LONGITUDINAL CHANGES IN RESTING-STATE CONNECTIVITY DURING RECOVERY FROM TRAUMATIC AXONAL INJURY

APPROVED BY SUPERVISORY COMMITTEE

_____
Carlos Marquez de la Plata, Ph.D.

_____
C. Munro Cullum, Ph.D., ABPP

_____
Sina Aslan, Ph.D.

_____
Wendy Ringe, Ph.D.

_____
Jeffrey Spence, Ph.D.

DEDICATION

To my parents, Jayashree Krishnan and Krishnan Narayanan, who have always encouraged me to pursue my dreams and have sacrificed so much for me to be where I am today.

LONGITUDINAL CHANGES IN RESTING-STATE CONNECTIVITY DURING RECOVERY FROM TRAUMATIC AXONAL INJURY

by

Kamini Krishnan

DISSERTATION

Presented to the Faculty of the Graduate School of Biomedical Sciences

The University of Texas Southwestern Medical Center at Dallas

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

The University of Texas Southwestern Medical Center at Dallas

Dallas, Texas

August, 2014

ACKNOWLEDGEMENTS

This dissertation and my academic career thus far could not have been possible without the guidance and support from my parents, mentors, friends, and family. To Amma and Appa, I feel privileged to be your daughter. I am deeply thankful that you believed in me at age 18 to facilitate my move to a foreign country. The unwavering support and love I received as I found my passion has been an inspiration, especially when I didn't take the stereotypical medical degree route! My parents' willingness to learn about neuropsychology is something I hope to emulate when I encounter unchartered territories.

I am so grateful for my amazing team of mentors, who have been supportive yet challenging throughout my graduate career. I want to express my sincere gratitude to Dr. Carlos Marquez de la Plata for teaching me how to think and write like a scientist, and for being laidback when I wasn't. Our lab motto, "there's gotta be a way to do that" will follow me throughout my career. I owe a depth of gratitude to Dr. Cullum for his speedy feedback and pearls of wisdom. His guidance throughout my graduate career has been invaluable. Supervision with Dr. Wendy Ringe, whether it was for clinical or research work, was akin to visiting a wise sage. Her guidance and feedback was challenging yet calmed my graduate school anxiety. I am indebted to Dr. Sina Aslan for his invaluable input on imaging analyses. I appreciate his patience with my questions as I learned to navigate the world of neuroimaging. My sincere thanks to Dr. Spence, for his statistical prowess, his teaching made challenging statistical concepts easier to tackle. I appreciate the North Texas North Texas Traumatic Brain Injury Research Center staff for allowing me to use their data for my dissertation. Last but not the least; I owe a depth of gratitude to the patients that consented to be a part of this study at a time when they were critically ill.

The last four years would not have been as rewarding without my classmates. I am so glad graduate school brought us together because it has made this journey that much more meaningful. I have to acknowledge my war buddies, Dailyn, Kristine, Lian, and Rachel, for spending countless nights together working on our respective dissertations. I will miss the group therapy. I owe a special thanks to Leigh and Sheila, for sharing their love of neuropsychology and for making me a part of their lives. To Asha and Colin Vas, thank you for being my family away from family. My sincere gratitude to ChiChi, Judith, Mili, Rex, Sheena, Shreya, and Vinod for celebrating the highs and lows of the last four years, especially for sticking with me when my life mostly revolved around sitting in front of a computer. I want to extend a big thank you to my extended family for supporting me through the thick and thin, I could not have asked for more compassionate family members.

And most of all, I am thankful to God, for bringing all these individuals in my life, and for providing me not only the joys and challenges but also the grace to accept my mistakes and continue my growth.

LONGITUDINAL CHANGES IN RESTING-STATE CONNECTIVITY DURING RECOVERY FROM TRAUMATIC AXONAL INJURY

Publication No._____

Kamini Krishnan, Ph.D..

The University of Texas Southwestern Medical Center at Dallas, 2014

Supervising Professor: Carlos Marquez de la Plata, Ph.D.

Little is known about neural network connectivity immediately after a traumatic axonal injury (TAI). This is the first longitudinal study in TAI to examine functional connectivity in the Default Mode Network (DMN) and Central Executive Network (CEN) within 48 hours after traumatic brain injury with repeat imaging 7 months later. Aims: (a) characterize connectivity in these networks at the sub-acute stage of injury, (b) evaluate longitudinal change in networks with recovery, and (c) explore how this change might be associated with structural connectivity and

neurocognitive outcome. Resting-state fMRI and diffusion tensor imaging (DTI) scans were acquired from 21 patients with moderate-severe brain injuries consistent with TAI compared with 8 non-injured controls. Neurocognitive outcome was assessed at 7 months. Results revealed lower resting-state DMN connectivity 48 hours after TAI compared to non-injured controls, and this persisted 7 months after injury. CEN connectivity was comparable between acutely injured patients and controls, though patients demonstrated increased CEN connectivity at 7 months. These patterns of functional connectivity in patients were associated with alterations in structural connectivity, where areas of decreased functional connectivity were associated with decreased integrity of white matter tracts connecting those regions. However, some regions within these networks demonstrated increased functional connectivity despite presence of structural damage. Taken together, results suggest disruptions in functional and structural connectivity are present as early as 48 hours after a TAI. Alterations in functional connectivity during the recovery period may be explained either by structural damage or could suggest the presence of neural compensation in functional connectivity.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF DEFINITIONS

AD	Axial Diffusivity
BOLD	Blood Oxygen-Level Dependent
CEN	Central Executive Network
COWAT	Controlled Oral Word Association Test
CVLT-II	California Verbal Learning Test, Second Edition
DLPFC	Dorsolateral prefrontal cortex
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
FC	Functional Connectivity
FSE	Functional Status Exam
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale – Extended
IPC	Inferior Parietal Cortex
MD	Mean Diffusivity
MFC	Medial Frontal Cortex
MVA	Motor vehicle accident
LPL	Lateral Parietal Cortex
PCC	Posterior Cingulate Cortex
RSFC	Resting-state functional connectivity
RD	Radial Diffusivity
SC	Structural Connectivity

TAI	Traumatic Axonal Injury
TBI	Traumatic Brain Injury
TMTA	Trail Making Test A
TMTB	Trail Making Test B

CHAPTER ONE
Introduction

Every year, an estimated 1.7 million individuals sustain a traumatic brain injury (TBI) in the United States (Faul, Xu, Wald, & Coronado, 2010). Traumatic Axonal Injury (TAI), prevalent in all types of TBI, commonly occurs as a result of shearing of white matter due to the presence of rotational acceleration-deceleration forces. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) techniques demonstrate poor sensitivity for TAI (Bigler et al., 2005), whereas advances in neuroimaging modalities have found certain methods capable of distinguishing integrity of white matter and functional connectivity between healthy and compromised brains after TAI. Neuroimaging modalities such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) demonstrate potential for improving clinical interventions post TAI by aiding in the identification of pathology. To date, most studies examining the utility of neuroimaging as a biomarker for TAI have typically utilized task-based paradigms (e.g. working memory) focused on task-specific alterations in the neural networks (Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008). However, in the last decade, neural connectivity during off-task periods has become a focus in neuroimaging research (Edlow and Wu, 2013).

Resting-state functional connectivity (RSFC) data can examine the temporal synchronicity of functionally related brain regions. Regions demonstrating synchronous activity are collectively known as resting-state functional networks. Among these networks are the default mode network (DMN) and the central executive network (CEN). The DMN is typically associated with internally focused tasks such as self-reflection or mind wandering (i.e., when the

brain is not engaged in a directed task). This network includes regions such as medial frontal cortex, posterior cingulate, medial temporal cortex, and angular cortices. Functional connectivity in the CEN has been associated with tasks involving working memory and aspects of attention (Menon & Uddin, 2010). Neural regions in the CEN include the inferior parietal lobe and the dorsolateral prefrontal cortex, which demonstrate increased neural connectivity during externally focused tasks such as working memory fMRI paradigms and can also be measured at rest.

One hypothesized relationship between DMN and CEN is a complementary function, where the DMN activity decreases during active task demands, thereby allowing for increased neural activity in regions of the brain required for that task (Fox, Snyder, Vincent, & Raichle, 2007; Kelly et al., 2008, Hillary et al., 2011). This relationship has been demonstrated in working memory tasks involving regions of the CEN (Sanchez-Carrion et al., 2008). These networks are also present and active when the brain is not actively involved in a task (during rest). It is unclear how the relationship between DMN and CEN changes during non-task periods following brain injuries involving significant white matter compromise such as TAI.

To explore the relationship between brain injury and functional connectivity, Hillary et al. (2011) designed a longitudinal study to examine a cohort of 10 with moderate to severe TBI characterized by predominant focal lesions three and six months post-injury. Compared to controls in their sample, patients demonstrated decreased DMN connectivity and increased CEN connectivity at the acute stage. As patients recovered from injury, they demonstrated increased RSFC in DMN and decreased connectivity in CEN over time, while controls demonstrated the opposite pattern during this 3 month period. However, these changes in connectivity were not

associated with neurocognitive outcome. These results suggest that altered coherence in functional connectivity after TBI may not be directly associated with functional abilities.

Arenivas et al., 2012 demonstrated compromised functional connectedness of the DMN after chronic TAI, although there have been no longitudinal studies examining changes in RSFC in TAI. The current study aimed to extend previous findings and evaluated RSFC in acutely injured patients with TAI. Furthermore, longitudinal change in RSFC in the DMN and CEN was investigated, and the associations between RSFC, structural integrity, and neurocognitive outcome were explored.

CHAPTER TWO
Review of the Literature

TRAUMATIC BRAIN INJURY

Traumatic brain injury is a serious public health concern and predicted to be the third cause of death and disability by 2020 (Edlow & Wu 2012; Humphreys, Wood, Phillips, & Macey, 2013). Annually, nearly 10 million individuals are affected by brain injury worldwide (Humphreys et al., 2013). In the United States alone, 1.7 million Individuals sustain a TBI every year. Eight percent of those injured are evaluated and released from the emergency department, while 230,000 are hospitalized long-term, with approximately 50,000 deaths every year (Faul et al., 2010). The prevalence of TBI is likely a conservative estimate given recent increase in TBI-related combat injury and widespread awareness of the neurological impact of sports-related concussions (Edlow & Wu, 2012; Ling et al., 2013).

Traumatic brain injury is referred to as an "epidemic" due to the growing number of cases reported and the prevalence of neurological, behavioral, and cognitive consequences after a brain injury (Jennekens, Casterlé, Dierckx, & Dobbels, 2010; Kraus & McArthur, 1996; Lehmkuhl, Hall, Mann, & Gordan, 1993; Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). TBI is the leading cause of mortality and morbidity in individuals under the age of 35 (Jennekens et al., 2010; Werner & Engelhard, 2007). Over 5.3 million individuals in America are left with long-term TBI-related physical, psychological, and cognitive disabilities that can partially or totally impede the individual's ability to participate in activities of daily living (Alexander, 1995; Langlois & Cramer, 2004). Direct medical costs and indirect costs including loss of work

productivity due to TBI are estimated to be at least 76.5 billion in the United States alone (Faul et al., 2010, Meythaler et al., 2001).

Mechanism of Injury. TBI involves insult to the brain where a substantial physical force is exerted by an external object (e.g. blunt objects) or due to inertial forces from rapid acceleration/deceleration of the brain within the cranial vault.

Physical injury to the brain can be divided into two types, penetrating and non-penetrating injury (or closed head injury). Penetrating or open head injuries ensue when objects (such as a bullet) penetrate the skull or cause bone fragmentation. In a majority of cases, open head injuries lead to localized damage such as focal lesions/bruises/contusions. Cognitive losses in these cases can be estimated by identifying the function associated with the area of penetration (Morris, 2010). This type of injury can impact specific long-term cognitive and functional abilities (Hanlon, Demery, Kuczen, & Kelly, 2005). For example, lesions in prefrontal cortex have been associated with deficits in decision-making skills (Gläscher et al., 2012; Stuss et al., 2002).

Closed head injuries are the most common type of TBI which can occur after falls, motor-vehicle accidents (MVAs), or blast-related injuries (Ling et al., 2013; Morris, 2010). Approximately 35% of TBIs occur either due to falls in older adults or due to sports-related concussions in the general population (Faul et al., 2010). However, the largest percentage of TBI-related deaths arises from MVAs (Centers for Disease Control and Prevention, 2006; Langlois et al., 2006). Furthermore, the World Health Organization reports MVAs as the 3rd largest contributor to the global burden of disease and disability (Thornhill, 2000), likely because

the development of safety features in automotive industry has reduced the extent of mortality but contributed to the severity of injury leading to disability. Nevertheless, despite technological advancements, TBIs tend to produce significant functional consequences (Benson et al., 2012; Ling et al., 2013).

Closed head injuries typically involve inertial forces associated with the acceleration-deceleration movement during a collision. This movement can result in brain contusions in two primary neural locations; at the site of impact (as known as coup) and to the contralateral neural region as the brain moves away from the initial site of impact and collides with the opposite side of the skull (contra-coup; Ling et al., 2013; Morris, 2010).This rapid acceleration and deceleration of the head can also cause subcortical white matter compromise commonly referred to as Traumatic Axonal Injury (TAI).

Traumatic Axonal Injury. TAI is characterized by microscopic axonal lesions secondary to the disruption of neurofilaments and microtublues within each axon that occur due to shearing and tearing of axons, a common consequence of the inertial forces involved in MVAs (Morris, 2010; Smith, & Meaney, 2000). Research has shown TAI to be the predominant mechanism of injury in 40-50% of TBI's requiring hospitalization (Arfanakis et al., 2002; Meythaler et al., 2001; Ng et al., 1994). Axonal disruptions caused by TAI commonly affect centroaxial white matter structures located in the frontal and temporal regions, the upper brainstem, and deep white matter such as the corpus callosum and fornix (Adams, Graham, Murray, & Scott, 1982; Meythaler et al., 2001). This is thought to occur because the cerebral

commissures and white matter tracts of the brainstem are vulnerable to stretching and shearing as a result of mechanical forces involved in MVAs (Gennarelli, 1986).

TAI can have profound consequences including permanent brain damage, coma, or death (Povilshock and Katz, 2005; Sharp et al. 2011). The severity of a TBI (mild, moderate, or severe) is typically indicated by clinical measures assessing depth and duration of coma, length of post-traumatic amnesia, or Glasgow Coma Scale (GCS) scores (Wilson, Pettigrew, & Teasdale, 1998; Xu, Rasmussen, Lagopoulos, & Haberg, 2007). These clinical indicators, while useful in the characterizing a TBI, do not provide information regarding the integrity of grey and white matter regions affected after TAI. This information is particularly relevant as injury to axon bundles may cause impairments in cognitive functioning that are not readily apparent when relying solely on the clinical measures stated above (Wilson, Morgan, Lin, Turner, & Blumhardt, 2001; Xu et al., 2007). Additionally, the underlying pathology or mechanism(s) involved that result in cognitive impairments post-TAI are unclear. Neuroimaging modalities, as discussed below, may assist in elucidating this relationship.

Neuroimaging and TAI

From a global perspective, study of brain networks and changes in both intra- and inter-network interactions may provide insight into the functional consequence of neural disruption (Ham & Sharp, 2012; Brier et al., 2012). Furthermore, literature provides research support of imaging research being one of the avenues that may help identify the presence of compensatory neural activity (Ham & Sharp, 2012; Papa et al., 2013). To this end, neuroscience and related fields have undertaken the task of describing brain networks and their interactions with

endeavors such as the Human Connectome Project (Ham & Sharp, 2012; Sporns, 2012). Prior to the current wide-scale use of neuroimaging, scans of the brain were primarily used in acute care settings to identify pathology requiring urgent surgical intervention.

Conventional imaging modalities such as CT and MRI have greatly improved the ability to detect the presence of skull fractures and hemorrhages but are less sensitive to diffuse white matter damage that is characteristic of TAI (Benson et al., 2012; Bigler et al., 2005; Edlow & Wu, 2013). Over the past 15 years, advanced neuroimaging techniques have demonstrated utility in identifying white matter compromise after TBI and have showed moderate correlations with clinical outcomes (Bigler, 2013; Edlow & Wu, 2013; Ham & Sharp, 2012), providing modest support for using these measures as biomarkers that may aid in detection of pathology.

TAI is often suspected when a patient's cognitive and neuropsychiatric deficits are worse than CT findings (Adams et al., 1989; Chan et al., 2003), as microstructural injuries are impossible to detect on CT. TAI occurs in majority of closed head injuries and can present with significant cognitive, physical, and emotional sequelae (Chan et al., 2003). Therefore, recent research has focused on the application of advanced neuroimaging techniques to enhance the ability to detect TAI immediately post-injury (Bigler, 2013; Edlow & Wu, 2013; Ham & Sharp, 2012). Advanced neuroimaging techniques that demonstrate significant change in neural connectivity following TAI can be divided into structural and functional modalities. While many techniques exist under both categories, this review will focus on diffusion tensor imaging (DTI) as a measure of white matter structural integrity and resting-state functional connectivity (RSFC) as a measure of grey matter connectedness. Both techniques will be discussed below in the context of TBI with references to TAI when applicable.

Structural MRI-Diffusion Tensor Imaging. The diffusion of water molecules in the brain, specifically the directionality of magnetized hydrogen protons in the MRI scanner is the basis of image acquisition of DTI scans (Huisman et al., 2004). Each voxel in the brain is assessed in terms of rate of hydrogen atom diffusion and direction of diffusion (Bigler, 2005). Water molecules are thought to travel in 3 primary directions: anterior-posterior, laterally, and inferior-superior (Ramnani, Behrens, Penny, & Matthews, 2004). The protons can be relatively isotropic (non-directional as in grey matter) or anisotropic (restricted by myelin and membranes). DTI describes the diffusion process using three eigenvectors that provide information about diffusion in three orthogonal directions (Sidaros et al., 2009). The following metrics, fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) are used to infer the structural integrity of white matter (Bigler, 2005). FA values vary from 0 to 1, where higher values are suggestive of higher white matter integrity. MD represents the extent of diffusion of the water molecules and is derived by calculating the average of 3 eigenvalues. RD is a measure of diffusion perpendicular to axons and is influenced by the presence of myelin in white matter, whereas AD is a measure of diffusion parallel to axons and is more specific to axonal degeneration (Song et al., 2002; Beaulieu, 2002).

DTI has been posited as a biomarker for white matter injury (Edlow & Wu, 2013) partly because this modality has shown differences between healthy and clinical pathology and has also demonstrated associations between white matter disruption and neuropsychological outcome in various neuropsychiatric conditions including Alzheimer disease (Sexton, Kalu, Filippini, Mackay, & Ebmeier, 2011), schizophrenia (Ellison-Wright & Bullmore, 2009), bipolar disorder

(Adler et al., 2006), and TBI (Benson et al., 2012; Marquez de la Plata et. al., 2011b). DTI studies in TAI demonstrate hyperintensities in diffuse subcortical WM regions which is consistent with results from MRI studies in individuals with TAI as well as animal and human histopathological studies of TAI (Adams et al., 1982; Adams et al., 1989; MacDonald, Dikranian, Bayly, Holtzman, & Brody, 2007; Meythaler et al., 2001). This suggests DTI as a technique detects disruptions in white matter that have been seen in other modalities and across clinical populations, and may provide additional information regarding the integrity of the microstructure of the neural make-up in humans.

DTI in TAI. DTI demonstrates utility in distinguishing individuals with TBI from healthy brains based on pathology that affects the microstructure of white matter tracts. For example, research demonstrates lower FA in patients with TBI compared to healthy populations (Benson et al., 2007; Marquez de la Plata et al., 2011b; Newcombe et al., 2007). An FA decrease is associated with myelin disruptions, axonal swelling, and increased extracellular space (Wilde et al., 2006). Increases in MD and AD in patients with TBI have been linked to demyelination and localized edema (Beaulieu, 2002).

Studies using DTI can detect disruptions in white matter tracts including the corpus callosum, forceps major, forceps minor, cingulum, and fornix in patients with TAI (Arfanakis et al., 2002; Huisman et al.,2004; Inglese, et al., 2005; Marquez de la Plata et al., 2011b; Wang et al., 2011). Reductions in FA have been evident within the first 24 hours after injury, typically related to significant edema that eventually resolves but results in long-term white matter disruptions (Arfanakis et al., 2002; Bendlin et al., 2008; Sidaros et al., 2008; Wang et al., 2011).

Furthermore, compromise to white matter structural integrity is associated with decrements in neurocognitive functions including memory, attention, and executive functions (Lipton et al., 2008; Marquez de la Plata et al., 2011b). However, other studies have demonstrated no change or even improvement in neurocognitive functions despite presence of white matter damage in TBI (Kelly et al., 2008; Sharp et al., 2011; Sidaros et al., 2008). Age may play a role in integrity of white matter, as DTI studies have shown declines in FA in white matter with increasing age (He et al., 2013).

One possible interpretation for the contradictory results is the presence of a compensatory neural mechanism that can account for the lack of cognitive deterioration despite structural damage. For example, in a review of neuroplasticity in TBI, Levin (2003) cites multiple studies where patients with TAI with average performance on working memory tasks demonstrated greater diffuse activation in cortical regions compared to controls and patients with poor performance on the same task. This increased activation in patients was thought to represent reorganization of tissue microstructure (Sidaros et al., 2008). Neural network reorganization may also play a role in these results as demonstrated by Johnston et al. (2008) who showed preserved intrahemisphereic correlations after a complete callosotomy.

Functional MRI. Functional imaging techniques such as task-based fMRI and resting-state MRI rely on the supply of glucose and oxygen to the brain via the vascular system (Huettel, Song, & McCarthy, 2004). The differing magnetic properties of oxygenated and deoxygenated hemoglobin allows for a contrast in the brain that can be used to assess blood-oxygen level-

dependent (BOLD) signal and evaluate temporal synchronicity between two or more neural regions (Huettel et al., 2004).

An initial body of research in brain imaging focused on task-related paradigms, which described a one-to-one relationship between brain areas and specific cognitive functions (Bresler & Menon, 2010; Gratton, Nomura, Pérez, & D'Esposito, 2012). For example, studies with a focus on working memory or other frontal tasks in the scanner show increased involvement of prefrontal cortex and anterior cingulate cortex in patients with TBI compared to healthy controls (Flashman, & Saykin, 2001; McAllister, Sparling, Newsome et al., 2007; Scheibel et al., 2007). fMRI studies in TBI demonstrate that task-based paradigms can differentiate clinical populations from healthy controls based on BOLD activity during the task (Anderson, Taber, & Hurley, 2005; Edlow & Wu, 2013; Hillary et al., 2011). These task-based studies have enriched our understanding of cognitive function associated with brain regions involved in the selected task. However, investigations into resting-state functional connectivity patterns prior to task engagement may provide important information regarding the impact of atypical functional connectivity on patients' functional abilities. Neural network studies are one such modality that may provide information about the brain as a whole as opposed to specific regions, with additional insights into inter- and intra-network connectivity and lend insight into the impact of neural network connectivity on clinical outcome (Bressler & Menon, 2010; Hillary et al., 2011).

In recent years, imaging research has focused on examining the synchrony of different brain networks through examination of functionally related regions. Neural network studies posit that the ability to execute a cognitive task involves integrating multimodal information from various brain regions (Bressler & Menon 2010, Fornito, Harrison, Zalesky, & Simons, 2012;

Gläscher et al., 2012). Therefore, a task is completed as a result of different neural areas working in concert with one another and forming a functional network. Furthermore, brain regions that are within a network are thought to interact with regions in other networks to accomplish desired functions (Bressler & Menon 2010). The study of neural networks has increasingly blossomed as a means to examine the neural correlates of pathology and its relationship with cognition.

The architectural framework of a large-scale functional network primarily consists of nodes (i.e., neural regions) and edges (i.e., white matter pathways connecting the nodes). A group of nodes that are concomitantly activated (increased BOLD activity) or deactivated in response to stimuli can represent a large-scale network involved in that function. Functional interdependence between nodes can be identified through functional connectivity (FC) analysis. Typically, large-scale functional networks are identified as non-directional group of nodes using independent component analysis (ICA) or seed-based techniques (Bressler & Menon, 2010; Broyd et al., 2009; Bucker, 2008; Edlow & Wu, 2013).

Resting-State Functional Connectivity

Resting-state functional connectivity (RSFC) MRI relies on the fact that functionally correlated neural regions will demonstrate temporally synchronous fluctuations in BOLD activity, even when the individual is not actively engaged in a task. BOLD fluctuations can be detected at a low frequency (<0.1 Hz) as shown by Biswal et al. (1995) in a study demonstrating spatial overlap of BOLD response in regions comprising the primary motor cortex. RSFC studies investigate intrinsic or endogenously generated neural activity whereas task-based studies aim to measure evoked or induced responses to specifically designed stimuli (Snyder & Raichle, 2012).

"Rest" in the scanner is defined as the absence of challenging goal-directed behavior or presence of a simple and observable goal-directed behavior (such as visually fixating on a cross-hair). In the early RSFC studies, sequences were acquired during tasks and compared to periods of "rest," when the participant was not actively performing the task. Areas not involved in the task being examined demonstrated negative correlations or decreased BOLD signal which has been referred to as "deactivations" in the literature (Damoiseaux et al., 2006; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001; Van den Heuvel, Mandl, Luigjes, & Pol, 2008).

Resting-state imaging has advantages over task-based studies, especially in clinical populations, as this paradigm does not require an additional sophisticated set-up to administer the task. Lack of a complex task also eliminates the need to design control tasks to ensure equivalent task performance between groups (example, task accuracy in TBI versus healthy controls; Heine et al., 2012; Hillary et al., 2011). Additionally, resting-state paradigms are suitable to study clinical populations with impairments that restrict a participant's ability to complete scanner tasks. This includes patients in coma, or those in a minimally conscious state (Heine et al., 2012; Vanhaudenhuyse et al., 2012). Ease of administration of resting-state scans has prompted research in various clinical populations including TBI, Multiple Sclerosis and Alzheimer disease (Audoin et al., 2006; Christodoulou et al., 2001; Cordes et al., 2001; Duong et al., 2005; Hedden et al., 2009; Lowe et al., 2002; Lowe et al., 2008; Wang et al., 2006; Wang et al., 2008; Xu et al., 2007). Furthermore, resting-state paradigms broaden the scope of FC studies to examine changes in neural networks in the whole brain as opposed to task-specific alterations based on a priori regions of interest (Hillary et al., 2011). These studies demonstrate the utility of resting-state imaging studies in clinical populations where patients may not be able to adequately engage in a

task. Furthermore, resting-state studies have three times more signal to noise ratio compared to conventional task based studies (Fox & Grecius, 2002), which allows for improved spatial resolution of the image. To better understand how connectivity may impact cognition, especially at the acute stage of injury, it is imperative to investigate the interdependence of networks independent of task demands (i.e., have a working knowledge of network interactions at "rest").

Default Mode Network. A series of publications by Raichle and colleagues (Gusnard & Raichle, 2001; Raichle et al., 2001) extended previous resting-state findings and demonstrated a network of distinctly connected neural regions. These regions were identified by the coherence of BOLD fluctuations during rest or off-task periods and came to be known as the "default-mode network" (Buckner et al., 2008; Raichle et al., 2001). This network includes regions such as medial prefrontal cortex (MFC), precuneus, posterior cingulate cortex (PCC), angular cortices, and medial temporal lobes (Buckner et al., 2008; Fransson, & Marrelec, 2008; Raichle et al., 2001; Snyder & Raichle, 2012).

The DMN is typically associated with internally focused tasks such as self-reflection (Buckner and Carroll, 2007), mind wandering, and free associations of the past experiences or future plans (Buckner et al., 2008; Snyder & Raichle, 2012). Resting-state imaging studies in controls have repeatedly demonstrated increased BOLD activity within the nodes of the DMN at rest compared to other neural networks, with subsequent decrease during goal-directed tasks (Greicius, Supekar, Menon, & Dougherty, 2009; Raichle et al., 2001). This pattern of activation is consistent across healthy and clinical populations (Broyd et al., 2009; Greicius, Srivastava, Reiss, & Menon, 2004; Hedden et al., 2009; Wang et al., 2006).

Whole brain network analyses also provide a better understanding of age-related functional connectivity changes, as some studies have demonstrated decrease in inter-network and intra-network resting-state connectivity with increasing age (He et al., 2013; Mowinckel, Espeseth, & Westlye, 2012; Tomasi & Volkow, 2011). Tomasi and Volkow (2011) evaluated age and gender effects in the resting-state networks of 913 healthy controls and demonstrated decreased functional connectivity among nodes of the DMN connecting regions further apart (such as MFC-PCC versus PCC-LLPC). The decrease in functional connectivity between these long-range connections may be related to the integrity of white matter tracts, which are known to be less intact with increasing age (Madden, Bennett, & Song; 2009; Marner , Nyengaard , Tang, & Pakkenberg, 2003).

While effects of age on FC have been extensively studied, less is known about the impact of gender on connectivity. One study demonstrated higher connectivity within nodes of the DMN in females than males (Tomasi & Volkow, 2011), which was thought to be associated with higher cerebral blood flow and glucose metabolism in females (Blackstone, O'Kane, & Reid, 2011). These studies suggest that age may impact the strength of the DMN FC and should be investigated in any analysis involving the DMN while effects of gender on FC are unclear but should be explored to assess potential impact of this factor on the connectedness of neural networks.

Resting-state functional connectivity has been used to study the DMN as a potential biomarker for Alzheimer disease (Allen et al., 2007; Brier et al., 2012; Grecius et al., 2004 Hedden et al., 2009; Lowe et al., 2008). For example, Hedden and colleagues (2009) demonstrated a negative association between amyloid accumulation in Alzheimer disease and FC

in the DMN, especially reduced FC of the hippocampal formation in patients with Alzheimer disease compared to controls. Other studies have demonstrated a relationship between DMN and episodic memory, a domain impaired in Alzheimer disease (Buckner, 2004; Cole et al., 2010). These studies underscore the importance of understanding the pattern of FC in the DMN at it relates to clinical populations primarily because the DMN maybe a potential biomarker of early disease indicators such as increased amyloid accumulation (Brier et al., 2012; Buckner, 2004; Cole et al., 2010). Since the initial DMN studies in Alzheimer disease, this network has been studied in various other clinical populations as well (e.g. see review by Broyd et al., 2009). The next section summarizes literature on the DMN in individuals with TBI.

Default-Mode Network and Traumatic Brain Injury. In TBI, alterations in connectivity between regions of the DMN have been observed when compared to healthy controls (Arenivas et al., 2012; Buckner et al., 2008; Edlow & Wu, 2013; Hillary et al., 2011; Marquez de la Plata et al., 2011a). However, these disruptions in DMN may vary across injury severity, types of injury, and timing of injury assessment. For example, Mayer et al. 2011 demonstrated decreased connectivity in the DMN in a sample with mild TBI without observable cognitive impairment whereas other studies (Hillary et al., 2011; Sharp et al., 2011) demonstrated increased DMN activity in a sample with moderate-severe TBI. These varying findings with respect to FC in the DMN underscore the importance of characterizing the sample based on clinical characteristics.

The type of injury, predominantly focal or axonal lesions, can influence the degree of synchronous BOLD activity in the DMN after brain injury. For example, a study comparing patients with predominantly subcortical white matter injuries and non-injured controls

demonstrated reduced DMN activity in the PCC-MFC edge in patients (Arenivas et al., 2012). This result was contradictory to findings by Hillary et al. 2011 who demonstrated increased DMN activity in a sample with focal injury compared to controls. This suggests that presence of grey matter injury in addition to axonal injury may impact the pattern of resting-state connectivity.

Moreover, the time since injury when scanned (acute versus chronic) is another factor to consider when investigating the pattern of DMN connectivity post-TBI. In a study of acute TBI (<3 weeks post-injury) Mayer and colleagues (2011) demonstrated reduced FC within the DMN compared to healthy controls. In contrast, a study evaluating patients with moderate-severe TBI 6 months after injury demonstrated increased FC within the DMN compared to controls (Sharp et al., 2011). It has been hypothesized that disruptions in functional connectivity between nodes of a neural network might be accompanied by presence of white matter disruptions in fiber pathways connecting the nodes of the DMN. As such, Sharp and colleagues (2011) demonstrated lower functional connectivity in DMN nodes in patients with greater extent of TAI in the corpus callosum. Despite wide-spread evidence that alternations within the DMN nodes occur in TBI, the basic physiological mechanism remains unclear and the interpretation of changes of its intensity remains uncertain (Edlow & Wu, 2012).

The Central Executive Network. The CEN is thought to play a critical role in mediating attention, maintenance and manipulation of working memory, and judgment and decision making (He et al., 2013; Menon & Uddin, 2010; Sridharan, Levitin, & Menon, 2008). Working memory paradigms in the scanner demonstrate increased activity in dorsolateral prefrontal

cortices, anterior cingulate, and inferior parietal cortices, which form the nodes of the Central Executive Network (He et al., 2013; Sridharan et al., 2008). The nodes of this network typically demonstrate increased activity during challenging cognitive tasks, and activity attenuates during rest (Fornito et al., 2012; He et al., 2013; Hillary et al., 2011; Sridharan et al., 2008; Stevens et al., 2012). Neuroimaging studies have reported functional alteration in CEN in various clinical populations including Alzheimer disease (Brier et al., 2012) and TBI (Hillary et al., 2011). However, most studies have focused on functional connectivity during goal-directed tasks where patients typically demonstrate lower activation in CEN nodes compared to healthy controls (Fornito et al., 2012; Hillary et al., 2011).

Central Executive Network in Traumatic Axonal Injury. The literature on TBI has focused on studying task-based FC in the CEN as the function of the CEN corresponds to the cognitive impairments typically seen in TBI. Cognitive impairments in TBI commonly include deficits in attention, processing speed, working memory [the ability to maintain and manipulate a limited amount of information "in mind" (Morris, 2010)]. Neural regions involved in the CEN such as DLPFC are thought to be associated with these cognitive domains (Hillary et al., 2011). In patients with TBI, working-memory tasks have demonstrated increased involvement of regions critical for working memory including ACC (Hillary et al., 2011; Sanchez-Carrion, 2008). Stevens et al. (2012) demonstrated a link between post-concussive symptom severity and reduced functional connectivity in the anterior cingulate in individuals with moderate-severe TBI compared to controls.

Relationship between DMN and CEN. DMN and CEN are thought to interact inversely, mediating between endogenous and cognitively demanding activity (Bressler & Menon, 2010; Hillary et al., 2011). It is hypothesized that the reduced activation of DMN during task-oriented activities and increased activity in CEN nodes allows for the reallocation of cognitive resources to the CEN regions in order to help focus on the task at hand, and away from self-referential activity (Duan et al., 2012). This inverse relationship between DMN and CEN is also apparent in resting-state analyses, as evidenced by anti-correlations between the two networks such that when BOLD signal is strongly synchronized within each network and negatively correlated between neural networks. That is, the DMN and CEN demonstrate positive associations within the nodes in each network and are negatively correlated between each other (Calhoun & Hugdahl, 2012).

Researchers have hypothesized the interaction between the two networks as collaborative rather than competitive. This is contradictory to the inverse DMN- CEN relationship described previously. The collaborative approach is further elucidated by two recent studies. Fornito et al. (2012) suggest the presence of a scaling in neural activity between these two networks, as opposed to the on-off approach. To demonstrate scaling in neural networks, Fornito et al. 2012 showed co-active functional connectivity between these networks during a memory recall task, with the PCC playing a critical role in modulating between the networks, thereby suggesting a collaborative role rather than a competitive interaction between the two networks. Furthermore, Cole et al. (2010) demonstrated reduction in DMN activity in accordance with complexity of task demands. They hypothesize that the extent of reduction in DMN connectivity during a task is based on the level of difficulty of that task.

TAI and Neural Networks

In TBI, disruption in white matter has been associated with alterations in functional connectivity, as well as decline in functional abilities (Johnson et al., 2012; Hillary et al., 2011; Marquez de la Plata et al., 2011a; Mayer et al., 2011; Sharp et al., 2011). However, variability exists in the relationship between structural integrity, network connectivity, and neurocognitive outcome. For example, Sharp et al. 2011 demonstrated structural disconnection in moderate to severe as measured by decreased FA in white matter regions. These areas of reduced white matter integrity in TBI were accompanied by higher activation in DMN nodes versus healthy controls in the resting-state. The authors hypothesized that initial effects of injury as well as compensatory response to injury may have led to functional changes seen after chronic TBI (also seen in Hillary et al., 2011). In contrast, Arenivas et al. 2012 and Stevens et al. 2012 demonstrated decreased DMN connectivity in patients TBI.

When comparing the four investigations described above, there are some similarities in study characteristics that may help explain the results. One possible factor contributing to the variation in results may be the differences in type of TBI included in the study. Arenivas et al. 2012 and Stevens et al. 2012 excluded individuals with focal lesions, while Sharp et al. 2011 and Hillary et al. 2011 included more heterogeneous samples with focal and diffuse injury. Another factor is the severity of brain injury. Global white matter deficits may be present in severe injuries, whereas only specific white matter tracts maybe disrupted in milder forms of TBI (Stevens et al., 2012).

Longitudinal studies may provide information regarding systemic changes in network connectivity during recovery from TBI (Hillary et al., 2010; Sanchez-Carrion et al., 2008). To explore the relationship between brain injury and functional connectivity, Hillary et al. (2011) designed a longitudinal study to examine a cohort of moderate to severe TBI with predominant focal lesions three and six months post-injury. They demonstrated increased functional connectivity in the nodes of the DMN and decreased connectivity in CEN. This suggests that altered neural connectivity after a TBI may not have direct cognitive consequences. Similar results were demonstrated in a longitudinal design by Venkatesan et al. (2014) where patients with moderate-severe TBI were evaluated at three months and again two years after injury.

In contrast to these results, a different pattern of resting-state connectivity was observed in a mild TBI sample. Mayer et al. (2011) evaluated patients with mild TBI eleven days and three months after injury. The longitudinal analyses revealed decreased FC in DMN and task-positive network in patients compared to controls. Over time, there was no change in FC within the DMN. However, regions of the CEN showed increased connectivity over time. These alternations in FC were associated with integrity of the white matter structures. To date, there are no longitudinal studies examining change in RSFC among patients with predominant subcortical white matter injuries (i.e., TAI).

Neuropsychological Correlates of RSN in TBI

The extent of cognitive impairment after a brain injury depends on multiple factors such as severity of TBI (mild, moderate, or severe), presence of focal lesions and/or hematomas, length of post-traumatic amnesia and/or coma, time of assessment (acute versus chronic), and

extent of cortical atrophy (Morris, 2010; Stevens et al., 2012; Wilson et al., 1998; Xu et al., 2007). Neuroimaging studies in TBI have generally focused on the working-memory domain and aspects of executive functioning, attention, and episodic memory (Hillary et al., 2011; McDonald et al., 2002). Results have demonstrated impairments in these cognitive domains after a TBI (McDonald et al., 2012), which is consistent with neurocognitive literature. Although resting-state studies do not directly assess cognitive abilities compared to tasks in the scanner or traditional neuropsychological tests, investigating the relationship between cognitive function and the brain at rest may provide some insight into the complex relationship between on- and off- task networks and cognition. Given that neuropsychological impairment after TBI is typically observed in the areas of attention, information processing speed, and learning and memory, these areas are reviewed below as an overview of the cognitive sequelae of TBI (Brooks, Campsie, Symongton, Beattie, & McKinlay, 1986; Levin, 1990; Mathias & Wheaton, 2007; McAllister, Flashman, McDonald, Brenna, & Saykin, 2002; Ylvisaker & Feeney, 1996).

Attention. Attention is an important component of all aspects of cognition, as it plays a role in working memory, learning, memory, and problem solving (Morris, 2010). In TBI, impaired attention is a hallmark feature across all levels of injury severity and can include impairments in simple and sustained attention (Ponsford & Kinsella, 1992; Roebuck-Spencer & Sherer, 2008). Impaired attention is also observed in individuals with TAI as well as in TBIs that include large focal lesions (McCullagh & Feinstein, 2005). In a 3-back working memory scanner task, McAllister et al. 2006 found increased bilateral activation in frontal regions in patients with mild TBI whereas controls demonstrated increased activation in only the right

frontal region, suggesting that neural connectivity during cognitive tasks may differ for individuals with TBI.

Processing Speed. Patients with TBI often demonstrate slowed reaction time and reduced accuracy on timed-tasks (Morris, 2010). In a review of cognitive sequelae of severe TBI, deficits in processing speed were demonstrated in both simple and complex stimuli measuring reaction time (Mathias & Wheaton, 2007). Neuroimaging studies utilizing processing speed scanner tasks have demonstrated increased involvement of regions in the prefrontal cortex and anterior cingulate cortex (Rypma et al., 2006; Sweet et al., 2006). Increased activation in these regions for individuals with TBI is thought to be associated with decreased neural efficiency that impacts other areas of cognition such as attention and memory (Hillary et al., 2010).

Learning and Memory. Impairment of episodic memory is another hallmark feature of TBI. Deficits in this domain can be related to retrograde amnesia, post-traumatic amnesia or persistent difficulty recalling new information (McCullagh & Feinstein, 2005). Components of memory including encoding, storage, and retrieval can all be impacted by TBI (Morris, 2010), and may be affected by impaired attention and processing speed (for example, inattention reduces ability to encode and therefore impacts retrieval of information; Curtiss, Vanderploeg, Spencer, & Salazar, 2001).

Summary

Traumatic axonal injury is a common form of TBI. Understanding the neurobiology of this microstructural injury may have implications for detection of functional and cognitive consequences of TBI, recovery from TBI, and for developing targeted clinical interventions post-brain injury. To explore the neural impact of TBI, research in the last two decades has focused on advanced neuroimaging techniques such as functional MRI (task-based) and structural modalities (DTI) that are more sensitive to detecting presence of TAI and have demonstrated a relationship with functional outcome (Buckner et al., 2008; Ham and Sharp, 2012).

Resting-state functional connectivity has also shown promise as a neuroimaging biomarker for TAI, as several studies have demonstrated distinct differences in neural connectivity among brain injured patients when scanning the brain at rest and have showed a relationship between abnormal connectivity and cognitive outcome (Broyd et al., 2009, Hillary et al., 2011; Marquez de la Plata et al., 2011a). Few studies have investigated longitudinal change in the functional connectivity of resting-state networks among patients with TAI; however, there is literature that suggests compromise to white matter structures at the chronic stage is associated with compromised functional connectedness of the DMN (Sharp et al., 2011).

This pilot study investigated resting-state functional connectivity in two neural networks approximately 48 hours after a brain injury with repeat imaging 7 months post-injury. Differences between acutely injured patients and normal controls based on resting-state functional connectivity were investigated. Next, the pattern of recovery in resting-state neural networks as the individuals recover from injury was investigated. The relationship between functional connectivity, structural connectivity, and neurocognitive outcome was explored.

Research Goals

Primary Aims

1. To investigate whether strength of functional connectivity differs between patients with acute TAI and healthy controls.
2. To investigate longitudinal change in DMN and CEN connectivity after TAI.

Exploratory aims

1. Explore the relationship between RSFC (DMN and CEN) and structural connectivity after TAI
2. Explore the relationship between RSFC (DMN and CEN) and neurocognitive outcome after TAI.

Hypotheses

1. RSFC among nodes of the DMN and CEN will be greater for controls than patients (at the acute stage of injury).

   Rationale: Reduced functional connectivity in nodes of DMN has been observed in various clinical samples including TAI (Broyd et al., 2009). In a related-sample, Arenivas et al. 2012 demonstrated reduced functional connectivity of the DMN in chronic TAI. While little is known about the pattern of RSFC in the CEN following TAI, studies have shown that structural damage to white matter negatively impacts the strength of functional connectedness between neural regions (Marquez de la Plata et al., 2011a; Mayer et al., 2011; Sharp et al. 2011). Therefore, we expected patients with TAI would demonstrate significantly lower functional connectivity in DMN and CEN at the acute stage.

2. RSFC in DMN and CEN will increase over time among patients with TAI.

   Rationale: As the individual recovers from injury, it is expected that resting-state networks will also demonstrate increased connectivity with the network. This is supported in part by a longitudinal study in individuals with TBI who demonstrated a similar pattern of recovery (Hillary et al., 2011). Additionally, given that improvement in cognitive functions has been observed in patients as they recover from injury (Laatsch et al., 2004), and neural regions are known to be involved in cognitive functions, it is hypothesized that synchronicity of resting-state connectivity will also improve over time. Furthermore, studies have demonstrated improvements in integrity of white matter connections as the edema resolves from the acute stage of injury (Sidaros et al., 2008). However, other studies have demonstrated consistent deterioration in the integrity of white matter structures (Marquez de la Plata et al., 2011b; Wang et al., 2008). Although these results are contradictory, prior functional connectivity literature and improvement in functional outcome point to the possibility of a neural compensatory mechanism that may compensate for any atypical structural connectivity changes post-injury. This statement was further investigated through the exploratory hypotheses outlined below.

Exploratory Hypotheses

1. At the acute stage, reduced white matter integrity (decrease in FA, increase in MD) will be associated with a reduction in RSFC of DMN and CEN in patients with TAI.

   Rationale: Research in TAI demonstrates presence of acute sub-cortical white matter edema. These areas with edema correlate to regions with atrophy at the chronic stage. Reduced white matter integrity at the chronic stage is frequently observed and correlated to decrease in DMN

connectivity. At the acute stage, we expect to see a similar negative association between white matter integrity and RSFC, as acute white matter edema is likely to impact the connectivity of functional neural networks.

2. RSFC in patients with TAI will be associated with reduced simple attention, processing speed, and episodic memory.

   Rationale: Disruption in functional connectivity of DMN after TBI negatively impacts neurocognitive ability, especially with cognitive functions involving the fronto-temporal systems, such as attention, processing speed, and memory. This relationship has been demonstrated in several task-based studies (Hillary et al., 2011; Sanchez-Carrion et al., 2008; Rypma et al., 2006). With respect to DMN, it is known that pattern of connectivity is significantly different in patients with TBI versus controls. Taken together, these findings support the hypothesis that disrupted functional connectivity may impact domains of cognition most susceptible to compromise after a TBI.

CHAPTER THREE
Methodology

Recruitment

Participants were recruited from Parkland Health and Hospital Systems, Dallas, Texas, as part of a study conducted at the North Texas Traumatic Brain Injury Research Center. All patients enrolled in this study met the following inclusion criteria. 1) sustained a closed-head TBI with a mechanism of injury consistent with TAI (involving high-velocity rotational or acceleration-deceleration forces involved in motor-vehicle collisions or motor vehicle-pedestrian collision), 2) demonstrated acute subcortical white matter lesions visible on T2, FLAIR MRI 3) had either subcortical injury seen on Computed Tomography (CT) scan at admission or had a post-resuscitation GCS 3-12 if CT was normal, 4) were hemodynamically stable so that transfer to the scanner was clinically safe, 5) enrolled within 7 days of injury, and 6) were at least 16 years old 7) English speaking.

Exclusion criteria included 1) Patients with previous brain injury or pre-existing neurologic disorders 2) any CT-visible focal lesion or cortical FLAIR hyperintensity greater than 10 mL in volume, 3) bilaterally absent pupillary responses, 4) requirement of craniotomy or craniectomy, 5) midline shift greater than 3 mm at the level of septum pellucidum, 6) contraindication to MRI (incompatible metal implants), 7) vulnerable population (i.e., prisoner or pregnant).

Participants

All subjects demonstrated acute subcortical white matter lesions visible on T2 fluid attenuated inversion recovery MRI. Once consent was obtained at the acute state, research imaging sequences were added to existing neuroimaging protocol conducted as part of the patient's standard of care in the hospital. These patients were not intubated at the time of the acute scan and no complications were experienced during scan acquisition. However, at the acute stage of injury, patients were minimally conscious and/or medicated. A convenience sample was recruited for comparison. All controls were in good general health with no known history of TBI or other neurocognitive disorders. Written informed consent was obtained from all study participants or their legally authorized representative. This study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center in Dallas, Texas. Resting-state fcMRI, DTI, and T1 scans were obtained from patients with TAI during the acute (0-2 days) and chronic stage (6-8 months) of recovery and from healthy volunteers.

MRI Acquisition

RSFC Image Acquisition and Processing. Magnetic resonance images were obtained for each participant using a General Electric Signa Excite 3T (General Electric Healthcare, Milwaukee, Wisconsin) scanner. For fcMRI scans, sequence parameters were FOV 210x210, matrix= 64 × 64, slice thickness of 3.5 mm, voxel size = 3.2 x 3.3 x 3.5, 36 axial slices, TR/TE = 2000/25 ms, flip angle = 90°, 128 image volumes, and scan duration = 268 seconds (4 min 28 seconds). Participants were asked to direct their attention to crosshairs projected onto a screen during image acquisition.

The DTI images were obtained with a singleshot, spin-echo, echo-planar imaging sequence with a FOV 240 x 240 mm, matrix= 128 x 128, voxel size of 1.87 × 1.87 × 3 mm^3, slice thickness = 3.0 with no gaps, 45 slices, echo time=75.5 msec, a flip angle = 90°, number of excitations =2, and acquisition time = 9 min. Diffusion-sensitizing gradients were applied using a b-value of 1000s/mm^2 per axis, number of directions = 19 directions, and three b0 images.

High-resolution structural images were obtained sagittally using a fast spoiled gradient-recalled acquisition in the steady state (GRASS) sequence, with FOV = 240 x 240mm, matrix = 256 x 256, voxel size of 1.3 × 0.93× 0.93 mm^3, slice thickness = 1.3 with no gaps, 130 slices, echo time = 2.4 msec, flip angle = 25°, number of excitations = 2, and a 6-min acquisition time.

fcMRI Preprocessing. The resting-state data were analyzed using Data Processing Assistant for Resting-State fMRI (DPARSF; Yan & Zang, 2010, http://www.restfmri.net), a MATLAB toolbox based on SPM8 (Statistical Parametric Mapping, Version 8 (http://www.fil.ion.ucl.ac.uk/spm), and Resting-state fMRI Data Analysis Toolkit (REST, Song et al., 2011. http://www.restfmri.net).

Images were converted from DICOM to Analyze readable format. The first four volumes were then excluded from further analysis to ensure stabilization of the magnetic field. T1 and RSFC images were co-registered and realigned and adjusted for varying slice acquisition time and to correct for any motion and linear drift artifacts. Next, all data were spatially normalized to the Montreal Neurological Institute (MNI) template (resampling voxel sixe = 3x3x3 mm^3). Voxels were spatially smoothed with a 6-mm full-width at half-maximum Gaussian kernel. Removal of linear trend was performed to enhance signal to noise ratio. Lastly, given that BOLD

signal fluctuations occur at low frequencies (0.01-0.08 Hz), images were band pass filtered to exclude higher frequencies. Prior to functional connectivity analysis, the following sources of variance in resting-state data were removed as covariates using linear regression, (a) 6 head motion parameters, (b) global mean signal, (c) white matter signal, and (d) cerebrospinal fluid.

The two resting-state networks, DMN and CEN, were analyzed using a seed-based approach to generate a correlation map based on the bilateral posterior cingulate [±10 −56 −12] (DMN) and dorsolateral prefrontal [±45 +16 +45] (CEN) cortices (Chapman et al., 2013; Sridharan et al., 2008). To ensure normal distribution of these correlation values and perform mathematical operations, Fisher's r-to-z transformation was applied to the data.

Based on this functional connectivity map for each network and a review of the literature, neural regions (nodes) for each network were identified. For the DMN, nodes included posterior cingulate (0, -51, 29), medial prefrontal cortex (MFC) (0, 61, 22), left lateral parietal cortex (LLPC) (-48, -66, 34), and right lateral parietal cortex (RLPC) (53, -61, 35). Using these coordinates as center points, 6 mm radius ROI spheres were defined from which BOLD time series data were extracted. For each participant, six between-node correlations were obtained (MFC to PCC, MFC to LLPC, MFC to RLPC, PCC to LLPC, PCC to RLPC, and LLPC to RLPC). Figure 1 illustrates these seed locations.

For the CEN, the regions identified included right dorsolateral prefrontal cortex (RDLPFC; 46, 51, -7), left dorsolateral prefrontal cortex (LDLPFC; -45, 50,-5), left inferior parietal cortex (LIPC; -51, -50, 49), and right inferior parietal cortex (RIPC; 53, - 49, 47). Similar to DMN analysis, for each participant six between-node correlations were obtained from a ROI sphere with a 6 mm radius (LDLPFC to RDLPFC, LDLPFC to LIPC, LDLPFC to RIPC,

RDLPFC to LIPC, RDLPFC to RIPC, and LIPC to RIPC). Figure 2 illustrates these seed locations.

The placement of these seeds was based on a recent paper by Brier and colleagues (2012) who investigated RSFC in 559 individuals enrolled in a memory and aging study. The authors identified these nodes based on an independent component analysis and also stated ROI coordinates in this paper (6mm radius) subsume ROIs used for these regions by other seminal papers. For example, a 6mm ROI sphere in the PCC identified by Brier and colleagues (2012) subsumes ROI coordinates cited in Grecius et al., 2004 and Sestieri et al., 2011.

To determine the degree of synchronicity or connectedness between the identified functional edges, the 6 between-mode correlates for each network were entered into a square correlation matrix. A determinant statistic was derived by computing the function of the square matrix. The negative logarithm and square root of the determinant were used to correct for symmetry and variance in the data. The resulting numerical value reflected the degree of cohesiveness within a network, where higher values indicate a more functionally connected network (Arenivas et al., 2013).

DTI preprocessing. DTI images were realigned, corrected for eddy current distortions, and deskulled using FSL (www.fmrib.ox.ac.uk/fsl/, University of Oxford, Oxford,UK) . Tensor calculation and diffusion map generation were performed using DTI Studio (www.mristudio.org, Johns Hopkins Medical Institute, Baltimore, MD). Fiber tracts connecting regions of DMN and CEN were identified by superimposing functional ROI's on JHU atlas. For the DMN, inferior fronto-occipito fasciculus (IFO) and inferior longitudinal fasciculus (ILF) were identified as

white matter tracts connecting MFC-LLPC and MFC-RLPC. Cingulum bundle and IFO/ILF were tracts between MFC and PCC edge. Forceps major was identified as one of the white matter tracts connecting the PCC to LLPC, PCC to RLPC, and LLPC to RLPC. For the CEN, IFO and ILF were identified as tracts connecting the DLPFC to SPC, forceps minor between the bilateral DLPFC nodes and uncinate fasciculus within the DLPFC.

Tractography was performed with DTI Studio (Johns Hopkins Medical Institute, http://lbam.med.jhmi.edu/) utilizing the Fiber Assignment by Continuous Tracking algorithm (Mori, Wakana, Nagae-Poetscher, & van Zijl, 1999). Ten WM fiber bundles were reconstructed using a minimum FA threshold of 0.25, turning angle of 70 degrees, and the z-axis was flipped to ensure appropriate orientation. A multiple ROI approach with the OR, CUT, and AND functions, following the guidelines by Wakana, Jlang, Nagae- Poetscher, van Zijl, and Mori (2004) and Wang et al. 2008 were utilized in DTIstudio and reconstructed white matter tracts were quantified by FA, MD, RD, AD values.

Outcome Measures

Neurocognitive outcome assessments were conducted on the day of the chronic scan, 7 months post-injury, by a trained research coordinator who was blinded to neuroimaging results, and under the supervision of a neuropsychologist. Neurocognitive results were adjusted for demographic factors (age, education, gender) where available. T-Scores for the selected measures were used throughout the statistical analyses (M=50, SD=10).

Functional Outcomes. Functional outcomes were assessed using the Functional Status Exam (FSE; Dikmen et al. 2001) and the Glasgow Outcome Scale-Extended (GOSE; Wilson, Pettigrew, and Teasdale, 1998). The FSE is semi-structured ten- item interview measuring an individual's ability to engage in activities of everyday life in physical, social, and psychological domains after a TBI. Severity within each area is measured along a four-point ordinal rating scale, ranging from zero to three, where lower ratings indicate minimal changes as compared to pre-injury functional ability. The values are summed, with scores ranging from 10 to 40, and a score of 41 designates the patient died prior to the outcome assessment. The GOSE is a brief-screening questionnaire designed to assess functional abilities in various domains after a TBI. Total GOSE scores range from one to eight, with higher scores associated with better outcome.

Learning and Memory. Memory functioning was assessed using the California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, and Ober, 2000). Learning was assessed using the total items learned across five trials, while short and long delay free recall trials were used to assess recall memory.

Attention and Processing Speed. Trail Making Test A (TMTA), Dodrill Stroop Word-Reading condition, and selected subtests of the WAIS-III (i.e., Digit-Symbol Coding and Symbol Search) were administered to assess information processing speed.

Planned Statistical Analyses

All statistical analyses were performed using Predictive Analytical Software (PASW v17.0.2) except the mixed model regression described below that was performed using SAS (v9.4).

Demographic data were examined for between-group differences. Age and education differences were examined using *t* tests whereas gender and ethnicity were analyzed using Chi-Square test. Differences in degree of functional connectivity of the DMN between controls and acutely injured patients were evaluated using Analysis of Covariance (ANCOVA), with connectivity measures derived for the 6 edges as dependent variables. In this analysis, diagnosis was a fixed factor and age was used as a covariate. Similar ANCOVA analysis was used to evaluate between-group differences in degree of functional connectivity of the CEN.

A mixed model approach was used to evaluate change in strength of functional connectivity connections in the DMN and CEN over time. This model, used in longitudinal analyses, allows the ability to retain individuals with missing data points. With respect to functional connectivity, BOLD time series data was collected for 21 patients at two time points resulting in a total of 42 data points per functional edge. In this sample, 13 data points were missing for each edge due to late initiation of fcMRI protocol (x two), lost to follow-up at chronic stage as patients moved out of state (x three) and movement in scanner threshold = 1.5x voxel size (x eight). Accounting for missing data has been used previously in multiple neuroimaging studies as loss to follow up and movement artifact are common causes of missing data in imaging research (Bowman and Kilts, 2003; Forsyth et al., 2014; Szaflarski et al., 2006).

On analysis, there were no differences between patients with follow-up scans versus those without with respect to gender, age, and GCS score ($p < 0.05$).Therefore, there is no clear pattern for the missing data and they are considered to be missing at random. A VARCOMP procedure in SAS (Version 9.4) using restricted maximum likelihood (REML) method was used account for within and between subject variance for data available at both time points. Unlike a repeated measures analysis, this method retains cases that are missing a data point instead of discounting all values for that participant.

Pearson correlations were used to examine associations between the strength of functional connections between nodes of the DMN and CEN to structural connectivity measures. Pearson correlation coefficients were used to determine the association between neuropsychological outcomes and RSFC in DMN and CEN at the chronic stage. Spearman's rho was used to examine associations between functional connectivity measures of DMN and CEN with functional outcome scores (i.e., GOSE and FSE). A false-discovery rate (FDR) of 0.05 was utilized to correct for multiple comparisons.

CHAPTER FOUR
Results

Sample Characteristics

Sample Size. Twenty-one patients with injuries consistent with TAI were included. At the acute stage, two subjects were enrolled prior to the implementation of the fcMRI scan and five demonstrated significant movement- related artifacts and were excluded. Therefore, a total of 14 patients had acute fcMRI scans for analyses. At the chronic stage, four patients did not return for a follow-up visit as they had relocated to another state. One patient's fcMRI images demonstrated significant movement related artifact. Therefore, chronic fcMRI scans were analyzed for fifteen patients. White matter tracts were reconstructed for all participants with viable fcMRI data. Imaging data were analyzed for eight healthy controls. The significant correlations in the analyses described below did not survive a multiple comparison correction (FDR = 0.05). Table 1and 2 illustrate the representation of the sample sizes in this study.

Demographic Characteristics. Independent sample t-test showed no significant differences in age between the groups ($p < 0.05$). However, there was a difference in median age between the controls (median age = 40) and patients (median age = 24). There were significant differences in education between controls (M= 16.50, SD = 3.51) and patients (M= 12.29, SD = 2.59), t (26) = 3.38, p = 0.003. Chi-square analysis demonstrated no differences in gender χ^2 (1, N=32) = 1.02, p=0.41 or race, χ^2 (4, N=32) = 5.10, p = 0.28. Table 3 lists all demographic variables for the two groups.

The TAI sample was characterized as moderately-severely injured at the acute stage of injury (M= 1.17 days, SD = 0.73 days), as 17/21 patients scored 8 or below on the GCS (M= 6.3, SD = 4.43, Median = 3, IQR = 3-8). These patients were in the ICU for an average of 5 days (SD = 6.44) and were discharged approximately 9 days after being admitted to the hospital (SD = 7.62). At the chronic stage of injury (M = 7.09 months, SD = 1.03 months; Table 4), these patients demonstrated good recovery as measured by the GOSE (M = 6.71, SD = 1.57) and FSE (M = 15.9, SD = 5.39; Table 11).

To characterize FC and SC in acutely injured patients, we compared connectivity between patients and controls. Following that analysis we investigated the pattern of change in resting-state connectivity in patients during the first 7 months of injury, and then investigated whether the pattern of functional connectivity at the acute stage in the two resting-state networks was associated with structural connectivity and/or with neurocognitive outcome.

Hypothesis 1: Patients with acute TAI will demonstrate reduced functional connectivity in DMN and CEN compared to controls.

Independent one-way ANCOVAs were conducted for functional connectivity edges in the DMN, using diagnosis as a fixed factor and age as a covariate. While education was significantly different between the groups, this variable did not meet the assumptions required for an ANCOVA analysis and was not used as a covariate. Specifically, education did not demonstrate any correlation with the functional connectivity measures. Also, this factor was not independent from the FC measures based on the highly significant differences between the groups ($p = 0.003$). Therefore, education was a confounding factor and was not used as a

covariate. This was further supported by results of two ANOVAs with and without education as a covariate that demonstrated a reduction in error df and in model mean square when education was used as a covariate, resulting in a smaller effect. Therefore, education when used as a covariate decreased error variance in the sample. Similarly, the suitability of gender as a covariate was evaluated and was also found to be a confounding factor.

Although mean age was not significantly different between the groups, median age for controls was 40 years whereas median age for patients was 24 years. Literature suggests that age has an impact on strength of functional connectivity, with younger individuals demonstrating greater BOLD synchronicity in neural networks compared to older individuals (He et al., 2013; Mowinckel et al., 2012; Tomasi & Volkow, 2011). Therefore, age was used as a covariate in these analyses. This variable met the assumptions for ANCOVA.

A main effect of diagnosis was observed for all DMN functional edges ($p<0.05$) except PCC to LLPC and PCC to RLPC, with controls demonstrating significantly higher level of synchronicity between the edges compared to patients with acute TAI (Table 5). The degree of functional connectedness within the DMN was also significantly higher in controls compared to patients with acute TAI, $F(1, 19) = 3.73$, $p < 0.03$ (Table 4). There were no significant group differences in functional connectivity for functional edges in the CEN (Table 6).

Hypothesis 2. RSFC for DMN and CEN will increase over time in patients with TAI

The REML estimation method used to analyze these data and account for missing variables has been utilized in research before for similar purposes (Bowman and Kilts, 2003; Forsyth et al., 2014; Szaflarski et al., 2006). Although the statistic is valid, it was used to

extrapolate missing data points and the following results should be interpreted with this caveat in mind.

Based on results for the mixed effects model using REML that accounts for missing variables, increase in FC was observed from the acute to the chronic stage of recovery for certain edges. With respect to the DMN, increase in FC between the LLPL and RLPL nodes was demonstrated between the acute and chronic stage of injury, $F (1, 27) = 7.96$, $p = 0.009$ (Table 7). For the CEN, FC between RDLPFC and LDLPFC demonstrated significant increase over time $F (1, 27) = 5.29$, $p = 0.03$. Similar increase was observed in the LDLPFC to LIPC node, $F (1, 14.1) = 4.64$, $p = 0.046$. There was a significant increase in within-network connectivity over time, as measured by the function of the determinant, $F (1, 15.9) = 7.44$, $p = 0.015$ (Table 8).

A subset analysis was conducted to investigate change in RSFC for 9 patients with complete longitudinal FC data. Results demonstrated no significant differences in FC within edges of the DMN or CEN. LLPL-RLPC edge trended towards significance, with greater functional connectivity at the chronic stage, $t (1, 8) = -1.60$, $p = 0.074$, which is consistent with results above. Similarly, significant increase over time was demonstrated in FC of RIPC-LIPC [$t (1, 8) = -1.85$, $p = 0.051$]. See tables 9 and 10.

Exploratory Hypothesis 1.At the acute stage, reduced white matter integrity (decrease in FA, increase in MD) will be associated with a reduction in RSFC of DMN and CEN in patients with TAI.

Association between functional and structural connectivity. With respect to the DMN, significant negative correlations were observed in FA of the right cingulum in acutely injured

patients for PCC-MFC edge (r= -0. 69, p = 0.009). In terms of mean diffusivity, negative correlations were observed in forceps major for PCC-LLPC (r = -0.67, p = 0.012) and LLPC-RLPC edge (r= -0.59, p = 0.034). Left IFO was significantly correlated with MFC-LLPC edge (r = -0.58, p = 0.038). A positive correlation was observed between the right cingulum and PCC-MFC edge (r = 0.71, p = 0.006).

With respect to AD, Left ILF was significantly correlated with MFC-LLPC (r = -0.58, p=0.037). AD of the forceps major was negatively correlated with PCC-LLPC (r = -0.62, p = 0.025) and LLPC-RLPC edge (r= -0.56, p = 0.046). With respect to RD, Left IFO was negatively correlated with MFC-LLPC (p=-0.60, r = 0.029). RD of the forceps major was correlated with PCC-LLPC (r = -0.61, p = 0.028) and LLPC-RLPC edge (r= -0.59, p = 0.032).

With respect to CEN, there were no significant correlations between FC of the CEN and white matter tracts connecting the CEN edges with respect to change in FA and MD.

Exploratory Hypothesis 2. Decreased RSFC in patients with TAI will be associated with reduced processing speed and episodic memory.

Clinical Outcome. Based on the functional measures, FSE (median= 15) and GOSE (median = 7), patients in this sample demonstrated good recovery. On neurocognitive tests, patients' performance fell in the low average to average range overall, except for mildly impaired performance on the COWA. However, it should be noted that there was a wide range in performance across measures, T-scores ranging from 18 to 68. Table 11 represents a summary of functional and cognitive scores.

Association between functional connectivity and NP. The strength of connectivity within the DMN, as measured by the function of the determinant, was negatively correlated to Trails A ($r = -0.60$, $p = 0.019$) and Trails B ($r = -0.52$, $p = 0.045$). There were no significant correlations between the strength of connectivity in the CEN and NP measures. Appendix B represents scatter plots illustrating the relationship between the DMN and the two trail making tests.

CHAPTER FIVE
Discussion

The current study investigated task-free (i.e. resting-state) neural network connectivity during a critical period of recovery in individuals with TAI. Twenty-one patients with moderate-severe TAI characterized by predominant white matter lesions and absence of large focal lesions were examined within 48 hours of injury and again approximately seven months post-injury. To our knowledge, this is the first study to explore resting-state FC changes as early as two days after injury in any TBI sample. Additionally, this longitudinal study provides insight into the pattern of neural recovery in relation to structural connectivity and neurocognitive outcome.

Acutely Injured Patients with TAI

Default-Mode Network 48 hours after injury. As hypothesized, results demonstrated group differences in the functional connectedness of the DMN between controls and patients with acute TAI, where 67% of DMN edges showed significant decreases in FC in acutely injured patients. This finding is consistent with a study of moderately-severely injured TBI that demonstrated decreased magnitude of resting-state DMN activity in patients 3 months after injury (Hillary et al., 2011). The present study further extends these findings and suggests alterations in functional connectivity of the DMN may be present within 48 hours after a TAI.

Decreased DMN connectivity in acute stages of recovery has also been reported in less severe TBI. In a study of mild TBI, Mayer et al. (2011) demonstrated decreased BOLD connectivity within the DMN 11 days after injury. Similarly, Johnson et al. (2012) demonstrated decreased overall strength in DMN connectivity in athletes with a grade one mild TBI

approximately two days after concussion. Subjects were noted to be symptom free 24 hours prior to the scan, which suggests that functional connectivity can be affected even in concussed individuals with minimal to no clinical symptoms. Therefore, it is not surprising that the sample in our study consisting of moderately-severely injured participants with a median GCS score of 3 demonstrated significantly lower functional connectivity in the DMN compared to controls in the sub-acute stage of injury.

In addition to decreased DMN, the current study demonstrated significant hypoconnectivity in all functional edges involving the medial prefrontal cortex (MFC) in acutely injured patients. This finding suggests that MFC may be particularly susceptible to injury immediately after TAI, perhaps attributable in part to the mechanism of injury. This sample consisted of individuals with a TBI due to motor-vehicle accidents. The most common coup-contracoup mechanism of a TBI, seen in MVAs, often results in damage to the prefrontal regions of the brain (Morris, 2010). Importance of the MFC is further supported by investigations in the literature of decreased resting-state connectivity between the MFC and PCC in patients with TBI compared to controls (Mayer et al., 2011; Sharp et al., 2011; Sours et al., 2013). However, other studies have noted hyperconnectivity in nodes involving the MFC (Johnson et al., 2012; Hillary et al., 2011; Venketesan et al., 2014). This discrepancy may be due related to multiple factors such as difference in method for identification of the ROI, injury severity, age of participants, and timing of scan after injury.

Furthermore, impaired functional connectivity in the MFC may be influenced by compromised white matter structures in the frontal lobe, as studies have demonstrated a link between decreased functional connectivity in edges with injured white matter regions (Mayer et

al., 2011; Sharp et al., 2011; Grecius et al., 2008). To investigate this possibility, we explored the relationship between functional and structural connectivity at the acute stage and found that higher MD and RD values in the left IFO were correlated with lower functional connectivity in the MFC-LLPC edge. Similarly, a higher AD value was associated with lower functional connectivity in the left ILF. This finding provides partial support for the current study hypothesis regarding the impact of white matter damage to BOLD synchronicity of functional nodes. However, not all white matter structures that pass through the MFC were significantly correlated with functional connectivity. This suggests that factors other than structural connectivity may impact the BOLD synchronicity of functional nodes. There may be dynamic changes in blood perfusion and metabolism not apparent on MRI scans that can impact BOLD activity (Mayer et al., 2011).

Central Executive Network 48 hours after injury. Contrary to the initial hypothesis, there were no differences in resting-state CEN functional connectivity between controls and acutely injured patients. The hypothesis was based on DMN network components because there have been no published investigations of resting-state CEN at this acute stage of injury. First, given that decreased DMN connectivity is observed in patients with TBI with demonstrable structural decompensation (Sharp et al., 2011; Grecius et al., 2008), we expected a similar pattern in CEN, where damage to white matter tracts will be associated with decreased functional connectivity. Incorporating these findings, it was posited that damage to the white matter in this sample, due to edema or axonal injury typically present 48 hours after injury, would negatively affect the degree of functional connectedness of the CEN.

The absence of significant differences in CEN connectivity between controls and acutely injured patients was supported by the lack of an association between functional connectivity of the CEN and the white matter tracts connecting the neural regions involved in the CEN. This suggests that despite the presence of white matter damage in these tracts, strength of functional connectivity of the CEN was not directly associated with integrity of the tracts connecting the regions of the CEN. BOLD response is influenced by the combination of disruption in neuronal impulses and changes in metabolic activity due to pathophysiological changes (Mayer et al., 2011; Fox and Raichle, 2007). Therefore, it is possible that temporal coherence in functional regions is maintained by neural compensation, where BOLD data is transmitted via alternate means such as other white matter tracts not investigated in this study. This explanation is not novel as it has been posited by investigations that demonstrate incongruity between structural and functional connectivity results in TBI populations (Mayer et al., 2011; Palacios et al., 2013). Results in a chronic and severe TBI sample showed increased resting-state frontal connectivity within the DMN in the presence of damage to the cingulum (Palacios et al., 2013). Mayer and colleagues (2011) showed that cingulum bundle FA values predicted functional connectivity between right anterior cingulate cortex and posterior cingulate cortex in controls but not in patients with mild TBI. Taken together, these results raise the possibility of neural compensation in the presence of white matter damage in TAI. This hypothesis is further supported by results demonstrating increase in CEN connectivity at the chronic stage that is unaccompanied by an association with structural connectivity measures.

Longitudinal Network Connectivity

***Default-Mode Network over time*.** This network demonstrated minimal increase in functional connectivity longitudinally, with stable FC in 5/6 between-node regions. The overall dearth of increase in DMN connectivity, while contrary to expectations, is consistent with extant findings of lower resting-state functional connectivity in the DMN at the chronic stage of TBI compared to controls (Sanchez-Carrion et al., 2008, Palacios et al., 2013; Sharp et al., 2011). Additionally, our finding suggests that reduced functional connectivity seen 48 hours after injury persists with minimal increase over time.

Contrary to these results, however, Hillary et al. 2011 demonstrated increased DMN connectivity from 3 to 6 months post-injury. The difference between their findings and the present results may be related to differences in the samples studied, as their sample included a heterogeneous TBI group with both focal and axonal injuries and the present sample was restricted to individuals with white matter injuries in the absence of large focal lesions. Therefore, the emphasis on characterization of the sample is particularly relevant as it has been demonstrated that white matter injures significantly impact the extent of BOLD synchrony in grey matter regions (Mayer et al., 2011; Sharp et al., 2011). This is further supported by Mayer and colleagues (2011) who demonstrated decreased DMN FC twelve days after a mild TBI (vs controls) that remained stable four months post-injury. Conversely, in the heterogeneous TBI sample (Hillary et al., 2011), differences in functional connectivity may be attributed to white matter injury or damage to grey matter structures within the network of interest that resulted in abnormal functional connectivity. Additionally, neural regions cited in the literature have been investigated using a variety of MNI coordinates due to disparity in the methodological approach.

The studies mentioned above use different seed regions to investigate the DMN and CEN. Therefore, the contrary findings may be related to methodological approaches with regards to identification of the seed from which BOLD data is extracted for the study.

While the majority of DMN edges demonstrated stable functional connectivity, one edge, LLPC-RLPC, demonstrated a significant increase in functional connectivity during recovery. This is also the edge that showed the largest mean difference between patients and controls at the acute stage (LLPC-RLPC $F(1, 19) = 4.92$, $p = 0.019$). That is, the LLPC-RLPC edge demonstrated the lowest synchronicity of BOLD connectivity immediately after injury and is the only edge that showed improvement over time. Consistent with our finding, this edge was noted to be one of the few areas of the DMN with significantly lower resting-state functional connectivity in concussed athletes two days after injury compared to non-concussed teammates (Johnson et al., 2011). Thus, based on our current findings, it is possible that LLPC-RLPC edge experienced significant functional desynchrony early in the injury process, and therefore may have much more room for improved BOLD synchrony at the chronic stage of injury.

Furthermore, as previously noted, reductions in FC are often influenced by the integrity of white matter tracts connecting these areas. In case of LLPC-RLPC, forceps major is a white matter tract that runs through both regions, and the corpus callosum that includes the forceps major is sensitive to TBI (Arfanakis et al., 2002; Inglese et al., 2005). A similar pattern was observed in the current study, i.e. compromise to MD and AD in the forceps major was significantly associated with decreased functional connectivity between LLPC-RLPC at the acute stage. Therefore, for this node, the acute decrease in functional connectivity was associated with loss of structural integrity (i.e., edema) to the splenium of the corpus callosum. This hypothesis

is further supported by significant increase in AD of forceps major seven months after injury, which suggests continued deterioration in the structural integrity of the axon (Song et al., 2003). However, there was no change in FA or other DTI measures of the white matter tracts over time. These findings raise the possibility for a neural compensatory mechanism that should be further explored, as results demonstrate functional connectivity increases while a marker of axonal compromise (i.e., severed axons) increases.

***Central Executive Network over time*.** As noted previously, acutely injured patients with TAI demonstrated similar functional connectivity in the CEN compared to controls. However, these individuals showed significant increases in FC in the RDLPFC-LDLPFC and LIPC-RIPC edges during the recovery period. In addition, increased strength of functional connectivity in the network as a whole was observed over time. This suggests that while patients recover from injury, the synchrony of the BOLD fluctuations in their CEN increases over time. These results are in contrast to Hillary et al., 2011 who found a decrease in resting-state functional connectivity in ACC- parietal lobe and DLPFC- parietal lobe edges between the 3rd and 6th month after injury among a sample of moderate-severely injured individuals with mixed focal and axonal injuries. The CEN has not been previously studied at such a sub-acute stage of injury, which limits our ability to rely on the literature to explain the differences between studies. However, it should be noted that the increase in the current study was observed only in interhemisphereic functional connectivity (i.e. within contralateral DLPFC and IPC). In contrast, Hillary and colleagues (2011) demonstrated decreased *intra*-hemisphereic connectivity, i.e. within ipsilateral regions of the CEN (Left ACC- left parietal lobe). Studies have demonstrated reduced interhemesphereic connectivity in individuals with severe damage to their corpus

callosum (Quigley et al., 2003; Johnston et al., 2008). While the current study did not investigate the corpus callosum in its entirety, longitudinal analysis of the forceps minor demonstrates stable integrity of white matter in this tract over the recovery period. Interestingly, increased interhemispheric connectivity in DLPFC and IPC was observed despite the presence of white matter damage as demonstrated by increased AD in forceps major. It has been hypothesized that presence of interhemisphereic connectivity despite significant structural damage to a prominent white matter structure may be possible due to rerouting of electrical impulses through the commissures or other white matter tracts (Quigley et al., 2003; Johnston et al., 2008). This hypothesis was particularly illustrated in a study that showed presence of interhemispheric connectivity after a complete callosotomy (Johnston et al., 2008). Taken together, results from the current study suggest the possibility of a neural rerouting that leads to increased functional connectivity when structural tracts are compromised.

RSFC Association with Outcome. To investigate the relationship between resting-state functional connectivity and clinical outcomes, correlational analyses between connectedness of the DMN and CEN and performance on various neurocognitive tasks at seven months post-injury were conducted. Tests in the domains of processing speed, attention, and episodic memory were selected as they are shown to be impaired in individuals with TBI (Morris, 2010). In this study, the strength of the functional connectedness in the DMN during an off-task period was negatively associated with performance on the Trail Making Test. During any goal-directed task in the scanner, the DMN typically demonstrates reduced activation in order to allow the individual to engage in the required task with subsequent increased activation in the task-

positive network (such as the CEN). While RSFC does not permit direct analyses of cognitive ability, the results in this study suggest the possibility that a highly synchronized DMN may encumber the ability to engage in tasks assessing processing speed and mental flexibility. This is further supported by the scatter plot demonstrating a curvilinear relationship between performance on Trails A and connectedness of the DMN. However, due to the small sample size and large variability in neurocognitive scores, one must interpret these findings with caution.

The lack of significant relationship between functional connectivity and neurocognitive outcome in the CEN was contradictory to expectations. It was hypothesized that decreased connectivity at the chronic stage will predict neurocognitive outcome. This sample of moderately-severely injured individuals with predominant white matter injury demonstrated average performance observed on most all neuropsychological measures. However, there was a large variability in performance, with T-scores ranging from severely impaired to above average ability on the measures assessed. Furthermore, this sample demonstrated increased functional connectivity in the CEN over the recovery period with a stable decline in DMN connectivity. In this sample, the range in neurocognitive performance and mixed pattern of RSFC change in the two networks over time limits the interpretability of these results.

Limitations. While this is the first study to investigate disruptions in functional connectivity in DMN and CEN 48 hours post-injury in individuals with TAI, there are several limitations to be considered in this pilot study design. First, the study is likely underpowered, as the sample size is small with numerous statistical comparisons. Additionally, many of the significant findings did not survive multiple comparison correction. The median age was

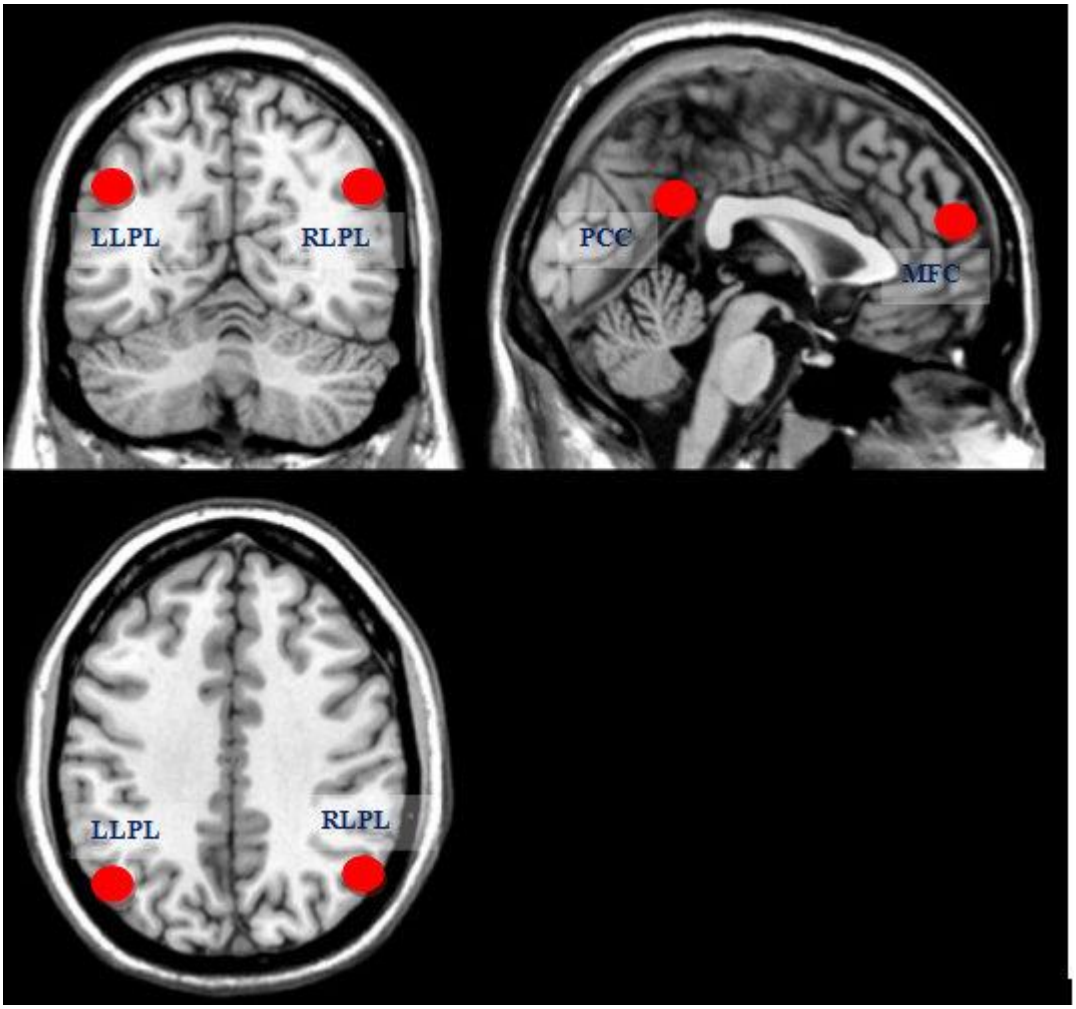
considerably dissimilar between patients and controls, as controls were significantly older than patients. While the present study attempted to account for variability explained by age (i.e., using age as a covariate) controlling for age-related variance through an age-matched design would be a more effective way to limit error variance. Replication of these findings is needed to compare the pattern of recovery in neural networks in larger sample sizes and across injury severity. Movement in-scanner is a concern in fMIR studies among acutely injured patients due to disorientation and/or restlessness present during the sub-acute stage; however, resting-state studies provide a distinct advantage over task-based fMRI studies among patients with acute TBI as these studies require less mental effort. This study recruited individuals with TAI to explore the impact of predominant white matter lesions on network connectivity. These results may not be easily generalizable to patients with TBI with predominant cortical injuries.

Conclusions. This study is unique in its investigation of network connectivity 48 hours after a traumatic brain injury. Additionally, this is the first *longitudinal* study in TBI that exclusively investigates resting-state connectivity in individuals with TAI. Acutely, the DMN demonstrates an altered pattern of connectivity that persists over time. CEN connectivity was not compromised within the first two days of injury but demonstrates a slight increase over time. Acute white matter compromise after TAI may influence degree of functional connectivity within the DMN to an extent; however, the degree and manner in which WM integrity influences FC is still unclear. Information processing speed appears to be inversely related to DMN synchrony, which was an unexpected finding. Taken together, these findings suggest alterations in brain connectivity occurring days and months post-TAI, possibly the result of neuroplasticity;

however, these changes are far from being understood. This pilot data lays ground for further studies to investigate the utility of the DMN and CEN as biomarkers to characterize acute and chronic TBI. Given the global increasing incidence of TBI and the presence of TAI in many of those injuries, gaining further insight regarding the impact of a brain insult on the intrinsic functional connectivity may shed light on recovery process after a traumatic injury.

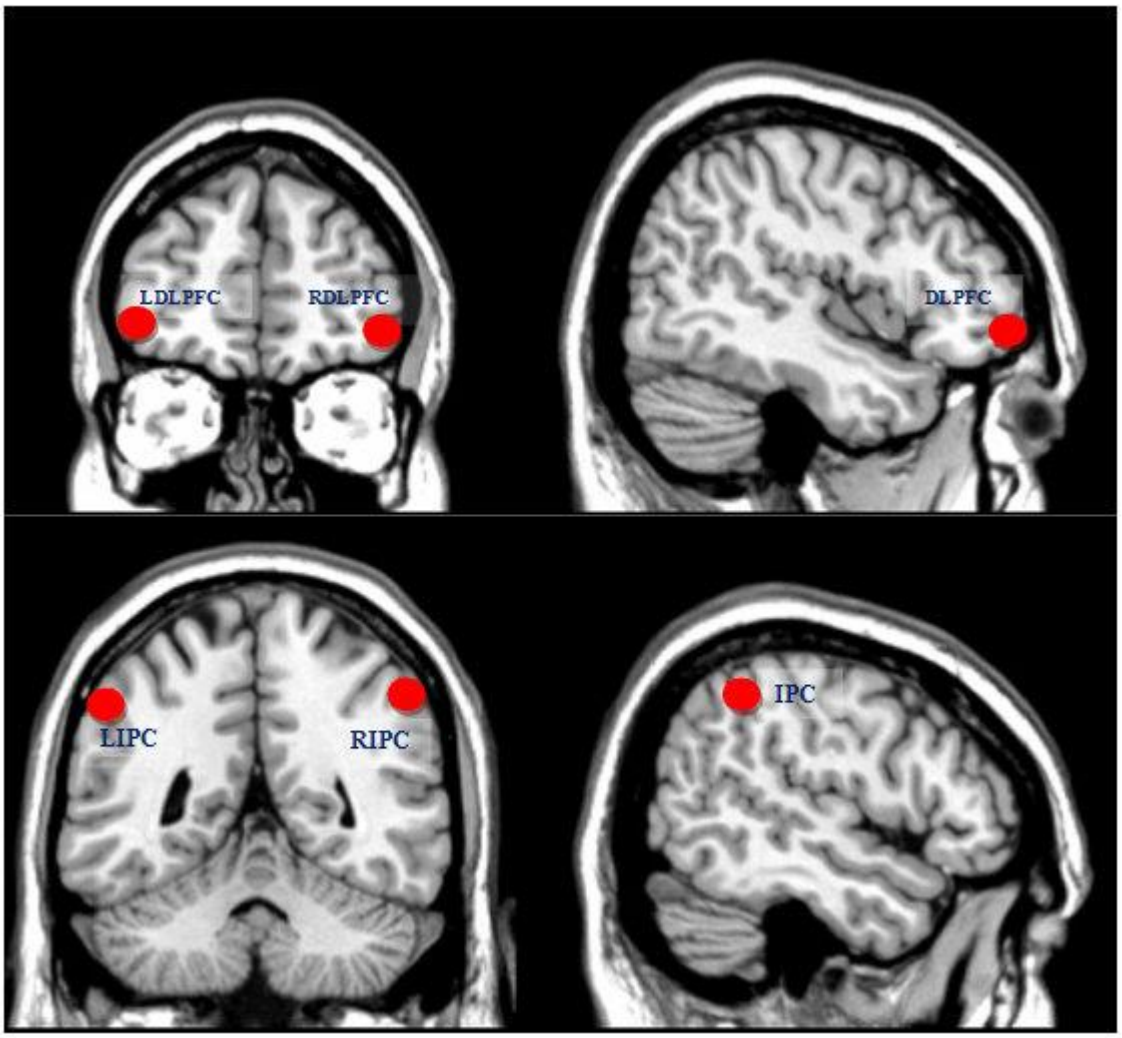
FIGURES

Figure 1: Seed placement for the DMN



Note: MNI coordinate for ROIs of 6 mm radius placed in regions of the Default Mode Network. Posterior cingulate cortex (PCC; 0, -51, 29), Medial Prefrontal Cortex (MFC; 0, 61, 22), Left Lateral Parietal Cortex (LLPC; -48, -66, 34), and Right Lateral Parietal Cortex (RLPC; 53, -61, 35).

Figure 2: Seed placement for the CEN



Note: MNI coordinate for ROIs of 6 mm radius placed in regions of the Central Executive Network. Right Dorsolateral Prefrontal Cortex (RDLPFC; 46, 51, -7), Left Dorsolateral Prefrontal Cortex (LDLPFC; -45, 50,-5), Left Inferior Parietal cortex (LIPC; -51, -50, 49), and Right Inferior Parietal Cortex (RIPC; 53, - 49, 47).

TABLES

Table 1: Numeric representation of data collected in this study

	rs-fMRI	**DTI**	**NP**
Controls	8	8	0
Acute	14	14	0
Chronic	15	15	15

Note: rs-fMRI= resting-state functional magnetic resonance imaging; DTI = Diffusion Tensor Imaging; NP= neuropsychological tests

Table 2: Numeric representation of patient data available for analyses

	Acute fMRI	Chronic fMRI
1	Not collected	1
2	Not collected	1
3	1	1
4	1	1
5	1	Lost to f/up
6	1	1
7	1	1
8	Motion	1
9	Motion	1
10	Motion	1
11	1	1
12	1	1
13	1	Lost to f/up
14	1	1
15	1	Lost to f/up
16	1	Motion
17	Motion	1
18	1	Motion
19	1	1
20	1	Lost to f/up
21	1	1

Note: f/up: follow-up

Table 3. Demographics all participants

	Normal Control (8)				TBI Patients (21)				*p*
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	
Age	39.63	16.34	40.00	25-54	29.00	11.41	24.00	21-36	0.12
Educatio	16.50	3.51	16.00	13-21	12.29	2.59	12.00	11-14	**0.003**
Gender	4 males (50 %)				16 males (76%)				0.17
Ethnicity	7 Caucasians (88%)				17 Caucasians (80 %)				0.19

Note: TBI: Traumatic Brain Injury, SD = Standard Deviation, IQR = Interquartile range

Table 4: Clinical characteristics of patients with TAI

		Age (years)	Education (years)	GCS at injury	ICU days	Hospital Days	Acute Scan (days)	Chronic scan (months)
Mean		29.00	12.29	6.30	5.00	9.38	1.17	7.09
Std. Deviation		11.41	2.59	4.43	6.44	7.62	0.73	1.03
Percentiles	25	21.00	11.00	3.00	2.00	2.50	0.50	6.00
	Median	24.00	12.00	3.00	3.00	7.50	1.00	7.00
	75	36.00	14.00	8.00	4.50	12.00	1.75	8.00

Note: GCS: Glasgow Coma Scale; ICU = Intensive Care Unit

Table 5. General Linear Model of FC in DMN

	Functional Connectivity			
	Controls M (SE)	Acute TAI M (SE)	*F*	*p*
PCC to MFC	0.72 (0.08)	0.53 (0.06)	3.32	0.042*
PCC to LLPC	0.63 (0.11)	0.44 (0.08)	1.67	0.106
PCC to RLPC	0.48 (0.08)	0.47 (0.06)	0.003	0.479
MFC to LLPC	0.62 (0.12)	0.33 (0.09)	3.56	0.037*
MFC to RLPC	0.55 (0.09)	0.32 (0.07)	3.70	0.035*
LLPC to RLPC	0.68 (0.08)	0.45 (0.06)	4.92	0.019*
DMN-Function of the determinant	1.55 (0.16)	1.12 (0.12)	3.73	0.034*

Note. *=$p<0.05$; FC= functional connectivity, DMN = Default Mode Network; PCC= Posterior Cingulate Cortex; MFC = Medial Prefrontal Cortex; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex

Table 6. General Linear Model of FC in CEN

	Functional Connectivity			
	Controls M (SE)	Acute TAI M (SE)	*F*	*P*
RDLPFC to LDLPFC	0.67 (0.08)	0.53 (0.06)	1.85	0.094
RDLPFC to RIPC	0.35 (0.11)	0.36 (0.08)	0.002	0.48
RDLPFC to LIPC	0.20 (0.10)	0.34 (0.07)	1.15	0.15
LDLPFC to RIPC	0.17 (0.10)	0.26 (0.07)	0.51	0.24
LDLPFC to LIPC	0.14 (0.10)	0.33 (0.07)	2.14	0.079
LIPC to RIPC	0.53 (0.10)	0.43 (0.07)	0.71	0.204
Determinant for CEN	1.26 (0.13)	1.06 (0.10)	1.308	0.13

Note. *=p<0.05; FC= functional connectivity; CEN = Central Executive Network; RDLPFC= Right Dorsolateral Prefrontal Cortex; LDLPFC = Left Dorsolateral Prefrontal Cortex; LIPC= Left Lateral Inferior Parietal Cortex; RLPC = Right Lateral Inferior Parietal Cortex

Table 7. Repeated Measures Mixed effects model DMN

	Functional Connectivity			
	Acute TAI Least Square Means (Estimate (SE)	Chronic TAI Least Square Means Estimate (SE)	*F*	*p*
PCC to MFC	0.55 (0.06)	0.52 (0.06)	0.16	0.697
PCC to LLPC	0.63 (0.11)	0.44 (0.08)	1.67	0.106
PCC to RLPC	0.43 (0.07)	0.49 (0.06)	0.98	0.350
MFC to LLPC	0.35 (0.08)	0.41 (0.08)	0.26	0.618
MFC to RLPC	0.34 (0.07)	0.50 (0.07)	3.51	0.084
LLPC to RLPC	0.45 (0.05)	0.66 (0.05)	7.96	0.009**
Determinant DMN	1.18 (0.11)	1.39 (0.10)	1.98	0.171

Note. **=p<0.01; DMN = Default Mode Network; PCC= Posterior Cingulate Cortex; MFC = Medial Prefrontal Cortex; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex

Table 8. Repeated Measures Mixed effects model CEN

	Functional Connectivity			
	Acute TAI Least Square Means Estimate (SE)	Chronic TAI Least Square Means Estimate (SE)	*F*	*p*
RDLPFC to LDLPFC	0.56 (0.05)	0.72 (0.05)	5.29	0.03*
RDLPFC to RIPC	0.34 (0.07)	0.42 (0.07)	0.88	0.37
RDLPFC to LIPC	0.32 (0.06)	0.35 (0.06)	0.14	0.71
LDLPFC to RIPC	0.25 (0.11)	0.27 (0.09)	0.11	0.74
LDLPFC to LIPC	0.34 (0.06)	0.44 (0.06)	2.09	0.17
LIPC to RIPC	0.25 (0.06)	0.40 (0.06)	4.64	0.046*
Determinant CEN	1.09 (0.08)	1.37 (0.08)	7.44	0.015*

Note. *=p<0.05; CEN = Central Executive Network; RDLPFC= Right Dorsolateral Prefrontal Cortex; LDLPFC = Left Dorsolateral Prefrontal Cortex; LIPC= Left Lateral Inferior Parietal Cortex; RLPC = Right Lateral Inferior Parietal Cortex

Table 9. Paired sample t-test for DMN in 9 patients with TAI

	Functional Connectivity			
	Acute TAI Means (SD)	Chronic TAI Mean (SD)	*t*	*p*
PCC to MFC	0.59 (0.20)	0.55 (0.22)	0.65	0.27
PCC to LLPC	0.48 (0.31)	0.63 (0.10)	-1.42	0.097
PCC to RLPC	0.48 (0.22)	0.56 (0.14)	-1.36	0.105
MFC to LLPC	0.43 (0.36)	0.56 (0.21)	-1.05	0.163
MFC to RLPC	0.40 (0.26)	0.43 (0.24)	-0.37	0.361
LLPC to RLPC	0.51 (0.22)	0.67 (0.14)	-1.60	0.074
Determinant DMN	1.25 (0.44)	1.42 (0.23)	-1.02	0.168

Note. DMN = Default Mode Network; PCC= Posterior Cingulate Cortex; MFC = Medial Prefrontal Cortex; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex

Table 10. Paired sample t-test for CEN in 9 patients with TAI

	Functional Connectivity			
	Acute TAI Mean (SD)	Chronic TAI Mean (SD)	*t*	*p*
RDLPFC to LDLPFC	0.64 (0.15)	0.73 (0.14)	-1.22	0.13
RDLPFC to RIPL	0.44 (0.26)	0.50 (0.19)	-0.61	0.28
RDLPFC to LIPL	0.42 (0.25)	0.42 (0.14)	-1.85	0.45
LDLPFC to RIPL	0.29 (0.30)	0.41 (0.18)	-1.33	0.11
LDLPFC to LIPL	0.42 (0.27)	0.45 (0.15)	0.12	0.33
LIPL to RIPL	0.40 (0.36)	0.61 (0.13)	-1.85	0.051
Determinant CEN	1.21 (0.44)	1.39 (0.16)	-1.50	0.09

Note. CEN = Central Executive Network; RDLPFC= Right Dorsolateral Prefrontal Cortex; LDLPFC = Left Dorsolateral Prefrontal Cortex; LIPC= Left Lateral Inferior Parietal Cortex; RLPC = Right Lateral Inferior Parietal Cortex

Table 11. Functional and Cognitive Outcomes in the TAI Sample (N= 17)

	Outcome Measure	Mean Score (SD)	Median Score	Range
Functional	FSE	15.9 (5.39)	15	10-26
	GOSE	6.7 (1.6)	7	3-8
Processing Speed	DSC	42.2 (6.9)	43	27-53
T-Scores	Stroop I	43.7 (12.6)	47	11-62
	SS	48.4 (8.3)	50	33-67
	TMTA	47.1 (13.1)	47	29-83
Executive	COWAT	40.7 (11.1)	39	18-68
Function	TMTB	51.35 (10.6)	50	31-69
T-Scores	Stroop II	53.8 (8.4)	56	30-63
Learning &	CVLT-II Total	47.7 (15.7)	47	5-73
Memory	CVLT-II SD	45.9 (14.1)	45	20-70
T-Scores	CVLT-II LD	45.6 (14.4)	45	15-65

Note: FSE = Functional Status Exam; GOSE = Glasgow Outcome Scale-Extended;; COWAT = Controlled Oral Word Association Test; TMTB = Trail Making Test B; Stroop II = Color Naming Condition; CVLT-II = California Verbal Learning Test – Second Edition; Total = Total Learning; SD = Short Delay; LD = Long Delay. DSC = Digit Symbol Coding; Stroop I = Reading Condition; SS = Symbol Search; TMTA = Trail Making Test A.

BIBLIOGRAPHY

Adams, J. H., Doyle, D., Ford, I., Gennarelli, T. A., Graham, D. I., & McLellan, D.R. (1989). Diffuse axonal injury in head injury: Definition, diagnosis and grading. *Histopathology, 15*(1), 49-59.

Adams, J. H, Graham, D. I, Murray, L. S., & Scott, G. (1982). Diffuse axonal injury due to non-missile head injury in humans: an analysis of 45 cases. *Annals of Neurology, 12*(6), 557-63.

Adler, C. M., Adams, J., DelBello, M. P., Holland, S. K., Schmithorst, V., Levine, A., ... & Strakowski, S. M. (2006). Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. *American Journal of Psychiatry, 163*(2), 322-324.

Alexander, M. P. (1995). Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology, 45*(7), 1253-1260.

Allen, G., Barnard, H., McColl, R., Hester, A. L., Fields, J. A., Weiner, M. F., ... & Cullum, C. M. (2007). Reduced hippocampal functional connectivity in Alzheimer disease. *Archives of neurology*, *64*(10), 1482-1487.

Arenivas, A., Diaz-Arrastia, R., Spence, J., Cullum, C. M., Krishnan, K., Bosworth, C., ... & de la Plata, C. M. (2012). Three approaches to investigating functional compromise to the default mode network after traumatic axonal injury. *Brain Imaging and Behavior*, 1-13.

Arfanakis, K., Haughton, V. M., Carew, J.D., Rogers, B. P., Dempsey, R. J., & Meyerand, M. E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. *American Journal of Neuroradiology, 23*, 794-802.

Audoin, B., Malikova, I., Confort-Gouny, S., Ibarrola, D., Cozzone, P. J., Pelletier, J., & Ranjeva, J. P. (2006). Functional magnetic resonance imaging and cognition at the very early stage of MS. *Journal of the neurological sciences*, *245*(1), 87-91.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR Biomedicine Journal,15,* 435-455.

Bendlin, B. B., Ries, M. L., Lazar, M., Alexander, A. L., Dempsey, R. J., Rowley, H. A., ... & Johnson, S. C. (2008). Longitudinal changes in patients with traumatic brain injury assessed with diffusion-tensor and volumetric imaging. *Neuroimage*, *42*(2), 503-514.

Blackstone, C., O'Kane, C. J., & Reid, E. (2010). Hereditary spastic paraplegias: membrane traffic and the motor pathway. *Nature Reviews Neuroscience*, *12*(1), 31-42.

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and princSPCes. *Trends in cognitive sciences*, *14*(6), 277-290.

Brier, M. R., Thomas, J. B., Snyder, A. Z., Benzinger, T. L., Zhang, D., Raichle, M. E., ... & Ances, B. M. (2012). Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. *The Journal of Neuroscience*, *32*(26), 8890-8899.

Benson, R. R., Meda, S. A., Vasudevan, S., Kou, Z., Govindarajan, K. A., Hanks, R. A., ... & Haacke, E. M. (2007). Global white matter analysis of diffusion tensor images is predictive of injury severity in traumatic brain injury. *Journal of Neurotrauma*, *24*(3), 446-459.

Benson, R. R., Gattu, R., Sewick, B., Kou, Z., Zakariah, N., Cavanaugh, J. M., & Haacke, E. M. (2012). Detection of hemorrhagic and axonal pathology in mild traumatic brain injury using advanced MRI: implications for neurorehabilitation. *NeuroRehabilitation*, *31*(3), 261-279.

Bigler, E. D. (2013). Neuroimaging Biomarkers in Mild Traumatic Brain Injury (mTBI). *Neuropsychology review*, *23*(3), 169-209.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537-41.

Bowman, F. D., & Kilts, C. (2003). Modeling intra-subject correlation among repeated scans in positron emission tomography (PET) neuroimaging data.*Human brain mapping*, *20*(2), 59-70.

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S. (2009). Default-mode brain dysfunction in mental disorders: a systematic review. *Neuroscience and Biobehavioral Reviews*, *33*, 279-296.

Brooks, N., Campsie, L., Symington, C., Beattie, A., & McKinlay, W. (1986). The five year outcome of severe blunt head injury: a relative's view. *Journal of Neurology, Neurosurgery & Psychiatry*, *49*(7), 764-770

Buckner RL (2004) Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron 44*, 195–208.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., ... & Mintun, M. A. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *The Journal of Neuroscience*, *25*(34), 7709-7717.

Buckner, R. L., & Carroll, D. C. (2007). Self-projection and the brain. *Trends in cognitive sciences*, *11*(2), 49-57.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network. *Annals of the New York Academy of Sciences*, *1124*(1), 1-38.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., ... & Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *The Journal of Neuroscience*, *29*(6), 1860-1873.

Calhoun, V. D., & Hugdahl, K. (2012). Cognition and Neuroimaging in Schizophrenia. *Frontiers in human neuroscience*, *6*.

Centers for Disease Control and Prevention. National Center for Injury Prevention and Control. (2006). Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths 2002-2006. Retrieved from http://www.cdc.gov/traumaticbraininjury/pdf/blue_book.pdf.

Chan, J., Tsui, E., Peh, W., Fong, D., Fok, K., Leung, K., ... & Fung, K. (2003). Diffuse axonal injury: detection of changes in anisotropy of water diffusion by diffusion-weighted imaging. *Neuroradiology*, *45*(1), 34-38.

Chao-Gan, Y., & Yu-Feng, Z. (2010). DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Frontiers in systems neuroscience*, *4*.

Chapman, S. B., Aslan, S., Spence, J. S., Hart, J. J., Bartz, E. K., Didehbani, N., ... & Lu, H. (2013). Neural Mechanisms of Brain Plasticity with Complex Cognitive Training in Healthy Seniors. *Cerebral Cortex*, bht234.

Christodoulou, C., DeLuca, J., Ricker, J. H., Madigan, N. K., Bly, B. M., Lange, G., ... & Ni, A. C. (2001). Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *Journal of Neurology, Neurosurgery & Psychiatry*, *71*(2), 161-168.

Cicerone, K. D. (2002). Remediation of working attention in mild traumatic brain injury. *Brain Injury*, *16*(3), 185-195.

Cole, M. W., Pathak, S., & Schneider, W. (2010). Identifying the brain's most globally connected regions. *Neuroimage*, *49*(4), 3132-3148.

Cole, D. M., Smith, S. M., & Beckmann, C. F. (2010). Advances and pitfalls in the analysis and interpretation of resting-state FMRI data. *Frontiers in systems neuroscience*, *4*.

Cordes, D., Haughton, V. M., Arfanakis, K., Carew, J. D., Turski, P. A., Moritz, C. H., ... & Meyerand, M. E. (2001). Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. *American Journal of Neuroradiology*, *22*(7), 1326-1333.

Curtiss, G., Vanderploeg, R. D., Spencer, J. & Salazar, A. M. (2001). Patterns of verbal learning and memory in traumatic injury. *Journal of the International Neuropsychological Society, 7,* 574-585.

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. *Proceedings of the national academy of sciences*, *103*(37), 13848-13853.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. (2000). California Verbal Learning Test: Manual (2nd ed.). San Antonio, TX: Psychological Corporation.

Dodrill, C. B. (1978). A neuropsychological battery for epilepsy. *Epilepsia,* 611-623.

Duan, X., Liao, W., Liang, D., Qiu, L., Gao, Q., Liu, C., ... & Chen, H. (2012). Large-scale brain networks in board game experts: insights from a domain-related task and task-free resting state. *PloS one*, *7*(3), e32532

Edlow, B. L., & Wu, O. (2012, September). Advanced neuroimaging in traumatic brain injury. In *Seminars in neurology* (Vol. 32, No. 4, p. 374). NIH Public Access.

Ellison-Wright, I., & Bullmore, E. (2009). Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophrenia Research*, *108*(1), 3-10.

Faul, M., Xu, L., Wald, M. M., & Coronado, V. G. (2010). Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta (GA): Centers for Disease Control and Prevention. *National Center for Injury Prevention and Control*, *2*, 1-9.

Fornito, A., Harrison, B. J., Zalesky, A., & Simons, J. S. (2012). Competitive and cooperative dynamics of large-scale brain functional networks supporting recollection. *Proceedings of the National Academy of Sciences*, *109*(31), 12788-12793

Forsyth, J. K., McEwen, S. C., Gee, D. G., Bearden, C. E., Addington, J., Goodyear, B., ... & Cannon, T. D. (2014). Reliability of functional magnetic resonance imaging activation during working memory in a multi-site study: Analysis from the North American Prodrome Longitudinal Study. *NeuroImage*,*97*, 41-52

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. *NeuroImage 42*, 1178-1184.

Gläscher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., ... & Tranel, D. (2012). Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. *Proceedings of the National Academy of Sciences*, *109*(36), 14681-14686.

Gratton, C., Nomura, E. M., Pérez, F., & D'Esposito, M. (2012). Focal brain lesions to critical locations cause widespread disruption of the modular organization of the brain. *Journal of Cognitive Neuroscience*, *24*(6), 1275-1285.

Greicius, M. D., Krasnow, B, Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, *100*(1), 253-258.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Science*, *101*, 4637-4642.

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., ... & Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological psychiatry*, *62*(5), 429-437.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R.F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral Cortex, 19*(1), 72-78.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience, 2*, 685-694.

Ham, T. E., & Sharp, D. J. (2012). How can investigation of network function inform rehabilitation after traumatic brain injury? *Current opinion in neurology*, *25*(6), 662-669.

Hanlon, R. E., Demery, J. A., Kuczen, C., & Kelly, J. P. (2005). Effect of traumatic subarachnoid haemorrhage on neuropsychological profiles and vocational outcome following moderate or severe traumatic brain injury. *Brain Injury*, *19*(4), 257-262.

He, X., Qin, W., Liu, Y., Zhang, X., Duan, Y., Song, J., ... & Yu, C. (2013). Age-related decrease in functional connectivity of the right fronto-insular cortex with the central executive and default-mode networks in adults from young to middle age. *Neuroscience letters*, *544*, 74-79.

Hedden, T., Van Dijk, K. R., Becker, J. A., Mehta, A., Sperling, R. A., Johnson, K. A., & Buckner, R. L. (2009). Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *The Journal of neuroscience*, *29*(40), 12686-12694.

Heine, L., Soddu, A., Gómez, F., Vanhaudenhuyse, A., Tshibanda, L., Thonnard, M., ... & Demertzi, A. (2012). Resting state networks and consciousness: alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness States. *Frontiers in psychology*, *3*.

Hillary, F. G., Slocomb, J., Hills, E. C., Fitzpatrick, N. M., Medaglia, J. D., Wang, J., ... & Wylie, G. R. (2011). Changes in resting connectivity during recovery from severe traumatic brain injury. *International Journal of Psychophysiology*, *82*(1), 115-123.

Huisman, T. A., Schwamm, L. H., Schaefer, P. W., Koroshetz, W. J., Shetty-Alva, N., Ozsunar, Y., ... & Sorensen, A. G. (2004). Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. *American Journal of Neuroradiology*, *25*(3), 370-376.

Huettel, S. A., Song, A. W., & McCarthy, G. (2004). Functional magnetic resonance imaging. Sinauer Associates, Inc., Sunderland, Massachusetts.

Humphreys, I., Wood, R. L., Phillips, C. J., & Macey, S. (2013). The costs of traumatic brain injury: a literature review. *ClinicoEconomics and Outcomes Research: CEOR*, *5*, 281.

Inglese, M., Makani, S., Johnson, G., Cohen, B. A., Silver, J. A., Gonen, O., & Grossman, R. I. (2005). Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *Journal of Neurosurgery*, *103*(2), 298-303.

Jennekens, N., Casterlé, D., Dierckx, B., & Dobbels, F. (2010). A systematic review of care needs of people with traumatic brain injury (TBI) on a cognitive, emotional and behavioural level. *Journal of Clinical Nursing*, *19*(9-10), 1198-1206.

Johnson, B., Zhang, K., Gay, M., Horovitz, S., Hallett, M., Sebastianelli, W., & Slobounov, S. (2012). Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. *Neuroimage*, *59*(1), 511-518.

Johnston, J. M., Vaishnavi, S. N., Smyth, M. D., Zhang, D., He, B. J., & Zempel, J. M. (2008). Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. *The Journal of Neuroscience*, *28*(25), 6453-6458.

Kelly, A.M., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., Milham, M.P., 2008. Competition between functional brain networks mediates behavioral variability. Neuroimage 39, 527–537.

Kraus, J. F., & McArthur, D. L. (1996). Epidemiologic aspects of brain injury. *Neurologic clinics*, *14*(2), 435-450.

Langlois, J. A., Rutland-Brown, W., & Thomas, K. E. (2004). *Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths*. Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Acute Care,

Rehabilitation Research and Disability Prevention, National Center for Injury Prevention and Control.

Langlois, M. W., & Cramer, K. M. (2004). The relationship between household composition and retirement stress. *Guidance & Counseling, 20*(1), 89-98.

Lehmkuhl, D. I., Hall, K. M., Mann, N., & Gordan, W. (1993). Factors that influence costs and length of stay of persons with traumatic brain injury in acute care and inpatient rehabilitation. *Journal of Head Trauma Rehabilitation, 8*(2), 88-100.

Levin, H. S. (1990). Memory deficit after closed-head injury. *Journal of Clinical and Experimental Neuropsychology, 12*(1), 129-153.

Levin, H. S. (2003). Neuroplasticity following non-penetrating traumatic brain injury. *Brain Injury, 17*, 665-674.

Ling, G. S., Hawley, J., Grimes, J., Macedonia, C., Hancock, J., Jaffee, M., ... & Ecklund, J. M. (2013). Traumatic brain injury in modern war. In *SPIE Defense, Security, and Sensing* (pp. 87230K-87230K). International Society for Optics and Photonics.

Lipton, M. L., Gellella, E., Lo, C., Gold, T., Ardekani, B. A., Shifteh, K., ... & Branch, C. A. (2008). Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury with cognitive disability: a voxel-wise analysis of diffusion tensor imaging. *Journal of neurotrauma, 25*(11), 1335-1342.

Lowe, M. J., Beall, E. B., Sakaie, K. E., Koenig, K. A., Stone, L., Marrie, R. A., & Phillips, M. D. (2008). Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. *Human Brain Mapping, 29*(7), 818-827.

Lowe, M. J., Phillips, M. D, Lurito, J. T., Mattson, D., Dzemidzic, M., & Mathews, V. P. (2002). Multiple sclerosis: Low frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity - initial results. *Radiology, 224*(1), 184-192.

Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging.*Neuropsychology review*, *19*(4), 415-435.

Mathias, J. L., & Wheaton, P. (2007). Changes in attention and information-processing speed following severe traumatic brain injury: A meta-analytic review. *Neuropsychology*, *21*(2), 212.

McAllister, T. W., Sparling, M. B., Flashman, L. A, & Saykin, A. J. (2001). Neuroimaging findings in mild traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology, 23*(6), 775-791.

McAllister T, Flashman LA, McDonald Brenna C, Saykin AJ (2006). Mechanisms of working memory dysfunction after mild and moderate TBI: Evidence from functional MRI and neurogenetics. *Journal of Neurotrauma*, 23, 1450–1467.

McCullagh, S., & Feinstein, A. (2005). Cognitive Changes. In J. M. Silver, T. W. McAllister, & S.C. Yodofsky (Eds.), *Textbook of traumatic brain injury*. Washington, DC: American Psychiatric Publishing, Inc.

McDonald, B. C., Saykin, A. J., & McAllister, T. W. (2012). Functional MRI of mild traumatic brain injury (mTBI): progress and perspectives from the first decade of studies. *Brain Imaging and Behavior*, *6*(2), 193-207.

Mac Donald, C. L., Dikranian, K., Bayly, P., Holtzman, D., & Brody, D. (2007). Diffusion tensor imaging reliably detects experimental traumatic axonal injury and indicates approximate time of injury. *The Journal of Neuroscience*, *27*(44), 11869-11876.

Marner, L., Nyengaard, J. R., Tang, Y., & Pakkenberg, B. (2003). Marked loss of myelinated nerve fibers in the human brain with age. *Journal of Comparative Neurology*, *462*(2), 144-152.

Marquez de la Plata, C. D., Garces, J., Shokri Kojori, E., Grinnan, J., Krishnan, K., Pidikiti, R., ... & Diaz-Arrastia, R. (2011). Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Archives of neurology*, *68*(1), 74.

Marquez de la Plata, C. D., Yang, F. G., Wang, J. Y., Krishnan, K., Bakhadirov, K., Paliotta, C., ... & Diaz-Arrastia, R. (2011). Diffusion tensor imaging biomarkers for traumatic axonal injury: analysis of three analytic methods. *Journal of the International Neuropsychological Society: JINS*, *17*(1), 24-35.

Mayer, A. R., Mannell, M. V., Ling, J., Gasparovic, C., & Yeo, R. A. (2011). Functional connectivity in mild traumatic brain injury. *Human Brain Mapping*, *32*(11), 1825-1835.

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5-6), 655-667.

Meythaler, J. M., Peduzzi, J. D., Eleftheriou, E., & Novack, T. A. (2001). Current concepts: Diffuse axonal injury-associated traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *82*, 1461-1471.

Mori, S., Crain, B. J., Chacko, V. P., & van Zijl, P. C. (1999). Three dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology*, *45*, 265–269.

Morris, T. (2010). Traumatic Brain Injury. In *Handbook of Medical Neuropsychology* (pp. 17-32). Springer New York.

Mowinckel, A. M., Espeseth, T., & Westlye, L. T. (2012). Network-specific effects of age and in-scanner subject motion: a resting-state fMRI study of 238 healthy adults. *Neuroimage*, *63*(3), 1364-1373.

Newcombe, V. F. J., Williams, G. B., Nortje, J., Bradley, P. G., Harding, S. G., Smielewski, P., ... & Menon, D. K. (2007). Analysis of acute traumatic axonal injury using diffusion tensor imaging. *British journal of neurosurgery*, *21*(4), 340-348.

Newsome, M. R., Scheibel, R. S., Steinberg, J. L., Troyanskaya, M., Sharma, R. G., Rauch, R. A., ... & Levin, H. S. (2007). Working memory brain activation following severe traumatic brain injury. *Cortex*, *43*(1), 95-111.

Ng, H. K., Mahaliyana, R. D., & Poon, W. S. (1994). The pathological spectrum of diffuse axonal injury in blunt head trauma: assessment with axon and myelin strains. *Clinical Neurology and Neurosurgery, 96*, 24-31.

Palacios, E. M., Sala-Llonch, R., Junque, C., Roig, T., Tormos, J. M., Bargallo, N., & Vendrell, P. (2013). Resting-state functional magnetic resonance imaging activity and connectivity and cognitive outcome in traumatic brain injury. *JAMA neurology*, *70*(7), 845-851.

Papa, L., Ramia, M. M., Kelly, J. M., Burks, S. S., Pawlowicz, A., & Berger, R. P. (2013). Systematic review of clinical research on biomarkers for pediatric traumatic brain injury. *Journal of neurotrauma*, *30*(5), 324-338.

Ponsford, J., & Kinsella, G. (1992). Attentional deficits following closed-head injury. *Journal of Clinical and Experimental Neuropsychology, 14*, 822-838.

Povlishock, J. T., & Katz, D. I. (2005). Update of neuropathology and neurological recovery after traumatic brain injury. *The Journal of head trauma rehabilitation*, *20*(1), 76-94.

Quigley, M., Cordes, D., Turski, P., Moritz, C., Haughton, V., Seth, R., & Meyerand, M. E. (2003). Role of the corpus callosum in functional connectivity.*American journal of neuroradiology*, *24*(2), 208-212.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, 98,* 676-682.

Ramnani, N., Behrens, T. E. J., Penny, W., & Matthews, P. M. (2004). New approaches for exploring anatomical and functional connectivity in the human brain. *Biological Psychiatry, 56,* 613-619.

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *Journal of Consulting Psychology*, *19,* 393-394.

Roebuck-Spencer, T., & Sherer, M. (2008). Moderate and severe traumatic brain injury. In J. E. Morgan & J. H. Ricker (Eds.), *Textbook of Clinical Neuropsychology* (pp. 411-429). New York, NY: Taylor & Francis.

Sanchez-Carrion, R., Gomez, P. V., Junque, C., Fernández-Espejo, D., Falcon, C., Bargallo, N., ... & Bernabeu, M. (2008). Frontal hypoactivation on functional magnetic resonance imaging in working memory after severe diffuse traumatic brain injury. *Journal of neurotrauma*, *25*(5), 479-494.

Sexton, C. E., Kalu, U. G., Filippini, N., Mackay, C. E., & Ebmeier, K. P. (2011). A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiology of aging*, *32*(12), 2322-e5.

Scheibel, R. S., Newsome, M. R., Steinberg, J. L., Pearson, D. A., Rauch, R. A., Mao, H., ... & Levin, H. S. (2007). Altered brain activation during cognitive control in patients with moderate to severe traumatic brain injury. *Neurorehabilitation and Neural Repair*, *21*(1), 36-45.

Sharp, D. J., Beckmann, C. F., Greenwood, R., Kinnunen, K. M., Bonnelle, V., De Boissezon, X., ... & Leech, R. (2011). Default mode network functional and structural connectivity after traumatic brain injury. *Brain*, *134*(8), 2233-2247.

Sidaros, A., Enberg, A. W., Sidaros, K., Liptrot, M. G., Herning, M., Peterson, P., et al. (2008). Diffusion tensor imaging during recovery from severe traumatic brain injury and relation to clinical outcome: a longitudinal study. *Brain, 131,* 559-572.

Sidaros, A., Skimminge, A., Liptrot, M. G., Sidaros, K., Engberg, A. W., Herning, M., ... & Rostrup, E. (2009). Long-term global and regional brain volume changes following severe traumatic brain injury: a longitudinal study with clinical correlates. *Neuroimage, 44*(1), 1-8.

Smith, D., & Meaney, D. (2000). Axonal damage in traumatic brain injury. *Neuroscientist, 6,* 483-495.

Snyder, A. Z., & Raichle, M. E. (2012). A brief history of the resting state: The Washington University perspective. *Neuroimage*, *62*(2), 902-910.

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*, *17*(3), 1429-1436.

Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., He, Y., Yan, C.G., Zang, Y.F., 2011. REST: A Toolkit for Resting-State Functional Magnetic Resonance Imaging Data Processing. *PLoS ONE 6,* e25031.

Sours, C., Zhuo, J., Janowich, J., Aarabi, B., Shanmuganathan, K., & Gullapalli, R. P. (2013). Default mode network interference in mild traumatic brain injury–A pilot resting state study. *Brain research*, *1537*, 201-215.

Sporns, O. (2012). The human connectome: A complex network. *Schizophrenia Research*, *136*, S28.

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569-12574.

Stevens, M. C., Lovejoy, D., Kim, J., Oakes, H., Kureshi, I., & Witt, S. T. (2012). Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. *Brain imaging and behavior*, *6*(2), 293-318.

Stuss, D. T. & Levine, B. (2002). Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annual Review of Psychology*, *53*, 401-433.

Szaflarski, J. P., Schmithorst, V. J., Altaye, M., Byars, A. W., Ret, J., Plante, E., & Holland, S. K. (2006). A longitudinal functional magnetic resonance imaging study of language development in children 5 to 11 years old. *Annals of neurology*, *59*(5), 796-807

Thornhill, S., Teasdale, G. M., Murray, G. D., McEwen, J., Roy, C. W., & Penny, K. I. (2000). Disability in young people and adults one year after head injury: prospective cohort study. *BMJ: British Medical Journal*, *320*(7250), 1631.

Tomasi, D., & Volkow, N. D. (2011). Aging and functional brain networks. *Molecular psychiatry*, *17*(5), 549-558.

Vanhaudenhuyse, A., Melanie Boly, M. D., Bruno, M. A., Gosseries, O., Demertzi, A., Kirsch, M., ... & Soddu, A. (2012). Functional Imaging and Impaired Consciousness. In *Coma and Disorders of Consciousness* (pp. 25-34). Springer London.

Van den Heuvel, M., Mandl, R., Luigjes, J., & Pol, H. (2008). Microstructural organization of the cingulum tract and the level of default mode functional connectivity. *The Journal of Neuroscience, 28* (43), 10844-10851.

Venkatesan, U. M., Dennis, N. A., & Hillary, F. G. (2014). Chronology and chronicity of altered resting-state functional connectivity after traumatic brain injury. *Journal of Neurotrauma,* (ja).

Wang, L., Zang, Y., He, Y., Liang, M., Zhang, X., Tian, L., ... & Li, K. (2006). Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. *Neuroimage*, *31*(2), 496-504.

Wang, J. Y., Bakhadirov, K., Devous, M. D., Abdi, H., McColl, R., Moore, C., et al. (2008). Diffusion tensor tractography of traumatic diffuse axonal injury. *Archives of Neurology, 65*(5), 619-626.

Wang, J. Y., Bakhadirov, K., Abdi, H., Devous, M. D., de la Plata, C. M., Moore, C., ... & Diaz-Arrastia, R. (2011). Longitudinal changes of structural connectivity in traumatic axonal injury. *Neurology, 77*(9), 818-826.

Wechsler, D. (1997). WAIS-III: Wechsler Adult Intelligence Scale (3rd ed.). San Antonio, TX: The Psychological Corporation.

Werner, C., & Engelhard, K. (2007). Pathophysiology of traumatic brain injury. *British journal of anaesthesia*, *99*(1), 4-9.

Wilde, E. A., Chu, Z., Bigler, E. D., Hunter, J. V., Fearing, M. A., Hanten, G. et al. (2006). Diffusion Tensor Imaging in the Corpus Callosum in children after moderate to severe traumatic brain injury. *Journal of Neurotrauma, 23,* 1412-1426.

Wilson, J. T., Hadley, D. M., Wiedmann, K. D., & Teasdale, G. M. (1995). Neuropsychological consequences of two patterns of brain damage shown by MRI in survivors of severe head injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 59, 328*-331.

Wilson, M., Morgan, P. S., Lin, X., Turner, B. P., & Blumhardt, L. D. (2001). Quantitative diffusion weighted magnetic resonance imaging, cerebral atrophy, and disability in multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 70,* 318-322.

Wilson, J. T. L., Pettigrew, L. E. L., & Teasdale, G. M. (1998). Structured interviews for the Glasgow Outcome Scale and Extended Glasgow Outcome Scale: Guidelines for their use. *Journal of Neurotrauma, 15,* 573–585.

Xu, J., Rasmussen, I., Lagopoulos, J., & Haberg, A. (2007). Diffuse axonal injury in severe traumatic brain injury visualized using high-resolution diffusion tensor imaging. *Journal of Neurotrauma, 24*(5), 753-765.

Yan C and Zang Y (2010) DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. *Front. Syst. Neurosci*. 4:13.

Ylvisaker, M., & Feeney, T. J. (1996, August). Executive functions after traumatic brain injury: Supported cognition and self-advocacy. In *Seminars in speech and language* (Vol. 17, No. 03, pp. 217-232). © 1996 by Thieme Medical Publishers, Inc..

APPENDIX A

Functional and Cognitive Outcome Measures

Functional Outcome Measures:

Functional Status Exam (FSE) (Dikmen et al., 2001). This measure, designed as a semi-structured interview, evaluates activities of daily living in 3 domains: physical, social, and psychological functioning, in individuals with TBI. Severity within each area is measured along a four-point ordinal rating scale, ranging from zero to three, where lower ratings indicate minimal changes as compared to pre-injury functional ability. The values are summed, with scores ranging from 10 to 40, and a score of 41 designates the patient died prior to the outcome assessment.

Glasgow Outcome Scale—Extended (GOSE) (Wilson, Pettigrew, & Teasdale, 1998). The GOSE is a brief-screening questionnaire designed to assess patient's ability to follow commands, perform activities of daily living, work, travel, and participate in recreational activities after a TBI. Total score ranges from one to eight, with higher scores associated with better outcome. Specifically, score of 2 suggests that the patient is in persistent vegetative state, scores of 3 and 4 indicate a severe disability, 5 and 6 indicate moderate disability, and 7 and 8 indicate good recovery.

Cognitive Outcome Measures:

California Verbal Learning Test—Second Edition (CVLT-II) (Delis, Kramer, Kaplan, & Ober, 2000): This measure assesses learning and recall (immediate and delayed; and free/cued recall) based on the oral presentation of a 16-word list (List A) over five trials, to facilitate

learning. An interference list consisting of another 16-word list is presented for one trial. This is followed by a short delay free-recall trial and cued-recall of the initial list (List A). Twenty minutes later, the participant is asked to recall List A (free and cued recall).

Dodrill Stroop (Dodrill, 1978). The Dodrill Stroop Color-Naming condition measures the ability to selectively attend to meaningful information while inhibiting an automatic response, i.e. name the color of the printed words as quickly as they can and not read the word. Time to complete the task and errors were examined.

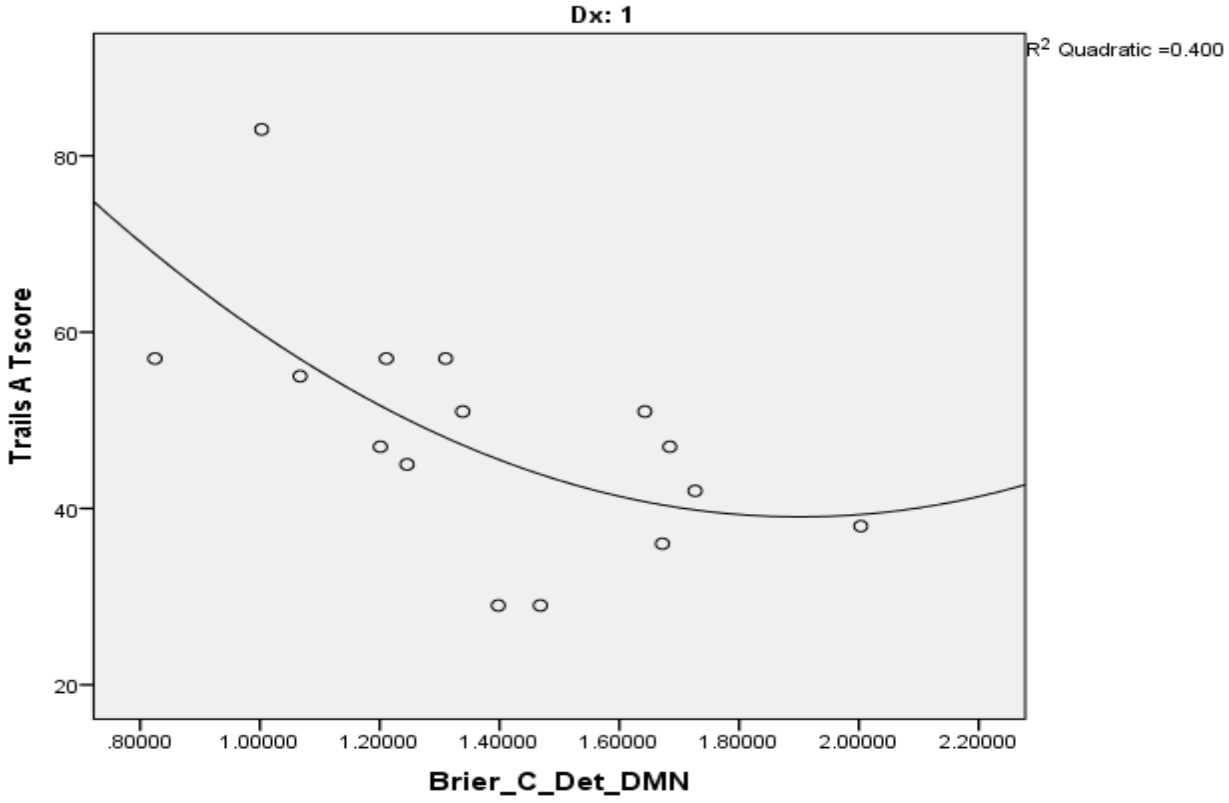
Trail Making Test (TMT) (Reitan, 1955). The TMT consists of two parts, A and B. Trail Making Test A (TMTA) is a processing speed task that requires the participant to draw lines to connect consecutively numbered circles (1 to 2, 2 to 3, 3 to 4, and so on) as quickly as they can. The total time to complete the task is recorded.

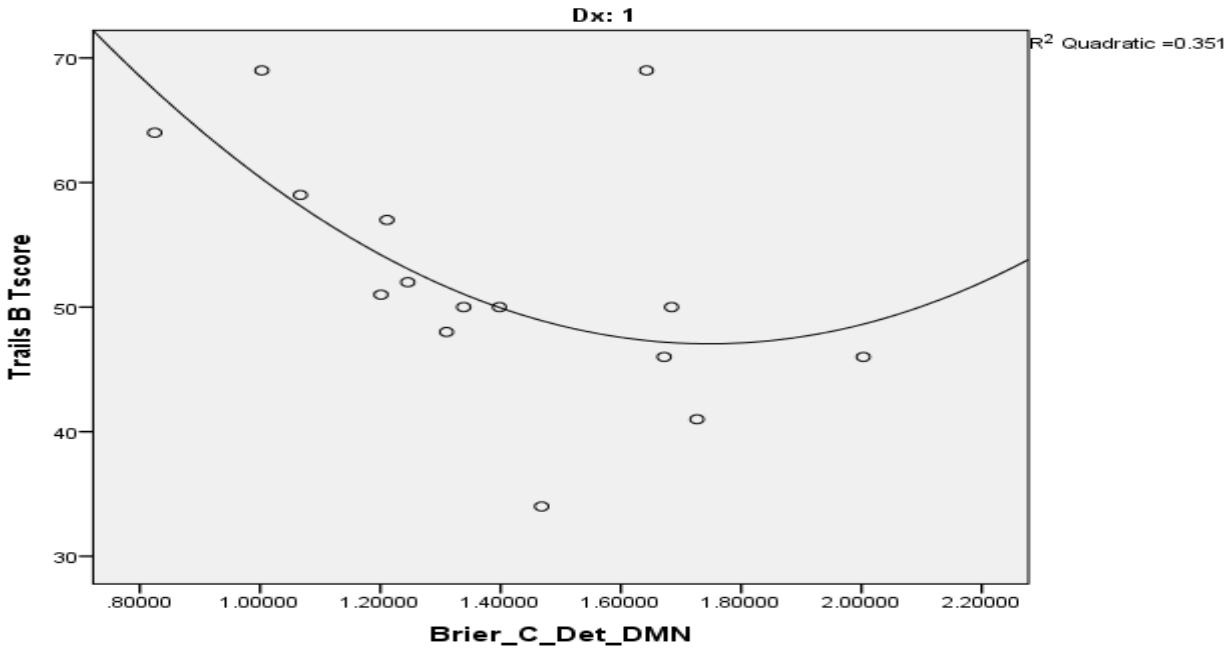
Trail Making Test B (TMTB) measures components of visual scanning, processing speed, and mental flexibility. In this test, participants are asked to alternate between sequentially numbers and alphabets (1 to A, A to 2, 2 to B, and so on) as quickly as they can. Again, the total time to complete the task is recorded.

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III, select subtests) (Wechsler, 1997). From the WAIS-III, Digit Span, Digit Span Backward (DSB), Digit Symbol Coding (DSC), and Symbol Search (SS) were administered. Digit span is a simple attention task where the participant is asked to attend to a string of digits presented orally and repeat them forwards.

In the latter half of this test, participants are presented digits orally and asked repeat them backwards (DSB). Digit Symbol Coding (DSC) is a visual-motor processing speed task where the participant is instructed to write in the number associated with presented symbols based on a key provided at the top of the page during the allotted time. Symbol Search (SS) is a similar task assessing visual-discrimination and visual-motor processing speed in which the participant is instructed to discriminate between symbols appearing in different groups by marking “yes” if a target symbol appears in the group of symbols from which they are to discriminate from or “no” if the target symbol does not appear in this group of symbols.

APPENDIX B
Additional Analyses




Dx: 1
R2 Quadratic =0.351
Trails B Tscore
70
60
50
40
30
.80000
1.00000
1.20000
1.40000
1.60000
1.80000
2.00000
2.20000
Brier_C_Det_DMN