in ongoing cognitive and behavioural sequelae (von Holst, 2007).

### 1.1.2 Pathophysiology

Blunt trauma to the head caused by some external force results in acceleration/deceleration forces leading to shifting of intracranial contents which causes primary brain injuries that are both focal and diffuse, as well as secondary brain injuries, which are initiated by the trauma however start to cause complications at a later time point (e.g. secondary oedema) (Ponsford, Sloan, & Snow, 2012).

#### 1.1.2.1 Primary Brain Injury

##### *1.1.2.1.1 Contusions*

Contusions are caused by blunt impact to the head. They are commonly seen in the basal and polar regions of the frontal and temporal lobes, two areas highly implicated in attention and working memory, as the skull surrounding these regions has bony protuberances that damage the brain during contact (Le & Gean, 2009). Contusions result in the death of local neurons as well as ischaemia, which leads to neuronal death due to deprivation of oxygen and glucose caused by the reduced blood supply.

##### *1.1.2.1.2 Diffuse Axonal Injury*

Shearing strains due to translational acceleration forces cause widespread axonal damage. This type of damage was initially described by Strich (1956, 1961) who termed it diffuse axonal injury (DAI). Given axonal damage is generally not diffuse, but stereotypically multifocal in nature the term 'traumatic axonal damage' is a more accurate description (Adams et al., 1989, 1991). DAI is, however, more commonly used to describe axonal injury following TBI and thus will be the term used in this thesis. DAI is caused by a cascade of events, starting with the deformation of axons and disruption in axonal

transport of critical elements (e.g. synaptic vehicles carrying neurotransmitters, proteins, lipids) which leads to accumulation of products causing axonal swelling and membrane rupture. Ultimately this may result in disconnection and Wallerian degeneration (Johnson, Stewart, & Smith, 2012). Axonal damage may take place over hours or days after injury. Petechial white matter haemorrhage can also accompany axonal injury (Povlishock & Katz, 2005). Junctions in which grey and white matter meet are particularly vulnerable to DAI due to the difference in tissue densities and tissue elastography. Areas that are commonly damaged include cortical areas, in particular the frontal and temporal poles, the corpus callosum, basal ganglia, hypothalamus, cerebellar peduncles and the fornices (Gaetz, 2004), many of which are known to be implicated in attentional function.

#### 1.1.2.2 Secondary Brain Injury

Secondary brain injury can be extensive and potentially more severe than that resulting directly from the injury itself (Kolb & Cioe, 2004). Cerebral ischemia, found to be the most significant secondary brain injury mechanism, is characterised by inadequate blood supply to the brain leading to hypoxia and cell death (Gennarelli, 1993; Venith et al., 2016). Cerebral ischemia is not limited to structually compromised regions and can occur in brain areas with no detectable structural damage (Venith et al., 2016). Mechanisms of secondary brain injury also include brain swelling caused by either cerebral oedema or hyperemia (Gaetz, 2004; Miller, 1991). This increases the pressure within the skull and can result in midline shift and also lead to hypoxic damage. Attenutating the permeability of the blood brain barrier following TBI has shown promising results with regard to the management of cerebral oedema and associated brain swelling (Donkin & Vink, 2010). Haemorrhaging in the brain caused by the tearing of blood vessels at the time of impact causes focal cell death and may lead to downstream hypoxic damage (Cassidy, 1994). Cerebral oxygenation may be compromised following TBI due to acute lung injury (a known complication of TBI) (Holland et al., 2003). Both vasoconstriction and reduction in

cerebral blood flow can result as a consequence of reduced O2 saturation leading to hypoxic injury (Madden, 1993; Werner & Engelhard, 2007). In addition, reductions in metabolism and utilisation of glucose have also been shown to occur post-TBI, these changes can be diffuse and may have a significant effect on brain functioning (Kolb & Cioe, 2004). Patients with TBI are also at risk of developing post traumatic epilepsy (PTE). The severity of the TBI as well as the presence of intracranial bleeding appear to increase the risk of developing PTE (Cavazos & Verellen, 2010).

#### 1.1.2.3 Dopamine Disturbance Following Traumatic Brain Injury

Focal and diffuse damage to midbrain and frontal regions can disrupt various neurotransmitter systems. Alterations to the DA (Bales et al., 2009), Norepinephrine (NE) (Kobori, Hu, & Dash, 2011), serotonin (5HT) (Rosenthal, Christensen, & Ross, 1998) and acetylcholine (Salmond, Chatfield, Menon, Pickard, & Sahakian, 2005) systems are implicated in the development of psychiatric and cognitive sequelae following TBI. Catecholamines DA and NE are crucial for attention, with DA believed to be the prominent neurotransmitter and neuromodulator that underpins attention (for review see Nieoullon, 2002). As the aim of this thesis is to investigate specific changes to the DA system post-TBI, it will be the main focus of this discussion. NE will be covered to a lesser extent.

Dopamine (DA) is a key neurotransmitter and neuromodulator within the brain, subserving many aspects of cognition and behaviour, including attention and working memory. Experimental research has provided evidence for the disturbance of catecholamine neurotransmission after TBI. Depletion in catecholamine (both DA and NE) concentrations have been identified in the cortex of rats up to two weeks post injury (McIntosh, Yu, & Gennarelli, 1994), whereas others studies have identified an increase in DA levels. Massucci et al. (2004), found an increase in DA levels and metabolism within the contralateral frontal cortex one hour post-injury, and within the ipsilateral frontal

cortex one day post-injury. Additionally, a delayed decrease in the dopamine transporter (DAT) protein within the frontal cortices has been demonstrated at seven and 28 days post-injury, but not at one day post injury (Yan et al., 2002). These changes may be attributable to nerve terminal damaged caused by DAI or down regulation of DAT (Yan et al., 2002).

An increase in tyrosine hydroxylase (TH) concentration, an enzyme necessary for the synthesis of DA in neurons and terminals, has been identified in rats' frontal cortices (Yan et al., 2001), and the nigrostriatal system (Yan et al., 2007), twenty-eight days post-injury. Similar changes have been identified within the prelimbic/infralimbic cortices in rats. Following cortical impact, increased TH concentration as well as increased DA and NE cortical levels were identified for up to two weeks post-injury (Kobori, Clifton, & Dash, 2006). Interestingly, a decrease in DA synthesis has been identified within the striatum at one week post-injury due to deficits in TH activity (Shin, Bray, Zhang, & Dixon, 2011). These findings suggest an initial reduction in DA neurotransmission in the first week following injury, followed by a compensatory response to augment extracellular levels of DA in the chronic phase (Massucci et al., 2004; Yan et al., 2001; Yan et al., 2007).

In humans, functional imaging investigations into dopaminergic (DAergic) neurotransmission post-TBI have revealed downregulation of dopamine-transporter (DAT) binding and dopamine 2-receptor within the striatum (Donnemiller et al., 2000). This is believed to be caused by DAI distrupting DA white matter pathways. Clinical studies have also demonstrated alterations in monoamine metabolites following TBI. Markianos, Seretis, Kotsou, and Christopoulos (1996), investigated cerebrospinal fluid (CSF) concentration of NE and DA, as well as serotonin metabolites methoxyhydroxyphenylglycol (MHPG), homovanillic acid (HVA) and HVA/5-hydroxyindole-acetic acid (5HIAA) in individuals with severe TBI. Concentrations of the metabolites were found to be associated with the patient's clinical state. For all participants, metabolites were high on the first day. They remained at high levels in the

patients whose conditions deteriorated, however, were found to decline in those whose clinical state improved. Urine catecholamine metabolite concentrations, however, do not reliably reflect severity or clinical outcomes in TBI, with no significant associations identified between metanephrine and normetanephrine concentrations and injury severity or outcomes following severe TBI (Salehpoor, Bazzazi, Estakhri, Zaheri, & Asghari, 2010).

In summary, animal models and clinical studies have provided evidence for the disturbance of the DA system, as well as the NE and 5HT systems, following brain injury. Change to DA neurotransmission is attributed, at least in part, to the cascade of events triggered by DAI. Research investigating catecholamine white matter pathology and attentional outcomes following TBI is lacking, however, and the association between the integrity of the MFB, an integral pathway in the DA system, and attentional performance following TBI is yet to be investigated.

### 1.1.3 Classification of Severity of Brain Injury

Understanding the extent of the pathophysiology and severity of TBI is important for the formulation of appropriate rehabilitation plans as well as predicting likely outcomes. Several measures have been developed to categorise TBI severity. Commonly used measures include duration of post-traumatic amnesia (PTA) which is characterised by a state of confusion, disorientation and an inability to lay down new memories. The *Westmead PTA Scale* (Shores, Marosszeky, Sandanam, & Batchelor, 1986) is a standardised measure of PTA that is used daily to assess a person's ability to make new memories, and orientation to time, date and place. Patients with mild TBI may experience duration of PTA from minutes to hours, whereas patients with severe TBI may take days to months to recover from PTA (Povlishock & Katz, 2005). Duration of PTA of greater than four weeks has been associated with moderate to severe disability in adults (Asikainen, Kaste, & Sarna, 1998; Tate et al., 2006). For the purposes of the present study, severity of

injury, as indicated by PTA duration, is defined as follows: <24 hours = mild; 24 hours – 1 week = moderate; 1-4 weeks = severe; > 4 weeks = very severe (Arlinghaus, Shoaib, & Price, 2005).

Another commonly used severity measure is the Glasgow Coma Scale (GCS), developed by Teasdale and Jennett (1974). It measures the level of consciousness by assessing eye movement, verbal and motor abilities. Scores ranging between 3-8 indicate severe TBI, 9-12 indicating moderate TBI, and 13-15 mild injury (Jennett & Teasdale, 1981). The GCS and PTA have been shown to be reliable predictors of neuropsychological and functional outcomes in TBI (Cattelani, Tanzi, Lombardi, & Mazzucchi, 2002; Ponsford, Spitz, & McKenzie, 2015; Tate, Broe, Cameron, Hodgkinson, & Soo, 2005). PTA has been found to be the more accurate predictor of long term outcomes, as well as likelihood of returning to work within the first year post injury (Cattelani et al., 2002; Tate et al., 2005). More recently, research has demonstrated that using PTA as a continuous variable, rather than a categorical variable, was more accurate in predicting prognosis (Ponsford et al., 2015)

### 1.1.4 Cognitive and Behavioural Sequelae Following Traumatic Brain Injury

Sequelae associated with mild injuries generally resolve within three to six months (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). However, cognitive and behavioural deficits following moderate to severe TBI are on-going, and although there is some recovery over time, residual deficits pose significant challenges for return to work and school, as well as pre-injury recreational and social activities (Bercaw et al., 2010; Draper et al., 2007; Hoofien, Gilboa, Vakil, & Donovick, 2001).

The previously discussed neuropathology associated with TBI underpins the cognitive and behavioural deficits commonly experienced following TBI. The neural networks, including the DA system, which subserve attentional abilities are made up of anatomically separate

brain regions connected by long white matter tracts. These brain areas, as well as the white matter pathways, are vulnerable to both focal and diffuse white matter damage caused by TBI. Thus, it is not surprising that attentional and working memory deficits are some of the most frequently reported impairments following TBI (Mathias & Wheaton, 2007; Ponsford & Willmott, 2004; Willmott et al., 2009). Slowing of processing speed is a prominent finding post-TBI and is thought to underlie other attentional abilities (e.g. selective attention) (Dymowski, Owens, Ponsford, & Willmott, 2015; Mathias & Wheaton, 2007). Deficits in this domain may have flow-on effects to other more complex attentional abilities. Individuals also experience problems with the strategic control of attention such as effectively dividing attention over two or more tasks, sustaining attention, ignoring competing stimuli, holding and manipulating information in the mind and appropriately shifting attention in a goal directed fashion (Dell'Acqua, Stablum, Galbiati, Spannocchi, & Cerri, 2001; Leclercq & Azouvi, 2002; Ziino & Ponsford, 2006a, 2006b). A more detailed discussion of attentional and working memory deficits following TBI is presented in following sections.

Executive functioning refers to an individual's ability to perform purposeful, goal-directed actions (Lezak, Howieson, & Loring, 2004). Skills such as planning, mental flexibility, abstract thinking, logical reasoning, and problem solving are necessary for individuals to be able to adapt to their environment. Many individuals with TBI experience executive dysfunction of some kind which can greatly affect their ability to reintegrate into the community (Donders & Larsen, 2012; Heled, Hoofien, Margalit, Natovich, & Agranov, 2011; Konrad et al., 2010).

Memory deficits are also frequently reported, with patients with TBI experiencing anterograde episodic memory deficits affecting the acquisition, consolidation and retention of new episodic memories (Konrad et al., 2010), as well as problems with prospective memory, for example, forgetting to buy milk on the way home (Pavawalla, Schmitter-Edgecombe, & Smith, 2012). Although some retrograde memory loss is often

experienced (Whiting & Hamm, 2008), long term remote memory is generally well preserved (McKinlay & Watkiss, 1999).

Communication problems such as word finding difficulties, impaired comprehension, tangential speech, excessive talking, and problems with the production of speech due to motor impairment are also common following TBI (Olver, Ponsford, & Curran, 1996; Snow, Douglas, & Ponsford, 1997). As the neuropathology associated with TBI is widespread, language problems can arise without focal damage to the language centres of the brain (Roa, 1996). Personality changes including increased self-centeredness, impulsivity, irritability, and disinhibition are also experienced following TBI and can cause significant difficulties for carers and families (Brooks & McKinlay, 1983). Empirical research has shown that as many as 61.1% of patients with TBI experience personality changes (Deb, Lyons, Koutzoukis, Ali, & McCarthy, 1999; Olver et al., 1996; Trevena & Cameron, 2011).

## 1.2 ATTENTION FOLLOWING TRAUMATIC BRAIN INJURY

Attentional deficits caused by TBI are heterogeneous and can include reduced speed of information processing, problems with selective attention, such as dividing and focusing attention, impairments of arousal and sustained attention, and executive control of attention. The complexity of attentional deficits seen post-TBI is not surprising given that attention itself is a complex multidimensional construct. Many theories of attention have been proposed over the years (Baddeley, 1986; Norman & Shallice, 1980; Posner & Petersen, 1990; Posner & Rothbart, 1992), however, when taken together, a common model of attention emerges. Firstly, there is the distinction between conscious and automatic processing of information. Shiffrin and Schneider (1977) define conscious processing as the voluntary control over information processing that is limited in capacity and rate, and therefore involves serial processing. Automatic processing, however, is the process of carrying out well learnt tasks, that are unaffected by load, and involve parallel

processing. Selective attention, sustained attention and strategic control of attention all involve conscious control of processing and thus are limited in capacity and rate. Mechanisms of controlled processing can be further broken down into the anterior system, which regulates strategic control of attentional resources, and the vigilance system, responsible for general arousal, alertness and sustained attention (Posner & Petersen, 1990; Posner & Rothbart, 1992). The current thesis will focus on non-spatial attention deficits as they are more frequently experienced following brain injury.

### 1.2.1 Orienting Attention

One of the most basic attentional abilities is the orientation of attention. This is thought to be carried out by the posterior attention network, which includes the posterior parietal lobes (Heilman, Watson, Valenstein, & Damasio, 1983; Mesulam, 1987), the pulvinar nucleus of the thalamus (Petersen, Robinson, & Morris, 1987), the reticular nuclei and the superior colliculus (Posner & Rothbart, 1992). The functions carried out by this network include the automatic disengaging from one point of focus, direction of movement to the new stimulus and the subsequent allocation of attention to the new stimulus for the purpose of serial processing. This usually occurs when there is an unexpected stimulus, for example a loud bang caused by an object falling, and is referred to as *overt spatial orienting*. Individuals can also engage in *covert orienting of attention* which includes shifting attention to a visual scene represented in memory, rather than the environment (Posner & Petersen, 1990). Damage to the posterior attention system has been implicated in unilateral neglect (Mort et al., 2003; Ringman, Saver, Woolson, Clarke, & Adams, 2004), and problems with recognition of objects, as well as disengaging from stimuli (Posner, Walker, Friedrich, & Rafal, 1984). As orienting of attention is a bottom-up cognitive ability, deficits may influence other higher order cognitive skills such as memory, executive functioning and other aspects of attention (Drew et al., 2007).

When investigating covert attention in a group of individuals with TBI, no difference was found with regard to the ability to disengage, reorientate and re-engage attention, however, reduced processing speed on the Posner's Covert Orienting of Attention Task (COAT: Posner, 1980), was identified within the TBI group when compared to controls (Bate, Mathias, & Crawford, 2001). Using a dual task paradigm in which a phoneme detection task was administered simultaneously to the COAT, participants' covert orienting ability was also assessed. Results showed that addition of a secondary task did not affect TBI participant's ability to reorient their attention. However, when compared to controls, the participants with TBI were found to perform significantly worse on the phoneme detection task, indicating an auditory-verbal attention impairment under the dual task condition.

### 1.2.2 Arousal and Sustained Attention

The vigilance system modulates the level of alertness and arousal and is responsible for sustained attention. Whilst in a vigilant state an organism is aware of its spatial orientation and is able to sustain attention for an extended period of time in order to process high priority stimuli (Posner & Petersen, 1990). The locus coeruleus in the brain stem reticular formation and its norepinephrine inputs into the parietal lobes, the pulvinar nucleus of the thalamus, and the colliculus have been proposed as the structures involved in these functions. This system is also thought to be affected by motivation and fatigue. The limbic system is proposed to influence the motivational aspects of attention, with the amygdaloid nuclei and septal regions influencing the importance of stimuli and the hippocampus being responsible for the memory (Cohen, 1993). In addition, the right lateral frontal lobe is proposed to modulate and maintain an alert state in a goal direct manner (Daffner et al., 2000; Siddiqui, Chatterjee, Kumar, Siddiqui, & Goyal, 2008; Wilkins, Shallice, & McCarthy, 1987), however there are some discrepancies in the literature (van Zomeren & Brouwer, 1994).

Both tonic and phasic arousal affect an organism's overall alertness (Posner, 2008; Stuss & Benson, 1984, 1986). The Frontal-Diencephalic-Brainstem System describes tonic arousal as the receptivity to slow moving changes throughout the day, such as sleep/wake cycles and food intake, and is regulated by the ascending reticular activating system. Phasic arousal, in contrast, is responsible for the more rapid changes in arousal that occur in response to the environment (e.g. increased heart rate in response to a more difficult task) and is modulated by diffuse thalamic projections (Stuss & Benson, 1984, 1986).

Difficulty sustaining attention is frequently reported by individuals with TBI including problems with maintaining concentration, and becoming easily distracted by noise or other stimuli (Mateer & Mapou, 1996). Alterations to alertness and/or damage to the vigilance system could results in these deficits. Disruptions to phasic arousal, as measured by physiological responses (e.g. alterations in cortical electrical potential and electrodermal responses) to changes in the environment, have been demonstrated post-TBI (Cremona-Meteyard & Geffen, 1994; Fuller, Sherman, Pedersen, Saper & Lu, 2011) Nativ, Lazarus, Nativ, & Joseph, 1994). Research into sustained attention deficits following TBI, however, has shown mixed results, partly related to the differing tasks purporting to measure this aspect of attention. Classical vigilance tasks which measure participants' response to infrequent, target stimuli randomly presented amongst non-target stimuli over extended periods of more than 30 minutes often fail to find a significant decrement in performance in individuals with TBI (Brouwer & van Wolffelaar, 1985; Parasuraman, Mutter, & Molloy, 1991; Spikman, van Zomeren, & Deelman, 1996; Ziino & Ponsford, 2006b). A different paradigm purporting to assess sustained attention is *The Sustained Attention to Response Task* (SART: Robertson, Manly, Andrade, Baddeley, and Yiend, 1997). This task requires participants to respond to target and non-target stimuli presented on a screen and aims to capture lapses in attention as measured by number of errors. Performance on this task by individuals with TBI is generally characterised by significantly fewer targets being selected and more errors when compared to healthy controls (Chan, 2002; Manly et al., 2003). However, sustained

attention is the ability to sustain performance on a task over an extended period of time. In contrast to the vigilance tasks, the SART is a relatively short task, taking under five minutes to complete. Additionally, it records errors rather than decline in performance over time, thus may not be measuring sustained attention deficits *per se*.

### 1.2.3 Selective Attention

Selective attention involves focused attention which is the ability to maintain attention to selected objects whilst ignoring conflicting stimuli, as well as the ability to effectively divide attention across tasks (Posner & Petersen, 1990; Posner & Rothbart, 1992). Speed of information processing is highly implicated in selective attention, as a reduction in speed of processing results in a decrease in the amount of information that can be processed in any given timeframe, due to limited capacity of the short term store (Cohen, 1993). Selective attention is thought to be performed by the anterior system which consists of the basal ganglia and the mid-prefrontal cortex including the cingulate gyrus and supplementary motor areas (Cohen, 1993; Posner & Rothbart, 1992).

Impairments in the ability to selectively attend to information following brain injury have been demonstrated using the Computerised Selective Attention Task (SAT; Ziino & Ponsford, 2006a). This task requires participants to selectively attend to presented stimuli and respond in accordance with a set of rules. Ziino and Ponsford (2006a) found the TBI group made more errors and were slower to complete the Complex Selective Attention Task (CSAT), when compared to controls. Similarly, Willmott et al. (2009) and Dymowski et al. (2015) demonstrated participants with TBI were slower to respond to stimuli on all conditions of the SAT, providing support for the role of information processing speed in selective attention.

#### 1.2.3.1 Information Processing Speed

Slowed speed of information processing is one of the most prominent findings following TBI(Dymowski et al., 2015; Felmingham, Baguley, & Green, 2004; Ponsford & Kinsella, 1992), and has been found to be the most prominent cognitive deficit 10 to 20 years folllowing TBI (Hoofien et al., 2001). A decline in processing speed can greatly affect the rate at which tasks are completed and may potentially underlie the more complex cognitive deficits seen after TBI (Mathias & Wheaton, 2007). In fact, reductions in speed of information processing have been found to account substantially for selective attention deficits seen post-TBI (Brouwer, Ponds, Van Wolffelaar, & Van Zomeren, 1989; Dymowski et al., 2015; Spikman et al., 1996).Such deficits have been found to be proportionate to severity of injury (Spikman, Timmerman, Zomeren van, & Deelman, 1999), but many patients with TBI perform one standard deviation below that of healthy controls on various measures of processing speed (Mathias & Wheaton, 2007). *The Symbol Digit Modalities Test* (SDMT) developed by Smith (1991) is a timed task that requires participants to use a key to decode a set of symbols and is sensitive to reductions in processing speed post-TBI (Draper & Ponsford, 2008; Ponsford & Kinsella, 1992; Willmott & Ponsford, 2009; Willmott et al., 2009).Tasks assessing speed of information processing such as the SDMT are generally reliant on different modalities, thus performance is considered to be dependent upon numerous white matter pathways connecting these regions (Deary, Penke, & Johnson, 2010). Reduced information processing speed has been consistently linked with diffuse white matter damage following TBI (e.g. Kourtidou et al., 2013). A discussion on the association between white matter damage and reduced information processing speed is presented in subsequent sections

#### 1.2.3.2 Divided Attention

Divided attention is the ability to allocate attention to one or more tasks in a goal directed fashion. It has been proposed that selective attention deficits, in particular the inability to effectively divide attention over two or more tasks, are due to an inadequate rate of information processing (Cohen, 1993; Schneider & Shiffrin, 1977). As the brain has a limited capacity to process information at any given time, a decline in the speed of processing may result in the inability to deal with all the information needed for the completion of a task (Cohen, 1993; Schneider & Shiffrin, 1977). Therefore, in order to assess divided attention, a task must look at both speed and accuracy of performance (Ponsford & Kinsella, 1992).

*The Ruff 2 & 7* (Ruff & Allen, 1995) is a pen and paper cancellation task that measures accuracy and speed for both automatic and controlled processing tasks. Participants with TBI have been found to be slower on the cancellation task when compared to controls (Allen & Ruff, 1990; Levin, High, Goldstein, & Williams, 1988). More recently, Willmott et al. (2009) found that participants with TBI cancelled significantly fewer targets than controls under both conditions. Interestingly, it was also found that the difference in processing speed between the automatic and controlled conditions was smaller for the participants with TBI than for the controls. The authors proposed that participants with TBI may require controlled processing for the so-called “automatic” conditions as well as the controlled conditions, thus, they were disadvantaged in both aspects resulting in no significant difference between the controlled and automatic processing speed.

Dual task experiments have also been utilised to assess divided attention deficits in patients with TBI. These experiments require the participant to conduct two tasks simultaneously, for example generating random numbers between 1 and 10 whilst performing a visual reaction time task (Leclercq et al., 2000). A dual task decrement has consistently been found in patients with TBI (Brouwer, Verzendaal, van der Naalt, Smit, & van Zomeren, 2001; Brouwer et al., 1989; Leclercq et al., 2000; Spikman et al., 1996;

Toyokura, Nishimura, Akutsu, Mizuno, & Watanabe, 2012; Withaar, 2000). Some studies found that the dual task decrement could be accounted for by reduced speed of processing (Brouwer et al., 1989; Pare, Rabin, Fogel, & Pepin, 2009; Spikman et al., 1996), whereas other studies have found a dual task decrement exists above and beyond that which could be accounted for by processing speed alone (Azouvi, Jokic, Der Linden, Marlier, & Bussel, 1996; Brouwer et al., 2001; Brouwer, Withaar, Tant, & van Zomeren, 2002; Leclercq et al., 2000; Toyokura et al., 2012; Withaar, 2000). These studies employed a more complex experimental design, in which participants were required to complete multiple dual task conditions of varying difficulty (Azouvi et al., 1996; Brouwer et al., 2001; Brouwer et al., 2002; Leclercq et al., 2000; Withaar, 2000). Thus, reduced speed of processing may account for dual task decrements seen in simple tasks, however, for more complex tasks that include a high working memory load and strategic allocation of attentional resources, there appears to be a divided attention deficit that cannot be solely explained by speed of processing (Azouvi et al., 2004; Azouvi et al., 1996; Brouwer et al., 2001; Brouwer et al., 2002; Leclercq et al., 2000; Withaar, 2000) .

#### 1.2.3.3 Focused Attention

Focused attention is the ability to maintain attention to a selected object whilst ignoring conflicting or redundant stimuli. Neuropsychological testing has identified focused attention deficits in individuals with TBI, albeit with a strong influence of processing speed on task performance. The Stroop test is sensitive to focused attention deficits following TBI (Ben-David, Nguyen, & van Lieshout, 2011; Goethals et al., 2004; Ponsford & Kinsella, 1992). It requires participants to focus on the relevant stimuli whilst ignoring competing information. The cause of the Stroop effect in participants with TBI, however, is a matter of debate. While some researchers have concluded that the Stroop effect is caused by an inability to focus attention and ignore competing stimuli (Goethals et al., 2004), others have proposed that the effect seen may be accounted for by a reduction in

processing speed. Ben-David et al. (2011) conducted a meta-analysis of ten studies assessing the performance of participants with TBI on Stroop tasks. While they found that participants with TBI showed a significant Stroop interference effect when compared to controls, they demonstrated that the discrepancies can mainly be attributed to a reduction in processing speed and, to a lesser degree, changes in sensory processing in those with TBI.

Deficits in selective attention in individuals with TBI may be related to a working memory problem or an inadequate executive system responsible for the dividing and focusing of attention in a goal directed fashion. Problems with the allocation of attention are discussed in the next section.

### 1.2.4 Strategic Control of Attention

Norman and Shallice (1980) proposed that the dividing and focusing of attention was performed by the *Supervisory Attentional System (SAS)*. For any novel or complex activity both the posterior and anterior network system will be activated (Posner & Rothbart, 1992). In such situations the SAS becomes activated in order to effectively allocate attentional resources for the successful completion of a task (van Zomeren & Brouwer, 1994). Once a task becomes automatic, an action schema is formed which signals to the SAS that it is not needed when a specific stimulus is perceived. The SAS has two key aspects: firstly, selectivity, the filtering out of irrelevant sensory information, modulated by a top-down mechanism able to select relevant objects to attend to for completion of current goals; and secondly, intensity, the degree of attention underlying the efficiency of selection, related to the general level of alertness. The SAS is thought to be performed by the left prefrontal cortex (Burgess & Shallice, 1996), and the anterior cingulate (Posner & DiGirolamo, 1998). A key component that relates to the SAS is the Baddeley (1986) Central Executive which serves the purpose of temporally storing and manipulating

information during conscious information processing, skills required for working memory that are in turn required for the shifting, dividing and focusing of attention. The Baddeley (1986) model also included a phonological loop, a temporary store for information via sub-vocal rehearsal and a visuospatial sketch pad, a temporary store for visual or spatial information. In recent years Baddeley (2001) has added a limited capacity storage system to the model that sits in-between the two subsystems and the long term store called the episodic buffer.

Difficulties allocating attentional resources are common following TBI and can greatly impact daily functioning. Deficits in strategic control of attention following TBI generally appear when there is an increase in time pressure, difficulty level, or working memory load (Azouvi et al., 2004; Azouvi et al., 1996; Bohnen, Jolles, & Twijnstra, 1992; Brouwer et al., 2001; Brouwer et al., 2002; Leclercq & Azouvi, 2002; Withaar, 2000). Studies using the *n*-back, a task which requires participants to mentally keep track of the letter on the screen that was presented one screen back, two screens back and sometimes three screens back, have shown working memory deficits in participants with moderate to severe TBI (Perlstein et al., 2004; Slovarp, Azuma, & Lapointe, 2012). Using the *n*-back, Slovarp et al. (2012), found participants with TBI demonstrated a significantly lower hit rate and a significantly higher false alarm rate, when compared to healthy controls. Overall, it was found that participants with TBI had difficulty discriminating between targets and non-targets, indicating they were less able to mentally keep track of, and update, information required for successful task performance.

When investigating different functions of working memory, including the phonological loop, the visuospatial sketchpad and the central executive in individuals with severe TBI, Vallat-Azouvi, Weber, Legrand, and Azouvi (2007) found participants with TBI performed more poorly on executive aspects of attention including reading span, arithmetic span, Brown–Peterson paradigm (visual modality), and Brown–Peterson paradigm (verbal modality) (Brown, 1958; Peterson & Peterson, 1959). With regard to the two subsystems,

however, although differences were observed between the groups, this effect did not reach significance.

More recently, Azouvi et al. (2016) investigated the sensitivity of the Groupe de réflexion sur l'évaluation des fonctions exécutives (GREFEX: Godefroy, 2008) battery in identifying executive dysfunction following TBI. Although the individuals with TBI were found to perform significantly worse on all aspects of tasks assessed, the tasks found to be the most sensitive to executive impairments following TBI included verbal fluency, as well as two tasks measuring executive control of attention, Stroop reading and TMT-B. Stroop reading subtest requires participants to read aloud a list of colour names, and is predominantly a speed of information task. TMT-B, however, is the more difficult aspect of the Trail Making Test, requiring participants to switch their attention from numbers to letters. Although it does have a speed of information component, it also requires executive control of attention. Azouvi et al. (2016) have provided support for the use of this task in identfying executive dysfuntion following TBI.

In summary, the most common attentional deficit resulting from TBI seems to be reduced speed of information processing. A reduction in processing speed may underlie many of the more complex attentional problems reported after brain injury. Although information processing speed cannot ever fully be delineated from other aspects of attention, impairments of sustained and selective attention are also apparent when task complexity is increased, or under conditions of increased time pressure or working memory load. Problems with working memory and executive control of attention also appear to be present when individuals with TBI are assessed with tasks that measure the strategic control of attentional resources. The varied and profound nature of attentional deficits experienced after TBI is not surprising when considering the extensive neuropathological and neurochemical changes that occur following TBI. Disruption to catecholamine systems has already been explored in previous sections. Catecholamine neuroanatomy, as

well as the contribution of catecholamines to attention and working memory will be discussed in the following section.

## 1.3 CATECHOLAMINES AND ATTENTION

Multiple neurotransmitter systems exist within the brain and all play an important role in cognition and behaviour. Several different neurotransmitters have been linked to attentional and working memory functions. Acetylcholine, which has historically been linked with learning and memory, has been associated with attentional effort, top down control of orienting of attention and stimulus detection (for review see Klinkenberg, Sambeth, & Blokland, 2011). Serotonin signalling has been linked with selective attention (Carter et al., 2005). Attentional function has also been linked to glutamate levels, with reduced glutamatergic activation associated with impaired attention and working memory (Krystal et al., 2005). Catecholamines, including DA and NE, have long been shown to be crucial for attentional and working memory function (Bäckman et al., 2011; Clark et al., 1986b, 1987a, 1987b, 1989). As the focus of this thesis is DA, the following section will focus on DA, as well as NE to a lesser extent.

DA and NE are the major cerebral catecholamines. These neurotransmitters are involved in many different circuits. They underpin diverse sensory, motor and cognitive abilities and in particular have been found to play pivotal roles in attention and working memory function (Bäckman et al., 2011; Clark et al., 1986b, 1987a, 1987b, 1989).

DA is a key neurotransmitter and neuromodulator within the brain. There are five main subtypes of DA receptors, all of which are G-protein coupled. Rather than directly causing inhibitory or excitatory post-synaptic activity, they exert their effect by activating an intracellular secondary messenger system, modulating neuronal activity (Lachowicz & Sibley, 1997; Missale, Nash, Robinson, Jaber, & Caron, 1998; Yang & Seamans, 1996). DA receptors are disbursed throughout the brain, including regions involved in cognitive

functions. $D_5$ receptors are expressed in the hypothalamus and hippocampus, $D_4$ receptors are found in high quantities in the cortex, $D_3$ are located in the caudate, nucleus accumbens and the cortex and have a functional role in cognition (Bullock, 2007). $D_2$, $D_1$ and subtypes are found in high numbers in the putamen and caudate nucleus of the striatum as well as the nucleus accumbens (Feldman, Meyer, & Quenzer, 1997).

Several DA pathways have been identified. The nigrostriatal system contains cell bodies in the substantia nigra which connect to the corpus striatum before innervating the medial frontal lobes. This circuitry is involved in maintaining normal motor behaviour. DA is also involved in instinctive behaviour via the tuberoinfundibular pathway, which includes cell bodies in the arcuate nucleus and periventricular area of the hypothalamus that in turn connect to the anterior pituitary. Both the mesolimbic and mesocortical pathways have their cell bodies in the ventral tegmental area (VTA). DA subserves cognitive abilities via the mesocortical circuit (Nieoullon, 2002). This circuit projects from the VTA to the cortex, with many ascending fibres terminating in the pre-frontal cortex (Chandler, Waterhouse, & Gao, 2014; Ikemoto, 2007). The mesolimbic system projects from the VTA and innervates the nucleus accumbens, hippocampus, lateral septum and amygdala, and is highly implicated in reward processing (Chandler et al., 2014; Ikemoto, 2007). The mesocorticolimbic pathway comprises DA neurons with their cell bodies in the VTA and connects to the ventral striatum and nucleus accumbens, before projecting to the cortex and innervating the frontal cortices. DA within the mesocorticolimbic circuit is also implicated in cognitive function, particularly that undertaken by the prefrontal cortex, including attention and working memory (Nieoullon, 2002).

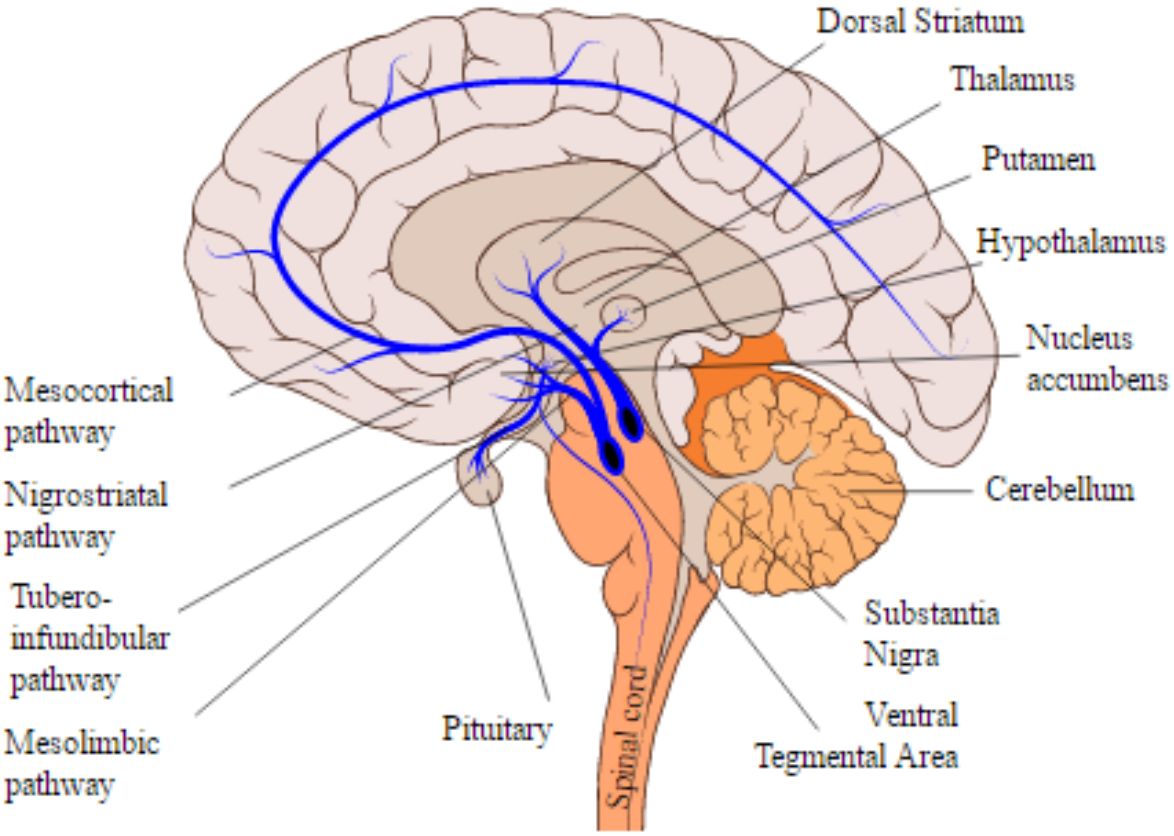


Figure 1.3 The mesolimbic, mesocortical, mesocortical and tuberoinfundibular dopaminergic pathways.

The medial forebrain bundle (MFB) is a crucial pathway in the DA system. It contains catecholamine fibres, including mesocorticolimbic fibres that project from cell bodies in the VTA to the ventral striatum/nucleus accumbens and terminate in the cerebral cortex. The MFB has two branches: 1) the inferior-medial branch (imMFB,) which follows the wall of the third ventricle, terminating in the lateral hypothalamus; and 2) the superolateral branch (slMFB) projects to the ventral striatum and nucleus accumbens before innervating the frontal cortex, specifically the dorsolateral prefrontal cortex and the orbitofrontal cortex (Coenen et al., 2009; Coenen, Panksepp, Hurwitz, Urbach, & Mädler, 2012; Coenen, Schlaepfer, Maedler, & Panksepp, 2011). This pathway, along with other catecholamine pathways, is particularly vulnerable to damage caused by TBI due to their physiological characteristics. Catecholamine fibres are poorly myelinated, long and project to many areas within the brain, placing them at a relatively high risk of injury due to the

shearing strains of blunt force trauma (Jenkins, Mehta, & Sharp, 2016; Staal & Vickers, 2011).

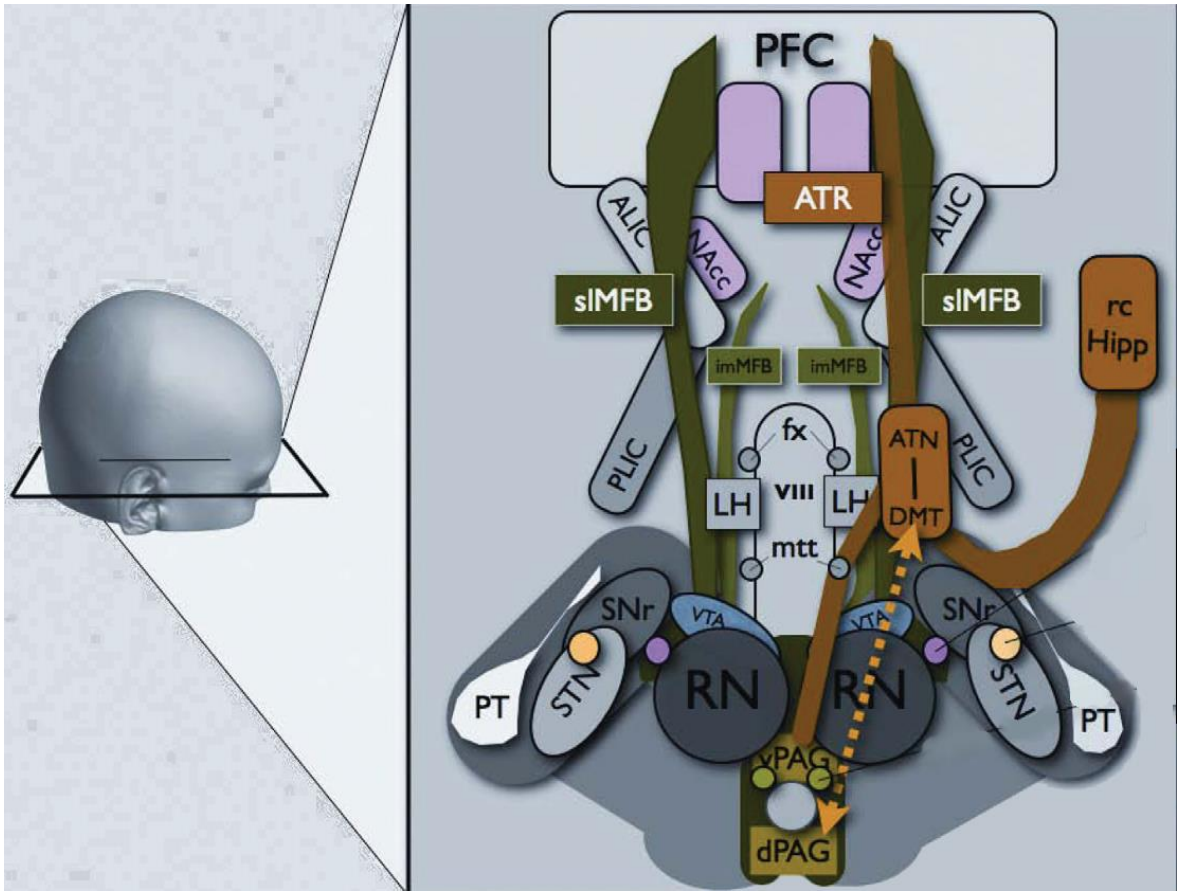


Figure 1.4 Depiction if the medial forebrain bundle (MFB).

The MFB divides into the inferior-medial branch (imMFB) which runs through the lateral third ventricle (VIII) and connects to the lateral hypothalamus (LH), and the superiorlateral branch (slMFB) which projects to the ventral striatum/nucleus accumbens (NAcc) before terminating in the prefrontal cortex (PFC). Further abbreviations ALIC = anterior limb of the internal capsule*;* ATN = anterior thalamic nucleus; ATR = anterior thalamic radiations; DM= dorsomedial thalamus; dPAG = dorsal peri-aqueductal gray; fx = fornix; LH = lateral hypothalamus; ot = optic tract; mtt = mammillo-thalamic tract; PAG = periaqueductal gray matter; PLIC = posterior limb of the internal capsule; PT = pyramidal tract; rc hipp = retrocommissural hippocampus; RN = red nucleus; STN = subthalamic nucleus; SNr = substantia nigra; VTA = ventral tegmental area. *Note*. Figure adapted from (Coenen, Schlaepfer, Maedler & Panksepp, 2011)

Norepinephrine is also implicated in attention, particularly arousal and vigilance. The system involved in arousal and vigilance is the locus coeruleus complex and its projections

into the thalamus and cerebral cortex. Other systems in which norepinephrine is involved include the lateral tegmental system, which is responsible for the regulation of visceral systems, and the dorsal medullary group.

Adrenergic receptors include alpha receptors (α1, α2) and beta receptors (β1, β2, β3). Receptor subtypes have different affinities to NE and thus variable responses can be elicited by either low or high doses of NE. Receptors α1 and β1 have a low affinity to NE; thus it takes high doses of NE to elicit a response. α2 receptors have a high affinity to NE and respond to low doses of NE. Therefore, pharmacological agents that cause increases in NE will have quite different effects from those that result in lower doses of extracellular NE. Within the PFC, DA and NE exhibit a U-shaped dose effect, in which a moderate amount results in optimal functioning, but too much or too little of either can impair cognitive function (Arsten, 2011).

### 1.3.1 Orienting of Attention

DA has been found to play a significant role in the orienting of attention in both animals and humans. In experimental models, unilateral neglect has been produced by lesioning the contralateral substantia nigra, striatum and ventral tegmental area (Clark et al., 1987a). Failure to orientate to visual, olfactory or tactile stimuli has been associated with bilateral loss of nigrostriatal dopamine in rats (Clark et al., 1987a; Iversen, 1979). With regard to NE, the locus coeruleus has been found to fire during the shifting of attention to novel stimuli as well as to food and other stimuli (Arnsten, 2011). It has also been found to increase the signal-noise ratio of neural firing in the sensory cortex in response to sensory stimuli, which indicates that NE may facilitate attention to particular sensory stimuli in the environment (Clark et al., 1987a). In humans, reducing levels of DA and NE by administering droperidol (a DA antagonist) and clonidine (an alpha-2 adrenoceptor agonist) to healthy participants improves orienting of attention, most likely in the

disengaging of attention from one stimulus in order to engage attention with another (Clark et al., 1989).

### 1.3.2 Selective Attention

Catecholamine activity also contributes to higher order attentional function. Simon, Scatton, and Moal (1980), demonstrated increased distractibility and a reduced ability to selectively attend to relevant stimuli during a T-maze alternation experiment following bilateral lesioning of the DAergic A10 nuclei, situated in the VTA. Lesions in ascending norepinephrine pathways in rats have been associated with impairments in discriminant task performance (Mason & Fibiger, 1979; Mason & Lin, 1980), as well as impairments on choice reaction time tasks, when compared to control rats (Carli, Robbins, Evenden, & Everitt, 1983).

Although specific catecholamine circuitry has not been investigated, using pharmacological studies, DA and NE have been found to influence selective attention ability in humans (Clark, Geffen, & Geffen, 1986a; Clark et al., 1986b, 1987b). Administration of clonidine - an alpha-2 adrenoceptor agonist shown to diminish locus coeruleus-cortical activation in animals (Aghajanian, 1982) - has been linked with reduced processing speed on a selective attention task, as well as reduced ability to detect targets. In contrast, methylphenidate has been associated with increased response rate on a selective attention task, resulting in increased target and error detection rate (Clark et al., 1986b). Droperidol (a DA antagonist) has been linked to reduced processing speed on selective attention tasks. No significant effect was identified on attentional performance when methylphenidate was administered separately. When administered after droperidol, however, methylphenidate reversed all the effects. (Clark et al., 1986a).

More recently, Kahkonen et al. (2001) investigated the effects of DAergic neurotransmission on selective attention. They used magnetoencephalography (MEG) and

electroencephalography (EEG) to study neural network changes associated with administration of haloperidol (a partially selective $D_2$ receptor antagonist) during a selective attention task. During both selective and involuntary attention conditions of the task, haloperidol was found to significantly impair selective attention by blocking DA $D_2$ receptors, providing evidence for the modulation of selective attention with DA neurotransmission.

### 1.3.3 Working Memory and Executive Control of Attention

The role of catecholamines in modulating executive control of attention and working memory, as well as other prefrontal cognitive abilities has been well established (Brozoski, Brown, Rosvold, & Goldman, 1979; Cai & Arnsten, 1997; Lee & Goto, 2015; Verma & Moghaddam, 1996). In one of the first studies of its kind, Brozoski and colleagues (1979) demonstrated the importance of DA in working memory. Using rhesus monkeys it was revealed that depletion of DA in the dorsolateral prefrontal cortex, by intracortical injections of selective catecholamine toxins, resulted in impairment of performance on delayed response performance, a spatial working memory task. Indeed, it was found that the impairment was as severe as surgical ablation of the dorsolateral prefrontal cortex. Treatment with drugs that increase DA , L-dopa or apomorphine, reversed the impairment (Brozoski et al., 1979).

Neuroimaging has proved to be an important tool for assessing the role of catecholamines in attentional functioning in humans. A Positron Emission Tomography (PET) study demonstrated an increase in the amount of DA released as a result of a working memory training program, aimed at improving the updating component of working memory (Bäckman et al., 2011). After five weeks of training, the healthy participants' working memory ability improved, as measured on letter-memory tasks and the *n*-back, and this was associated with an increase in DA release (Bäckman et al., 2011). Furthermore, it was

found that DA levels returned to normal after training, indicating that the increase in DA levels in response to working memory training was transient.

More recently, it has been demonstrated that NE also plays a critical role in working memory. Stimulation of alpha1 or beta receptors in the prefrontal cortex results in working memory impairment (Arnsten, 2000; Mao, Arnsten, & Li, 1999), however, stimulation of alpha2 receptors in the prefrontal cortex results in improvements in working memory (Jäkälä et al., 1999; Ramos et al., 2005; Swartz, McDonald, Patel, & Torgersen, 2008). Furthermore, blocking alpha2 receptors in the dorsolateral prefrontal cortex has been shown to result in working memory deficits in monkeys (Li & Mei, 1994). Administration of guanfacine (a NE agonist) to humans has also been found to improve working memory (Jäkälä et al., 1999; Swartz et al., 2008). Administration of methylphenidate, a psychostimulant that enhances both DA and NE concentrations in the prefrontal cortex, has shown to improve executive functions such as set shifting attention to novel stimuli (Rogers et al., 1999) as well as planning as assessed by the CANTAB (Elliott et al., 1997). Spatial working memory has also been shown to improve with administration of methylphenidate in healthy adults (Elliott et al., 1997; Mehta et al., 2000), providing further evidence for the roles of both DA and NE in working memory and executive attentional control.

In summary, DA and NE appear to play a role in orienting attention and, selective attention as well as working memory function. In both animal and human experiments depletion of catecholamine concentration in the frontal cortices has led to poorer attention and working memory performance, whereas increase in catecholamine concentration has led to improvement in attention functioning. Administration of medication that increases extracellular DA concentration has been associated with improvements in attentional performance following TBI, however, the underlying mechanisms are poorly understood. Further elucidating the nature and extent of injuries that disrupt the DA system post-TBI might inform pharmacological treatment of attentional deficits post-TBI.

### 1.3.4 Catecholamine Medication and Amelioration of Attentional Deficits

Pharmacological agents used to aid attentional rehabilitation post-TBI have included catecholamine agents and acetylcholine agonists. Commonly used catecholamine agents include methylphenidate and dextroamphetamine, which both increase extracellular concentrations of catecholamines by increasing the release of DA and NE into the synaptic cleft, as well as reducing presynaptic reuptake (Fleckenstein, Volz, Riddle, Gibb, & Hanson, 2007; Solanto, 1998; Volz et al., 2007; Volz, Farnsworth, Rowley, Hanson, & Fleckenstein, 2008). Amantadine, which increases the presynaptic release of DA, reduces the reuptake of DA and changes the number of DA receptors. Another agent, levodopa increases DA production. Bromocriptine, a postsynaptic receptor agonist for DA, has also been used with some success (McAllister, Flashman, et al., 2011). Commonly used acetylcholine (ACh) agonists include donepezil, physostigmine and CDP-choline, all of which increase extracellular ACh levels. Drugs that work to increase NE including atomoxetine, which inhibits reuptake of NE and guanfacine, a selective α-2A receptor NE agonist have also been trialled with mixed results (McAllister, McDonald, et al., 2011; Ripley et al., 2014). As the current study is evaluating the disruptions to the DA system post TBI, this review will focus on medications that work to influence extracellular DA levels.

Using a double-blind, placebo-controlled crossover trial, McDowell, Whyte, and D'Esposito (1998), investigated the effects of low-dose bromocriptine on attention and executive function in individuals with TBI. With administration of bromocriptine, individuals with TBI showed improved performance on tasks measuring strategic control of attention and, divided attention, as well as other domains of executive functioning including idea generation and reward based learning. No significant effect, however, was

evident on measures of working memory or information processing speed with administration of bromocriptine. In contrast, Whyte et al. (2008) did not observe a significant improvement on multiple aspects of attention, including processing speed, sustained attention, divided attention, and everyday aspects of attention (i.e. ratings of attention), with the administration of bromocriptine to individuals with TBI.

In individuals with TBI, administration of amantadine has been linked to improvements in focused attention (Kraus & Maki, 1997; Nickels, Schneider, Dombovy, & Wong, 1994), speed of processing (Kraus & Maki, 1997), sustained attention and alertness (Nickels et al., 1994). However, there is some discrepancy in the research findings, with Schneider (1999) failing to identify significant improvements in response to amantadine. In a controlled case study, both dextroamphetamine and methylphenidate were found to attenuate attention, memory and behavioural deficits, with dextroamphetamine associated with greater improvements than methylphenidate (Evans, Gualtieri, & Patterson, 1987). Methylphenidate, in its short release form, has been associated with improvement in speed of processing (Whyte et al., 1997; Whyte et al., 2004a; Willmott & Ponsford, 2009), alertness (Lee et al., 2005), selective (Gualtieri & Evans, 1988), divided (Gualtieri & Evans, 1988; Kaelin, Cifu, & Matthies, 1996; Plenger et al., 1996), and sustained attention (Gualtieri & Evans, 1988; Kaelin et al., 1996); as well as attention span (Kaelin et al., 1996; Plenger et al., 1996). More selective agents that only work on the DA system may be more effective in alleviating attentional impairment (McAllister, Flashman, Sparling, & Saykin, 2004).

In an attempt to provide insight into the effects of methylphenidate administration, Kim, Whyte, Patel, Europa, Wang, et al. (2012) used continuous arterial spin labelling (CASL), a type of perfusion magnetic resonance imaging (fMRI), in a double-blind placebo controlled crossover study to measure neural activity in participants with TBI receiving methylphenidate. Participants completed the visual sustained attention task and the 2-back whilst in the scanner. Accuracy and median reaction time significantly improved on

the visual sustained attention task with administration of methylphenidate. In addition, significantly faster responses were recorded on the 2-back during the treatment condition. Cerebral blood flow (CBF) was found to be lower during the treatment condition when compared to placebo; this was attributed to vasoconstriction caused by methylphenidate. The main effect of methylphenidate was not significantly related to CBF in particular regions of the brain. When subtracting the resting state image from the task image for the two conditions (i.e. methylphenidate task – methylphenidate resting state image, and placebo task – placebo resting state image), however, the left posterior superior parietal lobule was found to show a significant deactivation during the visual sustained attention task during the methylphenidate condition only, indicating a significant drug by condition effect. This relationship was not replicated in healthy controls, suggesting the deactivation of the left posterior parietal lobe may indicate a compensatory mechanism being switched off under treatment with methylphenidate (i.e. brain activation becoming similar to a non-injured brain with the administration of methylphenidate). More research is required, however, to determine why suppression of the posterior superior parietal lobule was associated with improved task performance.

This was one of the first studies to investigate the underlying mechanism responsible for improvements in attentional abilities with the administration of catecholamine medications. As discussed above, there are multiple investigations into the efficacy of medications that increase extracellular DA levels in augmenting attention function in TBI participants, yet the underlying disruption to the DA system is largely unknown. Advances in neuroimaging techniques have been crucial in furthering our knowledge of the neuropathology associated with TBI and related cognitive outcomes. Investigating the underlying neuropathological and neurochemical changes that give rise to attentional impairments is important to inform the development of new targeted treatments, as well as to select appropriate candidates for pharmacological trials

## 1.4 NEUROIMAGING, NEUROPATHOLOGY AND ATTENTION POST-TBI

Along with neurochemical changes associated with TBI, it is widely accepted that cognitive impairments are, at least to some extent, attributable to the focal and diffuse damage that occurs to the brain as a results of TBI (Bigler, 2001). Understanding the neuropathology that contributes to attentional impairments is vital, considering the deleterious effects they have on outcomes following TBI. Advancements in imaging techniques have allowed for better understanding of the neuropathology associated with TBI (Bigler & Maxwell, 2011; Le & Gean, 2009). Computed tomography (CT) provides accurate detection of intracranial haemorrhages and skull fractures. It is also widely available, has a short scanning sequence and does not interfere with life-support and monitoring equipment, making it a valuable imaging technique (Le & Gean, 2009; Shenton et al., 2012). When it comes to the detection of more subtle lesions caused by TBI, in comparison to CT, MRI is the superior technique (Le & Gean, 2009; Shenton et al., 2012). There are multiple sequences available when conducting MRI; broadly speaking they can be broken down into two main categories, structural and functional. Structural imaging investigates damage to brain tissue, including cortical and subcortical areas as well as white matter pathways. Functional imaging investigates brain activity through measuring physiological entities (e.g. blood flow). The next section reviews the brain changes that occur following TBI, as indicated using MRI, and the relationship of these abnormalities with attentional deficits. Although references to other imaging methods are made, for the purposes of this literature review, only the Diffusion Tensor Imaging (DTI) and Resting-State Functional Magnetic Imaging rs-fMRI sequences relevant to TBI will be described in detail.

### 1.4.1 Structural Pathology and Attention

Conventional MRI has been used to identify multiple associations between grey matter damage and attentional impairment. Children who have a history of TBI are at a greater risk of developing ADHD-like cognitive profiles (Yang, et al., 2016). Right putamen

pathology has been associated with the development of an ADHD like profile following TBI in children. Interestingly, damage to the left putamen and frontal lobes was most commonly seen in the children who did not go on to develop secondary ADHD (Herskovits et al., 1999). In a similar study by the same group, those demonstrating thalamic pathology were 3.64 times more likely to develop secondary ADHD after TBI, and children with basal ganglia pathology were 3.15 times more likely to develop secondary ADHD (Gerring et al., 2000). Max and colleagues (2004) demonstrated a link between orbitofrontal lesions and the development of secondary ADHD. In adults, information processing speed and divided attention, as measured by performance on Trail Making Test B, have been associated with atrophy in the left frontal region, as well as overall frontal atrophy at more than two years post injury (Bergeson et al., 2004). Grey matter atrophy within the right frontal, right temporal and right parietal regions, as well as the left anterior cingulate and left frontal regions has been associated with inattention on the Conners' Continuous Performance Test (Gale, Baxter, Roundy, & Johnson, 2005). For female participants only, performance on the SDMT was associated with genu volume following TBI (Johnson, Pinkston, Bigler, & Blatter, 1996). Wilkins et al. (1987) found participants with TBI who had right frontal lesions, but not those with left frontal or left/right posterior lesions, had difficulty with sustained attention.

Identifying the focal lesions which underpin cognitive deficits is vital for understanding TBI, however, focal damage does not always account for the type or severity of the deficits seen on neuropsychological testing (Bigler, 2001). White matter pathways connect these geographically separate regions, forming the attention neural network. Disruption to these pathways caused by DAI has the potential to disrupt these widely dispersed brain networks. Areas that remain relatively intact may not be receiving vital information from other areas due to damage to white matter pathways by DAI, resulting in poorer performance on measures of attention. Conventional magnetic resonance imaging (MRI) and computed tomography (CT) have long been used to detect abnormalities in the brain caused by TBI. They may, however, underestimate the true extent of DAI as they are not

sensitive enough to detect microstructural damage to white matter pathways (Arfanakis et al., 2002; Rugg-Gunn et al., 2001). Diffusion tensor imaging (DTI) is a relatively new technique that is able to assess changes in white matter microstructure such as that seen in DAI.

### 1.4.2 Diffusion Tensor Imaging

DTI assesses in vivo white matter integrity by measuring the rate of the diffusion of water in multiple directions at a specific point or voxel in the image. Microstructural damage to white matter tracts caused by DAI can include deformation of axons, neuronal swelling, retraction balls, increased or decreased extracellular space, or disconnection from downstream neurons which results in changes to the direction of diffusion of water or anisotropy that can be measured by DTI (Arfanakis et al., 2002; Ducreux et al., 2005; Rugg-Gunn et al., 2001). Fractional anisotropy (FA) is one common measure of white matter integrity. FA values range from values of 0 to 1, with higher values indicating that diffusion is restricted in movement to only one direction parallel to the axon, which is indicative of intact white matter. Lower values indicate that the diffusion of water is not restricted (i.e. due to increased extracellular space, swelling of axons or deformation of axons, water is no longer restricted in one direction along the axon and is able to diffuse in many directions), signifying white matter damage (Arfanakis et al., 2002; Rugg-Gunn et al., 2001). DTI produces other measures of white matter integrity, including an apparent diffusion coefficient (ADC), measuring the speed of diffusion in all directions, radial diffusivity (RD), which measures the speed and direction of diffusion perpendicular to the axon and mean diffusivity (MD), which measures the magnitude of diffusion in all directions. Alterations to white matter pathway microstructure have been consistently found in participants with TBI (for review see (Hulkower, Poliak, Rosenbaum, Zimmerman, & Lipton, 2013))

Methods used to analyse DTI images include voxel-based morphometry (VBM) . This is an automated technique that uses spatial normalisation to map participants' white matter pathways together in order to assess volumetric differences between groups at each voxel. This method is advantageous as it is automated and able to analyse white matter integrity of the whole brain (Ashburner & Friston, 2001). However, given the heterogeneous nature of injury caused by TBI, issues with image alignment and spatial smoothing may arise, potentially distorting results (Douglas et al., 2015).

Region of interest (ROI) analysis involves *a prior* selection of particular regions for investigation based on previous literature. This is a manual technique that allows for finer examination of white matter pathways. However, it is more time consuming and studies employing ROI will usually focus on a limited selection of tracts. Operators must be careful to correctly identify seed points and tracts. This can be difficult when investigating pathological brains where the underlying anatomy may be distorted (Marquez de la Plata et al., 2011).

DTI tractography involves selecting regions of interest as 'seeding points' to start the white matter tracking, then either automatically fusing the image data to a normalized cortical mask or alternatively, selecting ROI's and mapping tracts manually. Advantages of the automated method include the elimination of operator error and reduction in analysis time; however this method is not ideal for assessing brains that may be distorted due to injury, as issues with the alignment of images may arise. Manual tractography is, therefore, the more appropriate method for the analysis of pathological brains, yet problems with tractography arise when there are crossing fibres or noise (Alexander et al., 2001; Macovski, 1996).

Tractography requires accurate estimation of fibre orientation within a voxel. This can be difficult in areas where there are crossing fibres. Multiple methods have been developed to circumvent this, based on high angular resolution diffusion-weighted imaging (HARDI) data. Constrained spherical deconvolution (CSD), super-resolved CSD (super-CSD) and Q-

ball imaging (QBI) have all be found to resolve crossing fibres, with super-CSD being able to resolve fibres down to a crossing angle of 35 degrees (Tournier et al., 2008)

A relatively new method of analysis is tract-based spatial statistics (TBSS), a voxel-based technique that produces a virtual white matter skeleton from the common white matter tracts seen in all participants of a study (Smith et al., 2006). Once the virtual white matter skeleton has been formed, each individual's white matter pathways are applied to this skeleton. This allows for comprehensive analysis of tracts, whilst reducing misalignments, avoiding spatial smoothing and limiting partial volume effects (Kinnunen et al., 2011; Smith et al., 2006). In a study comparing ROI and TBSS, TBSS identified a greater number of tracts associated with outcome measures. This is likely due to the greater number of tracts assessed by the voxelwise method, as well as the fact that TBSS is capable of identifying reduced integrity for only a section of a tract, making it an advantageous technique for assessing the neuropathology of complex cognitive abilities (Spitz et al., 2013).

### 1.4.3 Diffusion Tensor Imaging and TBI

DTI is becoming an increasingly popular means of assessing pathology in TBI populations. Findings have identified DTI as a potential biomarker for injury severity as well as outcomes in TBI populations. Maller et al. (2010) conducted a review of the DTI literature investigating white matter changes after TBI. They found the pathways most commonly affected by DAI, as indicated by lower FA values, were the corpus callosum, white matter fibres of the anterior cingulate, and watershed regions including the anterior corona radiata and the internal capsule, all of which have been implicated in attentional function.

Cognitive abilities have been found to correlate with DTI measures. DTI metrics indicating white matter damage in the posterior cingulate, hippocampus and the frontal, temporal and occipital cortex have been found to be associated with learning and memory

performance in participants with TBI (Salmond et al., 2006). Reduced white matter integrity in the left superior frontal white matter has been found to be associated with impaired executive functions, including response inhibition, set-shifting, flexibility and word generation (Kinnunen et al., 2011). Lowered FA values in the white matter just below the left dorsolateral prefrontal cortex have also been found to be related to poorer performance on executive functioning tasks in participants with mild TBI (Lipton et al., 2009). Attentional and working memory deficits have also been found to be linked to white matter alterations, as indicated by DTI (e.g. Niogi et al., 2008), and are discussed in the next section.

### 1.4.4 DTI and Attention following TBI

Working memory and speed of processing have been shown to be related to white matter integrity in the fronto-parietal network in TBI populations. In a study looking at working memory as assessed by the Sternberg Item Recognition Task (SIRT; Sternberg, 1966), the relationship between white matter integrity and working memory performance in both children who had sustained a TBI and children with orthopaedic injuries only was investigated. In the orthopaedic injury group, a significant relationship between lower ADC (which indicative of healthy white matter) in the left frontal region and successfully rejecting false alarms was identified. The TBI group, however, exhibited a different pattern, with higher ADC in the left frontal lobe and cingulum bundle being related to slower reaction time, indicating that the reduced white matter integrity did not affect the working memory performance *per se,* rather it hindered the speed with which the patients could respond (Wilde et al., 2011).

When investigating thalamocortical projection fibres, Little et al., 2010 found integrity of fibres stemming from the anterior thalamic nucleus, ventral anterior thalamic nucleus and ventral lateral thalamic nucleus was associated with an attention domain score, which

included scores from Digit Span Forward, Spatial Span Forward, Trail Making Test – A, and number of omissions on Conners Continuous Performance Task. Niogi et al. (2008) investigated the relationship between white matter integrity, attention and memory in participants with mild TBI and healthy controls. Attentional performance was assessed using the *Attention Network Task* (ANT; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005) and memory performance was assessed using the California Verbal Learning Test, Second Edition (CVLT-II). For both the healthy controls and the participants with mild TBI, lower FA values in the uncinate fasciculus were correlated with poorer memory performance, and lower FA values in the left anterior corona radiata was correlated with attentional deficits. The participants with TBI did, however, exhibit more variability in their scores than controls.

Using TBSS, studies have identified a number of white matter tracts associated with attentional deficits post-TBI. Reduced white matter integrity within the superior longitudinal fasciculus, corpus callosum and cingulum has been found to be associated with impairment in executive control of attention, as measured by Hayling overall scaled score (Spitz et al., 2013), and Trail Making Test alternating switch cost (TMT-B minus TMT-A) (Kinnunen et al., 2011). Additionally, the left inferior longitudinal fasciculus has been associated with Hayling overall score (Spitz et al., 2013), and the right corticospinal tract and left frontal white matter have been linked to Trail Making Task alternating switch cost (Kinnunen et al., 2011). Interestingly, on the other hand, Kinnunen et al. (2011) found no significant association between any DTI metrics and performance on a speed of information processing task – a choice reaction task. Contrary to this, Spitz et al. (2013) found information processing speed to be associated with an extensive network of tracts throughout the brain including the left and right inferior longitudinal fasciculus, left and right superior longitudinal fasciculus, corpus callosum, and the cingulate bundle. However, on closer inspection of the tasks used, Kinnunen et al. (2011) used 'alternating-switch cost index' of the TMT (time to complete TMT-B - time to complete TMT-A) to investigate the strategic control of attention and white matter changes, a measure highly

influenced by information processing speed. As they did not control for information processing speed, the results may reflect an association between white matter pathology and processing speed, rather than executive functioning. With regard to working memory, Palacios et al. (2011) found a positive correlation between the 2-back d-index and FA in the superior longitudinal fasciculus, fornix, and corpus callosum using TBSS in conjunction with ROI masks.

In summary, DTI appears to be a valuable tool for assessing both the underlying white matter damage associated with TBI and the functional outcomes that follow. It is more sensitive than conventional MRI or CT scans for detecting microstructural damage to axonal pathways and provides more specific information about the relationships between this underlying damage and cognitive deficits seen after TBI. The contribution of white matter pathology to attentional impairments following TBI, however, has not yet been fully elucidated. Associations between white matter pathology and attentional deficits have been identified in the chronic phase of injury, but less is known regarding the more acute phase (< 12 months post injury). Additionally, limited studies have investigated multiple aspects of attention with the majority only utilising one or two attention measures. Given that attention and working memory deficits are so commonly seen after TBI it is important to ascertain the underlying causes. In addition, reductions in DA signalling have been identified post-TBI (Donnemiller et al., 2000), which may contribute to attentional impairment. However, there is limited research investigating DAergic white matter pathology following TBI. No study to date has investigated microstructural alterations to the medial forebrain bundle, and associated attention deficits post-TBI.

### 1.4.5 DTI and the Medial Forebrain Bundle

Due to the MFB's major role in the brain reward systems, past research has generally focused on its role in affective and addiction disorders (Alcaro & Panksepp, 2011; Bracht,

Doidge, Keedwell, & Jones, 2015; Coenen et al., 2009; Coenen et al., 2012; Wise, 2005). In humans, the supero-lateral branch (slMFB) of the MFB contains ascending catecholamine fibres and connects the ventral tegmental area (VTA) to the ventral striatum and nucleus accumbens, before terminating in the PFC (Coenen et al., 2009; Coenen et al., 2012; Coenen et al., 2011). The absence of the MFB on DTI neuroanatomical atlases makes it less accessible for investigation than other more prominent white matter tracts. Few studies have explicitly sought to examine the MFB using DTI and none have been undertaken in TBI. This is potentially due to the fact that the imaging of small white matter tracts is more readily compromised by machine and MR sequence variables than that of larger white matter tracts. Coenen and colleagues (2009) were the first to depict the MFB using DTI deterministic fibre tracking by placing a region of interest (ROI) seed in the ventral midbrain (Coenen et al., 2009). In a subsequent paper, by placing a single ROI seed in the ipsilateral VTA, Coenen et al., (2012) were also able to depict the MFB using deterministic tractography. Using a similar ROI, Bracht et al, (2015), depicted both the infero-medial (imMFB) and slMFB using probablistic tractography. Additionally, Anthofer et al. (2015) compared three different ROI pairs for deterministic fibre tracking of the MFB. The ROI with the most reliable and convincing results was the ipsilateral VTA and nucleus raphe dorsalis ROI pair. Using this method, Anthofer et al. (2015) found similar results to Bracht et al, (2015), Coenen et al., (2009) and Coenen et al., (2012), replicating the author's anatomical description of the MFB, as well as the seed regions used.

As previously discussed, catecholamine fibres are particularly susceptible to damage as a result of brain injury. Given that this MFB is a key catecholamine pathway carrying DA and NE fibres from the midbrain to the frontal cortices, damage to this pathway following TBI could potentially result in altered levels of extracellular catecholamines, disrupting the DA network and resulting in poorer working memory and attention performance. Previous studies have found white matter pathology to be associated with inefficient brain network functioning. Damage to white matter pathways disrupts connections between geographically separate brain regions, impairing functional networks and leading to

cognitive deficits (Palacios, Sala-Llonch, Junque, & et al., 2013; Pandit et al., 2013; Sharp et al., 2011). The following section will discuss functional imaging changes identified following TBI. Although other functional imaging techniques will be presented, the discussion will focus on rs-fMRI, a new technique able to investigate whole brain functional connectivity networks.

### 1.4.6 Functional Alterations and Attention in TBI

Neuronal activity and blood flow are associated. Therefore, when a brain region is activated blood flow to that are will increase. Functional imaging allows researchers to investigate physiological activity within the brain whilst participants are performing a task, giving an indication of which brain regions are involved in certain aspects of cognition. Functional magnetic resonance imaging (fMRI) techniques are sensitive to changes in regional blood flow, blood volume or blood oxygenation. Blood-oxygen-level dependent (BOLD) contrasts are able to measure changes in blood flow to brain regions (i.e. relative signal intensity changes), providing an indication of which areas are activated during a particular task. Other fMRI techniques exist which allow for the absolute measure of tissue metabolism, rather than regional change in blood flow that BOLD captures. These include PET which requires administration of a radiotracer and more recently, Arterial Spin Labelling (ASL), a similar method to PET, however, instead of a radiotracer, arterial blood is magnetically labelled and imaged making it less invasive.

With regard to attention, functional imaging studies have found a link between hypoperfusion in the occipital and temporal cortices and working memory deficits in those with TBI (Kim, Whyte, Patel, Europa, Slattery, et al., 2012). Increased errors on the Stroop task have been associated with hypoperfusion in the anterior cingulate cortex in participants with TBI, when compared to controls (Soeda et al., 2005). fMRI has proven to be useful in investigating possible compensatory mechanisms after injury.

Christodoulou et al. (2001) found that when compared to the control group, the participants with TBI showed a more dispersed pattern of activation. When performing a working memory task, healthy controls and participants with TBI demonstrated a similar pattern of activation, including the frontal, parietal and temporal lobes. However, the TBI group was found to display a more regionally dispersed pattern of activation that was more lateralised to the right hemisphere. Similarly, Rasmussen et al. (2008) found when performing a dual task experiment, TBI participants demonstrated a larger area of activation than controls, recruiting additional frontal and temporal structures. The same study, however, found the TBI group to show less activation in the occipital lobes and posterior cingulate compared to controls when completing a less taxing single motor task. Given the TBI group found the dual task experiment more difficult than the controls, the authors concluded TBI participants may have switched from automatic processing, to serial processing, recruiting additional brain regions (Rasmussen et al., 2008).

Although fMRI has proven to be useful in understanding neurofunctional abnormalities in individuals with TBI, it is not without pitfalls. Some individuals may be too severely impaired to perform cognitive tasks whilst in the scanner. Additionally, factors including motivation and cognitive strategies can influence results. More recently, researchers have turned their attention to resting-state functional magnetic imaging (rs-fMRI) as a means of investigating functional connectivity changes following TBI (Biswal et al., 1995; Fornito & Bullmore, 2010).

### 1.4.7 Resting State Functional Magnetic Imaging

In contrast to conventional functional imaging that investigates physiological brain changes when an individual is performing a task, rs-fMRI correlates spontaneous activation patterns of anatomically separated brain regions when individuals are not performing a task (i.e. “resting state”). As individuals are not required to perform a task,

this technique largely circumvents the fMRI pitfalls mentioned above. The coherent fluctuations observed during resting state are believed to mirror functionally related brain regions that underpin complex cognitive functions, including attention (Smith et al., 2009). The functional networks detected at 'rest' are highly consistent across individuals (Damoiseaux et al., 2006), stable across time points (Damoiseaux et al., 2006; Shehzad et al., 2009), and strongly influenced by genetics (Fornito & Bullmore, 2012; Fornito et al., 2011; Glahn et al., 2010). Additionally, they influence task-related neural activity as well as task performance (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Fox & Raichle, 2007), and are influenced by the structural integrity of the white matter pathways connecting the networks (Bonnelle et al., 2012; Bonnelle et al., 2011).

Several methods are available to process rs-fMRI. They can be broadly broken down into two categories, model-free and seed-based methods. Seed based methods involve selecting an *a priori* region of interest and correlating the resting-state time series of that particular region with the time-series of every other voxel within the brain. This method is advantageous as it is relatively straight forward and allows researchers to investigate the functional connectivity map of particular areas of interest within the brain.

Model-free methods do not require selection of a seed region and include principal components analysis (PCA), independent component analysis (ICA) and clustering. ICA methods are the most commonly used to investigate resting-state activity within the brain. ICA is a whole-brain voxel-wise technique that is able to detect multiple functional connectivity networks. It is highly data driven, however, has been found to consistently extract known functional networks (Beckmann, DeLuca, Devlin, & Smith, 2005a).

Commonly identified networks include the primary motor, primary visual, extra-striate frontal, left and right fronto-parietal and the default mode network (Beckmann, DeLuca, Devlin, & Smith, 2005b; Biswal et al., 1995; Damoiseaux et al., 2006; De Luca, Smith, De Stefano, Federico, & Matthews, 2005; Salvador et al., 2005; Van Den Heuvel, Mandl, & Pol, 2008). The default mode network (DMN) is of particular interest as regions within

this network are expressed when an individual is "at rest" and shows reduced activation (deactivation) during attentionally demanding tasks (Gusnard & Raichle, 2001; Shulman et al., 1997). Structures involved in the DMN include the posterior cingulate cortex/precuneus, medial prefrontal cortex and bilateral angular gyri (Gusnard & Raichle, 2001; Shulman et al., 1997).

As the DMN is active during rest it has been assumed that it reflects an internally focused state, in contrast to a goal-directed state (i.e. on-task). When an individual begins a cognitively demanding task, the DMN is deactivated and goal-directed networks become active. The salience network (SN) includes the anterior cingulate cortex, presupplementary motor area and insula, and becomes active when there is a need for behavioural change. It becomes active when rapid behavioural change is required (i.e. from off-task to on-task) and modulates other brain networks required for on-task behaviour. Efficient switching from DMN to goal-directed networks is vital for optimal cognitive functioning (Weissman et al., 2006). TBI has the potential to disrupt this interaction between networks. Research investigating the effects of TBI on resting state networks is presented in the following section.

### 1.4.8 Rs-fMRI and TBI

Neuropathological changes associated with TBI have been found to be associated with altered functional networks. Reduced connectivity in attentional, motor striatal, sensory motor, and frontal functional networks have been identified post-TBI (Hillary et al., 2011; Shumskaya, Andriessen, Norris, & Vos, 2012; Vakhtin et al., 2013), exemplifying the widespread damage which results from brain injury. Although multiple networks are found to be altered following TBI, the DMN has proven to be an important indicator of severity, as well as a predictor of cognitive function.

Alterations within the DMN following TBI have also been found to be linked to subclinical symptoms following a concussion, demonstrating the utility of rs-fMRI in assessing injury severity when traditional clinical methods are not as sensitive (Johnson, Zhang, et al., 2012). Additionally, changes to the DMN as a result of TBI appear to be most commonly associated with cognitive dysfunction, particularly attentional deficits, when compared to other resting state networks. Reorganisation of the DMN has been associated with cognitive recovery in severely brain injured individuals (Falletta Caravasso et al., 2015; Hillary et al., 2011).

Alterations to the DMN after brain injury are a robust finding within the literature. Increased functional connectivity between key DMN nodes, the medial prefrontal cortex and posterior cingulate cortex, has been found post-TBI (Hillary et al., 2011). Similarly, Bonnelle et al. (2011) observed increased functional connectivity within the DMN, particularly within the precuneus and posterior cingulate cortex, was associated with sustained attention deficits following TBI. Conversely, increased functional connectivity within the DMN post-TBI has been associated with better cognitive outcomes (Palacios et al., 2013; Sharp et al., 2011). Palacios et al. (2013) investigated the integrity of the cingulum bundle, a key tract connecting the posterior and anterior parts of the DMN, and its association to the DMN functional connectivity in chronic TBI patients. Increased functional connectivity was associated with better cognitive performance (as measured by an overall cognitive score made up of multiple tasks measuring attention, memory and executive functioning), as well as poorer white matter integrity within the cingulum bundle. It was postulated that this indicates a compensatory mechanism for the loss of structural connectivity.

TBI has also been found to alter the interaction between brain networks. Structural damage to white matter pathways connecting the SN to the DMN has been associated with reduced deactivation of the DMN, namely the precuneus and posterior cingulate cortex, following TBI. Furthermore, the DMN dysfunction has been linked to impaired inhibitory

control on a Stop-Signal Task in individuals with TBI (Bonnelle et al., 2012). Jilka et al. (2014) also demonstrated inefficient interaction between the SN and DMN. Again using a Stop-Signal Task, an increase in functional connectivity between the right anterior insula, a key SN node, and the DMN was observed in healthy controls when stopping. The same activation, however, was not seen in the TBI group, who demonstrated impaired inhibitory control. As with Bonnelle et al. (2012), damage to SN white matter pathways was negatively associated with the functional connectivity between the SN and DMN. The same pattern of results was found for switching of attention, demonstrating the importance of efficient interaction between SN and DMN for attentional tasks.

### 1.4.9 Rs-fMRI and Dopamine

DA neurotransmission modulates activity within the DMN. Greater DA levels are associated with efficient deactivation of the DMN during attention task performance (Tomasi et al., 2009), providing support for the use of stimulant medication (which increase DA) for the treatment of inattention (Tomasi et al., 2009). The DMN has been found to be functionally linked to the VTA in healthy controls and children with ADHD (Tomasi & Volkow, 2014). In addition, when compared to typically developing children, alterations in VTA functional networks have been observed in children with ADHD, possibly contributing to reduced motivation and inattention (Tomasi & Volkow, 2012). The impact that TBI has on functional connectivity of the VTA and the DMN, or with other brain regions, is, however, unclear. Evidence for VTA network disruption could provide further rationale for the use of medications that augment DA signalling to treat attentional deficits post-TBI.

In summary, DTI appears to be a valuable tool for assessing both the underlying white matter damage caused by TBI and the associated attentional impairments. DTI is more sensitive than conventional MRI or CT scans in identifying microstructural damage to

axonal pathways and, therefore, has potential to provide more specific information about the relationships between this underlying damage and cognitive deficits seen after TBI. The contribution of white matter pathology to attentional impairments following TBI, however, has not yet been fully elucidated. The majority of studies have investigated chronic samples and have only measured one or two aspects of attention. In addition, reductions in DA signalling have been identified post-TBI, and likely contribute to attentional impairments. Research into catecholamine fibre alterations following TBI is limited, however, and no study to date has assessed the relationship between white matter integrity of the medial forebrain bundle and its association with attentional deficits post-TBI. Damage to such pathways could potentially alter levels of extracellular catecholamines, disrupting the DA system, resulting in poorer working memory and attentional performance. Alteration to the functional connectivity of the VTA may also contribute to the frequent and severe attentional problems seen following brain injury by interacting with the DMN. Given the significant impact attentional impairments have on everyday life, understanding the neuropathological and neurochemical changes that lead to these problems is crucial.

## 1.5 AIMS AND HYPOTHESES

The aims of the present study were:

1) To compare, using Tract Based Spatial Statistics (TBSS), whole brain white matter integrity measured by FA and MD values, between individuals with TBI and healthy controls, and to assess association with performance on attentional measures.

2) To compare the structural integrity of the slMFB, as measured by FA and MD values, in individuals with TBI and healthy controls and to explore, in both

individuals with TBI and healthy controls, the relationships between white matter integrity of the slMFB and performance on attentional tasks.

3) To examine the functional connectivity of the VTA network with key DMN nodes in individuals with TBI and healthy controls, and the associations between injury-related changes and attentional performance.

It was hypothesised:

1) That participants with TBI would have lower FA values and higher MD in all regions of interest including the inferior longitudinal fasciculus, superior longitudinal fasciculus, inferior fronto-occipital fasciculus, forceps minor, forceps major, genu of the corpus callosum, splenium of the corpus callosum, cingulum, anterior limb of the internal capsule, posterior limb of the internal capsule, corticospinal tract, uncinate fasciculus, and medial forebrain bundle, than control participants. Additionally, it was hypothesised that attentional performance would be associated with DTI metrics; specifically, that for participants with TBI higher FA values and lower MD values in the attention neural network would be related to better performance on attentional tasks.

2) That participants with TBI, when compared to controls, would demonstrate lower FA values and higher MD values, indicative of white matter damage within their slMFB. Additionally, that for both the control and TBI group, higher FA values and lower MD values would be associated with better performance on attentional tasks.

3) That the VTA network would be functionally connected to DMN nodes and that alterations to this functional connectivity would be observed within the TBI group, when compared to controls. Finally, it was hypothesised that these alterations would be associated with poorer performance on attentional measures.

# CHAPTER TWO

## AN INVESTIGATION OF WHITE MATTER INTEGRITY AND ATTENTION DEFICITS FOLLOWING TRAUMATIC BRAIN INJURY

## 2.1 DECLARATION FOR THESIS CHAPTER TWO

**Monash University**

**Declaration for Thesis Chapter 2**

**Declaration by candidate**

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

| Nature of contribution | Extent of contribution |
|---|---|
| Formulation of experimental design, data collection, data analysis and preparation of full manuscript. | 70% |

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

| Name | Nature of contribution | Extent of contribution (%) for student co-authors only |
|---|---|---|
| Catherine Willmott | Consultation in formulation of experimental design, discussion of ideas expressed in manuscript and critical review of manuscript. | |
| Gershon Spitz | Involved in the conceptualisation, planning and design of the study, assisting with data analysis and reviewed the manuscript. | |
| Jennie Ponsford | Involved in the conceptualisation, planning and design of the study, and reviewed the manuscript. | |
| Alicia Dymowski | Assisted with recruitment and neuropsychological assessment of participants and revised the manuscript. | 5% |

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contribution to this work:

| | | |
|---|---|---|
| **Candidate's Signature** |  | Date: 17/11/2016 |
| **Main Supervisor's Signature** |  | Date: 17/11/2016 |

## 2.2 OVERVIEW

This chapter presents an empirical paper titled *"An investigation of white matter integrity and attention deficits following traumatic brain injury",* submitted to Journal of Neurotrauma. This paper investigated whole brain white matter changes following moderate to severe TBI and the association with attention deficits. By investigating a sample consisting of individuals predominantly within 12 months post-injury, we hoped to provide important information about the nature of white matter pathology and associated attention deficits in this critical time in recovery. Furthermore, we hoped to contribute to the literature by investigating multiple aspects of attention with the hope to extend upon previous DTI findings in TBI research.

## 2.3 ABSTRACT

Attention and working memory deficits are prominent following moderate-severe traumatic brain injury (TBI), however the mechanisms underpinning these deficits are poorly understood. This study aimed to investigate the association between white matter tracts and multiple aspects of attention and working memory deficits following moderate-severe TBI. Neuropsychological measures of attention and working memory were administered to 20 participants with moderate-severe TBI (post traumatic amnesia (PTA) M = 40.05 ± 37.10 days, median time since injury 10.48 months, range 3.72-87.49) and 20 control participants. Tract-based spatial statistics were used to assess fractional anisotropy (FA) and mean diffusivity (MD) of white matter tracts for 15 TBI participants and 20 controls. When compared to controls, participants with TBI were found to have lower FA ($p < 0.001$) and higher MD ($p < 0.001$) values in the majority of white matter tracts. TBI participants were also slower to complete tasks including Trail Making Task, Hayling, Computerised Selective Attention Task, *n*-back, and Symbol Digit Modalities Test ($p < 0.001$), when compared to controls. When controlling for age and estimated pre-morbid intelligence, slowed information processing speed following TBI was found to be associated with FA values in the corpus callosum, superior longitudinal fasciculus, cingulum, inferior fronto-occipital fasciculi, corona radiata, and cerebral white matter. The results highlight the widespread damage associated with TBI, as well as the impact of these alterations on information processing speed.

## 2.4 INTRODUCTION

Attention and working memory impairments are common following moderate to severe TBI(Mathias & Wheaton, 2007; Ponsford & Willmott, 2004), and can have a lasting impact on participation in life roles (Draper & Ponsford, 2008; Lewis & Horn, 2013). Deficits in these domains include difficulties sustaining attention, problems dividing

attention over two or more tasks, slowed processing speed, and reduced ability to hold and mentally manipulate information (Mathias & Wheaton, 2007; Olver et al., 1996). These attentional abilities rely on diffuse neural networks, connected by long white matter tracts (Pandit et al., 2013; Sharp, Scott, & Leech, 2014). Diffuse axonal injury (DAI) following TBI can damage these tracts which disrupts neural networks. This may result in on-going attention and working memory deficits (Arenth, Russell, Scanlon, Kessler, & Ricker, 2013; Palacios et al., 2011; Spitz et al., 2013).

Diffusion tensor imaging (DTI) is an imaging technique that estimates the integrity of tracts by measuring the directionality of water diffusion along white matter pathways, resulting in measures of fractional anisotropy (FA) and mean diffusivity (MD) (Le & Gean, 2009; Provenzale, 2010). Multiple techniques have been developed to analyse white matter structure. Region of interest (ROI) analysis is a commonly used technique that requires *a priori* selection of white matter tracts. Studies utilizing ROI analysis generally focus on a limited selection of tracts. Voxel-based morphometry (VBM) is an automated technique that enables the investigation of whole-brain changes, however, given the varied pathology associated with TBI (e.g. focal injuries), image alignment and spatial smoothing can be difficult (Ashburner & Friston, 2001; Davatzikos, 2004).

Tract-based spatial statistics (TBSS; Smith et al., 2006), a voxel-based technique, seeks to address spatial smoothing and misalignment issues that are inherent to VBM by creating a group mean white matter 'skeleton', representing the centre of white matter tracts common to each participant. This skeleton is applied to each individual's images to obtain measures of white matter integrity across the entire brain (Smith et al., 2006). This allows for comprehensive analysis of tracts, whilst reducing the risk of potential confounds associated with brain injury, including partial volume effects (Kinnunen et al., 2011). Additionally, when compared to ROI tractography analysis, TBSS has been found to identify a greater number of tracts associated with outcome measures (Spitz et al., 2013). This is likely due to the greater number of tracts assessed by the voxelwise method, and

because TBSS is capable of identifying reduced integrity for only a section of a tract (Spitz et al., 2013). These advantages are particularly important for assessing the neuropathology of complex cognitive abilities, such as attentional abilities, which rely on whole brain systems.

TBSS studies have identified a number of white matter tracts to be associated with attentional deficits post-TBI. Reduced white matter integrity in the superior longitudinal fasciculus, corpus callosum and cingulum has been found to be implicated in switching of attention (Kinnunen et al., 2011), as well as speed of initiation and response inhibition (Spitz et al., 2013). Additionally, the left inferior longitudinal fasciculus (Spitz et al., 2013), right corticospinal tract, and left frontal white matter (Kinnunen et al., 2011), were also found to be associated with attentional measures. Interestingly, Kinnunen et al. (2011) found no significant association between performance on a choice reaction task, a measure of processing speed, and DTI metrics. Contrary to this, using the Symbol Digit Modalities Test (SDMT), Spitz et al. (2013) found information processing speed to be associated with an extensive network of tracts throughout the brain, including the left and right inferior longitudinal fasciculus, left and right superior longitudinal fasciculus, corpus callosum, and cingulate bundle. Using TBSS, Palacios et al. (2011) investigated working memory using both TBSS and ROI analysis. Their TBSS analysis identified a positive correlation between the ability to discriminate between correct and incorrect responses on the 2-back and whole brain FA. These studies have provided preliminary evidence for involvement of a number of white matter pathways in attentional deficits post-TBI, particularly long association tracts.

It is important to investigate the multiple aspects of attention and the associated underlying neuropathology. The abovementioned studies focused only on one or two attention systems in their analyses. Additionally, most previous studies in this area investigated participants in the chronic phase following TBI. As the majority of recovery occurs within the first 12 months post-injury (Christensen et al., 2008), it is possible that

investigating a more acute sample will yield a clearer picture of injury-related pathology, potentially identifying neuroanatomical markers which may act as targets for future treatments. The current study aimed to (a) further elucidate TBI related white matter pathology in a more acute sample (predominately less than 12 months post-injury) and (b) explore the association between such pathology and attention and working memory deficits using TBSS.

## 2.5 METHOD

### 2.5.1 Participants

Twenty participants with a history of moderate to very severe TBI were recruited from the Acquired Brain Injury Rehabilitation service at Epworth HealthCare, Melbourne, Australia. Twenty healthy controls were recruited from the general public and matched to TBI participants during recruitment. The groups did not differ significantly with respect to gender, age, years of education, or estimated IQ (see Table 2.1). Median time since injury was 10.48 months, (interquartile range (IQR) = 10.83 months, range 0-87.5 months). Forty percent of participants underwent MRI and cognitive testing on the same day (median time lag between assessment and scan = 25 days, IQR =62.25 days, with the assessment done first in 86% of cases). Exclusion criteria included: (a) inadequate understanding of English, (b) insufficient cognitive ability or physical disabilities preventing completion of tasks, or previous: (c) severe psychiatric illness, (d) neurological disorder, (e) treatment for drug or alcohol dependence, (f) history of diagnosis of attention deficit disorder; or (g) Magnetic Resonance (MR) contraindications. Cause of injury included motor-vehicle accidents (60%), bicycle or pedestrian accidents involving motor vehicles (25%), falls (10%), one participant involved in an equestrian accident (5%). Average duration of post traumatic amnesia (PTA) was 40.05 days (SD = 37.10 days, range = 1-142 days). Glasgow Coma Scale (GCS) score distribution was as follows: GCS 13-15, 15%; GCS

9-12, 5%; GCS 3-8, 75%, not recorded, 5%. Considering PTA duration, the majority of TBI participants (50%) sustained a very severe injury (PTA >4weeks), 35% sustained a severe injury (PTA 1-4 week) and 10% sustained a moderate injury (PTA 1-7days) (Arlinghaus et al., 2005). One participant with a complicated mild injury (PTA <24hours with changes on Computed Tomography (CT) imaging, 5%; Arlinghaus et al., 2005) was included as research has demonstrated individuals with complicated mild TBI have poorer outcomes than those with uncomplicated mild TBI (Iverson et al., 2012; Lange, Iverson, & Franzen, 2009). All TBI participants had demonstrated pathology on CT brain scan.

Three TBI participants were excluded from the imaging data analysis due to severe pathology preventing accurate alignment, leaving an n of 17. One was excluded on the basis of large focal frontal lobe lesions, another had considerably enlarged ventricles and the third had significant hydrocephalus. Two TBI participants were excluded from the correlation analysis as their cognitive assessment and MRI were more than a month apart, rendering the association between DTI metrics and cognitive performance potentially invalid, resulting in n = 15 (median time post injury 8 months, IQR = 8.3 months, average 9 days between scan and cognitive assessment, 53% MRI and assessment were conducted on the same day). TBI participants (n = 20) were included in all comparisons for cognitive tasks, with the exception of the computerised selective attention task analysis, as one participant was partially colour blind and had difficulty distinguishing between the coloured stimuli (n = 19).

Table 2.1 Demographic characteristics and CT brain scan pathology

| | TBI ($n$ = 20) | Controls ($n$=20) | $p$ value |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | |
| Age (years) | 39.05 (16.44) | 33.45 (11.72) | .22 |
| Years of education | 13.58(2.53) | 13.43 (2.67) | .86 |
| Estimated FSIQ | 108.83 (8.81) | 107.71 (5.87) | .64 |
| | $n$ | $n$ | |
| Gender (male) | 15 | 12 | .31 |
| CT Brain Pathology | | | |
| Contusion | 8 | - | |
| Diffuse axonal injury | 3 | - | |
| Subarachnoid haemorrhage | 8 | - | |
| Subdural haemorrhage | 10 | - | |
| Epidural haemorrhage | 2 | - | |
| Intracranial haemorrhage | 3 | - | |
| Interventricular haemorrhage | 3 | - | |
| Haematoma | 4 | - | |
| Abscesses | 1 | - | |
| Petechial haemorrhages | 3 | - | |

Note. FSIQ = Full Scale Intelligence Quotient

### 2.5.2 Procedure

This study was approved by Monash University and Epworth HealthCare Human Research Ethics Committees. Participants were invited to undergo a neuropsychological assessment and a brain MRI scan once their treating neuropsychologist had determined they had emerged from PTA with daily administration of the Westmead PTA Scale (Shores et al., 1986). Prior to enrolment, all participants underwent CT scans as part of routine assessment and treatment at the acute hospital. Results from CT scans were reported by resident radiologists at the respective hospitals. MRI brain scans were undertaken at Monash Biomedical Imaging Centre.

### 2.5.3 Measures

#### 2.5.3.1 The National Adult Reading Test (NART)

The NART (Nelson, 1982), is a reading test which consists of 50 irregulary spelt words and was used to estimate pre-morbid IQ.

#### 2.5.3.2 The Symbol Digit Modalities Test

The SDMT (Smith, 1991), has previously identified reduced psychomotor processing speed in a TBI sample (Ponsford & Kinsella, 1992). Participants have 90 seconds to decode a series of symbols.

#### 2.5.3.3 Trail Making Test (TMT) - Parts A and B

The TMT (Reitan & Wolfson, 1985), Parts A and B measures processing speed, divided attention and mental flexibility and has been shown to differentiate individuals with TBI from healthy control participants (Spitz, Ponsford, Rudzki, & Maller, 2012).

#### 2.5.3.4 Digit Span subtest of the Wechsler Adult Intelligence Scale –Fourth Edition

Digits backwards, forwards and sequencing (Wechsler, 2008), were used to assess participants' immediate auditory attention span and working memory capacity. Digit span backwards has previously been shown to be sensitive to changes in attention after TBI (Chan, 2000; Kinsella et al., 1996).

#### 2.5.3.5 The Ruff 2&7 Selective Attention Task

The Ruff 2&7 Selective Attention Task (Ruff & Allen, 1995), is a pen and paper cancellation task which has previously been used to demonstrate selective attention deficits post-TBI (Willmott & Ponsford, 2009).

#### 2.5.3.6 The Hayling Sentence Completion Test from the Hayling and Brixton Tests

The Hayling Sentence Completion Test (Burgess & Shallice, 1996), Part A (response initiation) required participants to provide a word that completes the sentence as quickly as possible. In Hayling B (response inhibition), participants were required to complete the sentences with a word that is completely unrelated to the sentence. The tasks measure speed of initiation and response inhibition and have been found to be sensitive to change post-TBI (Draper & Ponsford, 2008).

#### 2.5.3.7 The Computerised Selective Attention Task (SAT)

The SAT (Ziino & Ponsford, 2006a), has two conditions, the Simple Selective Attention Task (SSAT) and Complex Selective Attention Task (CSAT). The CSAT assessed a higher working memory load as participants are required to retain additional rules. TBI patients have been found to respond more slowly and make significantly more errors than controls when completing this task (Willmott & Ponsford, 2009).

#### 2.5.3.8 The *n*-back

The *n*-back (Perlstein et al., 2004), has been found to be sensitive to working memory deficits in a TBI sample. Participants were required to correctly match the letter presented on the screen with the letter presented 0, 1 and 2 screens back.

### 2.5.4 Neuroimaging Acquisition

Neuroimaging was performed on a Siemens Magnetom Skyra 3 Tesla MRI scanner using a 32 channel head coil (Siemens Medical Imaging, Erlangen, Germany). A 3D T1-weighted MPRAGE sequence was acquired in the sagittal orientation (inversion pulse 900ms, TR 1540ms, TE 2.57ms, resolution 256 x 256 x 176, flip angle 9 degrees, FOV 250mm, slice thickness 1.00mm (176 slices)). A DTI sequence was acquired (TR= 10900, TE = 101, 64 diffusion encoding directions, Number of Excitations = 1, slice thickness = 2.0mm (64 slices), field of view = 256mm, matrix = 128 x 128, in-plane = 2.0 x 2,0mm, *b* value = 2000 s/mm$^2$).

#### 2.5.4.1 Tract-Based Spatial Statistics

TBSS (Smith et al., 2006), was performed using the FMRIB Software Library (Smith et al., 2004), First, each participant's FA data was registered into a standard space - the FMRIB58 FA space image by using nonlinear registration. Next, the mean FA image was created by averaging all aligned images to reveal the white matter tracts common to all participants. The mean FA image was then used to create an FA skeleton, which represents the centres of all tracts common to the group. The threshold values were set at 0.2 for the FA skeleton in order to exclude tracts containing high partial volume effects or that were highly variable amongst participants. Each participant's aligned FA image was projected onto the FA skeleton. Using the general linear model, data was then fed through

voxelwise statistics to compare white matter FA and MD between TBI and control groups. For the TBI group only, the GLM was then used to regress attentional performance onto the FA and MD values of white matter tracts, whilst controlling for age and estimated FSIQ. The 'randomise' tool was used to conduct group comparisons and significance testing, applying a threshold-free cluster enhancement (Smith & Nichols, 2009), with 5,000 permutations, after which a threshold of $p < .05$ was applied.

### 2.5.5 Data Analysis

Using a cut off of reaction time greater or less than two standard deviations from the mean for each group, three percent of *n*-back reaction times (RTs) across three conditions, as well as 8% SAT RTs across two conditions were removed from the analysis. This was similar to previous RT studies (Willmott et al., 2009). Univariate outliers were defined as Z-score >3.29 ($p < .001$, two-tailed test). Two outliers in the Hayling Test were identified (one TBI and one healthy control for number of errors) and assigned a score 1 unit greater than the next most extreme score (Tabachnick & Fidell, 2007). Independent sample *t*-tests were undertaken to compare groups for normally distributed test variables. Error data for the SDMT, 2&7, TMT, Hayling Test, *n*-back & SAT, and missed responses for the latter two tasks, was analysed using non-parametric test Mann-Whitney U. To control for Type I error, Bonferroni adjustments were made for multiple comparisons.

## 2.6 RESULTS

### 2.6.1 Neuropsychological Performance

Using a Bonferroni adjusted α level of .004, TBI participants were significantly slower to complete the TMT-A as well as the timed aspects of the Hayling Test when compared to controls (Table 2.2). In addition, they completed fewer items of the SDMT, cancelled fewer

targets on all conditions of the Ruff 2&7, and were slower to respond during all conditions of the *n*-back and SAT than control participants (Table 2.2). No significant group differences were found in terms of attention span or working memory performance as measured by Digit Span.

Table 2.2 Means, standard deviations, significance and effect sizes for attention measures for TBI and control groups

| | | TBI (*n*=20) | Control (*n*=20) | | |
|---|---|---|---|---|---|
| Task | Measure | Mean (SD) | Mean (SD) | *p*-value | Effect size[a] |
| Digit Span | DSF RS | 11.35 (2.56) | 11.40 (2.87) | .94 | 0.02 |
| | DSB RS | 9.25 (2.95) | 8.85 (2.76) | .66 | 0.14 |
| SDMT | Number correct | 44.30 (9.58) | 58.10 (10.20) | <.001 | 1.40 |
| TMT | TMT-A time (s) | 39.60 (15.02) | 23.05 (7.50) | <.001 | 1.40 |
| | TMT-B time (s) | 83.50 (39.65) | 59.90 (22.01) | .027 | 0.74 |
| Hayling | Initiation Time (s) | 16.70 (16.29) | 4.65 (4.49) | .004 | 1.01 |
| | Inhibition Time (s) | 49.05 (44.30) | 10.25 (9.39) | .001 | 1.21 |
| 2&7 | ASRS | 109.50 (30.54) | 158.80 (24.03) | <.001 | 1.80 |
| | CSRS | 102.30 (22.33) | 138.35 (20.23) | <.001 | 1.70 |
| SAT[b] | SSAT RT (ms) | 863.81 (178.04) | 654.48 (98.26) | <.001 | 1.45 |
| | CSAT RT (ms) | 1595.12(366.32) | 1205.40 (209.97) | <.001 | 1.31 |
| *n*-back | 0-back RT (ms) | 775.19 (186.97) | 611.57 (129.71) | 0.003 | 1.02 |
| | 1-back RT (ms) | 866.88 (189.67) | 690.30 (150.32) | 0.002 | 1.03 |
| | 2-back RT (ms) | 1111.63 (256.70) | 788.86 (190.89) | <.001 | 1.43 |

Note. [a] Effect size is Cohen's D; [b] SAT TBI (n=19); DSF = Digit Span Forward; RS = Raw Score; DSB = Digit Span Backward; TMT = Trail Making Test; ASRS = Automatic Speed Raw Score; CSRS = Controlled Speed Raw Score; SAT = Selective Attention Task; SSAT = Simple Selective Attention Task; RT = Reaction Time; CSAT = Complex Selective Attention Task; SDMT = Symbol Digit Modalities Test.

With regard to accuracy, Mann-Whitney *U* tests revealed no significant differences between TBI and control groups on number of errors on SDMT, TMT-A or TMT-B, or accuracy on any condition of the Ruff 2&7 ($p > .05$). In addition, no significant differences were found between groups on SAT number of errors or misses ($p > .05$). On the *n*-back, there were no significant group differences for number of false positives or misses on any condition ($p > .05$). TBI participants, however, made more errors on Hayling Inhibition than control participants (M = 14.60, SD = 17.61 and M = 3.05, SD = 2.42, respectively), U = 119, z = -2.20, $p = .03$, and missed more responses than control participants on the 1-back (M = 0.85, SD = 1.18, and M = 0.10, SD = 0.45, respectively), U = 121, z = -2.82, $p = .03$, and 2-back (M = 1.70, SD = 2.49, and M = 0.05, SD = 0.22 , respectively), U = 97, z = -3.45, $p = .005$, however these group differences did not survive the Bonferroni adjusted α level of .004.

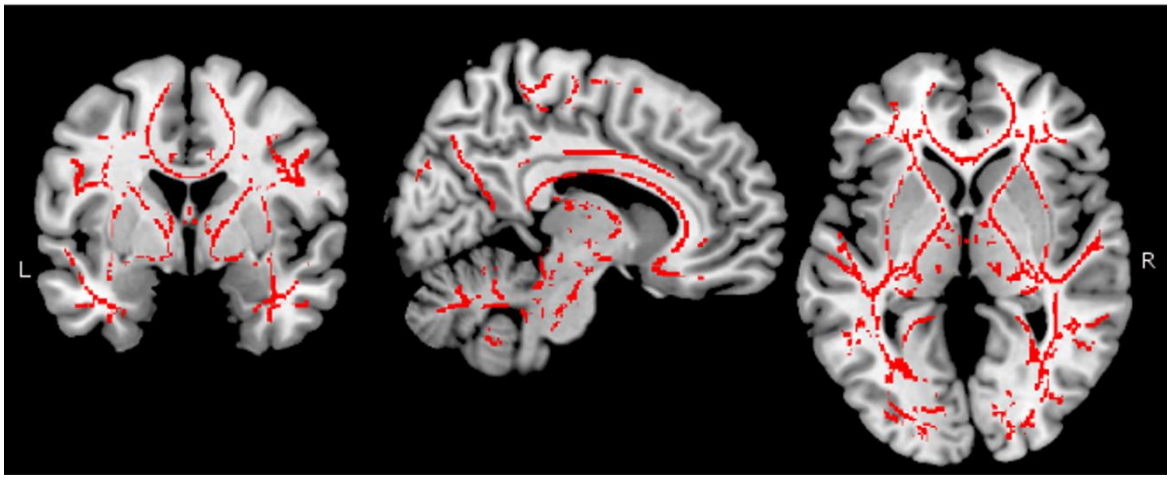


Figure 2.1 TBSS results demonstrating areas of significantly reduced FA in TBI participants when compared to controls thresholded at $p < 0.05$.

### 2.6.2 White Matter Integrity Following Traumatic Brain Injury

Investigation of group differences revealed that, when compared to controls, participants with TBI demonstrated reduced FA and increased MD values for the majority of white matter tracts, see Figure 2.1 and Figure 2.2. Lower FA was found in the TBI group in the corpus callosum (body, splenium, forceps major and forceps minor), uncinate fasciculi, inferior and superior longitudinal fasciculi, inferior fronto-occipital fasciculi, cingulum bundle, corticospinal tracts, thalamic projections, anterior and posterior limbs of the internal capsule, corona radiata, as well as cortical white matter in the temporal and frontal lobes. As with FA, higher MD was found in the majority of white matter tracts listed above in the participants with TBI when compared with controls. Peak clusters for MD and FA can be found in Table 2.3.

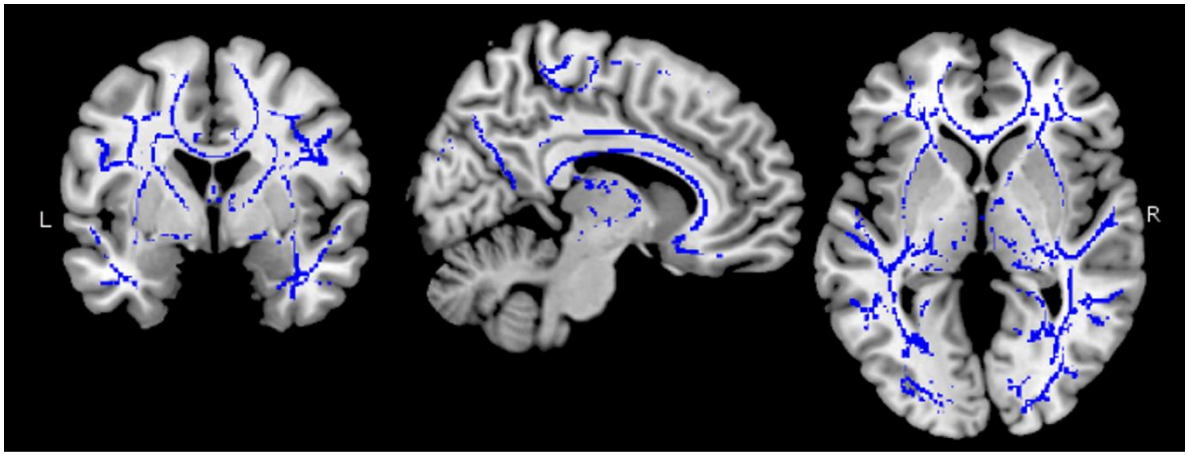


Figure 2.2 TBSS results demonstrating areas of significantly increased MD in TBI participants when compared to controls thresholded at $p < 0.05$

Table 2.3 Peak clusters for white matter changes following TBI

| | MNI Coordinates | | | |
|---|---|---|---|---|
| | x | y | z | Anatomical location |
| FA | | | | |
| | -2 | 0 | 6 | Left cerebral temporal white matter |
| | -13 | -3 | 57 | Left frontal cerebral white matter |
| | -15 | -51 | 20 | Left splenium of corpus callosum |
| | -21 | -32 | 32 | Left posterior corona radiata |
| | -17 | -51 | 24 | Left splenium of corpus callosum |
| | 8 | 22 | 26 | Right cingulate gyrus |
| MD | | | | |
| | -18 | 32 | 19 | Left forceps major |
| | -26 | 26 | 18 | Left anterior thalamic radiations |
| | 28 | 32 | 13 | Right inferior fronto-occipital fasciculus |
| | 34 | 24 | 21 | Right inferior fronto-occipital fasciculus |
| | 27 | 38 | 14 | Right anterior thalamic radiations |
| | -26 | 20 | 21 | Left anterior corona radiata |

Note: FA= Fractional Anisotropy; MD = Mean Diffusivity; MNI = Montreal Neurological Institute.

### 2.6.3 White Matter Integrity and Cognitive Performance

Significant associations were found between fractional anisotropy (FA) in the majority of white matter tracts and basic processing speed as measured by the SDMT, see Figure 2.3, and TMT-A, see Figure 2.4. The relationship was such that lower FA, indicative of reduced white matter integrity, was associated with slower performance on tasks. Anatomical locations and MNI coordinates of the peak clusters associated with SDMT and TMT-A are listed in Table 2.4.

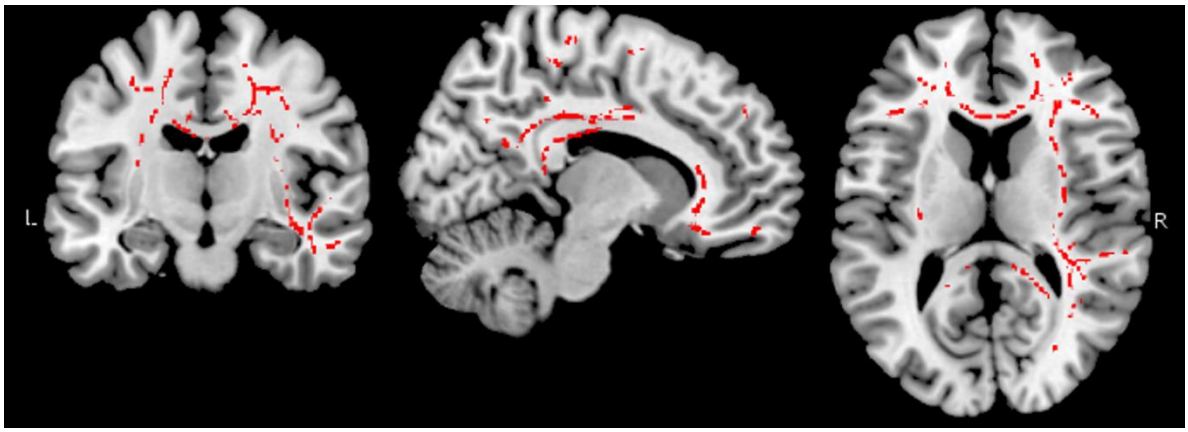


Figure 2.3 TBSS correlation analysis showing FA associated with SDMT performance in TBI participants thresholded at $p < 0.05$. SDMT = Symbol Digit Modalities Test

Table 2.4 MNI coordinates and anatomical locations of peak clusters associated with SDMT, and TMT-A in participants with TBI.

| | MNI Coordinates | | | |
|---|---|---|---|---|
| | x | y | z | Anatomical locations |
| SDMT | 27 | -59 | 29 | Right superior longitudinal fasciculus |
| | 33 | -58 | 30 | Right cerebral white matter |
| | -30 | 31 | 23 | Left cerebral white matter |
| | -8 | 26 | -3 | Left genu of the corpus callosum |
| | 22 | 37 | -5 | Right anterior corona radiata |
| | 28 | -59 | 31 | Right occipital white matter |
| TMT-A | 27 | -13 | 46 | Right parietal cerebral white matter |
| | 28 | -30 | 19 | Right posterior corona radiata |
| | 26 | -15 | 25 | Right superior corona radiata |
| | 26 | -15 | 47 | Right parietal cerebral white matter |
| | -24 | -41 | 34 | Left superior longitudinal fasciculus |
| | 15 | -29 | 33 | Right body of corpus callosum |
| | 34 | -13 | 1 | Right inferior fronto-occipital fasciculus |
| | 33 | -17 | 0 | Right inferior fronto-occipital fasciculus |
| | 35 | -11 | -4 | Right inferior fronto-occipital fasciculus |
| | 34 | -11 | 2 | Right inferior fronto-occipital fasciculus |
| | 34 | -9 | 4 | Right superior longitudinal fasciculus |
| | 7 | -62 | 28 | Right precuneous cortex |
| | 8 | -62 | 30 | Right cingulum |
| | 7 | -62 | 25 | Right cingulum |
| | 10 | -66 | 35 | Right precuneous cortex |

Note SDMT: Symbol Digit Modalities Test; TMT-A; Trail Making Test Part A; MNI = Montreal Neurological Institute.

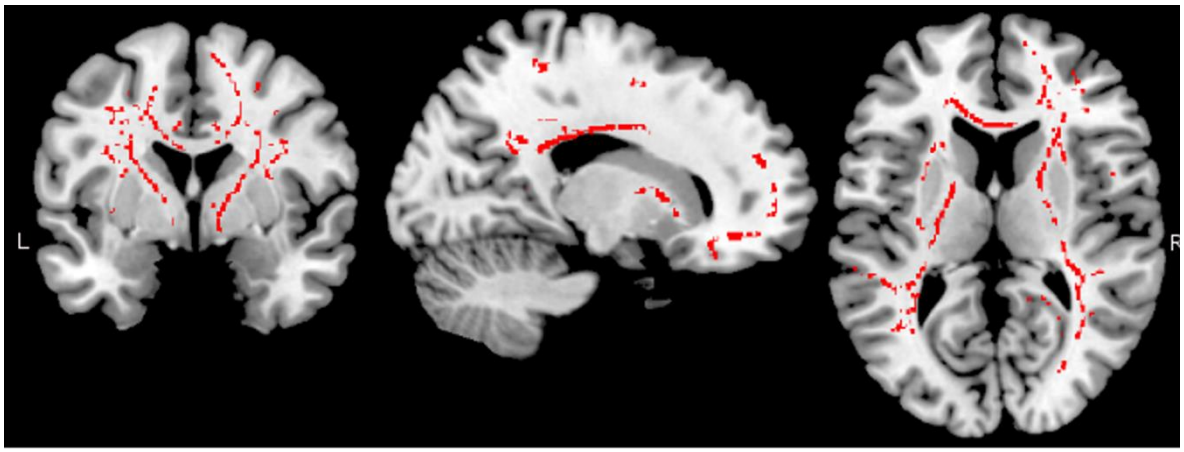


Figure 2.4 TBSS correlation analysis showing FA associated with TMT-A performance in TBI participants thresholded at $p < 0.05$. TMT = Trail Making Test-A

## 2.7 DISCUSSION

The aims of the current study were, firstly, to investigate whole brain white matter changes following TBI and, subsequently, to examine the associations between this pathology and attention deficits using TBSS. Previous research has identified white matter damage as key pathology following TBI (Hulkower et al., 2013). Consistent with this, when compared with a sample of matched controls, participants with TBI were found to have significantly reduced white matter microstructure, as measured by lower FA and higher MD, throughout the brain. This finding further supports the notion that diffuse and widespread white matter damage occurs following moderate to severe TBI (Büki & Povlishock, 2006). As focal injuries rarely account for the extent and type of functional and cognitive outcomes seen after TBI (Bigler, 2001), measuring the microscopic diffuse white matter damage is important for predicting outcomes. It can also provide information on injury severity and may help inform treatment planning (Hulkower et al., 2013)

With regard to performance on attentional tasks, when compared to controls, TBI participants were found to be slower to complete TMT, Hayling, SAT, *n*-back, and SDMT.

No differences were found between groups with regard to accuracy, suggesting participants with TBI may have been sacrificing speed for accuracy. These findings extend previous literature identifying slowed information processing speed as a prominent deficit following TBI (Dymowski et al., 2015; Mathias & Wheaton, 2007; Willmott et al., 2009).

As speed of information processing is typically reliant on different modalities, it is considered to be dependent upon numerous white matter pathways connecting geographically separate brain regions (Deary et al., 2010). In line with this notion, results indicated reduced white matter integrity in many major tracts connecting posterior and anterior brain regions (superior longitudinal fasciculi, inferior longitudinal fasciculus and inferior fronto-occipital fasciculi), as well as the left and right hemispheres (corpus callosum). Furthermore, these areas of altered white matter integrity were associated with slowed processing speed, as measured by SDMT and TMT-A. This finding supports previous observations within the TBI literature, linking slowed processing speed to reduced integrity of prominent white matter tracts within the brain (Arenth et al., 2013; Kourtidou et al., 2013; Spitz et al., 2013). It is, however, inconsistent with Kinnunen et al. (2011) who found no association between white matter integrity and information processing speed. It is possible the discrepancy in findings could be a result of the different tasks employed, as the current study Kourtidou et al. (2013) and Spitz et al. (2013) all included the SDMT, a complex task found to be more sensitive than other measures to slowed processing speed following TBI (Draper & Ponsford, 2008).

Inconsistent with previous observations, the current study found no association between white matter damage and measures of executive control of attention. Using TBSS, Kinnunen et al. (2011) identified an association between the 'alternating-switch cost index' of the TMT (time to complete TMT-B - time to complete TMT-A) and MD in the left superior frontal white matter, and radial diffusivity (RD) in the cingulum bundle, corpus callosum, right superior longitudinal fasciculus, and right corticospinal tract. Spitz et al. (2013) found speed of initiation and response inhibition, as measured by lower Hayling

overall score was associated with reduced integrity in the superior longitudinal fasciculus, corpus callosum, inferior longitudinal fasciculus, cingulum bundle, predominantly in the left hemisphere. Using ROI analysis Niogi et al. (2008) identified an association between the anterior corona radiata and attentional control, measured by the Attention Network Task, and others have demonstrated the Paced Auditory Serial Addition Test (PASAT) and time taken to complete TMT-B to be associated with multiple white matter pathways including the internal capsule, superior longitudinal fasciculus, inferior fronto-occipital fasciculi, posterior corona radiata, sagittal stratun and thalamic projection fibres (Little et al., 2010). Previous studies have, however, revealed attentional deficits following TBI to be linked to slowed speed of information processing (Dymowski et al., 2015), and performance on the abovementioned tasks is dependent on speed of processing to some degree. As the abovementioned studies did not control for speed of information processing, the results may be a reflection of reduced speed, rather than executive aspects of attention, which would be consistent with the current findings.

Similarly, no significant association was found between white matter integrity and working memory performance. Palacios et al. (2011) also used the *n*-back to assess working memory in TBI participants within 12 months of injury. They identified an association between the ability to accurately discriminate between targets and non-targets on a 2-back task and white matter microstructure of the superior longitudinal fasciculus, corpus callosum, fornix and arcuate fasciculus. The discrepancy may be explained by the different *n*-back metrics used, as the current study investigated the association between mean reaction time for accurate responses and white matter integrity. Previous research using ROI has identified a link between both spatial span and digit span and thalamic projection fibres (Little et al., 2010). Multiple thalamic seed regions were used to assess integrity of thalamic projections in the study by Little and colleagues. It is possible this more in-depth analysis yielded more detailed results of thalamic projection integrity than TBSS, which may account for the discrepancy in results.

It is important to note the study may have been limited by sample size. It is possible the analyses were not optimally powered to detect significant associations between white matter integrity and other aspects of attention function over and above that found for speed of information processing, leading to Type II error. In addition, it is possible the DTI metrics were contaminated by the inadvertent measurement of cerebrospinal fluid resulting in reduced FA and increased MD values (Alexander, Hasan, Lazar, Tsuruda, & Parker, 2001; Vos, Jones, Viergever, & Leemans, 2011). Each individual scan was, however, inspected and participants with problematic brain atrophy were excluded. In addition, TBSS measures the centre of white matter tracts (Smith et al., 2006), making it less likely to inadvertently measure CSF, as white matter junctions with grey matter and CSF which are prone to partial volume effects are not measured.

### 2.7.1 Conclusion

It is important for assessment of injury severity, treatment planning and outcome prediction to understand the full extent of DAI damage following TBI (Hulkower et al., 2013). Using TBSS, this study identified multiple white matter tracts showing microstructure pathology in a more acute TBI sample (majority <12 month post injury). In addition, the results suggest that prominent white matter pathways connecting spatially distinct brain regions are implicated in information processing speed deficits post-TBI. Attentional deficits are frequent following TBI and have deleterious effects of life roles (Mathias & Wheaton, 2007; Ponsford & Willmott, 2004; Willmott et al., 2009). Given the majority of recovery takes place within the first 12 months post injury (Christensen et al., 2008), understanding the mechanisms that underpin these deficits during this time is critical for the development of targeted interventions.

## 2.8 ACKNOWLEDGEMENTS

The authors would like to thank the participants and their families who generously gave their time. We are grateful to the staff at the Monash-Epworth Rehabilitation Research Centre for initially screening admissions for eligibility, and the Epworth HealthCare neuropsychology staff for providing additional information in the screening process. We would also like to thank the Epworth Health Care rehabilitation doctors, Dr Rose Acher, Dr Michael Ponsford, and Professor John Olver, for their assistance with identifying eligible participants and help with recruitment. We would also like to thank the staff at Monash Biomedical Imaging Centre for expertise and assistance with the use of their facilities. In particular, we would like to especially acknowledge Dr Qi-Zhu Wu for his assistance with developing the imaging sequence. We also acknowledge the assistance of Antonio Benci at the Monash Facility for Instrumentation & Technology Development for designing and building the computer response box and Mr Christopher Hocking for programming the *n*-back task.

# CHAPTER THREE

# WHITE MATTER INTEGRITY OF THE MEDIAL FOREBRAIN BUNDLE AND ATTENTION AND WORKING MEMORY DEFICITS FOLLOWING TRAUMATIC BRAIN INJURY

## 3.1 DECLARATION FOR THESIS CHAPTER THREE

**Monash University**

**Declaration for Thesis Chapter 3**

**Declaration by candidate**

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

| Nature of contribution | Extent of contribution |
|---|---|
| Formulation of experimental design, data collection, data analysis and preparation of full manuscript. | 65% |

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

| Name | Nature of contribution | Extent of contribution (%) for student co-authors only |
|---|---|---|
| Catherine Willmott | Consultation in formulation of experimental design, discussion of ideas expressed in manuscript and critical review of manuscript. | |
| Gershon Spitz | Assisted with the designing the imaging analysis protocol, and critical reviewed the manuscript. | |
| Jennie Ponsford | Involved in the conceptualisation, planning and design of the study, and reviewed the manuscript. | |
| Alicia Dymowski | Assisted with recruitment and neurological assessment of some participants. Also assisted with data entry and reviewed the manuscript. | 5% |
| Nicholas Ferris | Assisted with the imaging analysis as well as reviewed the manuscript | |

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contribution to this work:

| | | |
|---|---|---|
| **Candidate's Signature** |  | Date:17/11/2016 |
| **Main Supervisor's Signature** |  | Date:17/11/2016 |

## 3.2 OVERVIEW

This chapter presents an empirical paper titled *"White matter integrity of the medial forebrain bundle and attention and working memory deficits following traumatic brain injury"* accepted by Brain and Behavior on the 16th October 2016. Following on from Chapter Two which examined whole brain white matter pathology post-TBI and associated attentional deficits, this chapter focuses on the superior-lateral medial forebrain bundle (slMFB), a key dopaminergic (DAergic) pathway that has not yet been investigated following TBI. By investigating this pathway, we hope to provide important information about the type of damage that may lead to DA neurotransmission disruption following TBI, and the associated attention deficits. Understanding the type of damage that leads to disruptions to the DA system and attentional impairments is important as it may inform the use of DA agonists and other pharmacological treatments.

## 3.3 ABSTRACT


### Background and Objective

The medial forebrain bundle (MFB) contains ascending catecholamine fibres that project to the prefrontal cortex (PFC). Damage to these fibres following traumatic brain injury (TBI) may alter extracellular catecholamine levels in the PFC and impede attention and working memory ability. This study investigated white matter microstructure of the medial MFB, specifically the supero-lateral branch (slMFB), following traumatic brain injury (TBI), and its association with performance on attention and working memory tasks.

### Method

Neuropsychological measures of attention and working memory were administered to 20 moderate-severe participants with TBI (post traumatic amnesia (PTA) M= 40.05 ± 37.10 days, median time since injury 10.48 months, range 3.72-87.49) and 20 healthy controls. Probabilistic tractography was used to obtain fractional anisotropy (FA) and mean diffusivity (MD) values for 17 participants with TBI and 20 healthy controls.

### Results

When compared to controls, participants with TBI were found to have significantly lower FA ($p < 0.001$) and higher MD ($p < 0.001$) slMFB values, and they were slower to complete tasks including Trail Making Task-A, Hayling, Selective Attention Task, *n*-back, and Symbol Digit Modalities Test.

### Conclusion

This study was the first to demonstrate microstructural white matter damage within the slMFB following TBI. However, no evidence was found for an association of alterations to this tract and performance on attentional tasks.

## 3.4 INTRODUCTION

Attention and working memory deficits are prevalent cognitive impairments following moderate to severe traumatic brain injury (TBI) (Ponsford & Willmott, 2004; Willmott et al., 2009). These deficits adversely affect individuals' ability to work, socialise and function in everyday life (Bercaw et al., 2010; Draper et al., 2007). The dopamine (DA) system is thought to play a key role in persistent cognitive impairment following TBI, including attention deficits (for review see Bales et al., 2009). Elucidating TBI induced disruptions to the DA system and whether they are associated with attention deficits may assist in identifying those most likely to benefit from pharmacological interventions.

Experimental models (Brozoski et al., 1979; Montaron et al., 1982) and clinical studies specifically implicate the DA system in attention and working memory function (Clark et al., 1986; Clark et al., 1987a; Clark et al., 1987b; Clark et al., 1989). Dysfunction of DA circuitry has previously been found in other clinical groups demonstrating attentional deficits, particularly Attention Deficit/Hyperactivity Disorder (see del Campo et al. (2011) for review), with administration of DA agonists found to ameliorate attentional impairments (Arnsten, 2011; Nieoullon, 2002; Solanto, 1998; Willmott and Ponsford, 2009). TBI causes widespread damage that may disrupt the DA system, potentially leading to attention deficits.

Alterations to the DA system have previously been identified in TBI populations. Reduced DA levels have been found in cortical areas post-TBI (McIntosh et al., 1994). Alterations to the DA transporter protein have been identified in brain regions associated with attentional function following TBI, including the frontal cortices (Yan et al., 2002), and the striatum (Donnemiller et al., 2000). This is believed to be secondary to disruptions to catecholamine pathways via diffuse axonal injury (DAI) (Donnemiller et al., 2000). DAI is a common pathology in TBI that leads to a cascade of events, including denervation and degeneration of nerve terminals (Büki & Povlishock, 2006; Johnson et al., 2013). Disruptions to DA signalling seen after TBI, and the associated attention impairments,

may be somewhat attributable to alteration to DAergic pathways caused by DAI. Investigation into alterations to DA pathways following TBI and association with attention deficits, however, is lacking.

The medial forebrain bundle (MFB) is an important pathway within the DA system. It contains ascending catecholamine fibres that innervate the frontal cortices (Coenen et al., 2009; Coenen et al., 2012; Coenen et al., 2011). Due to its major role in the brain reward systems, past research has generally focused on the MFB in relation to affective and addiction disorders (Alcaro & Panksepp, 2011; Bracht et al., 2015; Coenen et al., 2009; Coenen et al., 2012; Wise, 2005). In humans, the supero-lateral branch (slMFB) of the MFB connects the ventral tegmental area (VTA) to the anterior limb of the internal capsule, the ventral striatum and nucleus accumbens, before terminating in the prefrontal cortex (PFC) (Coenen et al., 2009; Coenen et al., 2012; Coenen et al., 2011). Given that alterations to the slMFB may have secondary consequences for extracellular DA levels, and potentially underpin attentional impairments, investigation of the changes to the slMFB following TBI is important.

Diffusion tensor imaging (DTI) is a magnetic resonance technique that provides an indication of the microstructural damage to white matter pathways by measuring water diffusivity, resulting in measures of fractional anisotropy (FA) and mean diffusivity (MD) (Le & Gean, 2009; Provenzale, 2010). DTI has been successfully used to identify alterations to white matter microstructure associated with poorer attentional performance post-TBI. Reduced speed of information processing has been associated with microstructural alterations in frontal white matter, cingulum bundle, inferior longitudinal fasciculus, thalamic projections and corpus callosum (Arenth et al., 2013; Little et al., 2010; Spitz et al., 2013; Wilde et al., 2011). Attention span has been found to be associated with white matter microstructure within thalamic projections post-TBI (Little et al., 2010). Additionally, the superior longitudinal fasciculus, corona radiata and corpus callosum are implicated in attentional control (Arenth et al., 2013; Spitz et al., 2013).

The absence of the MFB on DTI neuroanatomical atlases makes it less accessible for investigation than other more prominent white matter tracts. It was not until 2009 that the MFB was first depicted using DTI (Coenen et al., 2009). In their initial DTI deterministic fibre tracking investigation of the MFB, Coenen et al. (2009) tracked the MFB by placing a region of interest (ROI) seed in the ventral midbrain. In a subsequent investigation, Coenen et al., (2012) again used deterministic tractography and tracked the MFB by placing a single ROI seed in the ipsilateral VTA. Bracht et al, (2015), employed a similar ROI to depict both the infero-medial (imMFB) and slMFB using probablistic tractography. Additionally, Anthofer et al. (2015) compared three different ROI pairs for deterministic fibre tracking of the MFB. The most reliable and convincing results were found when using the ipsilateral VTA and nucleus raphe dorsalis ROI pair. Using this method, Anthofer et al. (2015) found similar results to Bracht et al, (2015), Coenen et al., (2009) and Coenen et al., (2012), replicating the author's anatomical description of the MFB, as well as the seed regions used.

The aim of the current study was to: (a) explore the white matter microstructure of the slMFB in a TBI population in comparison with controls, and (b) explore the association between slMFB white matter microstructure and attentional function following TBI.

## 3.5 METHOD

### 3.5.1 Participants

Twenty participants with a history of moderate to very severe TBI (15 male) and twenty healthy controls (12 male) were recruited from the Acquired Brain Injury Rehabilitation service at Epworth HealthCare, Melbourne, Australia. Healthy controls were recruited from the general public and explicitly matched to TBI participants during recruitment. The groups did not differ significantly with respect to age, years of education, estimated IQ or gender (see Table I). For the TBI group, median time since injury was 10.48 months

(interquartile range (IQR) = 10.83 months, range 0-87.5 months). Forty percent of participants underwent MRI and cognitive testing on the same day (for the remainder median time lag between assessment and scan = 25 days, IQR =62.25 days, with the assessment done first in 86% of cases). Individuals were excluded if they had an inadequate understanding of English, insufficient cognitive ability or physical disabilities preventing completion of the tasks, previous history of treatment for psychiatric illness, past neurological disorder, history of treatment for drug or alcohol dependence, diagnosis of attention deficit disorder prior to injury, or Magnetic Resonance (MR) contraindications. Cause of injury included motor-vehicle accident (60%), bicycle or pedestrian accidents involving motor vehicles (25%), falls (10%), and one participant was involved in an equestrian accident (5%). Mean duration of post traumatic amnesia (PTA) was 40.05 days (SD = 37.10 days, range 0-142 days). With regards to GCS, 15% were classified as mild (GSC 13-15), 5% were moderate (GCS 9-12), 75% were severe (GCS 3-8), and 5% were not recorded. In terms of PTA duration, 50% of TBI participants had a very severe injury (PTA >4weeks), 35% a severe injury (PTA 1-4 week), 10% a moderate injury (PTA 1-7days), and one participant (5%) a complicated mild injury (PTA < 24 hours with changes on Computed Tomography (CT) imaging; Arlinghaus et al., 2005). All TBI participants demonstrated evidence of damage on CT brain scans (see Table 3.1)

Table 3.1 Demographic and brain pathology of the TBI and control groups

| | TBI (*n* = 20) | Controls (*n*=20) | *p* value | Effect size[a] |
|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | | |
| Age (years) | 39.05 (16.45) | 33.45 (11.72) | .22 | -0.40 |
| Years of education | 13.58 (2.53) | 13.43 (2.67) | .86 | -0.06 |
| Estimated FSIQ | 108.83 (8.81) | 107.71 (5.87) | .64 | -0.15 |
| | *n* | *n* | | |
| Gender (male) | 15 | 12 | .31 | 0.32 |
| Brain Pathology | | | | |
| Contusion | 8 (40%) | - | | |
| Diffuse axonal injury | 3 (15%) | - | | |
| Subarachnoid haemorrhage | 8 (20%) | - | | |
| Subdural haemorrhage | 10 (50%) | - | | |
| Epidural haemorrhage | 2 (10%) | - | | |
| Intracranial haemorrhage | 3 (15%) | - | | |
| Interventricular haemorrhage | 3 (15%) | - | | |
| Haematoma | 4 (20%) | - | | |
| Abscesses | 1 (5%) | - | | |
| Petechial haemorrhages | 3 (15%) | - | | |

Note. FSIQ = Full Scale Intelligence Quotient

Two TBI participants were excluded from the imaging data analysis due to severe pathology preventing accurate depiction of the MFB. One TBI participant had large focal frontal lobe lesions whereas the other participant had significant hydrocephalus. One participant was excluded from the analysis due to inconsistencies in DICOM images rendering them incompatible with the neuroimaging analysis, leaving 17 for analysis. Two further TBI participants were excluded from the correlation analysis as their cognitive assessment and MRI were more than a month apart, rendering the association between DTI metrics and cognitive performance potentially invalid, resulting in n = 15. TBI participants (n = 20) were included in all comparisons for cognitive tasks, with the

exception of one colour blind participant for the computerised selective attention task analysis.

### 3.5.2 Procedure

This study was approved by Monash University Human Research and Epworth HealthCare Ethics Committees. Written informed consent was obtained from all participants. Once they emerged from PTA according to their treating neuropsychologist, measured by daily administration of the Westmead PTA Scale (Shores et al., 1986), participants were invited to undergo a neuropsychological assessment of attention and working memory as well as a brain MRI scan. Prior to enrolment, all participants underwent CT scans as a part of routine assessment and treatment at the acute hospital. Results from CT scans were reported by radiologists at the respective hospitals.

### 3.5.3 Neuropsychological Measures

#### 3.5.3.1 The National Adult Reading Test (NART)

The NART (Nelson, 1982) is a reading test that consists of 50 irregularly spelt words and was used to estimate pre-morbid IQ.

#### 3.5.3.2 The Symbol Digit Modalities Test

The SDMT (Smith, 1991) has previously been used to show reduced psychomotor processing speed in a TBI sample (Ponsford & Kinsella, 1992). Participants have 90 seconds to decode a series of symbols.

#### 3.5.3.3 The computerised selective attention task (SAT)

The SAT (Ziino & Ponsford, 2006) has two conditions, the simple selective attention task (SSAT) and complex selective attention task (CSAT). The CSAT assessed a higher working memory load as participants are required to retain additional verbal rules. TBI patients have been found to respond more slowly and make significantly more errors than controls on this task (Willmott and Ponsford, 2009).

#### 3.5.3.4 The Ruff 2&7 selective attention task

The Ruff 2&7 selective attention task (Ruff & Allen, 1995) is a pen and paper cancellation task with two conditions, automatic speed (ASRS), controlled speed (CSRS). Participants cancelled the digits 2 and 7 amongst either letters or numbers, with the former being an automatic retrieval condition and the latter requiring controlled search and working memory abilities.

#### 3.5.3.5 The *n*-back

The *n*-back (Perlstein et al., 2004) has been found to be sensitive to working memory deficits in a TBI sample (Perlstein et al., 2004). Participants were required to correctly match the letter presented on the screen with the letter presented 0, 1 and 2 screens back.

#### 3.5.3.6 The Hayling Sentence Completion Test from the Hayling and Brixton Tests

The Hayling Sentence Completion Test (Burgess & Shallice, 1996) has two sets of 15 sentences with the last word missing. Hayling A (response initiation) required participants

to provide a word that completes the sentence as quickly as possible. In Hayling B (response inhibition) participants were required to complete the sentences with a word that is completely unrelated to the sentence. The tasks measures speed of initiation and response inhibition and has been found to be sensitive to change post-TBI (Draper & Ponsford, 2008).

#### 3.5.3.7 Trail Making Test (TMT) - Parts A and B

The TMT (Reitan & Wolfson, 1985), required participants to connect 25 numbers in ascending order (Trails A), and to switch between 13 numbers and 12 letters in sequence (Trails B), as quickly as possible while maintaining accuracy. It measures processing speed, divided attention and mental flexibility and has been shown to differentiate individuals with TBI from healthy control participants (Spitz et al., 2012).

#### 3.5.3.8 Digit Span subtest of the Wechsler Adult Intelligence Scale –Fourth Editions

Digits backwards, forwards and sequencing (Wechsler, 1997), was used to assess participants' immediate auditory attention span and working memory capacity. Digit span backwards has previously been shown to be sensitive to changes in attention after TBI (Chan, 2000; Kinsella et al., 1996).

### 3.5.4 Neuroimaging Acquisition

Neuroimaging was performed on a Siemens Magnetom Skyra 3 Tesla MRI scanner using a 32 channel head coil (Siemens Medical Imaging, Erlangen, Germany). A 3D T1-weighted MPRAGE sequence was acquired in the sagittal orientation (TI 900ms, TR 1540ms, TE

2.57ms, resolution 256 x 256 x 176, flip angle 9 degrees, FOV 250mm, slice thickness 1.00mm (176slices)). A diffusion tensor imaging (DTI) sequence was acquired (TR= 10900, TE = 101, 64 diffusion encoding directions, Number of Excitations = 1, slice thickness = 2.0mm (64 slices), field of view = 256mm, matrix = 128 x 128, in-plane = 2.0 x 2,0mm, *b* value = 2000 s/mm$^2$).

#### 3.5.4.1 Medial forebrain bundle tractography

Tractography of the medial forebrain bundle was conducted in MRtrix version 3 (J-D Tournier, Brain Research Institute, Melbourne, Australia, http://www.mrtrix.org/) (Tournier et al., 2012). Diffusion-weighted images initially underwent eddy-current correction in FSL version 5.0.8. The standard DWI processing was then undertaken in MRtrix, including estimating the response function before conducting the Constrained Spherical Deconvolution (CSD) based on the previously obtained response function. Using probabilistic tractography, the slMFB was tracked for each individual on the DWI image in subject-native space. The MFB seed regions outlined by Coenen et al. (2012) were used in the current study. The ipsilateral ventral tegmental area was used as the seed point, with the anterior margin being the mammillary body/mammillo-thalamic tract, the lateral margin the medial margin of the substantia nigra, and the posterior margin the red nucleus (see Figure 3.1). The first 10 resulting slMFB tracts were visually inspected by an experienced neuroradiologist NF, and authors GS and JO inspected the remainder to ensure correct depiction of the slMFB. Each individual's slMFB tract was converted to a slMFB mask, weighted on streamline length. Mean Fractional Anisotropy (FA) and Mean Diffusivity (MD) images were generated from the diffusion-weighted images in subject native space using an iteratively-reweighted linear least-squares solver (Veraart et al., 2013). FA and MD values for each participant were extracted by overlying the slMFB mask on each of the corresponding images.

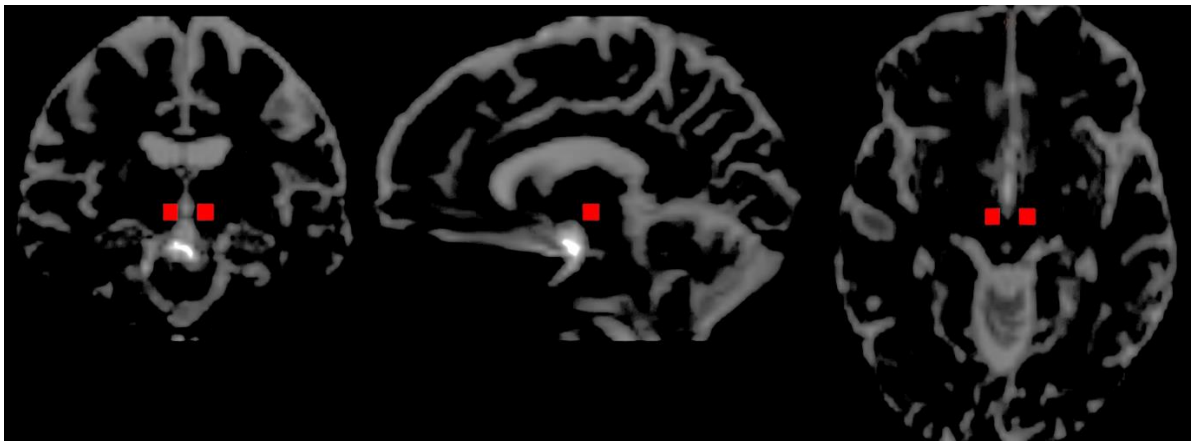

Figure 3.1 Region of Interest for the Ventral Tegmental Area.

Red square indicates the initial seed location used for probabilistic tractography in a single participant.

### 3.5.5 Data Analysis

Using a cut off of reaction times greater or less than 2 standard deviations from the mean for each group, 3% of *n*-back reaction times (RTs) across three conditions as well as 8% SAT RTs across two conditions were removed from the analysis, similar to previous RT studies (Willmott et al., 2009). Univariate outliers were defined as Z-score >3.29 ($p$ < .001, two-tailed test). Two outliers in the Hayling Test were identified (one TBI and one healthy control for number of errors) and assigned a score 1 unit greater than the next most extreme score (Tabachnick & Fidell, 2007). Independent sample T-tests were undertaken to compare groups for normally distributed test variables. Non-parametric test Mann-Whitney U was used to analyse error data for the SDMT, 2&7 accuracy data, TMT, Hayling Test, and errors, missed responses for the *n*-back and SAT. Pearson's correlations were run to explore the relationship between white matter microstructure of the medial forebrain bundle and performance on attention and working memory tasks. Partial correlation analysis controlled for age, years of education and estimated

Intelligence Quotient (FSIQ). To control for Type I error rate, Bonferroni adjustments were made for multiple comparisons.

## 3.6 RESULTS

### 3.6.1 Neuropsychological Performance

Using a Bonferroni adjusted α level of .004, when compared to control participants, TBI participants were found to complete fewer items on the SDMT, cancel fewer targets in both the controlled search and automatic detection condition of the Ruff 2&7, and were significantly slower to complete the TMT-A as well as the timed aspects of the Hayling Test (Table 3.2). With regard to computerised tasks, they were slower to respond during all conditions of the *n*-back and SAT, than controls (Table 3.2). No significant differences were found between the TBI and control group on any condition of Digit Span.

Table 3.2 Means, standard deviations, significance and effect sizes for performance on attention tasks for TBI and control groups

| | | TBI (*n*=20) | Control (*n*=20) | | |
|---|---|---|---|---|---|
| Task | Measure | Mean (SD) | Mean (SD) | *p* value | Effect size[a] |
| Digit Span | DSF RS | 11.35 (2.56) | 11.40 (2.87) | .94 | 0.02 |
| | DSB RS | 9.25 (2.95) | 8.85 (2.76) | .66 | 0.14 |
| SDMT | Number correct | 44.30 (9.58) | 58.10 (10.20) | <.001 | 1.40 |
| TMT | TMT-A time (s) | 39.60 (15.02) | 23.05 (7.50) | <.001 | 1.40 |
| | TMT-B time (s) | 83.50 (39.65) | 59.90 (22.01) | .027 | 0.74 |
| Hayling | Initiation Time (s) | 16.70 (16.29) | 4.65 (4.49) | .004 | 1.01 |
| | Inhibition Time (s) | 49.05 (44.30) | 10.25 (9.39) | .001 | 1.21 |
| 2&7 | ASRS | 109.50 (30.54) | 158.80 (24.03) | <.001 | 1.80 |
| | CSRS | 102.30 (22.33) | 138.35 (20.23) | <.001 | 1.70 |
| SAT[b] | SSAT RT (ms) | 863.81 (178.04) | 654.48 (98.26) | <.001 | 1.45 |
| | CSAT RT (ms) | 1595.12(366.32) | 1205.40 (209.97) | <.001 | 1.31 |
| *n*-back | 0-back RT (ms) | 775.19 (186.97) | 611.57 (129.71) | .003 | 1.02 |
| | 1-back RT (ms) | 866.88 (189.67) | 690.30 (150.32) | .002 | 1.03 |
| | 2-back RT (ms) | 1111.63 (256.70) | 788.86 (190.89) | <.001 | 1.43 |

Note. [a] Effect size is Cohen's D; [b] SAT TBI (n=19); DSF = Digit Span Forward; RS = Raw Score; DSB = Digit Span Backward; TMT = Trail Making Test; ASRS = Automatic Speed Raw Score; CSRS = Controlled Speed Raw Score; SAT = Selective Attention Task; SSAT = Simple Selective Attention Task; RT = Reaction Time; CSAT = Complex Selective Attention Task; SDMT = Symbol Digit Modalities Test.

Mann-Whitney *U* Tests revealed that number of errors on the Hayling SDMT, TMT-A or TMT-B, or accuracy on any condition of the Ruff 2&7 did not differ between groups (Table 3.3). In terms of the computerised tasks, the groups did not differ with regard to number of errors or misses on any condition of the SAT or the *n*-back (Table 3.3).

Table 3.3 Means, standard deviations and significance for errors score for TBI and control groups

| | | TBI M (SD) | Control M (SD) | *p*-value |
|---|---|---|---|---|
| SDMT | errors | 0.65(1.09) | 0.75(1.2) | 0.6 |
| TMT | TMT-A errors | 0.2(0.41) | 0.25(0.55) | 0.97 |
| | TMT-B errors | 0.6(0.75) | 0.60(0.94) | 0.8 |
| Hayling | initiation errors | 10.26(16.06) | 1.70(2.39) | 0.08 |
| | inhibition errors | 4.21(4.66) | 1.25(1.25) | 0.03 |
| Ruff 2& 7 | AS accuracy | 95.01(4.79) | 96.21(4.02) | 0.48 |
| | CS accuracy | 92.1(8.00) | 92.85(4.90) | 0.68 |
| SAT[a] | SSAT errors | 0.2(0.52) | 0.05(0.22) | 0.58 |
| | SSAT misses | 0 | 0 | 1 |
| | CSAT errors | 2.4(2.32) | 2.40(3.03) | 0.86 |
| | CSAT misses | 0.3(0.57) | 0.10(0.31) | 0.41 |
| *n*-back | 0-back errors | 1.25(2.00) | 0.25(0.44) | 0.09 |
| | 0-back misses | 0.65(1.79) | 0 | 0.11 |
| | 1-back errors | 2.95(2.33) | 1.40(1.73) | 0.04 |
| | 1-back misses | 0.85(1.18) | 0.10(0.44) | 0.03 |
| | 2-back errors | 6.6(4.36) | 3.25(3.04) | 0.014 |
| | 2-back misses | 1.7(2.49) | 0.05(0.22) | 0.005 |

Note. [a]SAT TBI (n=19); TMT = Trail Making Test; AS= Automatic Speed; CS = Controlled Speed; SAT = Selective Attention Task; SSAT = Simple Selective Attention Task; CSAT = Complex Selective Attention Task; SDMT = Symbol Digit Modalities Test.

### 3.6.2 Supero-Lateral Branch of the Medial Forebrain Bundle

Visual inspection of the results approximated that found by the Bracht et al., (2015) Coenen et al., (2009), Coenen et al., (2012) and Anthofer et al. (2015) depictions of the MFB when using the ipsilateral VTA and nucleus raphe dorsalis as ROIs. Thus, the slMFB identified follows the same path described in these previous studies running from the seed point placed in the VTA, the fibres courses along the lateral wall of the third ventricle connecting to the nucleus accumbens and anterior limb of the internal capsule, before terminating in the inferior-medial PFC, see Figure 3.2.

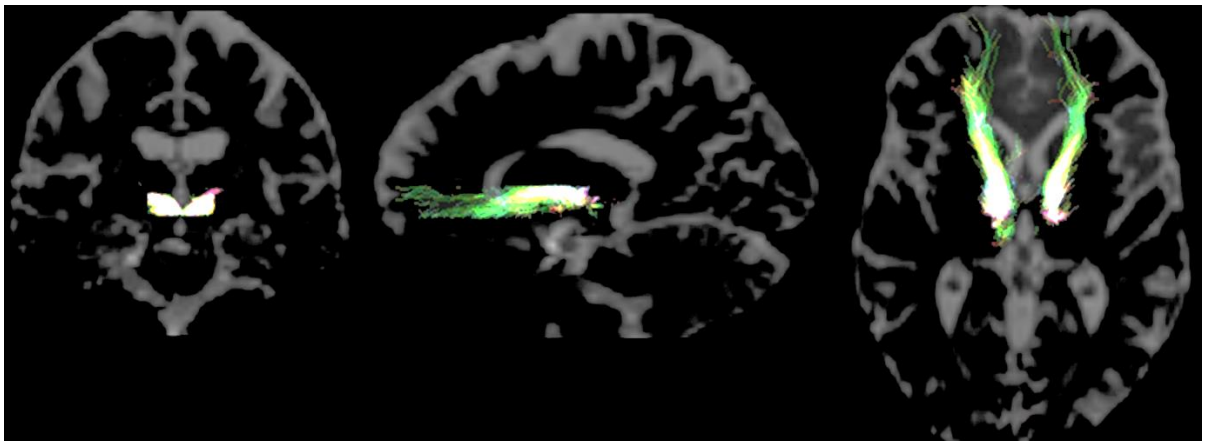

Figure 3.2. slMFB reconstructed for a single participant using probabilistic tractography

### 3.6.3 White Matter Microstructure Alterations within the slMFB following TBI

Using a Bonferroni adjusted α level of .025, bivariate comparisons revealed that TBI participants had significantly lower FA values and significantly higher MD values within the slMFB compared to the control group (Table IV). Participants with TBI also showed a larger range of slMFB FA and MD values than controls. When controlling for age and time since injury, no significant association was found between worst GCS or PTA duration and slMFB FA or MD values. In addition, no association was found between time since injury and DTI metrics when controlling for age.

Table 3.4 Means, standard deviations, significance and effect sizes for DTI metrics for TBI and control groups

| | TBI (*n*=17) | | Control (*n*=20) | | | |
|---|---|---|---|---|---|---|
| | Mean (SD) | Range | Mean (SD) | Range | *p* value | Effect size[a] |
| FA | .33(.03) | .256-.371 | .37 (.03) | .320-.426 | <0.001 | -1.56 |
| MD[b] | 7.43 (.50) | 6.5-8.5 | 6.74 (.29) | 6.1-7.2 | <0.001 | 1.69 |

Note. [a] Effect size is Cohen's D; [b] MD [X $10^{-4}mm^2/s$]; FA= Fractional Anisotropy; MD = Mean Diffusivity

Using a Bonferroni adjusted α level of $p > 0.001$, when controlling for age, years of education and gender, no significant correlations were found between neuropsychological performance and DTI metrics for TBI or control participants (Table 3.5).

Table 3.5 Correlation coefficient and p-values (in italics) for DTI metrics and cognitive measures, controlling for age, years of education and estimated full scale intelligence quotient.

| | | TBI | | Control | |
|---|---|---|---|---|---|
| | | FA | MD | FA | MD |
| SDMT | Number correct | 0.171 | -0.495 | -0.172 | 0.114 |
| | | *0.594* | *0.102* | *0.509* | *0.662* |
| Ruff 2&7 | ASRS | -0.428 | 0.085 | -0.433 | 0.294 |
| | | *0.165* | *0.792* | *0.083* | *0.252* |
| | CSRS | -0.418 | 0.129 | -0.300 | 0.215 |
| | | *0.176* | *0.690* | *0.242* | *0.406* |
| TMT | TMT-A (s) | -0.298 | 0.323 | 0.025 | 0.153 |
| | | *0.347* | *0.306* | *0.924* | *0.559* |
| | TMT-B (s) | 0.162 | -0.220 | 0.358 | -0.175 |
| | | *0.614* | *0.492* | *0.158* | *0.502* |
| Hayling | Initiation Time (s) | -0.224 | -0.005 | -0.029 | -0.023 |
| | | *0.485* | *0.987* | *0.911* | *0.930* |
| Hayling-B (rs) | Inhibition time (s) | 0.203 | -0.132 | -0.439 | 0.249 |
| | | *0.526* | *0.683* | *0.078* | *0.335* |
| | Initiation errors | -0.130 | -0.067 | -0.174 | 0.156 |
| | | *0.686* | *0.836* | *0.504* | *0.549* |
| | Inhibition errors | -0.002 | -0.125 | -0.458 | 0.275 |
| | | *0.995* | *0.698* | *0.065* | *0.285* |
| Digit Span | DSF | -0.220 | 0.595 | -0.039 | 0.182 |
| | | *0.492* | *0.041* | *0.882* | *0.484* |
| | DSB | -0.170 | 0.558 | 0.007 | 0.069 |
| | | *0.597* | *0.059* | *0.978* | *0.792* |
| | DSS | -0.243 | -0.023 | -0.270 | 0.221 |
| | | *0.447* | 0.943 | 0.295 | 0.393 |
| *n*-back | 0- back RT (ms) | -0.219 | 0.625 | -0.349 | 0.071 |
| | | *0.494* | 0.030 | 0.170 | 0.788 |
| | 1-back RT (ms) | 0.445 | -0.675 | -0.254 | -0.086 |
| | | *0.147* | *0.016* | *0.325* | *0.742* |
| | 2-back RT (ms) | -0.267 | 0.446 | -0.274 | 0.015 |
| | | *0.401* | *0.146* | *0.287* | *0.954* |
| SAT[a] | SSAT RT (ms) | 0.413 | -0.024 | -0.272 | -0.042 |
| | | *0.182* | *0.940* | *0.290* | *0.873* |
| | CSAT RT (ms) | 0.127 | 0.039 | 0.133 | -0.379 |
| | | *0.695* | *0.905* | *0.611* | *0.134* |

Note. [a] SAT TBI (n=19); p-values presented in italics; FA = Fractional Anisotropy; MD= Mean Diffusivity; DSF = Digit Span Forward; RS = Raw Score; DSB = Digit Span Backward; TMT = Trail Making Test; ASRS = Automatic Speed Raw Score; CSRS = Controlled Speed Raw Score; SAT = Selective Attention Task; SSAT = Simple Selective Attention Task; RT = Reaction Time; CSAT = Complex Selective Attention Task; SDMT = Symbol Digit Modalities Test.

## 3.7 DISCUSSION

To the best of our knowledge, this was the first study to investigate changes to the slMFB following TBI, and their association with attention and working memory deficits. As the slMFB contains ascending catecholamine fibres, damage as a result of DAI may disrupt extracellular concentrations of catecholamines within the PFC, potentially leading to attention and working memory deficits. Previous DTI deterministic fibre tracking research has described the slMFB as splitting from the trunk of the MFB in the VTA, coursing along the lateral wall of the third ventricle, connecting to the nucleus accumbens and anterior limb of the internal capsule, before terminating in the inferior-medial PFC (Anthofer et al., 2015; Bracht et al., 2015; Coenen et al., 2009; Coenen et al., 2012). Using probabilistic tractography and seed regions described by Coenen et al (2012), the slMFB was depicted as described by previous literature, replicating previous findings.

Using a well matched sample, TBI participants were found to have reduced FA and higher MD within the slMFB when compared to controls, indicating microstructural white matter damage caused by DAI. This is consistent with the many previous studies which have identified multiple damaged white matter pathways following TBI (for review see Hulkower et al., 2013). Disruption to axon terminals caused by DAI may affect DA transmission (Büki & Povlishock, 2006), and downregulation of the dopamine transporter protein has been identified post-TBI (Donnemiller et al., 2000; Yan et al., 2002). Although DA agonists have been associated with amelioration of attention deficits post-TBI (Whyte et al., 1997; Whyte et al., 2004; Willmott & Ponsford, 2009), the underlying disruption to the DA system is still not well understood. The current findings extend upon previous research identifying disruptions to the DA system following TBI (Bales et al., 2009; Fujinaka et al., 2003; Yan et al., 2002). Research into the type and extent of damage associated with TBI is important to further our understanding of the disorder and may help to identify individuals suitable for pharmacological trials.

Contrary to our hypothesis, no significant associations were found between slMFB FA or MD values and attentional outcomes in the TBI or control group, failing to provide evidence for a role of the slMFB in attention or working memory processes. This finding is inconsistent with experimental models which have demonstrated inattentive behaviour to be associated with lesioning of the mesocorticolimbic neurons (Salamone, 1991), DA neurons that project through the MFB (Moore and Bloom, 1978). Additionally, the DA pathways arising from the VTA, connecting to the striatum/nucleus accumbens and terminating in the PFC are believed to be linked to attention deficits in other disorders, particularly ADHD (del Campo et al., 2011; Kharas & Dafny, 2016). Research has identified reduced FA in orbitofrontal-striatal pathways in individuals with ADHD, however, associations with attention measures were not investigated (Schweren et al., 2016).

Given that TBI has been linked to complex, varied and interactive pathology (Werner & Engelhard, 2007), and the attentional system itself is diffuse and complex, perhaps it is not surprising that no association was found when focusing on a single pathway. Other pathology associated with TBI may have affected areas implicated in attentional abilities, giving rise to the deficits seen in the TBI group. However, no association was identified between slMFB microstructure and attentional performance in the control group either, failing to support the notion that the slMFB is implicated in attentional abilities. Specific interest in the slMFB was indicated by the strong association between catecholamines and attention (for review see Clark and Noudoost, 2014), the lack of research into the slMFB in a TBI cohort to date, and the potential benefit of identifying individuals who may benefit from pharmacological interventions known to moderate catecholamines within the PFC, such as methylphenidate. Additionally, other research has found associations between white matter microstructural alterations within a single pathway and complex cognitive abilities. For example Johnson et al. (2011) found that reduced FA in the uncinate fasciculus predicted emotional and behavioural regulation problems in children following TBI.

With regard to performance on attentional tasks, TBI participants were found to perform more poorly on cognitive tasks when compared to controls. They demonstrated slowed information processing speed on tasks including the TMT-A, SAT, *n*-back, Hayling and SDMT relative to the control group. As the majority of these tasks contain a motor component, it is difficult to determine if the TBI group demonstrated cognitive processing speed deficits alone, if it was a combination of both motor and cognitive slowing, or if the results reflect a slowing in motor speed only. The Hayling task, however, does not contain a motor component, and thus, is not reliant on motor speed, providing evidence for the presence of cognitive information processing speed deficits within the TBI group. This corroborates previous literature identifying slowed information processing speed as a major outcome following TBI (Felmingham et al., 2004; Willmott et al., 2009). Interestingly, after applying the Bonferroni correction, no significant difference was found between the two groups with regard to time to complete TMT-B. This is in contrast with previous findings (e.g. Spitz et al., 2012) and raises the possibility that the TBI group were only impaired on basic cognitive tasks (e.g. TMT-A). However, given participants with TBI demonstrated reduced processing speed on the SAT and *n*-back, two tasks carrying a high cognitive load, this is unlikely to be the case. It should be noted, however, that given the small sample size, the generalizability of these findings is limited.

Consistent with previous research (e.g. Ponsford and Kinsella, 1992; Willmott et al., 2009), no difference was found between the TBI and control group on Hayling, TMT, SDMT, or Ruff2&7 in terms of accuracy, suggesting participants with TBI may have been sacrificing speed for accuracy on these tasks. With regard to working memory, no significant difference was found between groups on any condition of Digit Span. Although working memory deficits have been identified following TBI (e.g. Willmott et al., 2009), other studies have also failed to differentiate between participants with TBI and controls on this task (Draper & Ponsford, 2008). Additionally, number of errors on all conditions of the *n*-back was comparable for the TBI and control group, indicating intact working memory. Similarly, no significant differences were found between groups with regards to

the number of errors or misses on any condition of the SAT. Previous literature has demonstrated individuals with TBI make increased errors and misses on the CSAT, but not the SSAT of the SAT, when compared to controls. This is believed to reflect deficits in selective attention (Ziino & Ponsford, 2006). The current findings are inconsistent with this, suggesting intact selective attention. Overall, the prominent finding within the TBI group was slowed processing speed, with little evidence for strategic control of attention deficits.

The current findings are consistent with previous research that has suggested slowed information processing speed may largely account for attention deficits following TBI (Dymowski et al., 2015; Felmingham et al., 2004; Mathias & Wheaton, 2007). Other research utilising more complex tasks carrying a higher working memory load (i.e. dual tasks experiments with multiple dual conditions of varying difficulty) has demonstrated strategic control of attention deficits not accounted for by processing speed (Asloun et al., 2008; Azouvi et al., 1996), suggesting our tasks may not have been sufficiently complex to capture higher level attention deficits.

### 3.7.1 Future Research

It is possible the tasks used in the current study were not sensitive to the type of deficits attributable to slMFB damage. Given the slMFB projects to the PFC, it is possible that this particular tract is associated with more executive aspects of attention, rather than basic processing speed. In addition, the slMFB is known to play a major role in both affective and addiction disorders due to its implication in the brain reward systems (Alcaro & Panksepp, 2011; Coenen et al., 2009; Coenen et al., 2012; Wise, 2005). Thus, future research using tasks such as the IOWA Gambling Task (Bechara et al., 1994), which encompasses a reward-based learning component (Fellows, 2004), may be more effective in elucidating the deficits and symptoms associated with damage to the slMFB.

### 3.7.2 Limitations

Although the sample was well controlled and well matched, it was relatively small, possibly missing significant associations and leading to Type II error. Additionally, given the TBI group consisted of mainly moderate to severe injuries, it is likely the majority of white matter tracts would exhibit white matter microstructure alterations to some extent. As the current study only investigated the slMFB, however, it is unknown whether the slMFB was more or less damaged than any other white matter tract within the brain. Furthermore, although no significant associations were identified between performance on attention tasks and FA or MD within the slMFB, as the study did not investigate a comparison tract, the specific relationship (or lack thereof) between attention performance and slMFB changes following TBI is unknown. As previously mentioned, however, the aim of the study was to explore whether the slMFB was damaged post-TBI and if it was associated with attentional performance, given its strong implication in the DA system. This was the first study to demonstrate the slMFB is indeed, damaged following TBI. However no association with attentional deficits was found in the current TBI cohort. Finally, it is important to note the potential influence of partial volume effects on the results (Alexander et al., 2001; Vos et al., 2011). Given individuals with TBI usually demonstrate some degree of brain atrophy, and that the pathway investigated runs along the lateral wall of the ventricles, it is possible the DTI metrics were contaminated by the inadvertent measurement of cerebrospinal fluid resulting in reduced FA and increased MD values. However, each individual scan was inspected and participants with problematic brain atrophy were excluded.

### 3.7.3 Conclusion

Attentional abilities have long been linked to DAergic activity. TBI is associated with disruptions to the DA system, which may contribute to attentional deficits. This is the first study to provide evidence of white matter damage to the slMFB following TBI, extending upon previous research demonstrating DA disruption following TBI. No association was found between attentional performance and slMFB microstructural alterations in either group, failing to provide evidence for the role of the slMFB in the attentional system. Investigating associations between outcomes such as impulsivity/inhibition or mood disturbance and slMFB microstructural alterations following TBI may provide further evidence of the role of the slMFB in cognition and the subsequent implications associated with damage to this pathway.

## 3.8 ACKNOWLEDGEMENTS

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# CHAPTER FOUR

# The Functional Connectivity between the Ventral Tegmental Area and Default Mode Network and Associated Attentional Deficits Following Traumatic Brain Injury

## 4.1 DECLARATION FOR THESIS CHAPTER FOUR

**Monash University**

**Declaration for Thesis Chapter 4**

**Declaration by candidate**

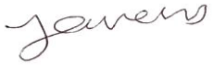
In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

| Nature of contribution | Extent of contribution |
|---|---|
| Formulation of experimental design, data collection, data analysis and preparation of full manuscript. | 70% |

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

| Name | Nature of contribution | Extent of contribution (%) for student co-authors only |
|---|---|---|
| Catherine Willmott | Consultation in formulation of experimental design, discussion of ideas expressed in manuscript and critical review of manuscript. | |
| Orwa Dandash | Assisted with designing the imaging protocol, imaging analysis, and reviewed the manuscript. | |
| Alex Fornito | Assisted with the designing the imaging analysis protocol, and critical reviewed the manuscript. | |
| Gershon Spitz | Assisted with the imaging analysis, discussion of ideas expressed in the manuscript and critical reviewed the manuscript. | |
| Jennie Ponsford | Involved in the conceptualisation, planning and design of the study, and reviewed the manuscript. | |

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contribution to this work:

| | | |
|---|---|---|
| **Candidate's Signature** |  | Date: 17/11/2016 |
| **Main Supervisor's Signature** |  | Date: 17/11/2016 |

## 4.2 OVERVIEW

This chapter presents an empirical paper titled “The Functional Connectivity between the Ventral Tegmental Area and Default Mode Network and Associated Attentional Deficits Following Traumatic Brain Injury” Submitted to Brain and Cognition. Subsequent to Chapter Three which investigated structural changes to the DA system (alterations to the slMFB) following brain injury and associated attention deficits, this chapter explores functional connectivity changes between the VTA (a region rich in DA cell bodies) and the default mode network (DMN; a key resting-state network that is highly implicated in attention function).

## 4.3 ABSTRACT

Attentional deficits are one of the most frequently reported problems following traumatic brain injury (TBI). Dopamine (DA) agonists have demonstrated preliminary efficacy in the amelioration of attentional deficits in individuals with TBI. Elucidating the underlying disruption to dopaminergic pathways is important to inform the rationale for such treatments. The present aimed to study i) investigate attentional deficits following TBI; ii) explore functional connectivity between the ventral tegmental area (VTA) (a region rich in DA cell bodies) and the default mode network (DMN) following TBI using rs-fMRI; and iii) determine whether functional alterations following TBI were associated with attentional performance in the TBI group. Twenty participants with a history of complicated mild to very severe TBI (post-traumatic amnesia (PTA) M = 40.05 ± 37.10 days, median time since injury 10.48 months, range 3.72-87.49) and 20 control participants were included in the study. A seed was placed in the VTA and the resting state analysis was conducted within a mask of the DMN. Participants also underwent neuropsychological assessment of attentional abilities. Results demonstrated reduced information processing speed was the main finding in the TBI group, when compared to controls. In controls, the VTA demonstrated functional connectivity with the angular gyrus and precuneus. No significant functional connectivity between the VTA network and DMN was observed in the TBI group. Between-group differences were, however, not found to be statistically significant. Damage associated with TBI likely weakened the coupling between these region to the point where it was no longer significant, although not enough to cause statistical differences between the two groups. No correlations analysis with attentional performance as run given the lack of between-group differences, however, it is unlikely the non-significant differences between the two groups would have accounted for the attention deficits observed in this sample.

## 4.4 INTRODUCTION

Pharmacological studies have provided preliminary evidence supporting the use of dopamine (DA) agonists to alleviate attentional deficits following traumatic brain injury (TBI) (McDowell, Whyte, & D'Esposito, 1998; Whyte et al., 1997; Whyte et al., 2004b; Willmott & Ponsford, 2009). The underlying disruption to DA systems associated with TBI and the associated effects on attentional abilities are, however, not well understood. Elucidating the DA disruption related to attentional deficits post-TBI would further inform the rationale for the use of DA agonists in treatment.

DA within the prefrontal cortex has been found to play a significant role in attention and working memory (Arnsten, 2011; Clark et al., 1987a, 1987b). Dysfunction of catecholamine circuitry has previously been linked to attentional deficits in attention deficit hyperactivity disorder (ADHD) (del Campo, Chamberlain, Sahakian, & Robbins, 2011) and schizophrenia (Lewis, 1997). Additionally, DA agonists, such as methylphenidate, have demonstrated efficacy in the ameliorating of attentional deficits (Arnsten, 2011; Nieoullon, 2002; Solanto, 1998; Willmott & Ponsford, 2009).

Resting-state functional magnetic imaging (rs-fMRI) has emerged as a valuable tool for investigating functional connectivity within the brain (Biswal et al., 1995; Fornito & Bullmore, 2010; Fox & Raichle, 2007; van den Heuvel & Hulshoff Pol, 2010). rs-fMRI can be used to measure the coherence of spontaneous fluctuations in brain activity recorded when no particular task is being. The coherent fluctuations observed under such a state are believed to reflect functionally related brain regions that underpin complex cognitive functions, including attention (Smith et al., 2009). The neural dynamics recorded under a 'rest' design are robust across individuals and time (Damoiseaux et al., 2006; Shehzad et al., 2009), influence task-evoked activity and performance (Fox et al., 2006; Fox & Raichle, 2007) and are under strong genetic control (Fornito & Bullmore, 2012; Fornito et al., 2011; Glahn et al., 2010).

Diffuse axonal injury (DAI) is a common pathology following TBI which results in widespread damage and deformation of axons (Büki & Povlishock, 2006; Johnson, Stewart, & Smith, 2013). Recent studies have revealed an association between altered functional connectivity and attentional deficits post-TBI (Bonnelle et al., 2011; Palacios et al., 2013; Pandit et al., 2013; Sharp et al., 2011). Alterations of default mode network (DMN) functional connectivity have featured prominently in these studies (Bonnelle et al., 2011; Sharp et al., 2011). The DMN includes the posterior cingulate cortex/precuneus, medial prefrontal cortex, temporal regions and bilateral angular gyri, and characteristically shows reduced activation, or deactivation, during performance of attentionally demanding tasks (Gusnard & Raichle, 2001; Shulman et al., 1997). Failure to suppress DMN activity during task performance can result in lapses in attention (Weissman et al., 2006). Dopaminergic (DAergic) transmission modulates activity within the DMN such that greater DA levels are linked to more efficient deactivation of the DMN (Tomasi et al., 2009). This finding supports the use of DA agonist medication for the treatment of inattention (Tomasi et al., 2009).

The ventral tegmental area (VTA) contains a large proportion of DAergic cells that provide neuromodulatory input to the ventral striatum (nucleus accumbens), the caudate and prefrontal cortex (Chandler et al., 2014; Ikemoto, 2007; Lammel et al., 2008). A recent study found the VTA to be functionally associated with the DMN in both healthy controls and children with ADHD (Tomasi & Volkow, 2014). Also, alterations in VTA functional networks have been found in children with ADHD, when compared to typically developing children, potentially underpinning reduced motivation and inattention (Tomasi & Volkow, 2012). However, the impact of TBI on functional connectivity of the VTA and the DMN, and associated attention deficits, is unclear. Evidence for alterations to the functional connectivity between the VTA and DMN could indicate disruption to DA neurotransmission, which may inform the use of DA agonists, and other pharmacological agents, to treat attentional deficits post-TBI.

The present study aimed to investigate i) attentional deficits following TBI; ii) functional connectivity between the VTA and the DMN following TBI, using rs-fMRI; and iii) whether functional alterations following TBI are associated with attentional performance in the TBI group We hypothesised that the VTA would be functionally connected with DMN nodes for both TBI and control participants. Additionally, we hypothesised participants with TBI would show altered functional connectivity between the VTA and DMN nodes when compared to controls. Finally, we hypothesised that any such alterations observed within the TBI group would be associated with poorer performance on attentional tasks, specifically, increased time taken to complete tasks and more errors resulting from lapses in attention.

## 4.5 MATERIALS AND METHODS

### 4.5.1 Participants

Twenty participants with a history of moderate to very severe TBI were recruited from the Acquired Brain Injury Rehabilitation service at Epworth HealthCare, Melbourne, Australia. MRI scanning took place a median of 10.48 months post injury, (interquartile range (IQR) = 10.83 months, range 0-87.5 months), see Table 1 for injury characteristics. Forty percent of participants underwent MRI and cognitive testing on the same day (for the remainder median time lag between assessment and scan = 25 days, IQR =62.25 days, with the assessment done first in 86% of cases). Participants were excluded if they had any of the following: (a) inadequate understanding of English, (b) insufficient cognitive ability or physical disabilities preventing completion of tasks, or previous: (c) treatment for psychiatric illness, (d) neurological disorder, (e) treatment for drug or alcohol dependence, (f) history of diagnosis of attention deficit disorder, or (g) Magnetic Resonance (MR) contraindications. All TBI participants had demonstrated pathology evident on CT brain scan. Also, 20 controls with no prior history of neurological or

psychological disorders were recruited by disseminating study flyers. During recruitment, control participants were matched to TBI participants with regards to age, gender, estimated full-scale intelligence quotient (FSIQ), and years of education.

Table 4.1 TBI participant causes of injury, injury severity and CT brain scan pathology

| | TBI participants (*N* =20) *n* (%) |
|---|---|
| Causes of injury | |
| Motor-vehicle accident | 12 (60%) |
| Bicycle/pedestrian | 5 (25%) |
| Falls | 2 (10%) |
| Other | 1 (5%) |
| PTA categories[a] | |
| Mild[b] (< 24 hours) | 1 (5%) |
| Moderate (1-7 days) | 2 (10%) |
| Severe (1-4 weeks) | 7 (35%) |
| Very severe (>4 weeks) | 10 (50%) |
| GCS categories | |
| Mild 13-15 | 3 (15%) |
| Moderate 9-12 | 1 (5%) |
| Severe 3-8 | 15 (75%) |
| Not recorded | 1 (5%) |
| CT Brain Pathology | |
| Contusion | 8 |
| Diffuse axonal injury | 3 |
| Subarachnoid haemorrhage | 8 |
| Subdural haemorrhage | 10 |
| Epidural haemorrhage | 2 |
| Intracranial haemorrhage | 3 |
| Interventricular haemorrhage | 3 |
| Haematoma | 4 |
| Abscesses | 1 |
| Petechial haemorrhages | 3 |

Note. a PTA categories defined using (Arlinghaus et al., 2005); b One participant with a complicated mild injury was included as individuals with complicated mild TBI have been found to demonstrate poorer outcomes than those with uncomplicated mild TBI (Iverson et al., 2012; Lange et al., 2009) ; PTA = Post Traumatic Amnesia; GCS = Glasgow Coma Scale.

### 4.5.2 Procedure

This study was approved by Monash University Human Research and Epworth HealthCare Ethics Committees. Once patients were cleared of PTA by their respective neuropsychologists, using daily administration of the Westmead PTA Scale (Shores et al., 1986), they were invited to undergo a brain MRI scan and a neuropsychological assessment of attention and working memory. All participants underwent CT scans as a part of routine assessment and treatment at the acute hospital. Results from CT scans were reported by radiologists at the respective hospitals. Written informed consent was obtained from all participants.

### 4.5.3 Neuropsychological Measures

#### 4.5.3.1 The National Adult Reading Test (NART)

The NART (Nelson, 1982) is a reading test which consists of 50 irregularly spelt words and was used to estimate pre-morbid IQ.

#### 4.5.3.2 The Symbol Digit Modalities Test

The SDMT (Smith, 1991) required participants to decode as many symbols as possible within 90 seconds. Studies have demonstrated that the SDMT is sensitive to reduced psychomotor processing speed following TBI (Ponsford & Kinsella, 1992).

#### 4.5.3.3 The Computerised Selective Attention Task (SAT)

The SAT (Ziino & Ponsford, 2006a) has two conditions, the simple selective attention task (SSAT) and complex selective attention task (CSAT). The CSAT required participants to

retain additional verbal rules and assessed a higher working memory load. When compared to controls, TBI participants have been found to respond more slowly and make significantly more errors on this task (Willmott & Ponsford, 2009).

#### 4.5.3.4 The Ruff 2&7 Selective Attention Task

The Ruff 2&7 selective attention task (Ruff & Allen, 1995) is a pen and paper cancellation task. Research has shown TBI participants performed worse on this task when compared to controls (Willmott & Ponsford, 2009).

#### 4.5.3.5 The *n*-back

The *n*-back (Perlstein et al., 2004) required participants to correctly match the letter presented on the screen with the letter presented 0, 1 and 2 screens back. It has been shown to be sensitive to working memory deficits post-TBI (Perlstein et al., 2004).

#### 4.5.3.6 The Hayling Sentence Completion Test from the Hayling and Brixton Tests

The Hayling Sentence Completion Test (Burgess & Shallice, 1996) is comprised of two sets of 15 sentences with the last word missing. Hayling A (response initiation) required participants to provide a word that completes the sentence as quickly as possible. Hayling B (response inhibition) required participants to complete the sentences with a word that is completely unrelated to the sentence. TBI participants have been found to make more errors on Hayling B than controls (Draper & Ponsford, 2008).

#### 4.5.3.7 Trail Making Test (TMT) - Parts A and B

The TMT (Reitan & Wolfson, 1985) measures processing speed, divided attention and mental flexibility. It required participants to connect 25 numbers in ascending order (Trails A) and to switch between 13 numbers and 12 letters in sequence (Trails B), as quickly as possible. TBI participants have been found to be slower on both conditions when compared to controls (Spitz et al., 2012).

#### 4.5.3.8 Digit Span Subtest of the Wechsler Adult Intelligence Scale –Fourth Editions

Digits backwards, forwards and sequencing (Wechsler, 2008), were used to assess participants' immediate auditory attention span and working memory capacity. Research has shown digit span backwards to be sensitive to changes in attention after TBI (Chan, 2000; Kinsella et al., 1996).

### 4.5.4 Neuroimaging Acquisition

Neuroimaging was performed at the Monash Biomedical Imaging Centre, Melbourne, Australia, on a Siemens Magnetom Skyra 3 Tesla MRI scanner using a 32 channel head coil (Siemens Medical Imaging, Erlangen, Germany). For each participant, a T1-weighted MPRAGE sequence was acquired in the sagittal orientation (inversion pulse 900ms, TR 1540ms, TE 2.57ms, resolution 256x256x176, flip angle 9°, FoV 250mm, slice thickness 1.00mm (176slices) with a voxel size of $1mm^3$). Resting state fMRI was acquired using the gradient echo EPI sequence and the following acquisition parameters: field of view, 192x192mm; data matrix, 64x64; 44 axial slices; isotropic voxel size, $3mm^3$; TR/TE = 2500ms/30ms; Flip Angle, 90°. During the resting-state sequence participants were asked to lie quietly in the scanner.

### 4.5.5 Imaging Preprocessing

To estimate functional connectivity maps for each participant, in accordance with a method employed by Tomasi and Volkow (2014) who successfully estimated the VTA functional connectivity network in an ADHD population, a seed region of 3.5 mm was placed in the VTA, centred in the midline just anterior to the red nuclei [MNI coordinates: (0, −15, −12) mm], see Figure 4.1. Data was analysed using Statistical Parametric Mapping version 8 (SPM8), running in Matlab version 2014a (Mathsworks Inc). Image preprocessing included slice-timing and head motion correction via affine transformation to the first image. The functional images were coregistered with subjects' anatomical scans, which were coregistered to the SPM-T1 template. For accurate spatial normalisation across individuals, the resulting transformation matrix was applied to the functional data. Segmentation of anatomical scans was carried out using a unified normalisation and segmentation approach (Ashburner & Friston, 2005).

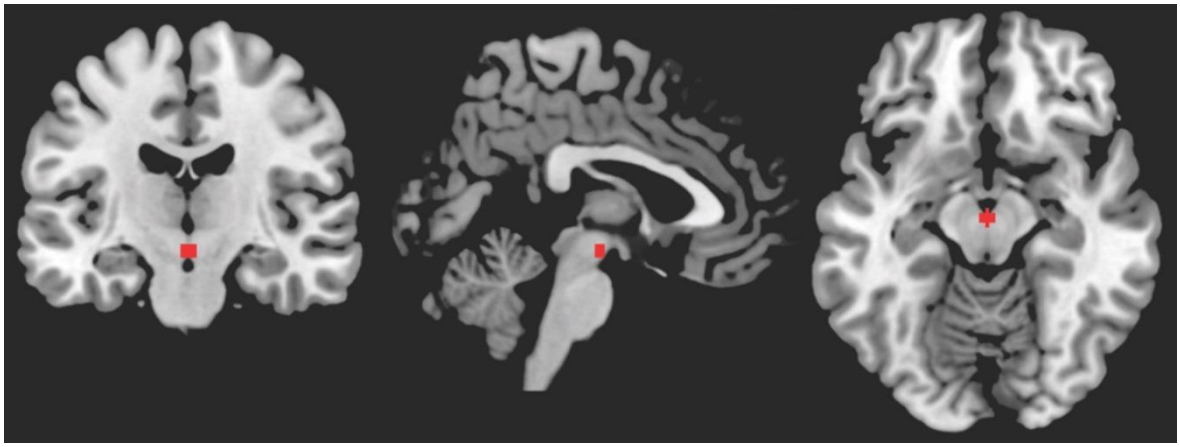


Figure 4.1 Ventral tegmental area seed region

[MNI coordinates: (0, −15, −12) mm].

The aCompCor method (Behzadi, Restom, Liau, & Liu, 2007) was used to correct for BOLD signal fluctuations caused by physiological fluctuations of a non-neuronal origin.

White matter and CSF masks were generated by thresholding the corresponding tissue images segmented from the T1 scan at 99% and 50% tissue probability, respectively. Any overlap with the grey matter mask was removed by image subtraction. Voxelwise time series were extracted from the white matter and CSF masks and subjected to separate principal component analyses in the time domain. The first five components were retained from each analysis. All data were linearly detrended, and a linear regression model was applied that included: ten component signals from white matter and CSF, the six head motion parameters (three rotation, three translation) that were estimated during the head motion correction procedure. The first-order derivatives of all sixteen signals were then fitted on a voxelwise basis. The residuals of this regression were retained for further analysis. This method has been shown to be effective for removal of physiological noise and subtle movement effects without the need for global signal regression or censoring of the data (Muschelli et al., 2014).

The noise-corrected data were then band pass filtered ($0.008 < f < 0.08$) and spatially smoothed with a Gaussian filter (8 mm full-width at half-maximum). All images were routinely inspected for potential normalisation artefacts. No participants were excluded following the inspection of head motion reports with excessive head motion, defined as >2 mm translation and >2° rotation. Mean time series were then extracted from the VTA seed region.

### 4.5.6 First-Level, Within-Subjects Analysis

For each participant, functional connectivity maps were estimated using general linear models as implemented in SPM8. Time courses extracted from the VTA seed were entered into a single general linear model with the VTA seed as a variable of interest in a regression analysis. The analysis was conducted within the mask of key DMN nodes including the medial prefrontal cortex (mPFC), angular gyrus, posterior cingulate cortex

and precuneus (Raichle et al., 2001; van den Heuvel & Hulshoff Pol, 2010). The DMN mask was created in the Anatomical Labelling Atlas *(N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou, F. Crivello, O. Etard, N. Delcroix, Bernard Mazoyer and M. Joliot)* built into the Wake Forest University WFU PickAtlas (http://www.fmri.wfubmc.edu/cms/software#PickAtlas) as implemented in SPM8. Contrast images were generated for each participant by estimating the regression coefficient between voxels within the DMN mask and VTA seed time-series.

### 4.5.7 Second-Level, Between-Group Analysis

A two sample t-test was carried out in SPM8, comparing TBI and control group contrast images for the VTA seed point. Within-group statistical maps were thresholded using a cluster-forming threshold of $p < 0.001$ and corrected for multiple comparisons using small-volume corrections, using the DMN mask to indicate voxels of interest. Clusters that survived a threshold of $p < 0.05$ were deemed significant.

### 4.5.8 Behavioural Data Analysis

Similar to previous reaction time (RT) studies (Willmott & Ponsford, 2009), 3% of *n*-back reaction times (across the three conditions) as well as 8% SAT RTs (across both conditions) were removed from the analysis using a cut off of RTs greater or less than 2 standard deviations from the mean for each group. Z-score >3.29 ($p < .001$, two-tailed test) was used to identify univariate outliers. Two outliers in the Hayling Test were identified (one TBI and one healthy control for number of errors) and assigned a score 1 unit greater than the next most extreme score (Tabachnick & Fidell, 2007). For normally distributed data, independent sample t-tests were undertaken to compare groups. Non-parametric test Mann-Whitney U was used to analyse error data for the SDMT, 2&7

accuracy data, TMT, Hayling Test, and errors and, missed responses for the *n*-back and SAT. To control for Type I error rate, Bonferroni adjustments were made for multiple comparisons.

## 4.6 RESULTS

The groups did not differ significantly on age, years of education, estimated IQ or gender (see Table 4.2.). One TBI participant was excluded from the analysis involving the computerised selective attention task, as they were partially colour blind and had difficulty distinguishing between the coloured stimuli.

Table 4.2 Control and TBI group characteristics

| | TBI ( *n* =20) | Control (*n* = 20) | *p*-value |
|---|---|---|---|
| | n | n | |
| Gender (male) | 15 | 12 | .31 |
| | Mean (SD) | Mean (SD) | |
| Age (years) | 39.05(16.45) | 33.45(11.72) | .223 |
| Years of education | 13.58(2.53) | 13.43(2.67) | .856 |
| Estimated FSIQ | 108.83(8.81) | 107.71(5.87) | .641 |

Note. FSIQ = Full Scale Intelligence Quotient.

### 4.6.1 Neuropsychological Performance

When compared to controls, using a Bonferroni-adjusted α level of .004, the TBI group was significantly slower to generate responses on the Hayling Test and took longer to complete TMT-A. Participants with TBI also identified fewer targets on both conditions of the Ruff 2&7, decoded fewer symbols of the SDMT, and were slower to respond during all conditions of the *n*-back and SAT, than controls (Table 4.3).

After applying a Bonferroni-adjusted α level of .004, no significant differences were evident in either digit span forward or backwards. No significant differences between the TBI and control groups were identified on accuracy scores for any condition of the Ruff 2&7, number of errors on SDMT, TMT, or Hayling, or with regard to number of errors or misses on any condition of the SAT or *n*-back.

Table 4.3 Means, standard deviations, significance and effect sizes for TBI and control groups on speed measures.

| | | TBI (*n*=20) | Control (*n*=20) | | |
|---|---|---|---|---|---|
| Task | Measure | Mean (SD) | Mean (SD) | *p*-value | Effect size[a] |
| SDMT | Number correct | 44.30 (9.58) | 58.10 (10.20) | <.001 | 1.40 |
| TMT | TMT-A time (s) | 39.60 (15.02) | 23.05 (7.50) | <.001 | 1.40 |
| | TMT-B time (s) | 83.50 (39.65) | 59.90 (22.01) | .027 | 0.74 |
| Hayling | Initiation Time (s) | 16.70 (16.29) | 4.65 (4.49) | .004 | 1.01 |
| | Inhibition Time (s) | 49.05 (44.30) | 10.25 (9.39) | .001 | 1.21 |
| 2&7 | ASRS | 109.50 (30.54) | 158.80 (24.03) | <.001 | 1.80 |
| | CSRS | 102.30 (22.33) | 138.35 (20.23) | <.001 | 1.70 |
| SAT[b] | SSAT RT (ms) | 863.81 (178.04) | 654.48 (98.26) | <.001 | 1.45 |
| | CSAT RT (ms) | 1595.12(366.32) | 1205.40 (209.97) | <.001 | 1.31 |
| *n*-back | 0-back RT (ms) | 775.19 (186.97) | 611.57 (129.71) | 0.003 | 1.02 |
| | 1-back RT (ms) | 866.88 (189.67) | 690.30 (150.32) | 0.002 | 1.03 |
| | 2-back RT (ms) | 1111.63 (256.70) | 788.86 (190.89) | <.001 | 1.43 |

Note. [a] Effect size is Cohen's D; [b] SAT TBI (n=19); DSF = Digit Span Forward; RS = Raw Score; DSB = Digit Span Backward; TMT = Trail Making Test; ASRS = Automatic Speed Raw Score; CSRS = Controlled Speed Raw Score; SAT = Selective Attention Task; SSAT = Simple Selective Attention Task; RT = Reaction Time; CSAT = Complex Selective Attention Task; SDMT = Symbol Digit Modalities Test.

### 4.6.2 VTA Functional Connectivity within the DMN

For the control group, the right angular gyrus and bilateral precuneus of the DMN were found to be functionally connected with the VTA seed (see Figure 4.2; Table 4.4). No

significant VTA functional connectivity was observed within the DMN mask for the TBI group (Table 4.4).

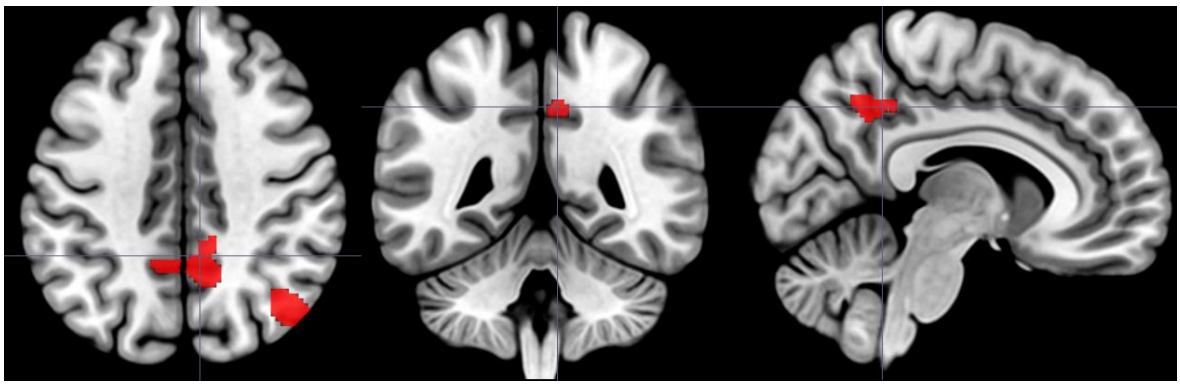


Figure 4.2 Functional connectivity maps of the ventral tegmental area (VTA) seed within the DMN for the control group ($p < 0.05$).

Images are displayed using neurological convention with right hemisphere shown on the right. Corrected for multiple comparisons through small-volume corrections.

### 4.6.3 Alteration in VTA Connectivity within the DMN following TBI

Although the control group demonstrated functional connectivity between the VTA and DMN nodes and the TBI group did not, there was no significant difference between the two groups ($p > 0.05$). The third aim was to investigate the association between significant alteration to functional connectivity between the VTA and DMN, and attentional performance in the TBI group. However, given no significant alterations were observed, no correlation analysis was performed.

Table 4.4 DMN nodes demonstrating functional connectivity with the VTA seed for the TBI and control group.

| Group | Anatomical Region | Hemisphere | MNI peak coordinates x,y,z | Z-score (*df*=1, 38) | No. of Voxels | *p*-value |
|---|---|---|---|---|---|---|
| Control | Angular gyrus | Right | 48, -66, 32 | 4.07 | 532 | 0.001* |
| | | | 52, -68, 32 | 4.05 | | |
| | | | 48, -60, 26 | 4.01 | | |
| | | | 40, -58, 34 | 3.75 | | |
| | | | 42, -70, 44 | 3.64 | | |
| | Precuneus | Right/Left | 10, -54, 42 | 3.66 | 149 | 0.049* |
| | | | 12, -40, 40 | 3.43 | | |
| | | | -8, -52, 40 | 3.41 | | |
| TBI | Medial frontal cortex | Left | -10, 24, 42 | 3.48 | 18 | 0.34 |
| | Medial frontal cortex | Left | -10, -42, 4 | 3.47 | 12 | 0.38 |
| | Angular gyrus | Left | -52, -58, 30 | 3.39 | 72 | 0.14 |
| | | | -42, -56, 24 | 3.37 | | |

Note * denotes significant clusters; MNI = Montreal Neurological Institute. Corrected for multiple comparisons; TBI = traumatic brain injury.

## 4.7 DISCUSSION

The current study aimed to investigate attentional deficits following TBI and to explore functional connectivity between the VTA and DMN following TBI using rs-fMRI. We also aimed to determine whether functional alterations observed in the TBI group were associated with performance on attention measures.

Consistent with the hypothesis, overall TBI participants performed worse than controls measuring on tasks different aspects of attention. In line with previous literature (Dymowski et al., 2015), the prominent finding was reduced information processing speed. This effect was observed on basic pen and paper tasks, tasks encompassing a motor element, (TMT-A, SDMT) as well as complex computerised tasks, carrying a higher cognitive load (SAT, *n*-back). TBI participants were also slower to respond to the verbal task (Hayling) which had no motor requirements, indicating a reduction in cognitive speed, rather than simply motor slowing.

Accuracy scores were comparable between groups suggesting the TBI group's poorer performance on attention measures was likely due to slowed processing speed rather than executive deficits. Although previous literature has also failed to find significant differences with regard to number of errors on Hayling, TMT, SDMT, or Ruff 2&7 (Ponsford & Kinsella, 1992; Willmott et al., 2009), Digit Span, the *n*-back and SAT have proven to be sensitive to attentional impairments following TBI (Chan, 2002; Kinsella et al., 1996; Perlstein et al., 2004; Ziino & Ponsford, 2006a). When considering the participant demographics, however, the current TBI group consisted of individuals who were well educated (mean years of education = 13.58, SD= 2.53), with a mean estimated IQ at the upper end of the average category (mean FSIQ = 108.83, SD = 8.81). Thus, the tasks may not have carried the appropriate degree of executive control/working memory load to capture executive type deficits in this cohort. Future research should consider using dual task experiments with multiple dual conditions of varying difficulty as they have previously demonstrated strategic control of attention deficits not accounted for by processing speed (Asloun et al., 2008; Azouvi et al., 1996).

rs-fMRI analysis revealed the VTA was functionally connected with the right angular gyrus and bilateral precuneus of the DMN in control participants. This finding is in line with previous research demonstrating functional connectivity between the VTA and the angular gyrus and precuneus in healthy adult controls, as well as typically developing children and children with ADHD (Tomasi & Volkow, 2014). DMN interaction with other functional networks has proven to be critical for optimal cognitive functioning (Bonnelle et al., 2012). Failure to deactivate the DMN can result in cognitive deficits, such as lapses in attention (Weissman et al., 2006).

Such an effect, has been shown to be under control of DA modulation of the DMN, with increased extracellular DA being associated with deactivation of the DMN during performance of an attentional task (Tomasi et al., 2009). Specifically, when healthy controls performed a visual attention task, lower dopamine transporter (DAT) availability

within the striatum (i.e. increased levels of DA) was associated with reduced activation within the DMN (specifically, the ventral precuneus/cuneus) (Tomasi et al., 2009). The finding from the current study provides further support for the notion that the precuneus, and perhaps the angular gyrus, are implicated in the interaction between a DA network and DMN in healthy controls. It is possible this interaction is underpinned by DAergic white matter pathways emerging from the VTA, innervating these regions and modulating neural activity as well as DMN deactivation.

In contrast to the control group, no statistically significant VTA functional connectivity was observed within the DMN mask in the TBI group. Damage associated with TBI may have disrupted neural networks connecting the VTA and DMN weakening the functional connectivity between these regions to a point where it is no longer statistically significant. Indeed, previous research has identified links between functional alterations within networks and white matter damage connecting network nodes (Bonnelle et al., 2012; Bonnelle et al., 2011; Palacios et al., 2013; Sharp et al., 2011). Damage to the salience network (SN) seen post-TBI has been found to impair the interaction between the SN and DMN, and is associated with reduced attentional function (Jilka et al., 2014). Additionally, reduced integrity of white matter tracts within in the SN has been associated with impaired DMN functioning following TBI (Bonnelle et al., 2012).

Although there appears to be some differences between the control and TBI group with regard to the functional connectivity between the VTA and DMN, these differences were not found to be statistically significant. Given TBI is a heterogeneous disorder, individual variability in the damage to the neural networks linking the VTA with the DMN may have caused variable disruption in the functional connectivity between these regions - potentially underpinning the non-significant results in this relatively small sample. This finding, however, is inconsistent with the hypothesis and previous literature observing disruptions to functional connectivity networks following TBI (Bonnelle et al., 2012; Bonnelle et al., 2011; Hillary et al., 2011; Sharp et al., 2011). In both mild and more severe

TBI, reduced connectivity in attentional, motor striatal, sensory motor and frontal networks have been identified (Hillary et al., 2011; Shumskaya et al., 2012; Vakhtin et al., 2013). Disruption of the DMN, in particular, has commonly been observed following TBI. Bonnelle et al. (2011) observed increased activation of the DMN in the post-acute/chronic phase of injury, particularly within the precuneus and posterior cingulate cortex, and this was associated with impairments in sustained attention post-TBI.

Stage of recovery may also have contributed to the difference in results. The current study investigated TBI participants who were predominately less than 12 months post injury and still within the crucial recovery stage. Sharp et al. (2011), Bonnelle et al. (2011) and Palacios et al. (2013) all investigated TBI participants in the more stable chronic phase of injury. Hillary et al. (2011) specifically looked at recovery in the DMN and goal-directed (external state) networks. They observed increased connectivity in both network between three and six months post-injury, indicating resting-state networks change with recovery. Thus, although no significant functional connectivity was found between the VTA and DMN nodes in the current sample, as individuals in the TBI group continue to recover the functional connectivity between these regions may change. In addition, the level of specificity of the aim, although theoretically driven, may account for the discrepancy in results. By masking the VTA functional network results within the DMN we limited the number of voxels within the brain being compared between the TBI and control group. In contrast to the studies mentioned above that compared whole functional network maps, the VTA functional connectivity map was masked within the DMN, thereby reducing the number of comparisons.

Although correlation analysis was not performed given there were no clusters of significant alterations following TBI, it is unlikely the non-significant functional connectivity alterations between the VTA and DMN nodes observed in the TBI group would have accounted for the attention deficits seen. Attention and working memory are complex cognitive abilities that rely on many brain areas connected by white matter

pathways. Damage to any aspect of this neural network could contribute to the attention deficits seen. Additionally, disruptions to other neurotransmitter systems implicated in attention (e.g. norepinephrine), may have led to the attention deficits observed. More research in much larger samples is needed to further elucidate the neuropathologies that give rise to the various attentional deficits associated with TBI to inform targeted treatments (Jenkins et al., 2016).

Although it was speculated that the VTA functional network influences DMN deactivation, and thus attentional performance for the control group, this association was not explicitly investigated. This presents an interesting line of enquiry for future studies. Additionally, the integrity of the functional connectivity between the VTA and DMN in the TBI group before injury in unknown. Thus, one cannot rule out the possibility that the lack of significant connectivity between these networks was not related to the damage caused by TBI, but rather, for this particular group of individuals, the DA and DMN were not functionally related. We believe this is less plausible, however, when considering the previous evidence demonstrating the strong association between the DA system and the DMN (Dang, O'Neil, & Jagust, 2012; Tomasi & Volkow, 2014; Tomasi et al., 2009).

## 4.8 CONCLUSION

Our results suggest the VTA network interacts with the DMN via the angular gyrus and precuneus in healthy controls. The absence of such association in the TBI patients suggests that other neuropathology caused by TBI may have led to the cognitive deficits observed. More research is required with a larger sample to further elucidate the association between the VTA network and DMN, as well as other possible causes of attention deficits following TBI.

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# CHAPTER FIVE

# GENERAL DISCUSSION

## 5.1 INTRODUCTION

There is evidence suggesting a link between white matter pathology and attentional deficits associated with TBI. The small numbers of DTI studies investigating this association have, however, generally focused on patients in the chronic phase of recovery from TBI (more than 12 months post-injury). While an association has been established between white matter pathology following brain injury and information processing speed deficits (Arenth et al., 2013; Spitz et al., 2013), less in known regarding pathology underpinning impairment of other aspects of attention. Given the significant impact attentional deficits can have on an individual's ability to function in their everyday lives, investigating the neuropathology underpinning the full array of attentional impairment is critical.

In addition to resultant neuropathology, neurochemical changes following TBI likely also contribute to persistent cognitive deficits. The dopamine system plays a significant role in attention and working memory (Clark et al., 1986b, 1987a, 1987b, 1989; Clark & Noudoost, 2014), and has been shown to be altered following TBI (Massucci et al., 2004). Alterations to catecholamine white matter pathways connecting regions of the DA system are believed to contribute to DA system disruption following TBI (Bales et al., 2009; Donnemiller et al., 2000; Yan et al., 2002); however, investigations into DAergic white matter pathology post-TBI have been limited. The slMFB is a key white matter pathway in the DA system. It contains ascending catecholamine fibres and connects the VTA, a region containing a large proportion of DA cell bodies, to the ventral striatum and nucleus accumbens, before terminating in the PFC (Coenen et al., 2009; Coenen et al., 2012; Coenen et al., 2011). No study to date has investigated the integrity of the slMFB following TBI and the association with attentional deficits.

DA disruption impacts many brain systems that underpin attentional function. Efficient DMN deactivation is critical for optimal attentional functioning (Weissman et al., 2006), and extracellular DA levels influence DMN deactivation efficiency (Tomasi et al., 2009).

Thus, the interaction between the DA system and DMN may be a key factor contributing to attentional performance. Damage to the brain as a result of TBI has the potential to disrupt this delicate interaction leading to attentional deficits. Multiple studies have identified alteration to the DMN following TBI (Bonnelle et al., 2011; Jilka et al., 2014; Sharp et al., 2011). There has, however, been no research assessing TBI-related functional connectivity alterations between the VTA and key nodes of the DMN, and associated attention deficits.

The aim of the present thesis was therefore to: (1) investigate whole brain white mater changes following TBI, and their association with different aspects of attention in a more acute sample (<12 months post-injury); (2) explore whether TBI is associated with alterations within the slMFB white matter microstructure, a critical white matter pathway within the DA network and to explore the association between the slMFB and performance on attentional tasks; and (3) to examine the functional connectivity of the VTA network with the major DMN nodes in individuals with TBI and healthy controls, and the associations between injury-related changes and attentional performance.

## 5.2 ATTENTION DEFICITS FOLLOWING TBI

To assess the neuropathological and neurofunctional changes that underpin attentional impairments following TBI, first, we investigated the nature and severity of attentional deficits experienced by this cohort. Multiple aspects of attention were examined in both the TBI and healthy control groups. This included speed of information processing and strategic control of attention including selective attention, divided attention, working memory and inhibition. When considering documented TBI-related neuropathology and neurochemical alterations (Bigler, 2001), it was hypothesised that individuals with TBI would demonstrate slowed speed of information processing and make more errors or missed responses on higher order tasks, including Ruff 2&7, TMT, Hayling, Digit Span, SAT and *n*-back, relative to control participants.

Overall, TBI participants demonstrated poorer performances on attentional tasks, when compared to controls. Consistent with previous research, reduced speed of information processing was the prominent finding in this TBI cohort. Slowed information processing speed was observed across different modalities - on complex computerised tasks, carrying a high cognitive load (SAT, *n*-back), as well as more basic pen and paper tasks, encompassing a motor element, (TMT-A, SDMT). The TBI group also demonstrated reduced response rate on the Hayling. Given the Hayling is performed verbally, with no motor requirements, slowing on this task indicates a reduction in cognitive speed, rather than simply motor slowing.

With regards to accuracy, no differences were found between groups on number of errors on processing speed (SDMT or TMT), selective attention (Ruff 2&7 and SAT), inhibition (Hayling) or working memory (*n*-back or Digit Span) tasks. Previous studies have also failed to identify a significant difference between TBI participants and controls with regard to number of errors on Hayling, TMT, SDMT or Ruff2&7 (Ponsford & Kinsella, 1992; Willmott et al., 2009). Digit span, the *n*-back and SAT have, however, been shown to identify attentional impairments following brain injury.

When investigating performance on the SAT, both Ziino and Ponsford (2006a) and Willmott et al. (2009) found TBI participants made significantly more errors and misses on the CSAT, but not the SSAT condition. The CSAT carries a higher cognitive load as participants are required to attend to both number/letter and colour, in comparison with the SSAT, in which participants only need to attend to colour. This suggests the TBI group were having difficulty selectively attending to the appropriate information. When investigating whether it was speed of information processing or impaired working memory that underpinned the selective attention deficits identified, Willmott et al. (2009) concluded that information processing speed was a main contributor, although the influence of other aspects of executive control of attention were not assessed.

Working memory deficits have also been commonly identified following brain injury. Digit Span Backwards been found to be sensitive to working memory change following TBI (Chan, 2002; Kinsella et al., 1996). With regard to the *n*-back, Perlstein et al. (2004) found no significant difference with regard to information processing speed on the *n*-back, however, load-related (2- and 3- back) working memory deficits in error rates were observed, suggesting deficits in strategic control rather than speed.

According to Shiffrin and Schneider (1977), conscious processing requires serial processing of information and is limited in capacity and rate. Working memory allows for temporary storage and manipulation of information during conscious processing (Baddeley, 1986). Due to the limited capacity of the short-term store, slowed information processing speed reduces the amount of information that can be processed at any given time (Cohen, 1993), which can result in deleterious effects on more complex aspects of attention.

Reduced speed of information processing does not, however, underpin all aspect of attentional impairment following TBI. Higher order executive abilities may also be disrupted, leading to attentional errors. In the Baddeley (1986) model of working memory, the 'central executive' is believed to control working memory, and its role is purported to be comparable to the supervisory attentional control system proposed by Shallice (1982). These executive processes are believed to subserve the ability to maintain concentration; shift/switch attention between multiple stimuli; inhibit distracting information to complete tasks in a goal-directed fashion.

The current study failed to identify executive control deficits of attention. Other studies employing tasks with a high working memory load (e.g. dual task experiments with multiple dual conditions of varying difficulty) have documented deficits of these higher order attentional processes which are not accounted for by processing speed (Asloun et al., 2008; Azouvi et al., 1996). Additionally, Perlstein et al. (2004) observed working memory deficits following TBI at higher working memory loads (2- and 3-back). Although the

current study included the 2-back, it did not include the more difficult 3-back condition. Given the current TBI sample consistent of individuals who were well educated (mean years of education = 13.58, SD= 2.53), with a mean estimated IQ at the upper end of the average category (mean FSIQ = 108.83, SD = 8.81), it is possible that the cognitive load/degree of executive control required for the tasks used was not sufficiently challenging to elicit strategic control of attentional deficits.

In summary, TBI participants performed more poorly on tasks measuring different aspects of attention, with reduced information processing speed being the prominent finding. Accuracy scores were comparable between groups indicating the impairment was likely due to slowed processing speed rather than executive type deficits.

## 5.3 WHITE MATTER PATHOLOGY AND ATTENTIONAL IMPAIRMENT FOLLOWING TBI

Since the initial use of CT, and later MRI, neuroimaging has made significant contributions to the understanding and management of TBI (Bigler & Maxwell, 2011). Recent advances in imaging techniques, such as DTI which measures white matter pathology, have allowed a more in-depth understanding of the neuropathology associated with TBI. As focal injuries rarely account for the extent and type of functional and cognitive impairments seen after TBI (Bigler, 2001), measuring the microscopic diffuse white matter damage is important in identifying the full extent of underlying neuropathology.

DTI is more sensitive than CT or conventional MRI to microstructural white matter changes seen following brain injury. Previous research has identified links between white matter pathology and attentional performance (Little et al., 2010; Niogi et al., 2008; Spitz et al., 2013). The majority of previous studies investigating this association have, however, only measured one or two aspects of attention. Additionally most have been undertaken in

the chronic phase post-injury (>12 months). Chapter 2 contributed to the literature by investigating multiple aspects of attention in a more subacute sample (majority of TBI participants <12 months post injury). Given the majority of recovery and axonal reorganisation takes place within the first year (Bigler, 2001; Büki & Povlishock, 2006), studies investigating chronic samples may miss vital information regarding white matter pathology and its association with attentional deficits.

Using TBSS, a voxel-wise DTI analysis technique, Chapter 2 aimed to: (1) investigate whole brain white matter microstructure alterations following TBI; and (2) explore the association between such pathology and performance on attentional and working memory tasks using TBSS. Given that TBI causes widespread damage, it was hypothesised that the majority of white matter tracts within the brain would show some level of microstructural alterations and that these TBI-related white matter changes would be associated with poorer performance on attentional tasks.

Consistent with the hypotheses and previous research (Hulkower et al., 2013), the TBI group demonstrated lower FA and higher MD values in the majority of white matter tracts within the brain, indicative of damage due to DAI. The most significant alterations were identified in the frontal and temporal white matter, the cingulate, corpus callosum, corona radiata, thalamic radiations and inferior-fronto-occipital fasciculus. Damage to frontal and temporal white matter is common post-TBI (Gaetz, 2004), potentially due to the bony skull protuberances that damage the brain during impact (Le & Gean, 2009). Grey-white matter junctions and the midline of the brain are also vulnerable to DAI. Consistent with our findings, studies have generally found the corpus callosum to show damage, as well as the long white matter pathways connecting anterior and posterior parts of the brain (Gaetz, 2004; Hulkower et al., 2013; Le & Gean, 2009).

The neural networks that support attention and working memory function consist of anatomically separate brain regions connected by white matter tracts. White matter pathology associated with DAI can disconnect nodes within neural networks and interfere

with the transportation of information throughout the brain (Arenth et al., 2013; Palacios et al., 2012; Spitz et al., 2013). Reduced efficiency of neural networks may lead to attentional deficits including reduced processing speed as well as problems with strategic control of attention. Consistent with previous research, results from the current study identified a link between alterations in microstructure in prominent white matter tracts connecting anterior and posterior brain regions (superior longitudinal fasciculi, inferior longitudinal fasciculus and inferior fronto-occipital fasciculi), as well as the left and right hemispheres (corpus callosum), and processing speed deficits.

Speed of information processing is considered to be dependent upon multiple white matter pathways connecting anatomically separate brain regions (Deary et al., 2010). Whilst some previous studies have supported this notion (e.g. Kourtidou et al., 2013; Spitz et al., 2013), there is some discrepancy in the literature, with Kinnunen et al. (2011) failing to find a significant association between white matter pathology and slowed information processing speed following TBI. As discussed in Chapter 2, it is likely that task differences account for the discrepancy in results. The SDMT has previously been found to be superior at differentiating individuals with TBI and control participants when compared to other cognitive tasks measuring attention and speed of information processing (Draper & Ponsford, 2008). Thus, the SDMT may have been more sensitive to speed of information processing deficits than the choice time reaction task employed by Kinnunen et al. (2011).

No significant associations were identified between white matter pathology and strategic control of attention in the current study. Similar to the current study, Arenth et al. (2013) found a significant association between processing speed deficits and white matter pathology, but not higher order attentional dysfunction. Using ROI the authors specifically investigated the FA and RD of the corpus callosum in TBI and control groups, and the association with various cognitive measures. Significant links were identified between speed of information processing and corpus callosum DTI metrics on tasks including

TMT-A, TMT-B; however, no significant associations were identified with executive control of attention measures, including the Stroop Inference T-score, or Wisconsin Card Sorting Task perseverative errors T-score.

Nevertheless, some previous TBSS studies have identified an association between strategic control of attention and white matter pathology. Reduced white matter integrity within the superior longitudinal fasciculus, corpus callosum and cingulum have been found to be implicated in executive control of attention (Kinnunen et al., 2011; Spitz et al., 2013). Additionally, reduced white matter microstructure integrity of the left inferior longitudinal fasciculus (Spitz et al., 2013), right corticospinal tract and left frontal white matter (Kinnunen et al., 2011) have also been linked with deficits in executive control of attention. Although the tasks used included 'alternating-switch cost index' of the TMT (time to complete TMT-B - time to complete TMT-A) (Kinnunen et al., 2011) and overall Hayling score (Spitz et al., 2013), speed of information processing was not controlled for in either of these studies. Thus the results may reflect an association between white matter pathology and processing speed, rather than executive functioning, which would be consistent with the current result.

The significant association between white matter pathology and strategic control of attention has, however, been observed in other studies that have used tasks not reliant on speed of information processing. Palacios et al. (2011) found a positive correlation between the 2-back d-index (the ability to accurately discriminate between targets and non-targets on a 2-back task) and global FA using TBSS. When further investigating this association using ROI analysis, FA in the superior longitudinal fasciculus, fornix, and corpus callosum was found to be associated. Additionally, using ROI Little et al. (2010) observed an association between thalamic projection fibres, but not the corpus collusion or cortical white matter, and spatial span and digit span. These studies provide evidence for the association between white matter pathology and strategic control of attention deficits.

Perhaps the more in-depth ROI technique was required to identify these types of associations. As demonstrated in Palacios et al. (2011), only global FA was associated with the task, which is non-specific, whereas when further investigated with ROI microstructural alterations of multiple tracts were found to correlate with strategic control of attention measures. Although TBSS can assess all white matter tracts throughout the brain and has been found to be more sensitive to outcomes measures, research has shown ROI tractography to provide additional information about the microstructure of the tracts (Spitz et al., 2013). Perhaps using ROI to further investigate the significant white matter tracts identified in the current study and the associations with attention deficits, would have identified additional associations.

Given that the prominent attentional deficit identified in the current study was slowed information processing speed, perhaps it is not surprising we did not find an association between white matter pathology and strategic control of attention. Apart from an increase in time taken to complete the task, the TBI group did not differ from controls on tasks assessing higher order attentional function. For future research, it would be beneficial to investigate a group of individuals who demonstrated this type of deficit on testing or who reported such deficits on neurobehavioral interviewing.

In summary, the mechanisms underpinning attentional and working memory deficits are poorly understood. Although there is evidence to suggest these deficits are associated with white matter pathology, most studies have been conducted using chronic samples and have only investigated a single aspect of attention. Chapter 2 contributed to the literature by assessing alterations to white matter tracts, and the associated attentional deficits within a more acute sample (majority < 12 months post injury). Slowed information processing speed following TBI was found to be related to an extensive network of tracts. The results highlight the widespread damage associated with TBI, as well as the impact of these alterations on information processing speed. It is essential for assessment of injury

severity, treatment planning and outcome prediction to understand the full extent of DAI damage following TBI.

### 5.3.1 Limitations and Future Research

Although the majority of individuals with TBI included in the study were within 12 months post injury, there were a few that were at least one year post-TBI. In future research, it may be beneficial to investigate a more homogenous sample, comprising only individuals within the subacute phase of injury to more accurately characterise the type of deficits experienced and associated white matter pathology shortly after injury. Additionally, although the two samples were well matched, there is the possibility the analyses were not optimally powered to detect significant associations between white matter integrity and other aspects of attentional function such as strategic control of attention, leading to Type II error. In future, investigating these associations in a larger sample size may provide more generalised findings, with the possibility of identifying links between strategic control of attention and white matter pathology. TBI is a heterogeneous condition and this heterogeneity, combined with the relatively small sample size likely limited the power to detect changes that may have been present in some individuals. Finally, there is a possibility that partial volume effects may have contaminated the DTI metrics resulting in reduced FA and increased MD values (Alexander et al., 2001; Vos et al., 2011). Partial volume effects were, however, controlled for by inspecting each individual's brain images and excluding those with problematic brain atrophy. Additionally, by measuring the centre of white matter tracts (Smith et al., 2006), TBSS is less likely to inadvertently measure CSF, as white matter junctions with grey matter and CSF which are prone to partial volume effects are not measured.

## 5.4 WHITE MATTER INTEGRITY OF THE MEDIAL FOREBRAIN BUNDLE AND ATTENTION AND WORKING MEMORY DEFICITS FOLLOWING TRAUMATIC BRAIN INJURY

Neurochemical changes are common following TBI and have potential to result in significant cognitive sequelae. Multiple studies have observed disruption to the DA system following TBI (Donnemiller et al., 2000; McIntosh et al., 1994; Yan et al., 2001; Yan et al., 2002). Alterations to DA signalling post-TBI are believed to be somewhat attributable to DAI of DAergic pathways (Bales et al., 2009; Donnemiller et al., 2000; Yan et al., 2002). There is, however, little known with regards to changes to DAergic white matter tracts, such as the slMFB, post-TBI and the associated cognitive deficits. Chapter 3 contributes to the literature by exploring the microstructure alteration to the MFB and related attention deficits post-TBI.

Using DTI and an ROI approach, Chapter 3 investigated: (a) alterations to white matter microstructure of the slMFB following TBI, and (b) the association between slMFB white matter microstructure and attentional function following TBI. It was hypothesised that, when compared to healthy controls, participants with TBI would demonstrate lower FA and higher MD values, indicative of white matter damage within the slMFB. Given the strong involvement of catecholamine in attentional abilities, it was hypothesised that for both the control and TBI group higher FA values and lower MD values would be associated with better performance on attentional tasks.

Consistent with the hypothesis, when compared to control participants, alterations in white matter microstructure of the slMFB were observed in the TBI group as indicated by lower DA and higher MD values. This was the first study to provide evidence for the damage to the slMFB following TBI, adding to the multitude of DTI literature identifying white matter pathology following TBI (for review see Hulkower et al., 2013). Additionally, the result provides evidence for the disruption of the DA system following TBI, extending

upon previous research identifying changes to other aspects of the DA system following brain injury (Bales et al., 2009; Donnemiller et al., 2000; Yan et al., 2002).

Although the TBI group were found to have reduced integrity of the slMFB and performed worse on attentional tasks, no significant associations were identified between slMFB FA and MD and attentional deficits. This finding is at odds with previous research linking DA to attention and working memory function in healthy controls (Arnsten, 2011; Clark et al., 1987a, 1987b, 1989; Clark & Noudoost, 2014), as well as research associating DA system dysfunction and inattention in other clinical groups (e.g. ADHD) (del Campo et al., 2011; Salamone, 1991). Studies in animals have found lesioning DA neurons which project though the slMFB to be associated with poor attention (Salamone, 1991). Additionally, in humans, reduced integrity of orbitofrontal-striatal pathways has been linked to ADHD, suggesting these pathways underpin attentional impairments - although associations with attention deficits were not specifically investigated (Schweren et al., 2016).

The discrepancy between the findings from Chapter 3 and the studies mentioned above is possibly due to the heterogeneous nature of damage caused by TBI. Damage to any part of the brain involved in the attentional neural network could contribute to the attentional impairments seen post-brain injury. Furthermore, compensatory mechanisms may have mitigated the association between slMFB damage and attentional deficits. Animal models demonstrate that compensatory responses to DA disruption occur approximately one month after injury. For example, at 28 days post-injury, an increase in tyrosine hydroxylase (TH) concentration, an enzyme necessary for the synthesis of DA in neurons and terminals, has been identified in rats' frontal cortices (Yan et al., 2001), and the nigrostriatal system (Yan et al., 2007). Given the TBI sample were all at least one month post-injury, perhaps they had already undergone some such cortical reorganisation to compensate for disruptions to DA signalling. However, the fact that medication which increases the concentration of DA levels demonstrates efficacy in alleviating attentional

impairments in cohorts more than three months post-injury (Whyte et al., 2004a), suggests that disruptions to DA transmission may be present for some time after injury.

With regard to performance on attentional tasks, the primary finding was reduced information processing speed. Given the slMFB projects to the prefrontal cortex, and DA within the prefrontal cortex is highly associated with executive aspects of attention (i.e. inhibition and working memory) (Bäckman et al., 2011), perhaps the tasks used in the current study were not sensitive to the type of deficits attributable to slMFB damage. As previously mentioned, other studies requiring a higher level of executive control/carrying a higher working memory load, like those referred to above, that are better able to differentiate individuals with TBI from control participants may have shown a significant effect. However, no significant associations were found between slMFB microstructural integrity and performance on attentional tasks for healthy controls, suggesting slMFB integrity does not play a substantial role in these attentional abilities. Other types of damage (including disruption to other neurotransmitter systems) should be considered in future studies. This topic is discussed in a later section.

In summary, DAergic activity has long been associated with attentional abilities. TBI can result in disruptions to the DA system, which may underpin attentional deficits. Extending upon these previous findings, Chapter 3 is the first study to provide evidence of white matter damage to the slMFB following TBI. No association was found between attentional performance and slMFB microstructural alterations in either group, failing to provide evidence for the role of the slMFB in the attentional system.

### 5.4.1 Limitations

As discussed in Chapter 2 the lack of a comparison tract meant that, although no significant associations were identified between performance on attention tasks and FA or MD within the slMFB, the uniqueness of the relationship (or lack thereof) between

attentional performance and slMFB changes following TBI is unknown. Furthermore, the relative damage to the slMFB in comparison to other white matter tracts is unknown. The purpose of the study, however, was not to compare the slMFB with other white matter tracts, but rather to explore whether the slMFB was damaged post-TBI and contributed to attentional impairment, given its strong implication in the DA system. This was the first study to demonstrate the slMFB does show microstructure alterations following TBI, indicative of damage due to DAI.

In addition, given the MFB's strong involvement in the DA network it was inferred that damaged to the MFB could potentially disrupt DA neurotransmission. Alterations to DA neurotransmission, however, were not directly measured thus any link to DA signalling alterations is only speculative. Moreover, the cholinergic system has previously been implicated in attention and working memory deficits following TBI (Arciniegas et al., 1999), and has a similar anatomical pathway to the DA system (arising from the midbrain and connecting to the frontal cortex). It is possible the attention deficits seen within this TBI cohort were somewhat attributable to damage to the cholinergic system. Future research may wish to assess the damage to both the DA and cholinergic systems following TBI and the associated attention deficits in order to better understand the origin of these impairments and how best to treat them.

As with all DTI studies, there may have been some influence of partial volume effects on the results (Alexander et al., 2001; Vos et al., 2011). The slMFB runs along the lateral wall of the third ventricle. Given individuals with TBI usually demonstrate some degree of brain atrophy, it is possible the DTI metrics were contaminated by the inadvertent measurement of cerebrospinal fluid resulting in reduced FA and increased MD values. However, each individual's images were inspected, and participants with problematic brain atrophy were excluded in order to control for this. Finally, the sample was relatively small, possibly missing significant associations and leading to Type II error.

### 5.4.2 Future Research

The slMFB is an important aspect of the brain's reward system and is often associated with motivation, mood, impulsivity and addiction (Alcaro & Panksepp, 2011; Coenen et al., 2009; Coenen et al., 2012; Wise, 2005). Tasks tapping into these areas may more accurately capture the type of deficits produced by damage to the slMFB. Future research may consider using tasks such as the IOWA Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994), which encompasses a reward-based learning component (Fellows, 2004), or the Go/No-go tasks coupled with a reward component, which involves both reward-based learning as well as inhibitory control (Guitart-Masip et al., 2012). Additionally, mood disturbances are common following TBI (Gould, Ponsford, Johnston, & Schönberger, 2011), and hedonic capacity has previously been found to be associated with slMFB microstructure in people with remitted depression (Bracht, Doidge, Keedwell, & Jones, 2015). Investigating the link between slMFB microstructure and depression symptoms following TBI may help to provide insight into the neuropathogenesis of mood disturbance associated with brain injury. As mentioned above, the TBI group investigated in Chapter 3 did not show evidence of strategic control of attention deficits on testing. Given DA has been strongly linked with higher order attentional abilities (e.g. working memory), in future it may be worthwhile to investigate the associations between attention and slMFB in a sample who demonstrate evidence of strategic control deficits on testing.

## 5.5 FUNCTIONAL CONNECTIVITY OF THE VENTRAL TEGMENTAL AREA AND ATTENTIONAL DEFICITS FOLLOWING TRAUMATIC BRAIN INJURY.

White matter pathology following TBI can result in disruption to brain networks, resulting in functional connectivity alterations (Bonnelle et al., 2012; Bonnelle et al., 2011; Jilka et al., 2014; Sharp et al., 2011). As mentioned above the DA system involves many subcortical and cortical areas connected by white matter tracts. DAI causes widespread

damage which can alter these DA pathways, disrupting the neural networks, leading to changes in functional connectivity networks. The DMN is a resting state functional network that is active at rest (when an individual is not performing a task) and is deactivated upon commencing a task. Efficient switching off of the DMN and switching to other on-task networks is critical for optimal cognitive functioning (Weissman et al., 2006). The VTA contains a large proportion of DAergic cells that provide neuromodulatory input to the ventral striatum (nucleus accumbens), caudate and the prefrontal cortex (Chandler et al., 2014; Ikemoto, 2007; Lammel et al., 2008). Previous research has observed the VTA functional network to include aspects of the DMN (Tomasi & Volkow, 2014). Additionally, levels of extracellular DA have been associated with efficient DMN deactivation (Tomasi et al., 2009). Multiple studies have found the DMN to show alteration following TBI (Bonnelle et al., 2011; Palacios et al., 2013; Sharp et al., 2011), however, no study to date has investigated alteration to functional connectivity between the VTA and key DMN nodes. Chapter 4 contributed to the literature by examining the TBI related functional network changes between the VTA and DMN, and associated attentional deficits. Results from this study may have implication for the use of DA agonists to treat attentional deficits post-TBI. Drugs such as amantadine work to increase the amount of extracellular DA; thus may have beneficial effects on the efficient deactivation of the DMN and associated attentional abilities.

The aims of Chapter 4 were to i) investigate attentional deficits following TBI; ii) using rs-fMRI explore functional connectivity between the VTA and the DMN following TBI; and iii) determine whether functional alterations following TBI are associated with attentional performance in the TBI group. We hypothesised that the VTA would be functionally connected with the DMN for both TBI and control participants. Additionally, we hypothesised participants with TBI would show altered functional connectivity between the VTA and DMN when compared to controls. Finally, we hypothesised that these alterations observed within the TBI group would be associated with poorer performance

on attentional tasks, specifically increased time taken to complete tasks, and more errors resulting from lapses in attention.

rs-fMRI was used to investigate the functional connectivity of the VTA with the principal DMN (medial prefrontal cortex, angular gyrus, precuneus, and posterior cingulate cortex). VTA was observed to be functionally connected to the right angular gyrus and bilateral precuneus in the control group, two important aspects of the attentional system. The angular gyrus has previously been associated with reorienting and shifting of attention (Gottlieb, 2007) and the precuneus has been found to underpin working memory ability (LaBar, Gitelman, Parrish, & Mesulam, 1999). Our findings supported previous research by Tomasi and Volkow (2014) who, when investigating the VTA functional network in healthy adults, typically developing children and those with ADHD, observed the VTA to be functionally connected to many brain regions, including key DMN nodes – the angular gyrus and precuneus.

The DMN is activated when an individual is not focused on the outside world (i.e. not performing a task). It represents internally directed thought. When a person engages in a task, thought needs to be directed externally in order to appropriately attend to and complete the task. The salience network (SN) which is made up of anterior cingulate cortex, pre-supplementary motor area and insula becomes activated when rapid behavioural change is required (i.e. from off-task to on-task) and influences other brain networks needed for on-task behaviour. Efficient switching from DMN to goal-directed networks is vital for optimal cognitive functioning (Weissman et al., 2006), with failure to deactivate the DMN linked to cognitive deficits, such as lapses in attention (Weissman et al., 2006). As previously mentioned, extracellular levels of DA play a key modulatory role in the deactivation of the DMN. When investigating healthy controls, Tomasi et al. (2009) used PET neuroimaging to demonstrate that DAT availability within the caudate and putamen is negatively associated with DMN activation during an attention task. That is, greater DAT availability (i.e. less extracellular DA), was associated with less efficient

deactivation of the DMN, and vice versa. Moreover, it appears DA also influences interaction between the DMN and other resting-state networks. When an individual's attention is directed internally, the DMN is activated, and the SN is deactivated. High levels of DA synthesis capacity has been linked with increased correlation between activity in the DMN and activity within the fronto-parietal network, and decreased coupling between the fronto-parietal network and SN. The fronto-parietal network is believed to mediate the allocation of resources between the "off-task" DMN and "on-task" SN. This suggests that DA may modulate the interaction between these three large-scale networks (Dang et al., 2012). The results from Chapter 4 suggest the VTA may interact with the DMN via DAergic inputs to the angular gyrus and precuneus. This association may have implications for DMN deactivation and thus attentional ability, although more research is needed to clarify this.

No significant VTA functional connectivity was observed within the DMN regions for the TBI group, suggesting the varied and complex damage caused by TBI weakened the functional connectivity between the VTA and DMN to the point it was no longer statistically significant. Haemorrhagic contusions to cortical areas involved in the DMN or the midbrain (where the VTA is situated) have the potential to disrupt normal brain activity leading to asynchronous spontaneous activation between these regions. DAI could damage pathways connecting the VTA to the DMN, altering flow of communication between these areas. Indeed, catecholamine fibres arising from the VTA may be at particular risk of DAI as they are poorly myelinated (or not myelinated at all), placing them at a higher risk of physical injury (Reeves, Phillips, & Povlishock, 2005; Staal & Vickers, 2011). Furthermore, findings from Chapter 3 provided evidence for DAergic white matter damage following TBI. As discussed in Chapter 4, reduced integrity of white matter tracts connecting functional connectivity networks has previously been linked to impaired resting-state connectivity. Specifically, SN white matter pathology has been associated with impaired DMN functioning following TBI (Bonnelle et al., 2012), and is associated with reduced attentional function (Jilka et al., 2014). Thus, there are multiple ways in

which TBI could have affected the functional connectivity between the VTA and DMN, leading to the non-significant finding.

Inconsistent with expectations, these differences in functional connectivity between the VTA and DMN nodes for the control and TBI group were not found to be statistically significant. Differences in disruption to the neural network connecting VTA and DMN nodes could result in individual variability in the alterations seen after TBI and possibly underpin the non-significant finding in this cohort. However, this is at odds with multiple studies observing significant alterations in the resting-state network following TBI. As discussed in Chapter 4, many studies have found TBI-related changes to the DMN. Following TBI, increased connectivity within the DMN has been observed in the frontal lobes (Palacios et al., 2013), the precuneus (Bonnelle et al., 2011; Sharp et al., 2011) and posterior cingulate cortex (Bonnelle et al., 2011; Sharp et al., 2011). Both impairments in sustained attention (Bonnelle et al., 2011), as well as improvements in cognitive abilities (Palacios et al., 2013; Sharp et al., 2011), have been associated with increased connectivity of the posterior cingulate cortex and precuneus, with the latter suggesting a compensatory response to loss of structural connectivity (Palacios et al., 2013; Sharp et al., 2011). Other brain networks including visual processing, motor, limbic, and networks underpinning executive control have also been observed to show both increases and decreases in functional connectivity post-brain injury (Stevens et al., 2012).

These studies used ICA to analyse the resting-state data, however. ICA is a voxel-wise technique used to identify common resting state networks amongst participants. It is highly data driven but allows for direct comparison between subject groups. In contrast, seed-based methods require a prior selection of regions of interest. Seed-based methods correlate spontaneous brain activity fluctuations of the particular regions chosen with every other voxel in the brain (unless a mask is implemented). Given this technique will only investigate functional connectivity with the ROIs, it is more specific than ICA, perhaps accounting for the lack of findings in the current study. However, other studies

using seed-based approaches have managed to detect changes to functional connectivity maps post-TBI. In a mild TBI sample, Iraji et al. (2014) observed significant alteration in functional connectivity network maps of the thalamus, hippocampus, precuneus and posterior cingulate cortex using a seed-based approach. Also, subsequent to investigating the DMN with ICA, Palacios et al. (2013) observed frontal and parietal nodes of the DMN to show increased connectivity with nearby regions (i.e. the mPFC was observed to show increased connectivity with other areas within the mPFC, and the parietal lobe showed increased connectivity to other parietal regions) using seed-based analysis. As discussed in Chapter 4 the specificity of the aim may have accounted for the discrepancy in findings. Unlike the studies mentioned above we did not investigate the whole VTA network. As we had a specific a priori aim based on previous research, we only compared VTA network clusters that were situated within the DMN. It is possible the specificity of the investigation within a relatively small sample accounted for the lack of differences between the two groups, particularly when taking into account the inherent heterogeneity of TBI as a disorder.

The difference in time since injury of participants may also have contributed to the differences in findings. The majority of studies investigating moderate to severe TBI included TBI participants mainly in the chronic phase of injury (Bonnelle et al., 2011; Palacios et al., 2013; Sharp et al., 2011). Chapter 4, on the other hand, examined TBI participants who were predominately less than 12 months post injury. The brain undergoes the majority of recovery within the first 12 months, and changes to resting-state networks have been observed within the first six month post-injury. When specifically investigating resting-state functional network recovery, Hillary et al. (2011) examined within-subject changes from three to six months post-injury for an “external-state” network and the DMN. Increased functional connectivity was observed at six months compared to three moths post-injury for both networks. Thus, is possible as this TBI group continue to recover, compensatory mechanisms may evolve and functional connectivity between the VTA and DMN nodes may change.

As there were no significant alterations of the VTA and DMN nodes following TBI, we were unable to perform the correlation analysis with attentional tasks. However, we believe it is unlikely that the mild, non-significant disruption to this connectivity would have accounted for the substantial changes in attentional ability experienced by the TBI group. It is possible that damage to other aspects of the attention neural network, or disruption to other neurotransmitter systems (e.g. NE), underpinned the deficits observed. This notion is explored further in the section following.

In summary, Chapter 4 extends upon previous literature identify a link between the VTA and DMN nodes in healthy controls. No such association was evident in the TBI group, suggesting disruption to this network due to TBI, although between-group differences were not statistically significant. More research is required with a larger sample to further elucidate the association between the VTA network and DMN, as well as other possible causes of attention deficits following TBI.

### 5.5.1 Limitations and Future Research

As with Chapters 2 and 3, although the sample was well controlled and well matched, it was relatively small, possibly missing significant associations and leading to Type II error. Also, it was speculated that, in healthy controls, the DA function network interacts with the DMN via the angular gyrus and precuneus; however, this association was not explicitly investigated. To examine this potential association, studies could employ a similar approach to that of Bonnelle et al. (2012). DTI could be used to investigate the health of white matter tracts connecting the VTA with the DMN. The integrity of these tracts could then be correlated with DMN functional connectivity changes. Additionally, to investigate whether the VTA and DMN connectivity is associated with DMN deactivation, future research could examine the influence of white matter integrity connecting the VTA and DMN networks and efficiency of DMN deactivation when completing an attentional task.

## 5.6 DISRUPTION TO THE DOPAMINE SYSTEM AND ATTENTIONAL DEFICITS FOLLOWING TBI

Although there is good evidence to suggest DA disruption likely contributes to attention and working memory deficits in some individuals with TBI (Bales et al., 2009), evidence demonstrating a direct association between the two is limited. The findings from Chapter 3 and 4 demonstrated that although aspects of the DA system were damaged following TBI, this damage was not significantly associated with attentional performance. This is likely due to the following: 1) the association between DA and attention and working memory is intrinsically complex; 2) attention and working memory are complex cognitive processes that are subserved by integrated networks and multiple neurotransmitter systems; and 3) TBI itself is a heterogeneous disorder which causes complex and widespread damage that can disrupt any part of the attention neural network leading to damage.

Investigating the link between DA disruption and attentional dysfunction could have informed treatment. Currently many medications are available that augment DA levels, with methylphenidate and amantadine demonstrating efficacy in treating attention deficits post-TBI (Jenkins et al., 2016). Methylphenidate targets DA receptors and DAT proteins to increase the amount of extracellular DA available, whereas Amantadine may increase extracellular DA levels by blocking GABAergic interneuron activity associated with DA terminals resulting in increased DA signalling. Pharmacological trials in TBI groups have shown mixed results (McDowell et al., 1998; Schneider, 1999; Whyte, 2008). The variability in results may, in part, be due to differences in underlying neuropathology. TBI can disrupt the DA system in multiple ways; focal damage to the prefrontal cortex could influence the 'top-down' control it has over DA nuclei in the brainstem (Jenkins et al., 2016). Focal damage to brainstem nuclei may also have deleterious effects on DA neurotransmission. DAI to DAergic pathways is believed to affect DA neurotransmission

(Bales et al., 2009; Donnemiller et al., 2000; Yan et al., 2002), and may be associated with downregulating DAT proteins (Donnemiller et al., 2000; Yan et al., 2002) and dopamine 2-receptors (Donnemiller et al., 2000). Thus, the health of the DA system may differ between individuals with TBI which may be why these medications appear to work for some and not others.

Furthermore, recent research has provided evidence for an increase in DA levels as a result of cognitive training. Bäckman et al. (2011) used PET and radioligand raclopride to measure binding potential for D2 striatal receptors in healthy controls both before and after 5 weeks of working memory training. Training on a letter-memory updating task was associated with improved performance on this task (as well as the *n*-back) and enhanced striatal DA release. This may provide an alternative therapy to medication, although further research is required to confirm the results. As with the medication trials, investigating whether particular neuropathology predicts outcome on cognitive training would be beneficial for planning appropriate treatments. Future research could investigate whether damage to the DA system predicts how an individual responds to medications as well as cognitive training, as this could allow for effective targeted treatment plans.

Given the lack of association found between alterations to the DA system and attentional impairments, however, the influence of other types of damage and disruption to other neurotransmitter systems needs to be considered. Norepinephrine is another neurotransmitter that is highly implicated in attention and working memory (Ramos et al., 2005; Swartz et al., 2008), and is disrupted following TBI. Depletion of NE levels has been observed within the first 24 hours after injury (Prasad et al., 1994), at seven days and up to eight weeks after injury, indicating a chronic depletion in NE concentration post-TBI (Fujinaka, Kohmura, Yuguchi, & Yoshimine, 2003). As with DA, multiple medications are currently available that augment extracellular NE levels, with pharmacological trials demonstrating some efficacy in treating attentional impairments (McAllister, McDonald, et al., 2011; Ripley et al., 2014). More research is needed, firstly, to understand the nature

of damage associated with catecholamine disruption (both NE and DA) and its association with attentional impairments. It may then be possible to examine whether this damage is associated with the effectiveness or otherwise of different catecholamine agents. This could allow for more individualised treatment planning. Given the damage caused by TBI is diffuse and heterogeneous, investigating whole brain systems as well as multiple neurotransmitter systems simultaneously will likely lead to a better understanding of the damage that leads to attentional deficits and how best to treat them.

## 5.7 CONCLUSION

This thesis has demonstrated the consistent presence of impaired speed of information processing evident following TBI, with less evidence for strategic control of attention deficits in this sample. When investigating a more acute sample of individuals with TBI and assessing multiple aspects of attention, this study has overcome a number of methodological limitations of previous studies to demonstrate an association between a diffuse network of white matter tracts and speed of information processing in those with TBI. No evidence was found for the association of white matter tracts with higher order aspects of attention. However, this may have been because the TBI group did not show significant impairment in these areas.

White matter pathology of the slMFB was also observed within the TBI group. This was the first study to identify microstructural alterations to this crucial white matter tract within the DA network. This finding extends previous research documenting DA transmission disruption believed to be caused by DAI. Future research could further elucidate this association as this may have implications for pharamcological trials in TBI patients. No association was found with regard to attentional deficits and slMFB microstructure. The fact that no significant association was identified in either the TBI or control group suggests that perhaps this pathway does not underpin performance on the attentional measures used in this study. Tasks such as the IOWA gambling task, with a

reward based component, may have been more useful in identifying the type of deficits that damage to this pathway may cause.

Finally, the VTA was found to be functionally associated with DMN nodes, the angular gyrus and precuneus, providing evidence for the interaction between the VTA functional network and DMN in non-injured brains. No such association was found for the TBI group, suggesting damage caused by TBI disrupted the functional connectivity between these regions. Between-group differences were, however, not found to be statistically significant. It is likely that the individual variability in damage associated with TBI accounts for the non-significant finding in this relatively small sample. Further research in larger samples in required to further elucidate the association between the VTA and DMN in a TBI population.

In summary, this thesis extends and highlights the diffuse and severe damage that TBI causes to the brain, affecting both structural and functional connectivity. TBI is a devastating disorder that causes long-term impairment for individuals. Attention and working memory deficits are common following brain injury and have deleterious impacts on the return to previous life roles. Thus, understanding the neurological and neurochemical changes that underpin these outcomes is critical. Investigating dysfunction of catecholamine systems such as the DA system is promising as currently many therapies are available. However, the current thesis did not provide substantial evidence for the role of DA disruption in attentional deficits following TBI. More research in larger sample sizes is required to better understand the damage that is associated with dysfunction of the DA system, but also that associated with other neurotransmitter systems (e.g. NE), and their impact on attentional functions. With technological advances it is to be hoped that it will ultimately be possible to identify which neurotransmitter systems underpin or contribute to certain cognitive impairments and develop pharmacological treatments accordingly.

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