CONNECTIVITY WITHIN THE DEFAULT MODE NETWORK AFTER TRAUMATIC AXONAL INJURY

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DEDICATION

To my father, Anastacio Arenivas, who instilled in me the drive to do my best and provided me the support necessary to complete my educational pursuits.

In loving memory of Allison Oubre, the definition of a true friend, a patriot, and someone I can always count on for strength. She still provides her loved ones the motivation to do better and be better to each other.

CONNECTIVITY WITHIN THE DEFAULT MODE NETWORK AFTER TRAUMATIC AXONAL INJURY

by

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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, 2011

ACKNOWLEDGEMENTS

There are many people who I would like to thank for their guidance and support throughout my doctoral program and in the completion of my dissertation. First, I want to express my sincere gratitude to my dissertation chair, Dr. Carlos Marquez de la Plata, whose generosity, patience, and inspiration will never be forgotten. It is impossible to repay him the time, understanding, and care that he put into working with me throughout this research. His expertise and creativity made the process productive and enjoyable.

I am extremely grateful to the members of my All-Star dissertation committee. I deeply admire and respect each of them and I am humbled for the opportunity to have worked with such a remarkable team. I am honored that Dr. Ramon Diaz-Arrastia and the North Texas Traumatic Brain Injury Research Center staff permitted me to use their images for my research. Dr. Diaz-Arrastia's wisdom, energy, and direction across the dissertation are greatly appreciated. Throughout the dissertation and as I met program milestones, Dr. Betsy Kennard never failed to inspire me with her warmth, grace, and enthusiasm. I am also thankful for Dr. Munro Cullum and the encouragement and wealth of knowledge he shared across so many areas of my research and program. I owe special thanks to Dr. Jeff Spence, who provided invaluable assistance and statistical expertise in my learning and understanding of highly technical concepts. As a whole, my

committee never ceased to deliver challenging, creative, optimistic, and accommodating ideas, all of which improved this project.

It would be an unforgivable error of omission not to thank the "Los Group" for their selfless dedication and flexibility. I am so impressed by the tireless readiness put forth by Kamini Krishnan, Carlee Culver, and Chris Bosworth to make our lab's research happen through our motto, "there's gotta be a way [to do that]." I look forward to their future projects.

I would also like to acknowledge a special pair of individuals who substantially contributed to my clinical training, never tired of my questions, and provided support beyond expectation. Countless thanks are due to Dr. Lana Harder for her ongoing mentorship and promotion of my professional growth. I am blessed to know and to have worked with such a considerate, brilliant, and amazing person across clinical and research endeavors. For Dr. Crista Wetherington's limitless compassion and inspiration to think outside of the box, I am forever grateful.

Finally, I must thank my family, friends, and significant other, Eli Malamut, for their love, understanding, and unfailing support without which my achievements would not be complete.

June 2011

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Publication No. _____

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The University of Texas Southwestern Medical Center at Dallas, 2011

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Traumatic axonal injury (TAI) is a common consequence of TBI in which the brain's white matter is mechanically torn by deceleration and rotational forces. Injury to axons after this type of injury causes significant impairments in cognitive functioning, but the association between disruption of structural connections (i.e., axons) and the brain's functional connectedness is not well understood. Studies examining integrity of white matter after TAI have found significant compromise to structures likely involved in the connectivity of the default mode network (DMN), a reliably elicited functional neural network with clinical implications. The discriminant and prognostic utilities of the DMN following traumatic axonal injury (TAI) have not been previously investigated.

This broad investigation was comprised of two related studies examining the utility of neuroimaging modalities as biomarkers of TAI. Resting-state magnetic resonance imaging (RS-MRI) and diffusion tensor imaging (DTI) sequences were acquired 6-11 months post-injury using a 3T scanner from 25 patients with TAI and 17 controls. Functional and neurocognitive outcomes were assessed the same day. The first study examined the utility of three approaches analyzing DMN integrity using RS-fMRI. The purpose was to identify the utility of each approach to distinguish between healthy and brain-injured individuals, and determine whether observed differences have clinical significance. The second study integrated functional and structural connectivity measures of the DMN to determine whether compromise to functional connectivity within this network can be explained by the degree of white matter compromise commonly observed after TAI.

The first study concluded that connectivity within the DMN is compromised after TAI, as all three methods demonstrated good ability to discriminate between healthy and injured brains. The second study suggests the functional disconnectedness within the DMN is in part due to compromise in structural connections observed after TAI. Neither the degree of functional or structural compromise to the DMN has clinical implications in TAI. In general, the two investigations suggest the DMN undergoes compromise after TAI, and connectivity between nodes of the network are valid markers of axonal injury.

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LIST OF ABBREVIATIONS

BOLD	Blood Oxygen-Level Dependent
COWAT	Controlled Oral Word Association Test
CVLT-II	California Verbal Learning Test, Second Edition
CT	Computed Tomography
DMN	Default Mode Network
DSB	Digit Span Backward
DSC	Digit Symbol Coding
DTI	Diffusion Tensor Imaging
FC	Functional Connectivity
FMRI	Functional Magnetic Resonance Imaging
FSE	Functional Status Exam
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale - Extended
IFO/ILF	Inferior Fronto-Occipito Fasciculus/Inferior Longitudinal Fasciculus
LD	Long Delay
LLPC	Left Lateral Parietal Cortex
MFC	Medial Frontal Cortex
MRI	Magnetic Resonance Imaging
PCC	Posterior Cingulate Cortex

PPMC	Pearson Product Moment Correlation
RS-fcMRI	Resting-State Functional Connectivity Magnetic Resonance Imaging
ROI	Region of Interest
RLPC	Right Lateral Parietal Cortex
SD	Short Delay or Standard Deviation
SLF	Superior Longitudinal Fasciculus
TAI	Traumatic Axonal Injury
TBI	Traumatic Brain Injury
TMTA	Trail Making Test A
TMTB	Trail Making Test B

SECTION I: STUDY 1

Analysis of Three Approaches to Investigating Functional Compromise to the Default Mode Network after Traumatic Axonal Injury

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Abstract

The default mode network (DMN) is a reliably elicited functional neural network with potential clinical implications. Its discriminant and prognostic utility following traumatic axonal injury (TAI) have not been previously investigated. The present study used three approaches to analyze DMN integrity, including a whole-brain analysis [A1], network-specific analysis [A2], and between-node (edge) analysis [A3]. The purpose was to identify the utility of each method in distinguishing between healthy and brain-injured individuals, and determine whether observed differences have clinical significance. Resting-state fMRI was acquired using 3T MRI from 25 patients with TAI and 17 controls. Patients were scanned 6-11 months post-injury, and functional and neurocognitive outcomes were assessed the same day. Using all three approaches, TAI subjects revealed significantly weaker functional connectivity (FC) than controls. Clinical outcomes

were not correlated with FC using any approach. Results indicate that compromise to the integrity of the DMN after TAI can be identified using three approaches to analyzing resting-state FC; however, the degree of functional compromise to this network, as measured in this study, may not have clinical implications in chronic TAI.

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Introduction

The disease burden of traumatic brain injury (TBI), including functional and cognitive deficits, makes it a considerable public health concern in modern societies. In the United States alone, the annual incidence of TBI is estimated to range between 92 and 250 per 100,000 (Thurman et al., 1999). Brain injuries are estimated to account for 19.5% of all hospital admissions in the United States (Centers for Disease Control and Prevention, 2006). Traumatic axonal injury (TAI) most commonly occurs in motor vehicle collisions (MVCs), and is characterized by microscopic axonal lesions that commonly appear in subcortical white matter of patients with acceleration-deceleration type TBI (Buki & Povlishock, 2006). TAI is the predominant mechanism of injury in 40 to 50% of TBIs requiring hospital admission, and it is likely that TAI is a component of injury in all cases of TBI resulting from high-speed motor vehicle collisions (Meythaler et al., 2001).

Need for TBI Imaging Biomarkers

Despite numerous clinical trials, there are currently no effective treatments for TBI. Results of animal models have been successful but do not directly translate to human models due to the heterogeneous nature of human TBI (e.g., heterogeneity in injury location, severity, and mechanism) (Doppenberg et al., 1997). Biomarkers of TAI may aid in the selection of patients for participation in clinical trials of TAI-directed therapies or as surrogate measures in early stage

clinical studies. Neuroimaging biomarkers of TAI may be helpful in reducing heterogeneity of injury location by distinguishing between temporal or frontal lobe injuries, reducing variability of injury type (i.e., white or gray matter injury), and may be used to distinguish between different levels of injury severity. Biomarkers require discriminant and construct validity in order to be a useful measure of injury severity or a surrogate for clinical outcome. The utility of Magnetic Resonance Imaging (MRI) as a potential tool to obtain biomarkers in TAI is promising. For instance, the use of fluid-attenuated inversion-recovery (FLAIR) MRI has shown sensitivity to lesions in white matter after TAI, and the degree of compromise to white matter correlates to functional outcome (Marquez de la Plata et al., 2007). Diffusion tensor imaging (DTI) has also demonstrated sensitivity to compromise in structural connectivity (i.e., white matter) after TAI in the acute and chronic stage of injury (Basser et al., 1994; Hüppi et al., 2001; Marquez de la Plata et al., 2011; Wang et al., 2008). Furthermore, the degree of compromise to white matter detected by DTI correlates to functional outcome as well as neurocognitive outcome.

An advanced fMRI analysis involves examining the temporal correlation of blood oxygenation level-dependent (BOLD) signal during resting-state. Resting-state functional connectivity MRI (RS-fcMRI) offers the potential to investigate the neuronal connectivity of the brain by examining the coherence between spontaneous fluctuations that occur over time in distal gray matter areas

(Fox & Raichle, 2007; Friston et al., 1993; Horwitz, 2003; Skudlarski et al., 2008). RS-fcMRI may detect compromise to functionally connected regions and shows promise as a biomarker in clinical populations with compromise to white matter. Wang et al. (2006) found decreased functional connectivity between the right hippocampus and the medial prefrontal cortex, ventral anterior cingulate cortex right inferotemporal cortex, right cuneus extending into precuneus, left cuneus, right superior and middle temporal gyrus, and posterior cingulate cortex (PCC). They also found functional connectivity differences between the left hippocampus and the right lateral prefrontal cortex in AD. A recent study by Marquez de la Plata et al. (2011) suggests that RS-fcMRI may be useful in studying TBI as well, particularly given this population tends to have compromised anatomical/structural connections. They showed that patients with TAI demonstrated significantly lower interhemispheric functional connectivity for the anterior cingulate cortex and hippocampus when compared to controls.

DMN in TBI

Numerous studies have investigated RS-fcMRI in healthy controls and found consistent resting-state networks (Cordes et al., 2001; Damoiseaux et al., 2006; Lowe et al., 2010). The DMN is a reliably-elicited, high metabolism, and robust resting state brain network that may be involved in important functions of human cognition (Biswal et al., 1995; Cordes et al. 2001; Greicius et al., 2003; Raichle et al., 2001; Raichle & Snyder, 2007) The precise functions subserved by

the DMN are still largely unknown, but collectively, the DMN is considered to be involved in the integration of autobiographical memory retrieval, envisioning the future, perspective-taking, and "mind wandering" (Buckner et al., 2008; Mason et al., 2007). It is deactivated *during* cognitively demanding tasks (Raichle et al., 2001; Shulman et al., 1997); however, the aforementioned functions are *active* in the resting brain.

The recognition of the importance of the DMN has increased interest in resting-state correlations as a tool for defining functional systems in the human brain (Greicius et al., 2004). Functional connectivity patterns among healthy individuals at rest demonstrate a link between various regions known to be functionally connected, including the posterior cingulate cortex (PCC), medial frontal cortex (MFC), and lateral parietal cortices (Raichle et al., 2001). While little is presently known about the pattern of connectivity in the DMN following TAI, compromises to functional connectivity between nodes of the DMN have been shown to occur in various clinical conditions, such as Alzheimer's disease (Firbank et al., 2007; Greicius et al., 2004; Greicius et al., 2007; He et al., 2007, Rombouts et al., 2005; Sorg et al., 2007; Wang et al., 2006;), major depression (Liang et al., 2006), schizophrenia (Bluhm et al., 2007; Garrity et al., 2007; Pomarol-Clotet et al., 2008; Swanson et al., 2011; Zhou et al., 2007), post-traumatic stress disorder (Bluhm et al., 2006; Lanius et al., 2010), and mild TBI (Mayer et al., 2011). In patients with AD, reduced connectivity between medial

prefrontal cortex (MPFC) and PCC regions of the DMN is associated with aging, and the anterior region of the DMN is correlated with cognitive decline (Broyd et al., 2009). Additionally, Hedden et al. (2009) found that functional disruption of the default mode network (DMN) is correlated with amyloid accumulation in Alzheimer's disease (AD).

Neurocognitive Outcome after TBI

TBI typically results in a complex mixture of focal and diffuse axonal injuries (Gennarelli, 1986). Despite variability in the pattern of cognitive dysfunction in individual patients with moderate to severe TBI, the most commonly affected areas of cognitive functioning include attention, executive functioning, processing speed, and learning and memory.

Impairment in attention and information processing speed are prevalent after TBI across all levels of severity. Patients with TBI consistently demonstrate impairment on tests of divided attention, simple and choice reaction time, color naming, and symbol- digit coding (Mathias & Wheaton, 2007; Ponsford & Kinsella, 1992; Roebuck-Spencer & Sherer, 2008; Stuss et al., 1989). Memory difficulties are also common after TBI. Memory problems have been noted to occur across different aspects of memory processing, including encoding, consolidation, and retrieval (Curtiss et al., 2001; Levin, 1990; Levin et al., 1976; Niogi et al., 2008).

Executive dysfunction following TBI is common and considered to be one of the critical cognitive determinants of independent functioning and employability (Crepeau & Shezer, 1993; Hart et al., 2003; Roebuck-Spencer and Sherer, 2008; Sherer et al., 2003). Deficits in performance on tasks of verbal and design fluency, conceptual reasoning/flexibility, working memory, and planning have been reported (Christodoulou et al., 2001; Roebuck-Spencer & Sherer, 2008; Scheid et al., 2006).

The relationship between DMN connectivity and cognitive function is not yet well understood, but studies among healthy participants suggest the degree of functional connectivity of the DMN is associated with aspects of neurocognitive function. Sambataro et al. (2010) investigated functional connectivity within the DMN in older and younger participants during an n-back working memory task with increasing task load. Their findings revealed that older adults showed decreased connectivity and "ability to suppress low frequency oscillations" of the DMN during the task. Additionally, they found that in older adults the strength of the functional connectivity between the PCC with MFC correlated positively with working memory and was lower than younger participants. Damoiseaux et al. (2007) found a correlation between reduced activity of the "anterior part of the DMN" and difficulties in executive functioning (i.e., inhibition and set-shifting) in older adults compared to younger participants. Deactivation of DMN has also

been observed during semantic classification (Lustig et al., 2003) and verbal memory tasks in the elderly (Grady et al., 2006).

Objectives

The goals of this investigation were to: (1) identify the utility of three fcMRI approaches to distinguish between healthy and chronic brain-injured individuals, and (2) determine whether observed differences have clinical significance by assessing the relationship between the integrity of functional connectivity and neuropsychological outcomes. We hypothesized that functional connectivity of the DMN, using all three approaches, would be greater for controls than in patients following TBI. We also hypothesized that functional integrity measures from all three approaches would correlate with functional and neurocognitive outcome.

Materials and Methods

Participants

Data were collected as part of an investigation at the North Texas Traumatic Brain Injury Research Center within the University of Texas Southwestern Medical Center at Dallas. Twenty-five patients with TBI were recruited from Parkland Health and Hospital Systems, Dallas, Texas from 2006 to 2008. Inclusion criteria required that patients: 1) sustained closed head traumatic brain injury with a mechanism of injury consistent with TAI (i.e., high-velocity motor vehicle collision or MVC-pedestrian collision), 2) had either an abnormal

CT scan on admission or a post-resuscitation GCS 3-12 if CT was normal, 3) were hemodynamically stable so that transfer to the scanner was clinically safe, 4) enrolled within seven days of injury, and 5) were at least16 years old.

Exclusion criteria included: 1) Patients with previous brain injury or preexisting neurologic disorders (e.g., epilepsy, brain tumors, meningitis, cerebral palsy, encephalitis, brain abscesses, vascular malformations, cerebrovascular disease, Alzheimer's disease, multiple sclerosis, HIV, encephalitis), 2) any CT-visible focal low, mixed, or high density lesion 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) history of premorbid disabling condition that could interfere with outcome assessments, 7) previous hospitalization for TBI greater than one day, 8) contraindication to MRI (incompatible metal implants), 9) membership in a vulnerable population (i.e., prisoner), or 10) pregnancy.

Seventeen healthy volunteers of similar age- and gender were recruited as controls. All healthy volunteers had good general health and no known neurocognitive or psychiatric disorders. Informed consent was obtained from all participants or their legally authorized representative.

Functional and Structural Magnetic Resonance Image Acquisition and Processing

Image Acquisition and Processing. Functional and anatomical magnetic resonance images were obtained for each participant using either a Siemens Trio 3

Tesla (T) (Siemens AG, Erlangen, Germany) or a General Electric Signa Excite 3T (General Electric Healthcare, Milwaukee, Wisconsin) scanner. Resting state echo-planar images recorded BOLD fluctuation over 128 time-points two seconds apart (TR=2). Echo-planar image volumes were acquired at 36 axial slice locations for whole brain coverage. Specific echo-planar image data acquired by the Siemens scanner were obtained with single-shot gradient-recalled pulse sequence, TR = 2 seconds, echo time = 25 milliseconds, flip angle, 90^{o}; matrix, 64 X 64; field of view (FOV) 210 mm, and 3.5 mm slice thickness. Echo-planar sequence parameters for the GE scanner were comparable, as data were obtained with single-shot gradient-recalled pulse sequence, TR = 2 seconds, echo time = 25 milliseconds, flip angle 90^{o}; matrix, 64 X 64; field of view 210 mm, and 3.5 mm slice thickness. Participants were asked to keep their eyes open and not think of anything during image acquisition.

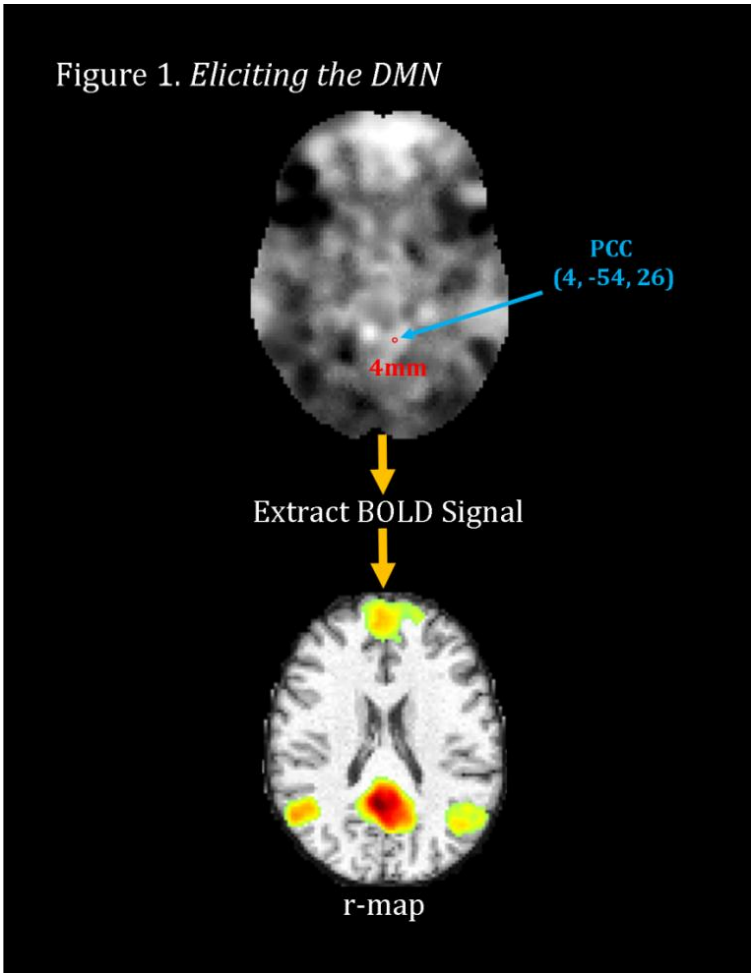
High-resolution T1-weighted structural images acquired by the Siemens scanner were acquired using MP-RAGE with slice thickness 1.0mm, FOV of 240 mm, and TE/TI/TR 4/900/2250ms, flip angle 9^{o}, NEX 1. High-resolution T1-weighted structural images acquired by the GE scanner were acquired using fast spoiled gradient-recalled (FSPGR) acquisition in the steady state with slice thickness 1.3 mm, FOV 240-280 mm, TR/TE 8.0/2.4 ms, flip angle 25^{o}, and NEX 2. All patient images were acquired 6 to 10-months post-injury.

MRI images were preprocessed using Statistical Parametric Mapping 5 (SPM5). Preprocessing of fMRI data included: coregistration, segmentation, normalization, smoothing, detrending, and temporal filtration. Images were converted from DICOM to Analyze readable format. The first four volumes were then excluded from further analysis. T1 and fMRI images were coregistered to each other. Next, fMRI images were segmented, where masks for gray matter, white matter, and CSF were created from T1 images. Normalization of echo-planar and T1 images to common space was accomplished with a resolution of 2 x 2 x 2 mm in order to account for differences in brain size and shape variations among participants. Spatial smoothing and detrending of the fMRI images took place to augment signal to noise ratio. Smoothing the fMRI data using 2 x 2 x 2 mm smoothing kernel reduced the spatial resolution. Detrending subtracted the background noise. Last, given that BOLD signal fluctuations are low-frequency waveforms, temporal filtration of the images was conducted to exclude the higher waveforms or frequencies. Low frequency oscillations in BOLD between 0.01-0.12 Hz were retained for analysis.

Description of Three Approaches

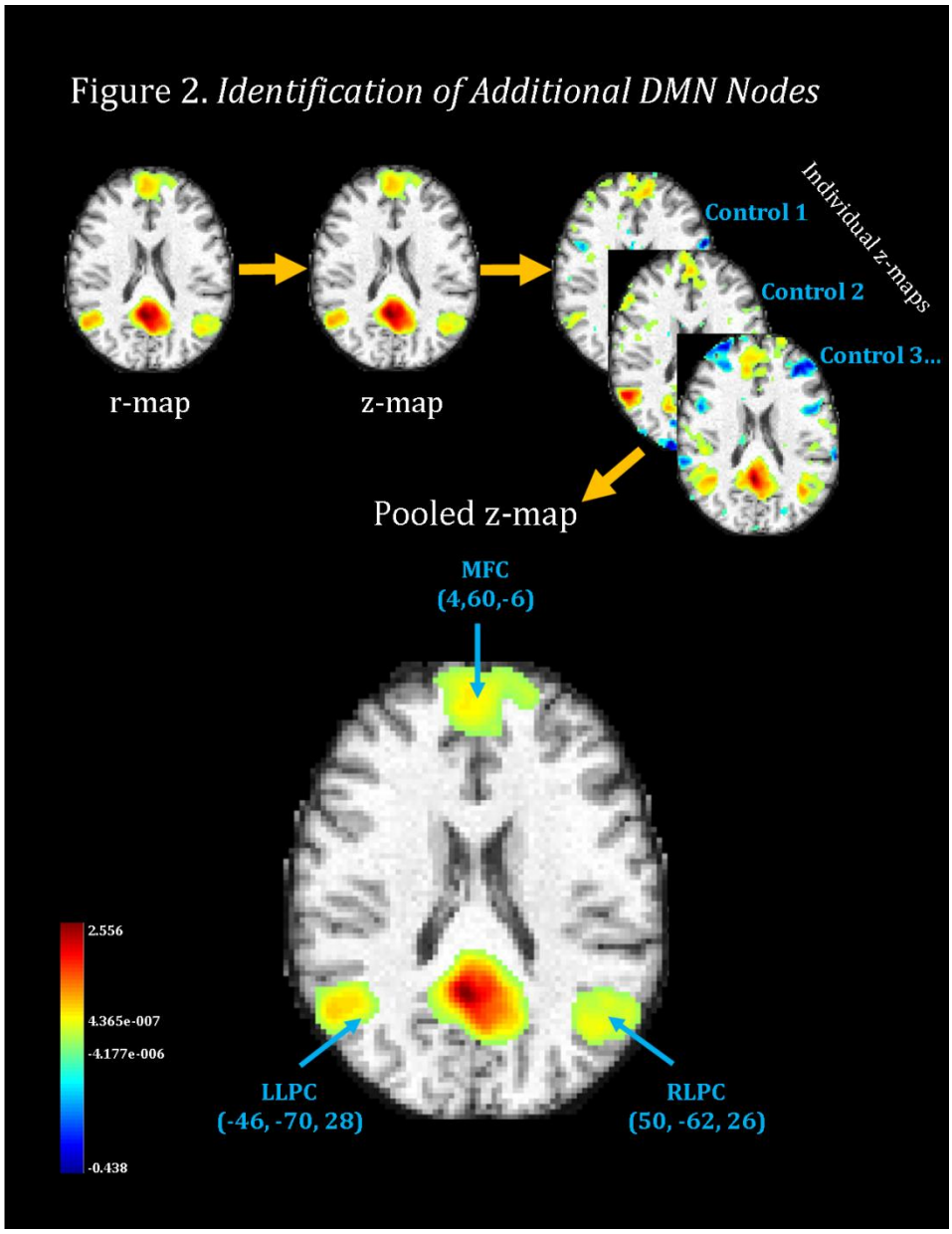
The present study utilized three approaches to analyze DMN integrity, which included a whole brain spatial correlation coefficient analysis [A1], a network-specific integrity measure [A2], and between-node (edge) correlations [A3]. In all three approaches, the following steps were used to elicit the DMN in

the healthy controls. Given that the PCC has been shown to play a central role in the DMN, (Buckner et al., 2008; Fransson & Marrelec, 2008; Greicius et al., 2009; Raichle et al., 2001; Shulman et al., 1997), a correlation map was computed using a reference seed region with a 4mm radius in the PCC. MNI coordinates for the PCC (4, -54, 26) were based on a previous study (Hedden et al., 2009) with an alteration of the x-coordinate value (i.e., from 0 to 4) to ensure that coordinate placement on the Cereb Cortex and avoid placing a region of interest (ROI) in cerebral spinal fluid between hemispheres. Among uninjured controls, we used the Resting State fcMRI Data Analysis Toolkit (REST; Beijing Normal University), to create spatial maps (i.e., r-maps) containing brain voxels with BOLD signal that fluctuated synchronously with BOLD signal in the PCC (i.e., correlated above a specified probability threshold of 0.05).



The following steps were specific to approaches 2 and 3. Previously obtained spatial correlation r-maps were converted to z-maps using Fischer's Z transformation [See Figure 2]. All of the z-maps for controls were pooled together to create an average z-map reflecting the spatial distribution and the strength of correlations with the PCC among healthy brains. The resulting pooled z-map was used to identify the peak voxels of the remaining nodes of the default network in this dataset. From this sample of controls, the coordinates of nodes of the DMN

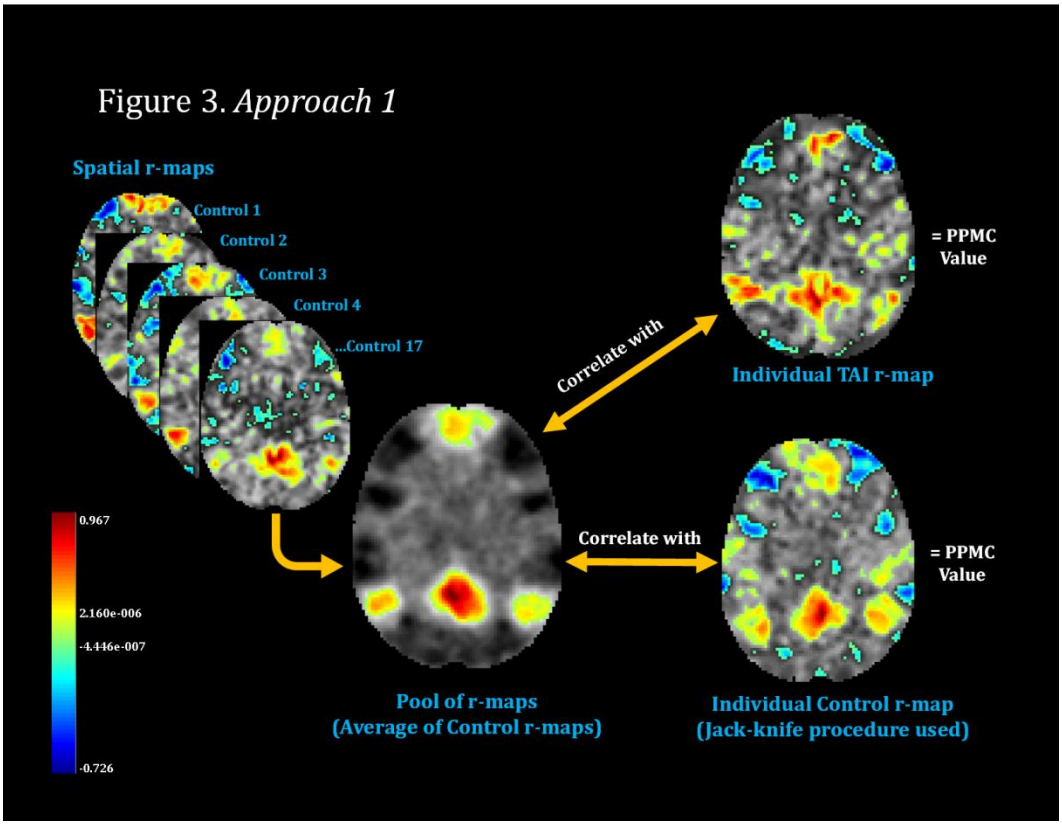
are: medial frontal cortex (MFC) (4, 60, -6), left lateral parietal cortex (LLPC) (-46, -70, 28), and right lateral parietal cortex (RLPC) (50, -62, 26) [See Figure 2]. These coordinates were used as center points for ROIs with a 4 mm radius from which BOLD time series data were extracted to determine functional connectivity between nodes required for A2 and A3.



Whole Brain Analysis

As previously mentioned, three approaches were employed to analyze DMN integrity. A1 was the broadest approach in that it assessed the synchrony of BOLD between the PCC and all voxels throughout the brain. In the TAI group,

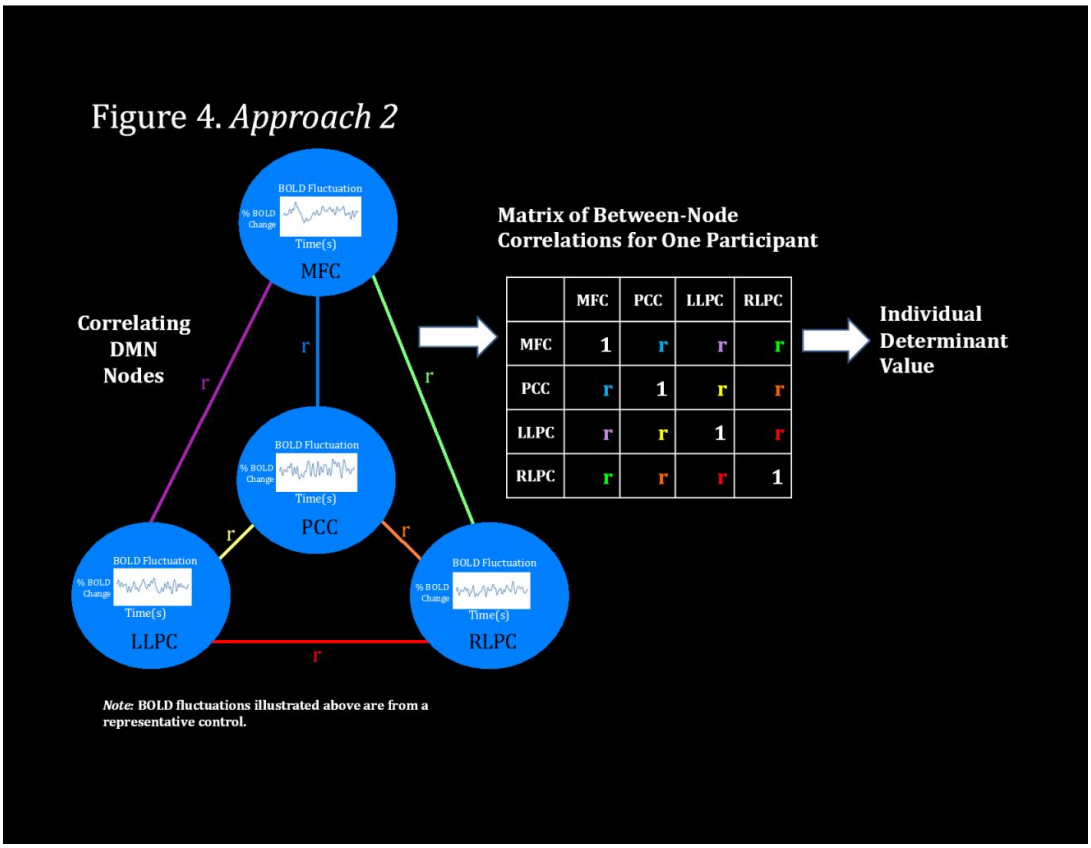
each individual's PCC spatial correlation map was correlated to the average of the control group's PCC spatial correlation maps, resulting in a single correlation value [i.e., Pearson Product Moment Correlation (PPMC)]. In the control group, each individual's PPMC was obtained by correlating their PCC spatial correlation map to the average of the control group's PCC spatial correlation map excluding their map (i.e., jackknifing procedure) in order to avoid artificially inflating the PPMC. Fisher's Z-transformation was applied to all PPMC values in order to normally distribute the values for group comparisons [See Figure 3].



Network-Specific Analysis

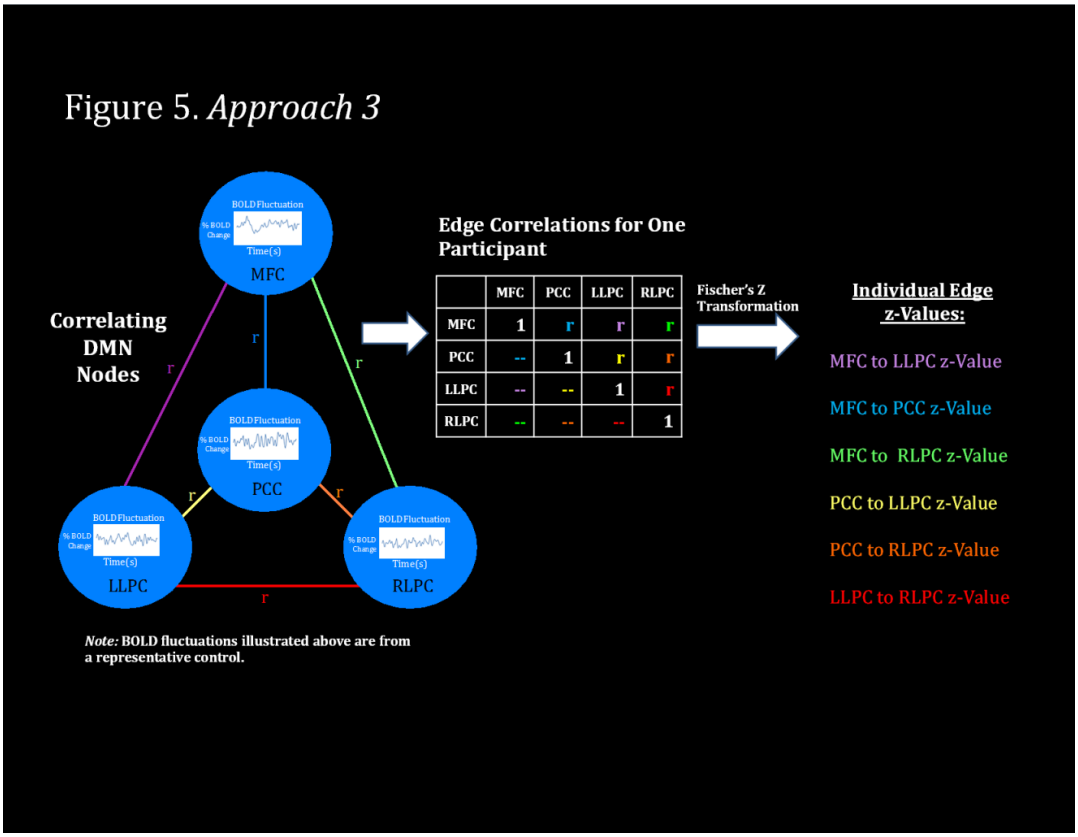
Using A2, all voxels across the entire network were included; therefore, this approach is more specific than A1 in that voxels unrelated to the DMN were not considered. Essentially, A2 measured the synchrony of BOLD fluctuations within the DMN nodes (PCC, MFC, LLPC, RLPC) only. The hippocampus was not included as part of the DMN for this study, as there is some debate regarding the extent of its involvement in this network (Mayer et al., 2011; Petrella et al., 2011; Van Eimeren et al., 2009). For each participant, functional connectivity between node pairs was accomplished by extracting the mean time course of the BOLD signal from the voxels of each node (using the aforementioned coordinates for each node). The time courses between nodes were correlated to each other to determine the synchronicity of the BOLD signal between these DMN regions. There were a total of six between-node correlations (MFC to PCC, MFC to LLPC, MFC to RLPC, PCC to LLPC, PCC to RLPC, and LLPC to RLPC). These correlation values were entered into a square correlation matrix. A determinant statistic indicating the degree of cohesiveness of the nodes within the network was obtained by computing the function of the square matrix. The function of determinant value was then statistically corrected for symmetry and variance (i.e., computation of the negative logarithm and square root of the determinant) to allow for comparison between groups. The result was a single numerical measure

of whole network integrity where a higher value indicates a more cohesive network for the individual [See Figure 4].



Between-Node (Edge) Analysis

A3 was similar to A2 in that between-node functional connectivity was computed for all four nodes, resulting in six correlation values corresponding to each functional edge per participant. Fischer's Z-transformation was applied to r values in order to normally distribute the values for group comparisons. Stronger correlations between nodes represent greater functional connectivity between them [See Figure 5].



Outcome Measures

Functional Outcomes. Functional outcomes were assessed at least six months post-injury using the Functional Status Exam (FSE) and the Glasgow Outcome Scale-Extended (GOSE). The Functional Status Exam (FSE), a structured interview, was used to evaluate change in activities of everyday life as a result of traumatic brain injury, including physical, social, and psychological domains (Dikmen et al., 2001). The degree of loss of independence in each area that has occurred as a result of the injury is used as the basis for the rating in those

domains. Severity within each area is measured along a four ordinal categories, ranging from a rating of zero, which signifies no change from preinjury status, to three, which signifies that the individual is completely dependent on others or that the individual does not perform that activity at all. The values are summed to yield scores between 10 and 40 for survivors, and a score of 41 designates the patient died prior to the outcome assessment. The GOSE is a commonly used structured interview that assesses functional abilities in multiple domains following a head injury in a less detailed manner than the FSE (Wilson, Pettigrew, and Teasdale, 1998). Total GOSE scores range from one to eight, with higher scores associated with better outcome.

Executive Functioning Outcomes. A series of neurocognitive tests were used to evaluate aspects of executive functioning. The Trail Making Test B (TMTB) was used to measure patients' ability to shift mental sets efficiently (Reitan, 1955). The Dodrill Stroop Color-Naming condition was used to measure ability to selectively attend to meaningful information while inhibiting a prepotent response (Dodrill, 1978), and the Controlled Word Association Test (COWAT) was used to assess phonemic verbal generativity (Spreen & Benton, 1977). The number of digits repeated backwards during the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Digit Span subtest was used to assess auditory working memory (Wechsler, 1997).

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

Processing Speed Outcomes. Trail Making Test A (TMTA) and selected subtests of the WAIS-III (i.e., Digit-Symbol Coding and Symbol Search) were administered to assess visual scanning and visual-motor speed. The Dodrill Stroop Word-Reading condition was used to measure reading speed (Dodrill, 1978).

Outcome interviews were conducted by a research coordinator who completed standardized training, was supervised by a neuropsychologist, and was blinded to imaging results. Neurocognitive results were adjusted for demographic factors (age, education, gender) where available. T-Scores for these measures were used throughout the statistical analysis (M=50, SD=10).

Statistical Analyses

Demographic data were examined for between - group differences with appropriate parametric or nonparametric tests. Age and education were examined with a *t* test and the categorical variables of gender and ethnicity were analyzed using Chi-Square tests. Between-group differences in the degree of functional connectivity of the DMN were evaluated using Analysis of Covariance (ANCOVA), with connectivity measures from each approach examined as

dependent variables. Diagnosis and scanner were considered fixed factors in this statistical model. Age was examined as a covariate, as it may be a proxy for injury severity given its correlation with acute injury severity. Pearson correlations were used to examine associations between the strength of connections between nodes and to determine the association between the functional connectivity measurement of each approach and neuropsychological outcome. Pearson correlations were also used to examine associations among connectivity measures. Spearman's rho was used to examine associations between connectivity measures and functional outcome scores (i.e., GOSE and FSE), as these measures yield ordinal data. To correct for effects of multiple comparisons, a false-discovery rate (FDR) of 0.05 was utilized to determine statistical significance. Statistical analyses were performed using Predictive Analytical Software (PASW v17.0.2; formerly known as SPSS, Chicago, IL). A probability value less than 0.05 was considered statistically significant.

Results

Demographic Characteristics

Demographic features and clinical characteristics for the participants enrolled in this study are shown in Tables 1 and 2. No significant differences in age existed between controls (M = 37.5, SD = 14.6) and patients (M = 29.7, SD =13.4), t (40) = 1.79, p = 0.08. Likewise, controls and patients did not differ by gender χ^2 (2, N = 42) = 1.674, p = 0.433. Controls and patients differed by

education, however, where controls (*M*= 15.8, *SD* = 3.3) were significantly more educated than patients (*M* = 12.7, *SD* = 2.6), *t* (39) = 3.41, *p* = 0.002. This difference resulted in the use of education as a covariate in analyses.

Table 1

Healthy Control and TAI Demographic Characteristics

Characteristic	17 Controls	25 TAI Chronic	*p*
Mean age in years (SD)	38 (15)	30 (13)	0.081
Mean education in years (SD)	15.9 (3.3)	12.7 (2.6)	0.002
Gender		Percent (*n*)	
Male	65% (11)	80% (20)	0.426
Race/Ethnicity			
Non-Hispanic, White	88% (15)	76% (19)	0.433
Hispanic	6% (1)	20% (5)	
Asian	6% (1)	4% (1)	
Handedness			
Right	100% (17)	92% (23)	0.261

The majority of patients sustained moderate to severe impairment as measured by GCS (Table 2).

Table 2

TAI Clinical Outcome Indices

	Mean	SD	Median	Range
GCS	8.4	5	8	3-15
GOSE	6.6	1.5	7	3-8

Note. GCS = Glasgow Coma Scale completed at acute injury; GOSE = Glasgow Outcome Scale-Extended completed 6 to 11 months post-injury.

Interscanner Variability

To investigate whether resting-state data are comparable between the two scanners used, we examined three measures of connectivity among controls in a between-scanner fashion. Nine controls were scanned using the Siemens magnet and eight using the GE magnet. The results of independent samples *t* tests showed that all three connectivity measures were similar between scanners (A1 average PPMC value, p=0.468; A2 average function of the determinant value, p=0.252; A3 average LLPC to RLPC between-node correlation, p=0.716), suggesting that the data from the two scanners were comparable.

Discrimination between Groups

Table 3 presents the results of eight ANCOVA tests. The following main effects were present after adjusting for age and education. The analysis of A1 yielded a significant main effect of diagnosis F (1, 41) = 4.918, p<0.05, with healthy controls exhibiting greater PPMC values (M = 0.641, SE = 0.040) than did patients with TAI (M = 0.530, SE = 0.032). Analysis of the second approach, A2,

yielded a significant main effect of diagnosis F (1, 41) = 19.55, p<0.001, with healthy controls exhibiting greater within network functional connectivity (M = 1.42, SE = 0.073) than patients with TAI (M = 1.013, SE = 0.058). Analyses of A3 were conducted for each functional edge. These analyses demonstrated a significant main effect of diagnosis for each functional edge as patients had significantly lower functional connectivity than controls.

Table 3

General Linear Model of 3 Approaches

	Functional Connectivity			
	Controls	TAI		
Approach	M (SE)	M (SE)	*F*	*p*
A1	0.641 (0.040)	0.530 (0.032)	4.918	**0.017**
A2	1.421 (0.073)	1.013 (0.058)	19.55	**0.00004**
A3: LLPC to RLPC	0.753 (0.109)	0.412 (0.087)	6.134	**0.009**
A3: MFC to LLPC	0.529 (0.102)	0.172 (0.081)	7.643	**0.005**
A3: MFC to RLPC	0.600 (0.087)	0.278 (0.070)	8.492	**0.003**
A3: MFC to PCC	0.683 (0.090)	0.397 (0.072)	6.290	**0.009**
A3: PCC to LLPC	0.607 (0.079)	0.416 (0.063)	3.628	**0.033**
A3: PCC to RLPC	0.747 (0.098)	0.459 (0.078)	5.373	**0.013**

Note. A1 = Whole-Brain Analysis; A2 = Network-Specific Analysis; A3 = Between-node (Edge) Analysis; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex.

Clinical Outcome

Overall, patients reported mild functional impairment at 6 months post-injury. The GOSE median score of 7 suggests an overall good recovery with current problems relating to the injury which affect daily life (e.g., headaches, dizziness, slowness). In terms of cognitive functioning, scores ranged widely across measures, including some patients with severe cognitive deficits and others scoring in the superior range. The means, however, were generally in the average range.

Table 4

Functional and Cognitive Outcomes in the TAI Sample

	Outcome Measure	Mean Score (*SD*)	Median Score	Range
Functional	FSE	16.5 (6.2)	14	10-31
	GOSE	6.5 (1.5)	7	3-8
Executive Function T-Scores	DSB	47.0 (8.9)	43	36-69
	COWAT	38.7 (13.0)	38	9-68
	TMTB	47.7 (12.2)	48	29-70
	Stroop II	53.1 (8.8)	56	30-63
Learning and Memory T-Scores	CVLT-II Total	48.4 (14.4)	47	5-68
	CVLT-II SD	45.7 (13.9)	45	20-65
	CVLT-II LD	45.0 (14.0)	45	15-65
Processing Speed T-Scores	DSC	42.2 (7.2)	43	27-53
	Stroop I	43.7 (12.6)	47	11-62
	SS	47.5 (7.8)	47	33-67
	TMTA	49.4 (15.3)	49	19-83

Note. All cognitive outcome scores presented are T-Scores. FSE = Functional Status Exam; GOSE = Glasgow Outcome Scale-Extended; DSB = Digit Span Backward; 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.

Associations with Outcome

Across all three approaches, neurocognitive test performance showed no association with functional connectivity as no correlation survived correction at 0.05 FDR.

Associations between Approaches

Additional analyses were carried out to examine the convergence of the three approaches when examining healthy DMN connectivity. Most associations between A1 and A3 were positive and significant. All associations between A2 and A3 were positive and significant. A1 and A2 were the most strongly associated. See Table 5.

Table 5

Correlations between fcMRI Edges and Global Integrity among Healthy Controls

	Global Integrity Measure	
	A1	A2
A2	0.820**	--
A3: LLPC and RLPC	0.348	0.674**
MFC and LLPC	0.767**	0.618*
MFC and RLPC	0.554*	0.756**
MFC and PCC	0.664**	0.684*
PCC and LLPC	0.538*	0.744**
PCC and RLPC	0.511	0.836**

Note. Significant associations: *=p<0.05, **=p<0.01. A1 = PPMC Approach; A2 = Function of the Determinant Approach; A3 = Between-node Correlation Approach; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex.

Discussion

We investigated the utility of examining the functional connectivity of the DMN as a biomarker post-TAI. We evaluated these potential biomarkers by whether they provide adequate discriminant validity, and whether the markers correlate with clinical outcome. To our knowledge this is the first study to examine three separate approaches to analyzing functional connectivity of the DMN after moderate to severe TBI compared to controls. Results revealed significant compromise to the integrity of the DMN after TAI in the chronic stage

after injury. We found that all three DMN analysis approaches adequately discriminated injured and uninjured brains, thus meeting the requirement that a biomarker must have discriminant validity to be useful. Furthermore, the integrity of DMN connectivity was robustly able to discriminate between patients and controls whether examining brain connectivity using a whole brain approach or a network specific approach. These findings are consistent with investigations using RS-fcMRI to study clinical populations with white matter integrity damage (i.e., AD, multiple sclerosis, TBI) (Audoin et al., 2006; Christodoulou et al., 2001; Duong et al., 2005; Hedden et al., 2009; Inglese et al., 2005; Lowe et al., 2002; Lowe et al., 2008), suggesting damage to white matter in chronic TAI negatively impacts the function of distinct cortical regions. These results are also consistent with the only other study to investigate the DMN in a brain injured population (Mayer et al., 2011).

Regarding construct validity, none of the approaches correlated to outcome. Results showed that while A1 significantly discriminated DMN-connectivity between patient and control groups, connectivity was not associated with clinical outcome measures. One potential reason for this finding is the nature of the approach, which examines voxels throughout the entire brain, and therefore it is possible that outcomes did not correlate with this measurement because it measures thousands of voxels unrelated to the DMN.

While A2 was sensitive to compromise in the DMN after brain injury, it also lacked correlation to clinical outcome. A2 was more specific to the integrity of the DMN than A1, as it only included the between-node correlations of voxels within regions specific to the DMN. A2 may have not correlated with outcome because it measures the functional integrity of the entire network, as opposed to predominant functional connections within the network. In other words, it can detect compromise to DMN as a whole, but the areas that are not compromised may dampen the effect of areas that are compromised, thus decreasing its correlation with outcome.

A3 examined the functional connectedness of individual node pairs of the DMN and adequately discriminated between injured and non-injured brains. This finding is consistent with the only other investigation examining the DMN among individuals with TBI (Mayer et al., 2011). In that study, the integrity of the DMN was examined by seeding the PCC and found that patients demonstrated lower functional correlations between this region and the rostral anterior cingulate cortex in mild TBI. The current study extends these findings to all DMN node pairs (i.e., MFC to PCC, MFC to LLPC, MFC to RLPC, PCC to LLPC, PCC to RLPC, and LLPC to RLPC). Furthermore, compromise to these additional nodes of the DMN may be a function of the more severely injured sample studied in the present investigation.

Of the three approaches, A3 examined the functional connectedness of individual node pairs and thus, was potentially more sensitive to damage to specific white matter tracks that run through the DMN regions. Within A3, all functional edges of the DMN discriminated between injured and non-injured brains, but none of the edges correlated with outcome in cognitive domains commonly affected after TAI (i.e., executive functioning, learning and memory, and processing speed) after correction for multiple comparisons. The lack of significant associations between edges of the DMN and outcome raise the possibility that degree of cortical connectedness is less important than degree of white matter integrity. Diffusion tensor imaging studies in this population have demonstrated degree of white matter compromise correlates to outcome (Huisman et al., 2004; Kraus et al., 2007; Marquez de la Plata et al., 2011; McCullagh and Feinstein, 2005; Niogi et al., 2008; Wang et al., 2008), suggesting integrity of white matter is more indicative of clinical outcome than the integrity of functional connectedness. This is in contrast to studies finding the integrity of the DMN at resting state is correlated to inhibition and set-shifting (Damoiseaux et al., 2007), semantic classification (Lustig et al., 2003), and verbal memory (Grady et al., 2006). One possible explanation is that white matter damage is the predominant type of injury in TAI, whereas cortical atrophy is the primary neuroanatomic insult in AD. This simple but important distinction in pathologies may result in structural connectivity integrity measures having a stronger association with

outcome in TAI than cortical connectedness measures; whereas for AD, functional connectivity measures may show a greater association with neurocognitive performance.

Finally, the lack of significant association with outcome could and DMN connectivity may suggest the DMN may not be the appropriate network to examine for use as a biomarker of outcome after TAI. The DMN is only one of nine commonly identified functional networks, and it is possible that the connectivity within the Central Executive Network (i.e., Task Positive Network) is associated with cognitive performance.

Limitations and Conclusions

Possible limitations to this study include a relatively small sample size and a control sample recruited by convenience resulting in a more educated group of healthy controls compared to patients. Future studies examining potential biomarkers should consist of larger samples and draw their control group in a manner that minimizes demographic variability. Our findings should be replicated in a longitudinal fashion to examine injury-related change in connectivity over time. Further, generalizations of our findings are limited by the lack of neuropsychological testing in the control group, as we are left to assume the directionality of associations between functional connectivity and outcome. Furthermore, our functional outcome measures demonstrate that patients in this study had recovered to a large degree. Given the degree of recovery observed in

this sample six months post-injury, the results may not generalize to a sample of more severely impaired patients with chronic TAI.

In conclusion, we demonstrated the integrity of the DMN is compromised after TAI, and the degree of compromise can be detected using three distinct approaches of analyzing RS-fcMRI data. However, none of the approaches of analyzing DMN connectivity showed that the degree of compromise to the DMN has clinical implications after TAI, thus only partially supporting the use of RS-MRI as an imaging-based biomarker in this population.

SECTION II: STUDY 2

Integration of Functional and Structural Connectivity to Investigate Compromise to the Default Mode Network after Traumatic Axonal Injury

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Abstract

Little is known about the functional and structural integrity of the default mode network (DMN) following traumatic axonal injury (TAI) and its relationship with clinical outcome. The present study sought to determine the utility of integrating resting state functional connectivity magnetic resonance imaging (fcMRI) and diffusion tensor imaging (DTI) as biomarkers after TAI by investigating: 1) whether the structural integrity between nodes of the DMN are compromised among patients with TAI, 2) the association between structural and functional connectivity, and 3) whether degree of structural integrity within the DMN is associated with clinical outcome.

Twenty-five patients with complicated mild to severe brain injuries were compared with 17 controls on resting state fMRI and DTI using 3T scanners.

Subjects were scanned an average of seven months post-injury, and a functional and neurocognitive outcome evaluation was conducted on the same day.

In general, results revealed minimal structural compromise to the integrity of the DMN after TAI, as participants with TAI showed reduced structural connectivity compared to controls in three DMN node-pairs [i.e., reduced fractional anisotropy (FA) in tracts connecting the Medial Frontal Cortex (MFC) to Left Lateral Parietal Cortex (LLPC) and Posterior Cingulate Cortex (PCC) to Right Lateral Parietal Cortex (RLPC), and increased Mean Diffusivity (MD) in tracts connecting the MFC to RLPC] as measured by DTI; however, none of the DMN-related structural connections showed compromise in both FA and MD values. Reconstructed DMN-related tracts were not associated with long-term clinical outcome measures. Structural and functional connectivity indices for this network were not strongly associated, suggesting integrating DTI and fcMRI in a monosynaptic manner may not be useful as a biomarker in chronic TAI.

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Introduction

Brain injuries are estimated to account for 19.5% of all hospital admissions in the United States (Centers for Disease Control and Prevention, 2006). Traumatic axonal injury (TAI) is a pathological feature characterized by microscopic axonal lesions that commonly appear in subcortical white matter of patients with acceleration-deceleration type traumatic brain injury (TBI) (Buki and Povlishock, 2006). Conventional magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) in the detection of axonal injuries (Gentry, Godersky, & Thompson, 1988; Ogawa et al., 1992); however, MRI is not as routinely used after TBI (Li et al, 2009; Azouvi, 2000). Further, CT and traditional MRI sequences only modestly predict outcome, perhaps due to their insensitive detection of axonal injury (Diaz-Marchan, Hayman, Carrier, & Feldman, 1996; Marquez de la Plata et al., 2007). As such, imaging biomarkers that provide adequate discriminant and construct validity are desired for improving diagnosis and prognosis of individuals with TBI.

Utility of DTI and RS-fcMRI in TBI

The understanding of neurologic illnesses with known damage to white matter such as TBI has greatly benefited from recent advances in magnetic resonance imaging technology. Following TBI, compromise to white matter pathways can be investigated using DTI tractography, an MRI analysis technique which enables brain white matter pathways to be reconstructed by determining the

primary diffusion direction of water molecules (Basser et al., 2000; Beaulieu and Allen 1994; Mori and van Zijl, 2002; Ramnani, Behrens, & Matthews, 2004). Diffusion can either be isotropic (free and equal in all directions) or anisotropic, restricted by barriers such as membranes. Fractional Anisotropy (FA) varies between 0 (maximal isotropic diffusion) and 1 (maximal anisotropic diffusion). FA is affected by factors such as the thickness of the myelin sheath and integrity of the axon membrane and cytoskeleton. The mean diffusivity (MD) is another commonly used measure derived from DTI. It represents the distance water molecules may freely diffuse" (Beaulieu, 2002). Increases in MD have been linked to demyelination and localized edema (Beaulieu, 2002).

DTI has been used to study populations with known white matter compromise, including multiple sclerosis and TAI (Kraus et al., 2007; Nakayama et al., 2006; Wang et al., 2008; Xu et al., 2007). In TAI, DTI has shown significant compromise to interhemispheric and long-range association tracts using several analytic techniques (Marquez de la Plata et al., 2011; Xu et al, 2007). Furthermore, the degree of compromise assessed by DTI correlates to clinical outcomes 6 months post-injury (Marquez de la Plata et al., 2011).

Functional connectivity from resting-state functional MRI (RS-fMRI) examines the correlation between spontaneous fluctuations that occur over time in distal gray matter areas, which allows the potential to investigate neuronal connectivity across the brain (Fox & Raichle, 2007; Skudlarski et al., 2008). RS-

fMRI can be used to identify functionally connected regions and can potentially be utilized as a biomarker for compromise to normal brain connectivity in clinical populations (Wang et al, 2006; Marquez de la Plata et al., 2011). Functional connectivity patterns among clinical populations with compromise to white matter deviate considerably from those observed among healthy brains. For example, the relationship between corpus callosum integrity and functional connectivity was demonstrated by Quigley and colleagues (2003), who found that patients with agenesis of the corpus callosum had significantly reduced interhemispheric connectivity as compared to healthy controls. Likewise, Johnston et al. (2008) demonstrated significantly reduced interhemispheric functional connectivity after a complete callosotomy, while intrahemispheric connectivity was relatively preserved. In TAI, Marquez de la Plata and colleagues (2011) demonstrated that individuals with TAI show reduced interhemispheric hippocampal functional connectivity, presumably the result of underlying structural damage to the corpus callosum; however, they did not incorporate the integrity of white matter structures in their investigation.

Studies examining both fcMRI and DTI in clinical populations have found functional connectivity is associated with structural connectivity. For example, in patients with multiple sclerosis, Lowe et al., (2008) demonstrated that functional connectivity between left and right primary motor regions were positively correlated with the integrity of corpus callosum connecting these regions.

Verstraete et al. (2010) found reduced FA of the corpus callosum and corticospinal tract, regions connecting regions of the motor network, in a sample of individuals with amyotrophic lateral sclerosis compared to controls.

DMN following TBI

The DMN is a reliably-elicited and robust resting state brain network that may be involved in important functions of human cognition (Raichle et al., 2001; Raichle & Snyder, 2007; Greicius et al., 2003; Biswal et al., 1995; Cordes et al. 2001). At rest, the DMN shows a pattern of functional connectivity between the posterior cingulate cortex (PCC), medial frontal cortex (MFC), and lateral parietal cortices (Raichle et al., 2001). The DMN shows a high resting metabolism and "deactivation" during cognitively demanding task performance (Raichle et al., 2001; Shulman et al., 1997). The collective function of the DMN regions remains unknown, but each region is presumed to relate to a unique set of functions. For example, Buckner and Carroll (2007) suggested that the PCC is activated during tasks involving autobiographical memory and self-referential processes. Leech et al. (2011) further suggested the PCC's involvement in "self-directed" thought. Amodio and Frith (2006) found that the MFC was associated with "social cognitive processes related to self and others." As a whole, the DMN is considered to be involved in the integration of autobiographical memory retrieval, envisioning the future, perspective-taking, and "mind wandering" (Buckner, Andrews-Hanna, and Schacter, 2008; Mason et al., 2007).

While little is presently known about the pattern of connectivity in the DMN following TAI, compromise to functional connectivity between nodes of the DMN have been shown to occur in various clinical conditions, such as Alzheimer's disease (Firbank et al., 2007; Greicius et al., 2004; He et al., 2007, Rombouts et al., 2005; Sorg et al., 2007; Wang et al., 2006; Greicius et al, 2007), major depression (Liang et al., 2006), schizophrenia (Bluhm et al., 2007; Garrity et al., 2007; Zhou et al., 2007; Pomarol-Clotet et al., 2008; Swanson et al., 2011), post-traumatic stress disorder (Lanius et al., 2010; Bluhm et al., 2009), and mild TBI (Mayer et al., 2011).

Combined DTI and fcMRI to study the DMN

The basic physiological mechanism of functional connectivity in the DMN is still not well understood, and the interpretation of changes of its intensity remains unclear (Skudlarski et al., 2008). It is speculated that for connectivity to be present between nodes of brain networks, there must be a structural or white matter fiber path connecting them, with the strength of the functional connectivity to depend on the strength of the anatomical connection (Greicius et al. 2009, Honey et al., 2009; Skudlarski et al., 2008; Supekar et al., 2010; van den Heuvel et al., 2009). DTI and temporal correlations in resting state fMRI offer the potential to investigate the neuronal connectivity of the working human brain (Skudlarski et al., 2008), as the former measures the integrity of white matter

tracts and the latter examines the functional connectedness of gray matter regions the tracts connect.

While centroaxial white matter structures are implicated in TAI (i.e., corpus callosum, fornix, internal capsule), it also impacts association tracts that may be involved in the DMN, including the cingulum bundle and longitudinal fasciculi (Lawes et al., 2008; Marquez de la Plata et al., 2011; Schmahmann et al., 2007; Wakana et al., 2004). Injury to white matter causes impairments in cognitive functioning in TBI (Felmingham et al., 2004), but the association between degree of white matter compromise and neuronal function is not entirely known (Kraus et al., 2007). Few studies have combined RS-MRI and DTI in the study of the DMN, and most have focused on healthy controls. However, these studies have demonstrated direct structural connections between functional nodes of the DMN. For example, Greicius et al. (2009) and van den Heauvel et al. (2008) showed direct white matter pathways between the functionally connected medial frontal cortex and posterior cingulate cortex, suggesting the cingulum bundle plays a role in connecting DMN regions.

Objectives

The goals of this investigation were to: (1) examine whether the structural integrity between the nodes of the DMN is associated with functional compromise among the nodes of the network apparent after TAI, and (2) to assess the relationship between connectivity measures and clinical outcomes. We

hypothesized structural integrity of the DMN would discriminate between healthy controls and patients with TAI. We also hypothesized that the degree of structural and functional connectivity would be significantly and positively correlated to each other among controls and among patients.

Furthermore, we expected that structural connectivity would correlate with functional and neurocognitive outcome. Among TBI patients, the FA value of reconstructed tracts between DMN nodes were expected to correlate positively with performance on functional and various neurocognitive tests. MD values between the nodes of the DMN were expected to correlate negatively with performance on functional and various neurocognitive tests.

Materials and Methods

Participants

Data for this study were collected as part of an investigation at the North Texas Traumatic Brain Injury Research Center within the University of Texas Southwestern Medical Center at Dallas. Twenty-five patients with TBI were recruited from Parkland Health and Hospital Systems, Dallas, Texas from 2006 to 2008. Inclusion criteria required that subjects: 1) sustained closed head TBI with a mechanism of injury consistent with TAI (i.e., high-velocity motor vehicle collision or MVC-pedestrian collision), 2) had either an abnormal CT scan on admission or a post-resuscitation Glasgow Coma Scale (GCS) 3-12 if CT was normal, 3) were hemodynamically stable so that transfer to the scanner was

clinically safe, 4) enrolled within seven days of injury, and 5) were at least 16 years old.

Exclusion criteria included: 1) Previous brain injury or preexisting neurologic disorders (e.g., epilepsy, brain tumors, meningitis, cerebral palsy, encephalitis, brain abscesses, vascular malformations, cerebrovascular disease, Alzheimer's disease, multiple sclerosis, HIV-encephalitis), 2) any CT-visible focal low, mixed, or high density lesion 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) history of premorbid disabling condition that could interfere with outcome assessments, 7) previous hospitalization for TBI greater than one day, 8) contraindication to MRI (incompatible metal implants), 9) membership in a vulnerable population (i.e., prisoner), or 10) pregnancy.

Seventeen healthy volunteers of similar age- and gender were recruited as controls. All healthy volunteers had good general health and no known neurocognitive or psychiatric disorders. Informed consent was obtained from all participants or their legally authorized representative.

Functional and Structural Magnetic Resonance Image Acquisition and Processing

Image Acquisition and Processing. Functional and anatomical magnetic resonance images were obtained for each participant using either a Siemens Trio 3 Tesla (T) (Siemens AG, Erlangen, Germany) or a General Electric Signa Excite

3T (General Electric Healthcare, Milwaukee, Wisconsin) scanner. Resting state echo-planar images recorded BOLD fluctuation over 128 time-points two seconds apart (TR=2). Echo-planar image volumes were acquired at 36 axial slice locations for whole brain coverage. Specific echo-planar image data acquired by the Siemens scanner were obtained with single-shot gradient-recalled pulse sequence, TR = 2 seconds, echo time = 25 milliseconds, flip angle, 90^{o}; matrix, 64 X 64; field of view (FOV) 210 mm, and 3.5 mm slice thickness). Echo-planar sequence parameters for the GE scanner were comparable, as data were obtained with single-shot gradient-recalled pulse sequence, TR = 2 seconds, echo time = 25 milliseconds, flip angle 90^{o}; matrix, 64 X 64; field of view 210 mm, and 3.5 mm slice thickness). Participants were asked to keep their eyes open and not think of anything during image acquisition.

High-resolution T1-weighted structural images acquired by the Siemens scanner were acquired using MP-RAGE with slice thickness 1.0mm, FOV of 240 mm, and TE/TI/TR 4/900/2250ms, flip angle 9^{o}, NEX 1. High-resolution T1-weighted structural images acquired by the GE scanner were acquired using fast spoiled gradient-recalled (FSPGR) acquisition in the steady state with slice thickness 1.3 mm, FOV 240-280 mm, TR/TE 8.0/2.4 ms, flip angle 25^{o}, and NEX 2. All patient images were acquired 6 to 10-months post-injury.

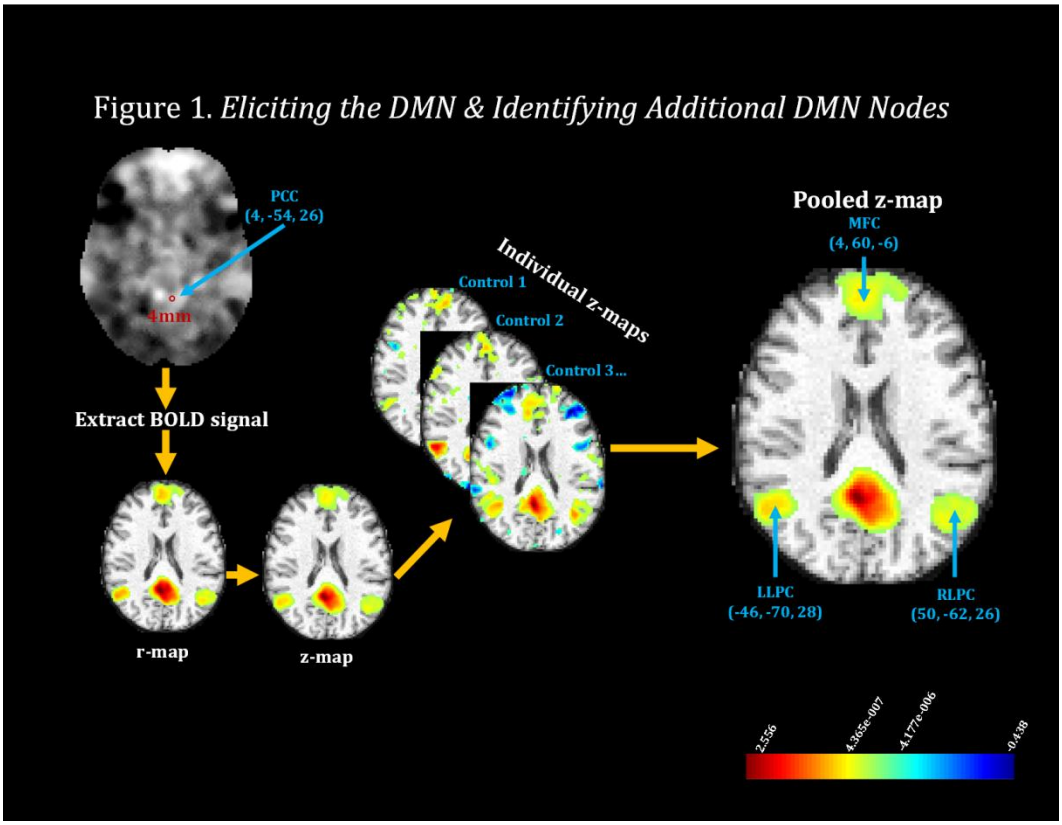
Statistical Parametric Mapping 5 (SPM5) was used to preprocess MRI images. Preprocessing of fMRI data included: coregistration, segmentation,

normalization, smoothing, detrending, and temporal filtration. Images were converted from DICOM to Analyze readable format. The first four volumes were then excluded from further analysis. T1 and fMRI images were coregistered to each other. Next, fMRI images were segmented, where masks for gray matter, white matter, and CSF were created from T1 images. Normalization of echo-planar and T1 images to common space was accomplished with a resolution of 2 x 2 x 2 mm in order to account for differences in brain size and shape variations among participants. Spatial smoothing and detrending of the fMRI images took place to augment signal to noise ratio. Smoothing the fMRI data using 2 x 2 x 2 mm smoothing kernel reduced the spatial resolution. Detrending subtracted the background noise. Last, given that BOLD signal fluctuations are low-frequency waveforms, temporal filtration of the images was conducted to exclude the higher waveforms or frequencies. Low frequency oscillations in BOLD between 0.01-0.12 Hz were retained for analysis.

Description of Functional and Structural Connectivity Analyses

Functional and structural neuroimaging were used to analyze DMN integrity. For the functional connectivity, the following steps were used to elicit the DMN in the healthy controls. Given that the PCC has been shown to play a central role in the DMN, (Raichle et al., 2001; Buckner et al., 2008; Fransson & Marrelec, 2008; Greicius et al., 2009; Shulman et al, 1997), a correlation map was computed using a reference seed region with a 4mm radius in the PCC. MNI

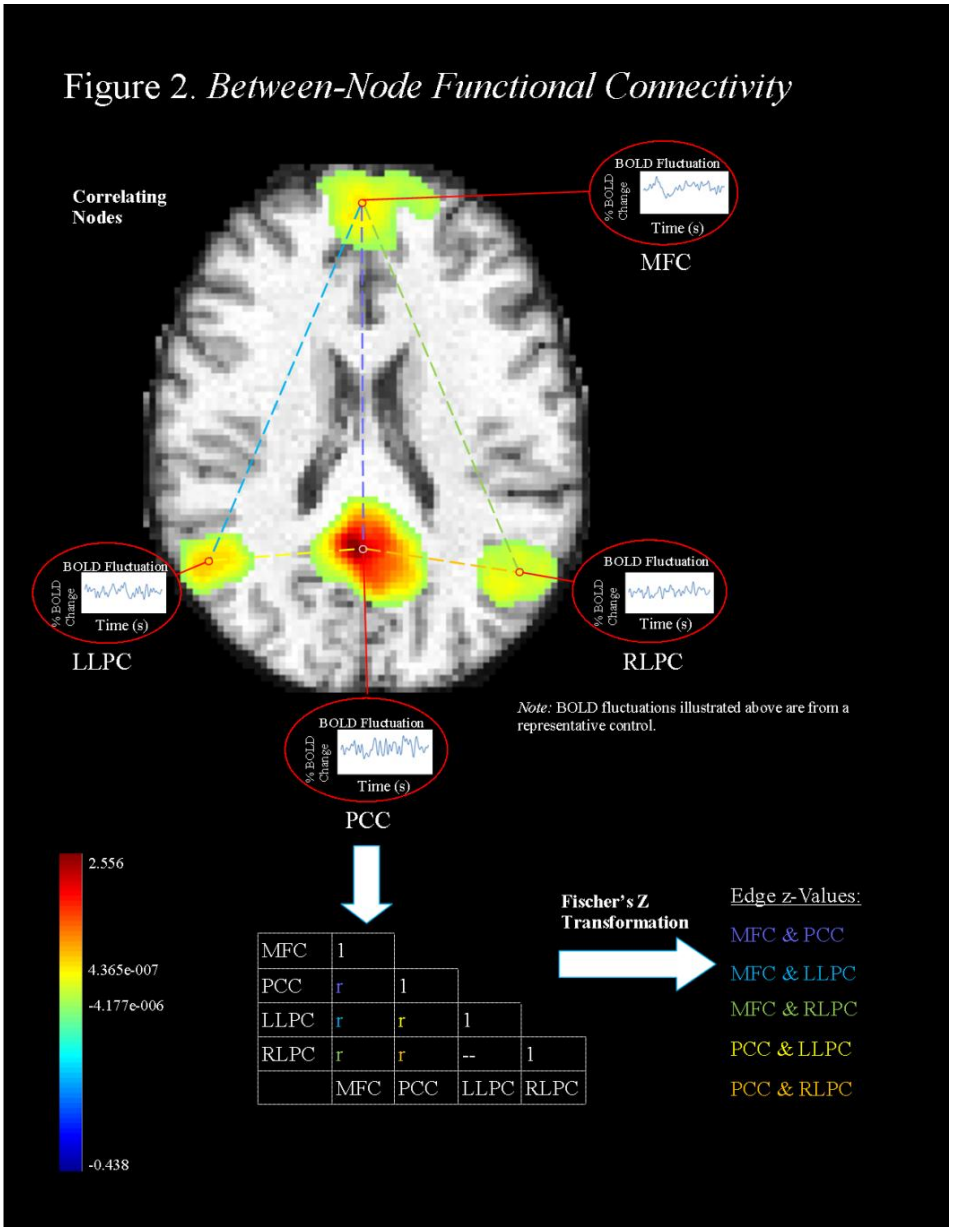
coordinates for the PCC (4, -54, 26) were based on a previous study (Hedden et al., 2009) with a modification of the x-coordinate value (i.e., from 0 to 4) to ensure that coordinate placement on the cerebral cortex and avoid placing a region of interest (ROI) in cerebral spinal fluid between hemispheres. Among uninjured controls, we used the Resting State fcMRI Data Analysis Toolkit (REST; Beijing Normal University), to create spatial maps containing brain voxels with BOLD signal that fluctuated synchronously with BOLD signal in the PCC (i.e., correlated above a specified probability threshold of 0.05).



Spatial correlation r-maps were converted to z-maps using Fischer's Z transformation (See Figure 1). All z-maps for controls were pooled together to create an average z-map reflecting the spatial distribution and the strength of correlations with the PCC among healthy brains. The resulting pooled z-map was used to identify the peak voxels of the remaining nodes of the default network in this dataset. From this sample of controls, the coordinates of nodes of the DMN are: medial frontal cortex (MFC) (4, 60, -6), left lateral parietal cortex (LLPC) (-46, -70, 28), and right lateral parietal cortex (RLPC) (50, -62, 26) (See Figure 1). These coordinates were used as center points for ROIs with a 4 mm radius from which BOLD time series data were extracted to determine functional connectivity between nodes.

Functional Between-Node (Edge) Analysis

Between-node functional connectivity was computed for all four nodes, resulting in four correlation values corresponding to each functional edge per participant. Fischer's Z-transformation was applied to r values in order to normally distribute the values for group comparisons. Stronger correlations between nodes represent greater functional connectivity between them (See Figure 2).



Diffusion Tensor Image Acquisition and Processing.

DTI deterministic tractography was used to reconstruct white matter tracts between DMN nodes using the areas of connectivity elicited in resting state fcMRI. For the GE scanner, fractional anisotropy (FA) and mean diffusivity (MD)

from these tracts were analyzed. DTI sequences were obtained using a single-shot spin-echo, echo-planar imaging sequence with FOV 240 mm, slice thickness/gap 3/0 mm, ~45 slices, TR/TE 12,000/75.5 ms, flip angle 90º, NEX 2, matrix 128×128. The diffusion sensitizing gradients were applied at a b-value of 1,000 s/mm2/axis with 19 noncollinear directions and 3 b0 images. The acquisition time was 9 min. The voxel size was 2×2×3 mm^3 interpolated (by default at the scanner) to 1×1×3 mm^3.

For the Siemens scanner, fractional anisotropy (FA) and mean diffusivity (MD) from these tracts were analyzed. DTI sequences were obtained using a single-shot spin-echo, echo-planar imaging sequence with FOV 240 mm, slice thickness/gap 3/0 mm, ~53 slices, TR/TE 6600/72 ms, flip angle 90º, NEX 2, matrix 256×256. The diffusion sensitizing gradients were applied at a b-value of 1,000 s/mm2/axis with 19 noncollinear directions and 3 b0 images. The acquisition time was 9 min. The voxel size was 2×2×3 mm^3 interpolated (by default at the scanner) to 1×1×3 mm^3.

Structural Between-Node (Edge) Analysis.

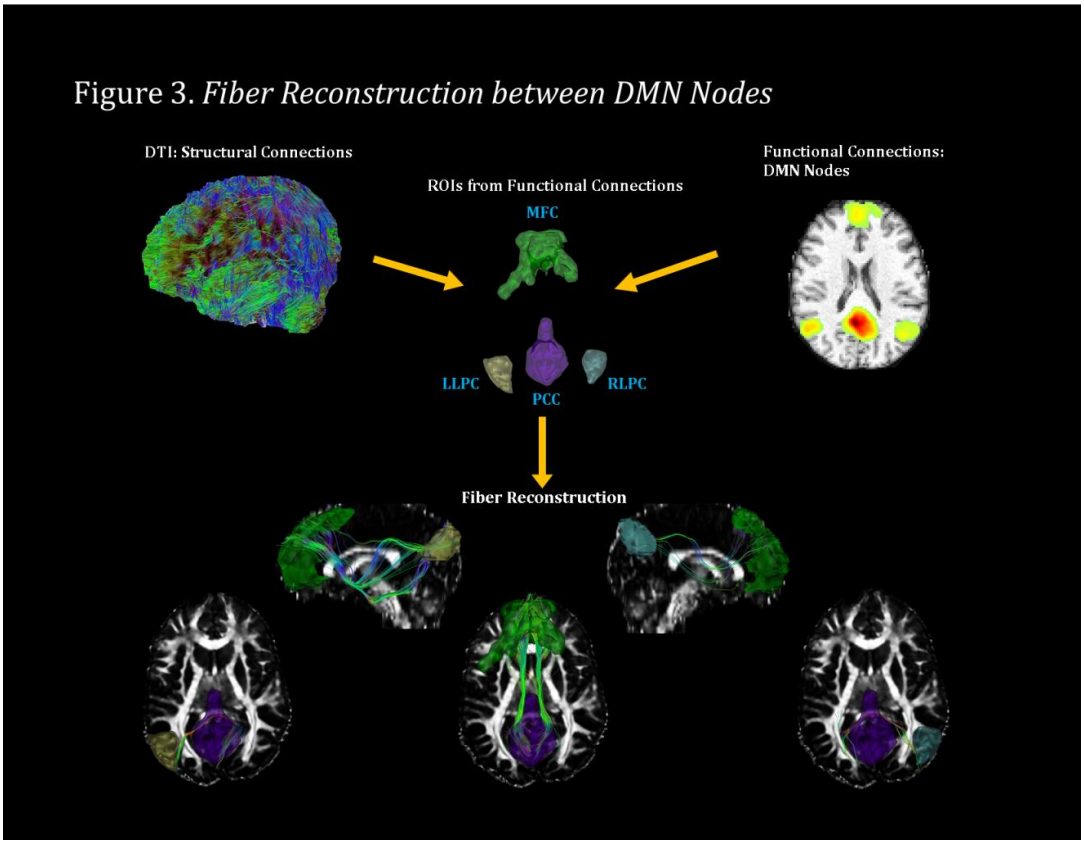
Between-node fiber reconstruction was computed for all four nodes, resulting in FA and MD values corresponding to each edge per participant. Preprocessing steps for DTI images used the MRIcron dcm2nii program to convert the DTI DICOM images into Neuroimaging Informatics Technology Initiative (NIfTI) data format while simultaneously extracting the gradient

directions (bvec and bval files). As part of standard preprocessing of DTI images, subsequent steps were carried out using Functional Magnetic Imaging for Brain Software Library, version 4.1.5 (FSL, University of Oxford, UK). Data underwent eddy current correction and B0 correction to correct for direction-dependent distortions (stretches and shears) in the diffusion weighted images caused by eddy currents in the gradient coils. Using the brain extraction tool, non-brain tissue was extracted from the eddy current-corrected image, B0 corrected-image, and the T1 image. Diffusion maps were generated using the DTI Fit function of MedINRIA. In order to ensure the DTI imaging (FA map, fcMRI activation map, and T1) were in the same dimensions, linear registration was performed using the functional linear registration tool (FLIRT) in which the fcMRI activation map and T1 image were normalized to the individual's FA map.

Fiber tractography and quantification were performed using DTI Track in Medical Image Navigation and Research Tool by INRIA 1.9.0 (MedINRIA v.1.9.0). Diffusion tensor tracing was performed on the brain-extracted, eddy-current corrected DTI data. Images were reoriented from the anterior to posterior position. Fiber tracking parameters included: 1) a fiber sampling rate in which a fiber was initiated at every voxel, 2) FA threshold of 0.3, and 3) a maximum angle deviation of 90º. Additional tracking parameters included fiber smoothness (80%) and a minimum length (12 mm) for each fiber for estimation of the diffusion tensor model.

Obtaining DMN Regions of Interest from Functional MRI

For each control, a threshold was applied to the individual's linearly registered functional pooled z-map. The activation map was then binarized so that it only contained regions of interest that above the set threshold. The binarized activation map was imported into the MedINRIA program, where ROIs could be selected through which fibers would be reconstructed. The threshold for each DMN node-pair was determined to be the threshold for which each control was able to reconstruct fibers between the node-pair (i.e., MFC to PCC) (See Figure 3). ROI thresholds varied by node pair (i.e., 0.2 for MFC to LLPC, MFC to PCC, and PCC to RLPC; 0.165 for MFC to RLPC and PCC to LLPC). After the determination of the threshold was made for the control node-pair, the same threshold and procedure for fiber reconstruction was applied to the node-pair for the patients. Patients were excluded from analysis of a particular node-pair if fibers were not able to be reconstructed between them.



Note. Structural connections between functionally connected regions of the DMN illustrated above are from a representative control. MFC = Medial Frontal Cortex, LLPC = Left Lateral Parietal Cortex, PCC = Posterior Cingulate Cortex, RLPC = Right Lateral Parietal Cortex; ROI = Region of Interest; Fibers reconstructed between the MFC and LLPC edge and MFC and RLPC edge included the inferior fronto-occipito fasciculus/inferior longitudinal fasciculus (IFO/ILF) and superior longitudinal fasciculus (SLF); Fibers reconstructed between the MFC and PCC edge included the cingulum bundle and IFO/ILF; Fibers reconstructed between the PCC and LLPC edge and PCC to RLPC edge included the splenium of the corpus callosum and posterior corona radiata.

Outcome Measures

Functional. Functional outcomes were assessed at least six months post-injury using the Glasgow Outcome Scale-Extended (GOSE) and the Functional Status Exam (FSE). The GOSE, a structured interview, assesses functional abilities in multiple domains following a head injury (Wilson, Pettigrew, & Teasdale, 1998). Total GOSE scores range from one to eight, with higher scores associated with better outcome. The Functional Status Exam (FSE) is a structured interview that assesses functional abilities following TBI in a more detailed manner than the GOSE. It was used to evaluate change in activities of everyday life resulting from TBI, including physical, social, and psychological domains (Dikmen et al., 2001). Ratings in these domains is based on the degree of loss of independence in each area that has occurred as a result of the injury. Severity within each area is measured along four ordinal categories, ranging from zero (i.e., no change from preinjury status) to three (i.e., the individual is completely dependent on others or does not perform that activity at all). Values are summed to yield scores between 10 and 40 for survivors, and a score of 41 indicates the patient died prior to the outcome assessment.

Executive Functioning. Aspects of executive functioning were measured by a series of neurocognitive tests. Auditory working memory was assessed by the number of digits repeated backwards during the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Digit Span subtest (Wechsler, 1997). The

Controlled Word Association Test (COWAT) was used to assess phonemic verbal generativity (Spreen & Benton, 1977), and the Dodrill Stroop Color-Naming condition was used to measure ability to selectively attend to meaningful information while inhibiting a prepotent response (Dodrill, 1978). Patients'ability to shift mental sets efficiently was measured by the Trail Making Test B (TMTB) (Reitan, 1955).

Learning and Memory. The California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) was used to assess memory functioning. Total items learned across five trials were used to measure learning. Memory was assessed by short and long delay free recall trials.

Processing Speed. Visual motor-speed and visual scanning were assessed with the Trail Making Test A (TMTA) and selected subtests of the WAIS-III (i.e., Digit-Symbol Coding and Symbol Search). Reading speed was measured by the Dodrill Stroop Word-Reading condition (Dodrill, 1978).

A research coordinator who conducted outcome interviews completed standardized training, was supervised by a neuropsychologist, and was blinded to imaging results. Where available, neurocognitive results were adjusted for demographic factors (age, education, gender) T-Scores (M=50, SD=10) for all neurocognitive measures were used throughout the statistical analysis.

Statistical Analyses

Demographic data were examined for between- group differences with

appropriate parametric or nonparametric tests. Age and education were examined with *t* tests, and gender and ethnicity were analyzed using Chi-Square tests. Between-group differences in the degree of structural connectivity of the DMN were evaluated using Analysis of Covariance (ANCOVA), with structural connectivity measures (FA and MD) of each edge examined as dependent variables. Diagnosis and scanner were fixed factors in this statistical mode. Age was found to be significantly correlated with acute injury severity, and was therefore used as a covariate in all analyses. A probability value less that 0.05 was considered statistically significant.

Pearson correlations were carried out separately by controls and patients to examine the correlation among functional and structural connectivity. Pearson correlations were also used to determine the association between the structural (FA and MD) connectivity of each DMN edge and neuropsychological outcome. Spearman's rho was used to examine associations between structural connectivity measures and functional outcome scores (i.e., GOSE and FSE). To correct for effects of multiple comparisons, a false-discovery rate (FDR) of 0.05 was utilized to determine statistical significance. Statistical analyses were performed using Predictive Analytical Software (PASW v17.0.2; formerly known as SPSS, Chicago, IL).

Results

Demographic Characteristics

Demographic features and clinical characteristics for the participants enrolled in this study are shown in Table 1. No significant differences in age existed between controls (M = 37.5, SD = 14.6) and patients (M = 29.7, SD =13.4), t (40) = 1.79, p = 0.081. Likewise, controls and patients did not differ by gender χ^2 (2, N = 42) = 1.674, p = 0.433. Controls and patients differed by education, however, with controls (M= 15.8, SD = 3.3) being significantly more educated than patients (M = 12.7, SD = 2.6), t (39) = 3.41, p = 0.002. This difference resulted in the use of education as a covariate in all analyses.

Table 1

Healthy Control and TAI Demographic Characteristics

Characteristic	17 Controls	25 TAI	*p*
Mean age in years (*SD*)	38 (15)	30 (13)	0.081
Mean education in years (*SD*)	15.9 (3.3)	12.7 (2.6)	**0.002**

Among controls, 65% (n=11) of subjects were male and among patients with TAI, 80% (n=20) were male. Regarding racial/ethnic background, the composition among control and patient groups were as follows: 88% (n=15) of controls and 76% (n=19) of patients were non-Hispanic, White; 6% (n=1) of controls and 20% (n=1) of patients were Hispanic; and 6% (n=1) of controls and

4% (*n*=1) of patients were Asian. Among controls, 100% (15) were right-handed and among patients 92% (23) were right-handed.

Generally, the group of patients was moderate to severely impaired, as 76% had acute GCS scores less than 12 (*M*=8.4, *SD* =5, *Mdn* = 8, Range = 3-15). At the chronic stage (i.e., 6 to 11 months post-injury), patients reported generally good recovery with some problems relating to the injury which affect daily life (e.g., headaches, dizziness, slowness) as measured by GOSE (*M*=6.6, *SD* = 1.5, *Mdn* = 7, Range = 3-8).

Interscanner Variability

To investigate whether resting-state data were comparable between the two scanners used, we examined functional and structural connectivity among controls in a between-scanner fashion. Nine controls were scanned using the Siemens magnet and eight using the GE magnet. The results of independent samples *t* tests showed that the functional connectivity measure was similar between scanners (Average LLPC to RLPC between-node correlation, *p*=0.716), suggesting that the functional data from the two scanners were comparable.

In contrast, the results of independent samples *t* tests showed that for some structural edges, either the mean FA or MD values were significantly different between scanners in the control group. To ensure scanner comparability for structural data of those edges, an adjustment was made to the FA or MD value.

The adjustment was determined by computing the ratio of the larger mean value for the DTI metric (by scanner) by the smaller value. The values for the scanner group with the smaller mean value for the particular DTI metric were then multiplied by that ratio. After this correction was applied to all participants, outliers in the control group were determined and removed before subsequent analyses were performed.

Group Discrimination Using Structural Connectivity Measures

Table 2 presents the results of ten ANCOVA tests. The following main effects were present after adjusting for age and education. FA for the MFC to LLPC edge yielded a significant main effect of diagnosis F (1, 34) = 3.578, $p<0.05$, with healthy controls exhibiting higher between-node functional connectivity (M = 0.377, SE = 0.008) than did patients with TAI (M = 0.358, SE = 0.006). FA for PCC to RLPC edge yielded a significant main effect of diagnosis F (1, 33) = 6.043, $p<0.05$, with healthy controls exhibiting higher between-node functional connectivity (M = 0.480, SE = 0.013) than did patients with TAI (M = 0.440, SE = 0.010). MD for the MFC to RLPC edge yielded a significant main effect of diagnosis F (1, 35) = 10.371, $p<0.01$, with healthy controls exhibiting higher between-node functional connectivity (M = 2.735, SE = 0.054) than did patients with TAI (M = 2.962, SE = 0.045).

Table 2

General Linear Model of Structural Integrity

	Functional Connectivity			
	Controls	TAI		
Edge	M (SE)	M (SE)	*F*	*p*
FA				
MFC & LLPC	0.377 (0.008)	0.358 (0.006)	3.578	**0.034**
MFC & RLPC	0.370 (0.007)	0.362 (0.006)	0.863	0.180
MFC & PCC	0.344 (0.005)	0.341 (0.004)	0.223	0.321
PCC & LLPC	0.402 (0.013)	0.394 (0.012)	0.205	0.327
PCC & RLPC	0.480 (0.013)	0.440 (0.010)	6.043	**0.010**
MD				
MFC & LLPC	2.838 (0.061)	2.890 (0.051)	0.414	0.263
MFC & RLPC	2.735 (0.054)	2.962 (0.045)	10.371	**0.002**
MFC & PCC	3.000 (0.051)	3.013 (0.043)	0.043	0.418
PCC & LLPC	2.716 (0.052)	2.730 (0.045)	0.042	0.419
PCC & RLPC	2.596 (0.056)	2.607 (0.046)	0.022	0.442

Note. FA = Fractional Anisotropy; MD = Mean Diffusivity; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex.

Associations between Functional and Structural Connectivity

Correlational analyses were carried out to examine the association between functional and structural connectivity in patients and controls. In the

control group, no associations were significant. In the patient group, associations between functional connectivity and FA were positive and significant for the PCC and RLPC edge. Associations between functional connectivity and MD were negative and significant for the MFC and LLPC edge and PCC and LLPC edge (See Table 3).

Table 3

Correlations Between Functional & Structural Connectivity in Patients with TAI

DTI Metric	Functional Connectivity				
	MFC & LLPC	MFC & RLPC	MFC & PCC	PCC & LLPC	PCC & RLPC
FA					
MFC & LLPC	0.059	0.203	0.135	-0.052	0.242
MFC & RLPC	0.517*	0.394	0.683*	0.246	0.243
MFC & PCC	0.061	0.088	0.435	0.316	0.337
PCC & LLPC	0.545*	0.408	0.660*	0.361	0.275
PCC & RLPC	0.249	0.274	0.476	0.610*	0.589*
MD					
MFC & LLPC	-0.569*	-0.396	-0.692*	-0.601*	-0.324
MFC & RLPC	-0.122	-0.147	-0.479	-0.272	-0.305
MFC & PCC	-0.006	-0.163	-0.313	-0.639*	-0.480
PCC & LLPC	-0.276	-0.195	-0.571*	-0.727*	-0.531*
PCC & RLPC	-0.024	-0.018	-0.418	-0.534*	-0.483

Note. *Significant at 0.05 FDR. Enclosed values indicate the correlations of interest (i.e., correlation between and edge's functional and structural integrity). FA = Fractional Anisotropy; FC = Functional Connectivity; MD = Mean Diffusivity; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex. FA *n* varies by edge (i.e., MFC & LLPC *n* =20; MFC & RLPC *n* = 21; MFC & PCC *n* = 22; PCC & LLPC n =21; PCC & RLPC *n* = 20). MD *n* varies by edge (i.e., MFC & LLPC *n* = 20; MFC & RLPC *n* =21; MFC & PCC *n* =22; PCC & LLPC *n* = 21; PCC & RLPC *n* = 20).

Clinical Outcome

Overall, patients reported good functional recovery at 6 months post-injury, as suggested by the GOSE median score of 7. In terms of cognitive functioning, these patients' cognitive scores fell within the average range except for performance on the COWAT, which was mildly impaired. Scores ranged widely across measures, including some patients with severe cognitive deficits and others scoring in the superior range. On average, however, scores were generally in the average range. These results are summarized in Table 4.

Table 4

Functional & Cognitive Outcomes in the TAI Sample

	Outcome Measure	Mean Score* (*SD*)	Median Score*	Range
Functional	FSE	16.5 (6.2)	14	10-31
	GOSE	6.5 (1.5)	7	3-8
Executive Function T-Scores	DSB	47.0 (8.9)	43	36-69
	COWAT	38.7 (13.0)	38	9-68
	TMTB	47.7 (12.2)	48	29-70
	Stroop II	53.1 (8.8)	56	30-63
Learning & Memory T-Scores	CVLT-II Total	48.4 (14.4)	47	5-68
	CVLT-II SD	45.7 (13.9)	45	20-65
	CVLT-II LD	45.0 (14.0)	45	15-65
Processing Speed T-Scores	DSC	42.2 (7.2)	43	27-53
	Stroop I	43.7 (12.6)	47	11-62
	SS	47.5 (7.8)	47	33-67
	TMTA	49.4 (15.3)	49	19-83

Note. *All cognitive outcome scores presented are T-Scores. FSE = Functional Status Exam; GOSE = Glasgow Outcome Scale-Extended; T-Score values were computed for the following measures: DSB = Digit Span Backward; 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.

Correlations with Outcome

Performance on tests of particular cognitive domains correlated with measures of structural connectivity (FA and MD) at a probability value of 0.05. After correcting for multiple corrections, no correlation survived correction at 0.05 FDR, suggesting the associations were not significant.

Discussion

This investigation integrated RS-fMRI and DTI to examine the DMN post-TAI to determine the utility of combining these imaging modalities for use as potential biomarkers. More specifically, we examined white matter structures between the functionally connected regions of the DMN by reconstructing fibers between them in healthy and injured brains. We evaluated this method as a potential biomarker by examining their ability to discriminate between healthy and injured brains and their association with clinical outcome.

White matter compromise in the chronic stage after moderate to severe TAI has been documented (Benson et al., 2007; Marquez de la Plata et al., 2011; Newcombe et al., 2007; Xu et al., 2007), including compromise to interhemispheric and long-range association fibers. Recent analyses by our group demonstrated functional compromise between all nodes of the DMN in chronic TAI, raising the possibility that white matter structures connecting these nodes may play a role in the connectivity of the DMN. The present study integrated these imaging modalities by reconstructing white matter tracts that connect each

of the functional nodes of the DMN utilizing the functional connectivity maps created by eliciting the DMN in resting state. To our knowledge, this is the first investigation to integrate structural and functional connectivity modalities of the DMN after TAI.

Using diffusion tensor tractography, we reconstructed several association fibers connecting the functional DMN node pairs, including the SLF, IFO/ILF and cingulum, and also reconstructed the posterior corona radiata and splenium of the corpus callosum. These findings are in agreement with previous studies which found white matter pathways that are associated with DMN connectivity in RS-fcMRI data (Greicius et al., 2009; Skudlarski et al., 2008; Teipel et al., 2010; van den Heuvel et al., 2008 (a); van den Heuvel et al., 2008 (b)). Our results extend these previous findings in that we reconstructed tracts between all DMN functional node-pairs in controls and patients with TAI (i.e., MFC to PCC, MFC to LLPC, MFC to RLPC, PCC to LLPC, and PCC to RLPC). Results revealed that some reconstructed tracts showed evidence of compromise, but most did not.

When examining group differences, we found decreased FA in tracts connecting the MFC to LLPC (i.e., IFO/ILF and SLF) and PCC to RLPC (i.e., splenium of the corpus callosum and posterior corona radiata) and increased MD in tracts connecting the MFC to RLPC (i.e., IFO/ILF and SLF) in patients with TAI compared to healthy controls. Thus, of the reconstructed tracts, the only DMN-related tracts that were compromised (by either MD or FA) were the

IFO/ILF and the splenium of the corpus callosum, which were previously found to be compromised in other TAI studies (Wang et al. 2007, Marquez de la Plata et al. 2011). However, it should be noted that none of the DMN-related structural connections showed compromise to both FA and MD values. This may suggest the method of tract reconstruction utilized in this study only identifies minimally compromised and intact white matter structures. Future studies should aim to integrate functional and structural connectivity and reconstruct more severely compromised white matter structures.

When we examined the association between DMN-related functional and structural integrity measures, we found there were no significant correlations among healthy controls. Likewise, among patients with TAI, only three of ten possible significant correlations were observed between DMN-related structure and function, suggesting this monosynaptic approach to connectivity may not be sufficient for examining the DMN.

We also examined the association between structural integrity and selected clinical outcome variables and found no significant associations after correction for multiple comparisons. Thus our investigation did not find that degree of white matter injury (i.e., structural integrity) between nodes of the DMN was associated with impairment in the functional and neurocognitive outcomes examined, which is in contrast with previous studies that have found that integrity of white matter after TAI was related to injury severity and functional outcome (Kraus et al.,

2007; Felmingham et al., 2004). Differences across studies may be related to sample characteristics, use of different outcome measures, and differences in neuroimaging analyses. For example, it is possible that we reconstructed only healthy tracts (i.e., those containing FA above the threshold value of 0.3) between DMN nodes. This procedural difference may have artificially reduced the association between structural integrity and outcome as only minimally injured tracts were available for analysis. The nature of our sample may have also contributed to fewer significant associations between structural integrity and outcome, as our TAI sample was evaluated on average more than seven months post-injury, and a majority was cognitively recovered at the time of evaluation.

In conclusion, we integrated advanced neuroimaging modalities to study the DMN after TAI to determine whether they can be used as potential neuroimaging biomarkers of TAI. Although the structural integrity of three DMN-related tracts showed some degree of compromise, the structural and functional connectivity measures for this network were not strongly associated in our sample, suggesting integrating DTI and fcMRI in a monosynaptic manner may not be useful as a biomarker in chronic TAI. Additionally, structural connectivity of the DMN was not correlated with the measures of clinical outcome that were examined.

SECTION III: INTEGRATED CONCLUSIONS

This broad investigation examined the usefulness of advanced neuroimaging modalities as potential biomarkers of TAI. Sahu et al. (2011) generally defined a biomarker as "anything that can be used as an indicator of a particular disease state or some other biological state of an organism." Biomarkers are necessary because they allow us to better understand disease spectrum with applications in epidemiological research, clinical trials, screening, and diagnosis and prognosis. Our studies emphasize that for a biomarker of TBI to be useful it must show discriminant and construct validity.

TBI is a considerable public health problem with limited effective treatments despite numerous clinical trials. Animal models are informative but are not generalizable to human TBI because of the heterogeneity of disease. Interest in imaging-based biomarkers of TBI has increased as they may reduce variability due to injury severity and location in a noninvasive manner, and may serve as a surrogate for clinical outcome. Pathological changes in white matter often occur following TBI and studies have shown that functional connectivity of cortical brain regions connected by disrupted white matter tracts are often compromised following TAI. Some of these cortical areas correspond to regions that comprise the DMN, a reliably elicited, low frequency resting -state network that is suppressed during a task and activated when at rest (Ames, 2000; Atwell et al., 2004; Raichle et al., 2001; Raichle et al., 2006; Shulman et al., 2004). The few

studies that have combined RS-MRI and DTI to specifically study the DMN have focused on healthy individuals (Greicius et al. 2009; Skudlarski et al., 2008; Supekar et al., 2010; van den Heuvel et al., 2009). Prior to this investigation, one study combined modalities and demonstrated their promise as useful biomarkers of TBI specifically focused on mild TBI (Mayer et al., 2011), however, little is known about the DMN connectivity disruption across the entire spectrum of TBI. As such, our studies have added to the literature, as we investigated the use of RS-MRI and DTI to better understand the DMN following complicated mild to severe TBI.

The first study examined three approaches to analyze DMN integrity from RS-fcMRI, including a global spatial correlation coefficient, network-wide integrity measure, and between-node correlations. The purpose was to identify the utility of each method to distinguish between healthy and brain-injured individuals, and determine whether observed differences have clinical significance. This study concluded that all three methods converged on the same finding: functional connectivity within the DMN is compromised after TAI. These findings support the hypothesis that all three approaches distinguish between TAI and healthy brains. These findings are consistent with existing literature studying the DMN in clinical populations, such as MS (Rocca et al., 2010) and AD (Firbank et al., 2007; Greicius et al., 2004; He et al., 2007, Rombouts et al., 2005; Sorg et al., 2007; Wang et al., 2006; Greicius et al, 2007),

which also show compromised functional connectivity of this network in patients compared to controls. The hypothesis that functional connectivity would be significantly and positively correlated with clinical outcome was not supported, as no significant correlations existed after correction for multiple comparisons.

The second investigation integrated fcMRI and diffusion tensor tractography to determine the relationship between structural and functional connections within the DMN. Additionally, reconstructed white matter tracts within this network were examined to detect compromise after TAI. Measures of structural and functional connectivity within the DMN were minimally correlated among patients. Furthermore, none of the reconstructed DMN tracts were significantly different between groups for both measures of white matter integrity (i.e., FA and MD). These findings only partially support our hypotheses that 1) integrity of DMN-related *functional* connectivity is positively associated with integrity of DMN-related *structural* connectivity, and 2) DMN-related tracts differentiate patients and controls. Our third hypothesis, that structural connectivity would be positively correlated to clinical outcome, was not supported as none of the correlations remained significant after correction for multiple comparisons.

This two-part investigation illustrated that imaging-based biomarkers of TAI are plausible through the use of RS-MRI and DTI technology. Study 1revealed compromise to the functional integrity of the DMN after TAI,

suggesting it may be used as a biomarker of TAI. The second study extended the first investigation by demonstrating that structural connections exist between functionally connected areas of the DMN, but our reconstructed tracts did not show much compromise in patients with chronic TAI. Both studies revealed that the degree of compromise to the DMN is not significantly associated with clinical outcome in chronic TAI, suggesting these markers may not have the clinical relevance necessary for use as a biomarker at the chronic stage of injury. These markers may have clinical significance at an earlier phase of injury, as these markers were assessed approximately seven months post-injury, and the sample was relatively well-recovered.

Limitations and Future Directions

While these studies shed light on compromise to a well-known resting-state network following TAI, the degree of recovery among our patients at the chronic stage, small sample size, and poorly matched controls limit generalization of our findings. Replication of these findings in combination with longitudinal studies are needed to examine disease progression at various time points beyond 6 months. Further, generalizations of our findings are limited by the lack of neuropsychological testing in the control group, as we are left to assume the strength and direction of associations between functional and structural connectivity measures. The use of two different scanners may be considered a limitation, as this may introduce additional variability to account for; however,

this may also be considered a strength, as neuroimaging biomarkers must be reliable across scanners for practical and clinical utility. Last, given known difficulties with executive function after TBI, other functional brain networks such as the central executive network (CEN) or salience network (SN) may have a stronger association with cognitive outcome after brain injury and be a more useful neuroimaging biomarker.

APPENDIX A

Additional Background

Statement of the Problem

The disease burden of traumatic brain injury (TBI) makes it a considerable public health concern. In the United States alone, the incidence of TBI is estimated to range between 92 and 250 per 100,000 annually (Thurman et al., 1999). Brain injuries are estimated to account for 19.5% of all hospital admissions in the United States (Centers for Disease Control and Prevention, 2006). Each year, approximately 275,000 patients are hospitalized with TBI and 1.5 million cases of milder TBI that do not require hospitalization (Centers for Disease Control and Prevention, 2006; Langlois et al., 2006). While falls are the leading cause of TBI (35.2%) and result in the greatest number of emergency department visits, the leading cause of TBI-related death is motor vehicle–traffic injury (Centers for Disease Control and Prevention, 2006; Langlois et al., 2006). Traumatic axonal injury (TAI) occurs in most motor vehicle collisions (MVCs), is characterized by microscopic axonal lesions that commonly appear in subcortical white matter of patients with acceleration-deceleration type TBI. DAI is the predominant mechanism of injury in 40% to 50% of TBIs requiring hospital admission, and it is likely that DAI is a component of injury in all cases of TBI resulting from high-speed motor vehicle collisions (Meythaler et al, 2001).

Over 5.3 million Americans live with TBI-related disabilities and it is the greatest cause of disability in males under 24 years of age (Choi & Bullock, 2001; Doppenberg, Choi, & Bullock, 1997; Alexander, 1995). On the modern battlefield, TBI is also a frequent cause of morbidity and mortality. Closed head injuries have become a common battlefield injury resulting from the use of improvised explosive devices in Operation Iraqi Freedom and Operation Enduring Freedom (Okie, 2005). A recent review by Meyer et al. (2008) indicated that TBI may account for up to one third of battle-related injuries in today's wars.

The costs of severe TBI to the individual, family, and society are extremely high (Lehmkuhl, et al., 1993; Kraus & McArthur, 1996; Meythaler, 2001). TBI frequently results in significant morbidity, and is responsible for a disproportionate loss of productive years of life. Despite major advances in the medical, surgical, and rehabilitative management of TBI over the past two decades, each year approximately 52,000 deaths result from TBI (Centers for Disease Control and Prevention, 2006). There are an estimated 26,000 trauma deaths per year due to TBI, with another 20,000 to 45,000 survivors suffering significant physical or neurobehavioral sequelae resulting in functional loss, and the direct costs are over $25 billion annually (Meythaler et al., 2001). As a consequence of TBI, approximately 50,000 individuals each year are left with long-term physical, cognitive, behavioral, and social limitations that impede their

independence, ability to work, and overall quality of life (Langlois & Cramer, 2004).

Clinical diagnosis of TBI is supported by neuroimaging techniques such as computed tomography (CT) scanning, magnetic resonance imaging (MRI), and single-photon emission CT scanning (Anderson, Taber, & Hurley, 2005; Bigler, 2005). However, these imaging modalities are limited in the extent to which they can visualize and diagnose axonal injury. For example, CT scanning has low sensitivity to diffuse brain damage, and these injuries are not always visible on T1- and T2-weighted magnetic resonance imaging (MRI) and CT (Bigler, 2005). In terms of functional imaging, single-photon emission CT scanning detects regional blood flow abnormalities that are not necessarily related to structural damage (Bigler 2005; Wang et al., 2005). Diffusion Tensor Imaging (DTI), however, can identify axonal injury acutely after TBI, and may be a useful biomarker for DAI as it correlates with functional and neurocognitive outcomes (Huisman et al., 2004; Sidaros et al., 2008; Wang et al., 2008).

TBI Subtypes

TBI is a heterogeneous condition. Despite the diverse circumstances under which brain injuries may be acquired, two principal mechanisms of brain injuries have been described.

Focal Injuries. The first mechanism includes contact injuries, which may occur when an object strikes the head or when the brain comes into contact with

the skull and affects a circumscribed area. This is also referred to as a focal injury (Roebuck-Spencer & Sherer, 2008). While focal injuries are not the focus of this study, a brief discussion on the topic is warranted given that they often co-occur in diffuse injuries.

Focal injuries may include scalp injury, skull fracture, surface contusions, and associated intracranial hematomas (Roebuck-Spencer & Sherer, 2008). Contusions often indicate brain damage following TBI, with characteristic distribution involving the frontal and temporal poles, the lateral and inferior aspects of the frontal and temporal poles, and less commonly the inferior aspects of the cerebellum (Adams et al., 1982; Gennarelli & Graham, 2005; Holbourn, 1943).

Intracranial hematomas often follow TBI and are the most common cause of serious clinical deterioration in patients who initially present well (Roebuck-Spencer & Sherer, 2008).They may include the following: 1) epidural hematoma (4%) or 2) intradural hematoma (56%), comprised of subdural hematoma, subarachnoid hematoma, discrete intracerebral or intracerebellar hematoma "not in continuity with the surface of the brain", or intracerebral or intracerebellar hematoma "in continuity with related subdural hematoma." (Silver, McAllister, & Yudofsky, 2005) In moderate to severe TBI, subarachnoid hematoma occurs in 3% of patients and typically occurs in conjunction with surface contusions (Roebuck-Spencer & Sherer, 2008). When present, subarachnoid hematoma is

related to worse outcome at time of discharge from the acute hospitalization and worse neuropsychological and vocational outcome at one year post-injury (Hanlon et al., 2005). Epidural hematoma is a convex shaped collection of clotted blood between the skull and dura. This type of hematoma often results from temporal bone fracture and tearing of the middle meningeal artery; however, it can also occur in relation to the frontal or parietal aspects of the brain (Roebuck-Spencer & Sherer, 2008). The source of bleeding is arterial, which causes the hematoma to develop rapidly. It can be life threatening if not treated quickly, but there is typically little associated underlying brain damage (Gennarelli & Graham, 2005). Subdural hematomas result from rupture to bridging veins between the upper surface of the brain to the sagittal sinus (Gennarelli & Thibault, 1982). Subdural hematomas tend to cover a large area and often appear crescent- shaped on neuroimaging because this blood can spread freely throughout the subdural space. Often, they are large enough to act as significant mass lesions and have been reported in between 26% to 63% of blunt head injuries (Roebuck-Spencer & Sherer, 2008).

Diffuse Injuries. A second mechanism includes acceleration/deceleration injuries which result from unrestricted movement of the head resulting in "shear, tensile, and compressive strain on brain tissues" (Gennarelli & Graham, 2005). These injuries affect the brain in a widespread pattern. In diffuse injuries, subsequent tissue injury is characterized by axonal stretching, disruption, and

eventual separation of fibers (Gennarelli & Graham, 2005; Xu et al., 2007). Diffuse axonal injury can include traumatic axonal injury, which often results from diffuse injuries with an acceleration/deceleration mechanism (Gennarelli & Graham, 2005). Traumatic axonal injury is likely the consequence of most TBIs after a high speed motor vehicle collision (Bennett et al., 1995).

Mechanism of TAI

TAI is the predominant mechanism of injury in 40% to 50% of traumatic brain injuries requiring hospital admission in the United States (Meythaler et al., 2001). Disruption of neurofilament subunits within the axonal cytoskeleton due to acceleration and deceleration inertial forces over time causes the structural (axonal/myelin) damage noted in these patients.

The sustained rotational acceleration force disrupts axolemma and cytoskeleton in multiple brain regions (Gaetz, 2004; Graham et al., 2000). The resulting loss of axonal transport may or may not lead to axonal swelling. Both loss of axonal microtubules leading to progressive axonal swelling, and neurofilament compaction without axonal swelling, have been observed within 30 minutes post-injury in experimental TBI (Goetz, 2004; Graham et al., 2000). Subsequent secondary axotomy starts to occur four hours post-injury (Graham et al., 2000; Stone et al., 2001). Direct tearing of axons by mechanical force is also possible in the most severe cases (Povlishock & Katz, 2005).

Human postmortem examinations show cytoskeletal disruption within 4-6 hours post-injury and "disconnection of swollen axons from their distal segment" between 1-7 days (Gaetz, 2004). The microscopic features correspond to Wallerian-type axonal degeneration as the axon disintegrates. This is thought to possibly be due to metabolic disruption from damage to the internal organelles and a loss of membrane integrity (Meythaler et al., 2001). Over several years, secondary Wallerian degeneration persists and results in degeneration and atrophy of gray and white matter in various brain areas (Williams et al., 2001; Wilson et al., 2004).

TAI is linked to coma of immediate onset and associated with low Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974) scores (Xu et al., 2007). The anatomical sites commonly affected by TAI are centroaxial white matter structures such as the corpus callosum and fornix, corticomedullary junctions located in the frontal and temporal regions, the upper brainstem, and deep gray matter (Adams et al., 1982; Amaral, Insausti, & Cowan, 1984; Meythaler et al., 2001; Ng, Mahaliyana, & Poon, 1994). TAI includes pathologies such as micro-hemorrhages, tissue tears, and diffuse vascular injury seen throughout the brain (Wang et al., 2005). The cerebral commissures and white matter tracts of the brainstem are vulnerable to stretching and shearing as a result of mechanical forces (Gennarelli, 1983). Injury to axon bundles causes disruptions in cognitive

functioning, but the association between degree of white matter compromise and neuronal function is not entirely known (Xu et al., 2007).

Neuroimaging and TAI

Neuroimaging is a common tool used to assist with clinical management of TAI; however, some neuroimaging modalities are less informative than others with this type of injury. Advanced magnetic resonance imaging technology is improving understanding of the pathophysiology underlying disease processes and neurologic conditions such as TAI.

Computed Tomography (CT). CT scanning has been part of the routine evaluation of acute and chronic TBI since the 1970s (Haydel et al., 2000). CT is the most common imaging modality used in the acute phase of head injury to detect skull fractures, hemorrhage, and parenchymal injury. Conventionally, CT has been used for: 1) the acute identification of focal injuries such as extra-axial or parenchymal hemorrhage which may require emergent neurosurgical interventions, 2) the exclusion of life threatening conditions such as midline shift or incipient herniation, or 3) the identification of conditions that may require intensive care monitoring, such as small hematomas that may subsequently expand or traumatic subarachnoid or intraventricular hemorrhages which may result in post-traumatic hydrocephalus (Corral et al., 2009; Kurka, Sivak, & Kucera, 2006; Suskauer & Huisman, 2009). CT scans also reflect the extent of vasogenic edema and depict the demarcation of boundaries between normal and

damaged brain tissue, information that may be useful prognostically during rehabilitation and community re-integration (Cenic et al., 2000; Schwartz, 1995). In patients with TBI, an understanding of the pathophysiology, informed by neuroimaging, helps to formulate clinical diagnosis during the rehabilitation and promote better understanding of clinical consequences (Povlishock & Katz, 2005). In turn, a better understanding of the clinical consequences informs prognosis, which can guide rehabilitation planning (Povlishock & Katz, 2005).

Clear advantages of CT imaging include how quickly and easily it can be performed on patients requiring life support or other medical equipment (e.g., heart pacemaker) (Bigler, 2005). As such, it is the method of choice for the acute assessment of patients with TBI. However, CT findings often do no relate well to neurobehavioral outcome at the time of discharge from rehabilitation, which makes the accurate prediction of outcome from acute CT findings alone difficult or impossible (Dikmen et al., 2001; Temkin et al., 2003). Assessment of injury severity through CT is critical for initial neurosurgical and ICU-based management of care, but these imaging results are only modestly associated with long-term functional outcome. CT is most beneficial in patients with severe TBI, as abnormalities identified by this modality have a predictive value of 77% -78% for favorable outcome (Corral et al., 2009; Naalt et al., 1999a). In mild to moderate brain injury, CT is useful in identifying focal traumatic lesions that may affect clinical disposition, but it is a poor tool for prediction of long-term

outcome. In this population, it has been shown that the number of abnormalities identified by acute CT is not associated with Glasgow Outcome Score (GOS; Jennett & Bond, 1975) or Glasgow Outcome Score - Extended (GOSE; Wilson, Pettigrew, & Teasdale, 1998) (Corral et al., 2009). Moreover, approximately 20% of patients who sustain mild to moderate brain injury with no significant abnormalities identified by acute CT have significant problems returning to work (Naalt et al., 1999b). This may be due, in part, to the inadequate sensitivity of CT to detect the presence of diffuse microstructural white matter damage that is characteristic of TAI.

Magnetic Resonance Imaging (MRI). While MRI has superior resolution and anatomic reliability than CT, it is often not used acutely because of its susceptibility to metal and motion artifact, incompatibility with certain life-support equipment within the MR environment, length of scan time, and decreased sensitivity (compared with that of CT) in detecting skull fractures (Bigler, 2005). The anatomic specificity of MRI approximates gross brain anatomy, can be done in any plane, and it is more sensitive to axonal shear injuries than CT (Bigler, 2005; Garnett, 2001). Functional MRI (fMRI) has led to improved understanding of the brain structures involved in aspects of cognitive functioning, and the deviation from normal brain activation among patients with TBI (Levin, 2003; McAllister et al., 2001). Using a working memory activation model, Christodoulou et al. (2001) reported diffuse, lateralized fMRI activation

among patients with moderate TBI as compared to healthy controls. They speculated the diffuse activation likely reflected the recruitment of additional cerebral resources to perform the task.

MRI is an imaging modality that provides higher spatial resolution than CT, allowing for improved detection of less obvious traumatic lesions such as microhemorrhages, small contusions, and TAI (Gentry, 1988; Lagares et al., 2009; Orrison et al., 1994; Suskauer & Huisman, 2009). This modality may be used within the subacute phase of injury or when the neurologic status of the patient indicates a more serious injury than suggested by CT findings. Conventional MRI sequences include T1, T2-weighted, and Fluid Attenuated Inversion recovery (FLAIR). T1-weighted sequences are susceptible to the presence of blood or fat in brain tissue depicted by high signal intensities. However, this imaging modality offers minimal diagnostic specificity as abnormalities seen on T1 sequences generally indicate the presence of multiple causes of injury such as hematomas, parenchymal lesions or vascular tumors (Cenic et al., 2000; Chan et al., 2003). T2*-weighted gradient-echo MR imaging detects brain hemorrhage better than T1 images, but high signal intensities from the cerebrospinal fluid (CSF) in these images complicates the identification of TAI lesions. FLAIR MRI imaging detects cerebral edema and allows for easier identification of injured tissue, as it nullifies CSF signal and greatly increases the contrast between normal and abnormal brain matter (Ashikaga, Araki, & Ishida,

1997; Chan et al., 2003; Lagares et al., 2009). In addition, FLAIR-weighted MRI can be used to quantify the degree of white matter damage after trauma (Marquez de la Plata, 2007; Pierallini et al., 2000; Scheid, 2006).

Functional Connectivity Magnetic Resonance Imaging (fcMRI).

Functional connectivity of blood oxygenated –level dependent (BOLD) signal between regions can be derived from fMRI. The mechanism that underlies fMRI begins with the vascular system, which supplies cells with glucose and oxygen (Huettel, Song, & McCarthy, 2004). Oxygen is bound to hemoglobin molecules and the magnetic properties of oxygenated and deoxygenated hemoglobin can be used to construct images based on the BOLD contrast (Huettel, Song, & McCarthy, 2004). The BOLD contrast results from changes in the magnetic properties of water molecules, which in turn reflect the influence of paramagnetic deoxyhemoglobin, a physiological correlate of oxygen consumption (Huettel, Song, & McCarthy, 2004). Oxygen consumption itself is a correlate of a change in "neural activity evoked by sensory, motor, and /or cognitive processes" (Huettel, Song, & McCarthy, 2004). FcMRI is defined as synchronized neuronal activity between anatomically separated but functionally related brain regions during a task or in the resting state (Biswal et al., 1995; Horwitz, 2003). It is based on determining brain regions that demonstrate temporally correlated BOLD signal (Biswal et al., 1995; Peltier & Noll, 2002).

It is known that at rest, healthy individuals demonstrate a pattern of functional connectivity in which various brain regions known to be functionally related show synchronous BOLD fluctuations. Clinical populations with compromised white matter tend to exhibit connectivity patterns that deviate considerably from those observed among healthy brains (Hedden et al., 2009; Wang et al., 2006). The use of fcMRI has led to improved understanding of the relationship between compromised white matter and associated function seen in various clinical populations, such as TBI, Multiple Sclerosis and AD (Lowe et al., 2008; Audoin et al., 2006; Duong et al, 2005; Lowe et al., 2002; Christodoulou et al., 2001). Wang et al., (2008) and Xu et al. (2007) examined the integrity of white matter after TAI and found significant compromise to structures likely involved in the connectivity of the DMN. Functional connectivity has also been shown to be reduced in patients with MS when compared to healthy age and gender matched controls (Lowe et al., 2002). Allen et al., (2007) found that patients with AD demonstrated reduced hippocampal functional connectivity, including an absence of connectivity with the frontal lobes, while healthy controls showed hippocampal functional connectivity with diffuse cortical, subcortical, and cerebellar sites. It is believed that for brain regions to be functionally related that there is an underlying structural or white matter connection between them. Advances in imaging have allowed for the noninvasive study of white matter, such as diffusion tensor imaging (DTI).

Diffusion Tensor Imaging (DTI). There is growing support for use of DTI as a diagnostic tool to identify and quantify the degree of white mater injury in patients with TBI. DTI is a relatively new MRI technique developed in the mid-1990s that provides information about white matter microstructure in vivo and is based on the technology used in MRI (Basser, Mattiello, & LeBihan, 1994; Huppi, 2001). DTI directly measures features of myelination that are functionally relevant as opposed to fMRI, which can indirectly measure myelination levels through changes in iron content (Klingberg et al., 1999). The term "diffusion tensor" refers to the matrix of vectors that describe the water molecule diffusion at each voxel in the magnetic resonance image (Mukherjee & McKinstry, 2006).

Two biological principles of brain organization underlie DTI: 1) White matter projections in the brain follow orderly projection routes (Bigler, 2005). More specifically, these are anterior-posterior, lateral, and inferior-superior projections; and 2) White matter integrity can be assessed by applying the principle of anisotropy. DTI yields anatomical images of structural integrity by measuring diffusion of water molecules (Ramnani, Behrens, & Matthews, 2004). Diffusion can either be isotropic (free and equal in all directions) or anisotropic, restricted by barriers such as membranes. Using DTI, the orientation of pathways and can be defined. Fractional Anisotropy (FA) maps of the brain can then be created in which brighter voxels represent greater anisotropy (Bigler, 2005). FA varies between 0 (maximal isotropic diffusion) and 1 (maximal anisotropic

diffusion). FA is affected by factors such as the thickness of the myelin sheath and integrity of the axon membrane and cytoskeleton. The mean diffusivity (MD) is another commonly used measure derived from DTI. It represents the distance water molecules may freely diffuse" (Beaulieu, 2002). Increases in MD have been linked to demyelination and localized edema (Beaulieu, 2002).

In pathologic conditions affecting microstructure of white matter tracts, FA decreases as a consequence of breakdown of myelin and downstream nerve terminals, axonal swelling, and increased extracellular space (Wilde et al., 2006). DTI has shown disruptions in the corpus callosum, internal capsule, and centrum semiovale in patients who have sustained mild TBI, (Inglese, et al., 2005). Investigators have used DTI to better characterize TAI. For example, Arfanakis et al. (2002) compared five patients with mild TBI scanned within 24 hours of injury and 10 healthy controls. They found differences in FA between the two groups in five white matter regions (anterior and posterior corpus callosum, external capsule, and anterior and posterior internal capsule). These differences were less evident when patients were scanned 1 month after injury. In 2004, Huisman et al. found significant reductions in FA in the internal capsule and splenium of the corpus callosum of 20 patients scanned within 7 days of injury. They further reported that FA correlated with acute GCS and modified Rankin Score ($r = 0.65$, $p < 0.001$; and $r = 0.74$, $p < 0.001$, respectively) upon discharge from the hospital. Both groups of investigators used a region of interest (ROI)

approach to identify FA abnormalities in regions known to be commonly affected in TAI. Diffusion tensor tractography is a technique used to three-dimensionally reconstruct white matter structures based on the directionality of water diffusion within each voxel. White matter tracts are reconstructed consistent with known neuroanatomy using either deterministic or probabilistic methods (Mori et al., 1999). Using ROIs and DTI tractography, which allows measurement of FA in specific white matter tracts, Wilde et al. (2006) reported similar results in children with TBI. They also found that FA was correlated with cognitive processing speed and performance on an interference resolution task (i.e., Flanker task).

The DMN

The concept of the DMN was first introduced into the literature in by Raichle et al. in 2001. Since then, it has quickly become a major theme in contemporary cognitive and clinical neuroscience. The concept of the DMN stems from a body of fMRI literature that demonstrates temporal correlations in the BOLD signal of spatially distinct brain regions which are presumed to reflect inherent functional connectivity (Raichle et al., 2001). This literature shows a consistent pattern of deactivation across regions of this network that occurs during the initiation of task-related activity and is sometimes referred to as a task-negative network (TNN) (Biswal et al., 1995; Cordes et al. 2001; Raichle et al., 2001). These regions include posterior cingulate cortex (PCC), medial frontal cortex (MFC) and lateral parietal cortices. The DMN shows a high resting

metabolism, "deactivation" during cognitively demanding task performance (Raichle et al., 2001; Shulman et al., 1997), and increased activity during social cognitive tasks (Harrison et al., 2008). The collective function of the DMN regions remains unknown, but the individual brain regions comprising it are believed to be involved in integration of autobiographical, self-monitoring and social cognitive functions (Spreng et al., 2009). Buckner and Carroll (2007) suggested that the PCC is activated during tasks involving autobiographical memory and self-referential processes and Amodio and Frith (2006) found that the MFC was associated with "social cognitive processes related to self and others." Even though each region presumably relates to a unique set of functions, it is important to note that this network is suppressed during cognitively demanding tasks and appears to be required for accurate behavioral performance (Kelly et al., 2008; Polli et al., 2005; Weissman et al., 2006). Activity during the resting state has been termed the "default-mode" of brain activity and refers to a state in which an individual is awake and alert, but not actively involved in an attention demanding or goal-directed task (Raichle et al., 2001).

The degree of functional connectivity between regions of the DMN is thought to be affected following TBI. The basic physiological mechanism of functional connectivity in the DMN is still not well understood and the interpretation of changes of its intensity remains uncertain (Skudlarski et al., 2008). It is speculated that for connectivity to be present between nodes of brain

networks, then there must be a structural or white matter fiber path connecting them and the strength of the functional connectivity depends on the integrity of the anatomical connection (Greicius et al. 2009, Skudlarski et al., 2008; Supekar et al., 2010; van den Heuvel et al., 2009).

Neuropsychological Correlates of TBI

The extent of cognitive impairment following TBI reflects several factors, including the severity of TAI as indicated by the length of LOC, posttraumatic amnesia (PTA), the extent of atrophy, and the location, depth, and volume of focal cerebral lesions (Katz & Alexander, 1994; Wilson et al., 1995). Additional important factors include the patient's age, preexisting morbidities, and the occurrence of significant extracranial or systemic injury (e.g., hypoxia or hypotension) (McCullagh & Feinstein, 2005). While variability exists in the pattern of cognitive dysfunction in individual patients with moderate to severe TBI, the most commonly affected areas of cognitive functioning include attention, processing speed, memory, language, and executive functioning.

Attention. Impairment in attention is prevalent after TBI across all injury level severity. During the early phases of recovery patients may demonstrate impaired awareness, distractibility, and an inability to concentrate for more than a few minutes (Katz, 1992). At later stages of recovery, attention deficits may only be revealed through more thorough testing (Katz, 1992).

Attention is believed to reflect the interactions of several widely dispersed neural networks. As such, focal or diffuse injury in TBI can impair different aspects of attention (McCullagh & Feinstein, 2005). Given that attention is considered to underpin all aspects of cognition, even mild impairments can inhibit other processes, such as the capacity for new learning (McCullagh & Feinstein, 2005). Mental slowing, difficulty following a conversation, losing "train of thought," and difficulty attending to more than one thing at once are common subjective complaints (McCullagh & Feinstein, 2005; Van Zomeren & Brouwer, 1994).

Processing Speed. Impairment in processing speed is also prevalent after TBI across all injury severity levels and is thought to result from diffuse white matter damage incurred during TBI (McCullagh & Feinstein, 2005). Impairments in processing speed correspond with the most robust psychometric findings after TBI (McCullagh & Feinstein, 2005). Patients consistently demonstrate impairment on tests of simple and choice reaction time, color naming and word reading time, and symbol digit coding tasks (Ponsford & Kinsella, 1992; Roebuck-Spencer & Sherer, 2008).

Learning and Memory. Memory impairment is common after TBI and is most apparent during the early intervals of retrograde amnesia and PTA. In the post-acute stage, too, however, it is a common subjective complaint (McCullagh & Feinstein, 2005; Van Zomeren & Van den Burg, 1985). Verbal and nonverbal

memory dysfunction has been shown across the range of TBI severity (McCullagh & Feinstein, 2005). Memory problems have been noted to occur across different aspects of memory, including encoding, consolidation, and retrieval (Curtiss et al., 2001).

Memory can be divided into declarative and implicit components. Declarative memory includes episodic memory of personal events and semantic memory for facts, whereas implicit memory refers to memory that occurs outside of conscious awareness, such as procedural learning (Markowitsch, 2000). Impairment in episodic memory is considered to be a characteristic feature following TBI (McCullagh & Feinstein, 2005). Dysfunction has been reported at all stages of episodic processing, including encoding, consolidation, and retrieval (Curtiss et al, 2001; Vanderploeg et al., 2001). One example includes failure to apply efficient learning strategies, such as grouping words by semantic categories (Curtiss et al., 2001). Overall, tasks requiring effortful and controlled processing show the largest degree of disruption following TBI. Implicit memory is thus is relatively spared following TBI, which is thought to occur because it requires minimal effort and controlled processing compared to declarative memory (Shum et al., 1996). Post-TBI, MRI findings have consistently showed hippocampal atrophy, a structure which plays a strong role in episodic memory (McCullagh & Feinstein, 2005; Tate and Bigler, 2000).

Executive Functioning. Executive dysfunction following TBI is common and largely involves the frontal lobes and their projections (Crepeau & Sherzer, 1993; Hart et al., 2003; Roebuck-Spencer & Sherer, 2008; Sherer et al. 2003; McCullagh & Feinstein, 2005; Stuss & Levine, 2002). Executive functions are said to "govern and use subordinate mental activities such as attention, memory, language, and perceptual functions in the mediation of real-world problems" (McCullagh & Feinstein, 2005) and are considered to be one of the critical cognitive determinants of independent functioning and return to occupational functioning (Crepeau & Sherzer, 1993; Hart et al., 2003; Roebuck-Spencer & Sherer, 2008; Sherer et al. 2003). More specifically, executive functions include tasks such as planning and establishment of goals; initiating, sequencing, and inhibiting responses; conceptual reasoning; and self-monitoring and self-regulation (McCullagh & Feinstein, 2005). In this domain, deficits in performance on tasks of verbal and design fluency, conceptual reasoning/flexibility, working memory, and planning have been reported (Roebuck-Spencer & Sherer, 2008). The dorsolateral prefrontal circuit is considered important for executive function, as impairments in planning, organization, and working memory have been noted following injury to this area (Alexander & Crutcher, 1990; Cummings, 1993). Similar impairments have resulted from damage at other points along this circuit involving projections to the striatum, pallidum, and thalamus, which return to the prefrontal cortex (Cummings, 1993).

Summary

Structural imaging methods such as CT and conventional MRI possess many limitations in their association with neurobehavioral outcome after TBI. They provide a gross inspection of the macroscopically visible brain; however TAI occurs at the microscopic (neuronal or synaptic) level and neuroimaging the question of brain pathology is not possible with this level or resolution. Despite this broad limitation, the understanding of neurologic illnesses impacting white matter has benefited from neuroimaging techniques such as RS-MRI and DTI tractography. Recent studies examining integrity of white matter after TAI have found significant compromise to structures which are likely involved in the connectivity of the DMN (Wang et al., 2008, Xu et al., 2007). Few studies have investigated the relationship between functional connectivity and white matter integrity in clinical populations, however. Of those, the focus has been on the AD and MS populations (Guye, Bartolomei, & Ranjeva, 2008). To date, only one study has investigated the relationship between functional connectivity and white matter integrity among patients following TBI, and their sample was comprised of individuals with mild TBI.

This investigation is twofold and corresponds to two separate studies for examining the utility of state-of-the-art neuroimaging modalities as biomarkers of TAI. The first study uses three approaches to analyze DMN integrity from RS-MRI (including a global spatial correlation coefficient, network-wide integrity

measure, and between-node correlations) to identify the utility of each method to distinguish between healthy and brain-injured individuals, and determine whether observed differences have clinical significance. The second study integrates functional and structural connectivity measures of the DMN to determine the relationship between and extent to which structural and functional connections of the DMN are present in controls and compromised in patients.

APPENDIX B

Aims and Hypotheses

Overarching Aim: Investigate the utility of using RS-MRI and DTI neuroimaging modalities as biomarkers of TAI in a twofold approach, with each part corresponding to a separate study.

Study 1

Aim 1: To identify the discriminant validity of three fcMRI approaches to distinguish between healthy and chronic brain-injured individuals

Hypothesis 1: Using all three approaches, functional connectivity of the DMN will be greater for controls than in patients following TBI.

Aim 2: To determine whether observed differences in connectivity have clinical significance (construct validity) by assessing the relationship between the integrity of functional connectivity and neuropsychological outcomes in patients following TAI.

Hypothesis 2: Functional integrity measures from all three approaches will significantly and positively correlate with functional and neurocognitive outcome.

Study 2

Aim 1: To characterize and distinguish between healthy and chronic brain-injured individuals by integrating functional and structural connectivity measures.

Hypothesis 1: Structural integrity of the DMN will be greater for controls than in patients following TBI.

Aim 2: To examine the relationship between functional and structural connectivity of DMN nodes in healthy controls and patients.

Hypothesis 2: Functional connectivity will significantly and positively correlate with FA and significantly and negatively correlate with MD in patient and control groups.

Aim 3: To examine the relationship between DTI metrics (FA and MD) and functional and cognitive outcomes in patients.

Hypothesis 3: Among patients, FA values between nodes of the DMN will correlate positively with performance on functional and various neurocognitive tests.

Hypothesis 4: MD values of patients between the nodes of the DMN will correlate negatively with performance on functional and various neurocognitive tests.

APPENDIX C

Functional and Cognitive Outcome Measures

Functional Outcome Measures:

Functional Status Exam (FSE) (Dikmen et al., 2001). The Functional Status Exam (FSE), a structured interview, is used to evaluate change in activities of everyday life as a function of traumatic brain injury, including physical, social, and psychological domains. The degree of loss of independence in each area that has occurred as a result of the injury is used as the basis for the rating in those domains. Severity within each area is measured along a four category ordinal scale, ranging from a rating of 0, which signifies no change from pre-injury, to 3, which signifies that the individual is completely dependent on others or that the individual does not perform that activity at all. The values are summed to yield scores between 10 and 40 for survivors, 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 commonly used questionnaire for assessing functional abilities in multiple domains after head injury. It contains questions regarding the patient's ability to follow commands, perform activities of daily living, work, travel, and participate in recreational activities. It also inquires about the presence of emotional disruptions and seizures that appeared after injury.

GOSE scores range from one to eight, with a score of 1assigned to individuals who are deceased at the time of the assessment. A score of, 2 is assigned to individuals 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). The CVLT-II involves the oral presentation of a 16-word list (List A) over five immediate-recall trials. The CVLT-II also includes an interference list (List B) that is then presented for one immediate-recall trial, 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 one last time. The test takes about 20 minutes to administer, excluding the 20-minute delay interval during which other nonverbal testing can be done.

Controlled Oral Word Association Test (COWAT) (Spreen & Benton, 1977). The COWAT is a generative verbal fluency task used to measure organization of concepts. Participants are asked to name as many words as possible that start with a specific letter within 60 seconds.

Dodrill Stroop (Dodrill, 1978). This measure consists of two timed trials. The Stroop Word-Naming trial presents the participant with the words red, green, and blue printed in an incongruous color. For example, the word red is printed in

green ink. The participant is instructed to read the words as quickly as they can. On the Stroop Color-Naming trial participants are asked not to read the word, but to name the incongruous color of the printed words as quickly as they can. This condition measures ability to selectively attend to meaningful information while inhibiting a prepotent response.

Trail Making Test (TMT) (Reitan, 1955). The TMT consists of two parts, A and B. Trail Making Test A (TMTA) requires the participant to draw lines to connect consecutively numbered circles (1 to 2, 2 to 3, 3 to 4, and so on). The participant is instructed to work as quickly as they can and the total time to complete the task is recorded. This test measures visual scanning and processing speed. Trail Making Test B (TMTB) requires the participant to alternate between sequentially numbered and alphabetically labeled circles (1 to A, A to 2, 2 to B, and so on). As in TMTA, the participant is instructed to work as quickly as they can and the total time to complete the task is recorded. This test is used to measure visual scanning, processing speed, and ability to shift mental sets efficiently.

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III, select subtests) (Wechsler, 1997). This investigation utilizes selected subtests from this popular measure of cognitive ability. In the Digit Span Backward (DSB) task, the participant is asked to attend to a string of digits presented orally and repeat them backwards. This task is part of a broader subtest, Digit Span, in which the

participant is required to the repeat number strings forward and backwards. DSB is used to assess auditory working memory. Digit Symbol Coding (DSC) is a timed task in which the participant is instructed to match numbers with symbols according to a key. This subtest measures visual-motor speed and short-term visual memory. Symbol Search (SS) is another timed task 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. This task is used to asses visual-motor processing speed and discrimination.

APPENDIX D

Additional Analyses

Study 1: Associations with Outcome

Correlations between A1 and A2 were not significantly associated with clinical outcome measures (Table 1). Performance on tests of particular cognitive domains was not associated with functional connectivity after correction for multiple comparisons. Prior to correction, the MFC and LLPC functional edge was positively and significantly associated with GOSE and negatively correlated with performance on a test of executive functioning (i.e., COWAT). The MFC and LLPC functional edge was positively and significantly associated with processing speed (i.e., DSC) (Table 2).

Table 1

Correlations between Global Network Integrity and Outcome

Outcome Measure		Global Network Integrity Measure	
		A1	A2
Functional	FSE	-0.109	-0.010
	GOSE	0.164	0.310
Executive Function	DSB	-0.142	0.044
	COWAT	-0.081	-0.077
	TMTB	-0.020	0.100
	Stroop II	-0.003	-0.221
Learning & Memory	CVLT-II Total	0.351	0.173
	CVLT-II SD	0.351	0.264
	CVLT-II LD	0.409	0.266
Processing Speed	DSC	0.112	0.010
	Stroop I	0.035	-0.262
	SS	0.125	0.061
	TMTA	-0.216	-0.174

Note. No significant associations. A1 = PPMC Approach; A2 = Function of the Determinant Approach; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex. FSE = Functional Status Exam; GOSE = Glasgow Outcome Scale-Extended. T-Score values were correlated for the following measures: DSB = Digit Span Backward; 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.

Table 2

Correlations between DMN Edges and Outcome

		FC					
Outcome Measure		LLPC & RLPC	MFC & LLPC	MFC & RLPC	MFC & PCC	PCC & LLPC	PCC & RLPC
Functional	FSE	-0.166	-0.279	-0.237	-0.008	-0.001	0.154
	GOSE	0.307	**0.488***	0.310	0.219	0.249	0.039
Executive Function	DSB	-0.070	-0.053	0.108	-0.192	0.083	-0.176
	COWAT	-0.365	**-0.413***	-0.319	-0.240	-0.050	0.040
	TMTB	-0.113	0.069	0.176	0.193	-0.209	-0.188
	Stroop II	-0.251	-0.277	-0.184	-0.066	-0.246	-0.024
Learning & Memory	CVLT-II Total	-0.030	0.132	0.117	0.234	0.319	0.141
	CVLT-II SD	0.075	0.185	0.160	0.221	0.376	0.220
	CVLT-II LD	0.072	0.351	0.290	0.328	0.281	0.173
Processing Speed	DSC	0.032	**0.536****	0.075	0.208	0.056	-0.195
	Stroop I	**-0.420***	-0.132	-0.279	-0.043	-0.031	-0.088
	SS	-0.055	0.300	0.176	0.223	-0.104	-0.242
	TMTA	-0.158	0.163	0.015	-0.128	-0.289	-0.236

Note. Significant associations prior to False Discovery Rate correction: * = $p<0.05$, **$p<0.01$. LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex. FSE = Functional Status Exam; GOSE = Glasgow Outcome Scale-Extended. T-Score values were correlated for the following measures: DSB = Digit Span Backward; 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.

Study 2 Associations with Outcome

Performance on tests of particular cognitive domains was not associated with structural connectivity after correction for multiple comparisons. Prior to correction, associations with FA were significant for structural edges which included the PCC (See Table 3). For example, all three edges including the PCC were negatively and significantly associated with processing speed (i.e., Stroop I). The FA value of the PCC and RLPC structural connectivity was negatively associated with performance on tests of executive functioning (i.e., Stroop II and COWAT).

Table 3

Correlations between Fractional Anisotropy and Outcome in Patients with TAI

		FA				
Outcome Measure		MFC & LLPC	MFC & RLPC	MFC & PCC	PCC & LLPC	PCC & RLPC
Functional	FSE	0.322	-0.017	**0.435***	0.205	0.107
	GOSE	-0.071	0.224	**-0.516***	-0.281	0.002
Executive Function	DSB	-0.046	0.103	-0.298	-0.023	-0.336
	COWAT	0.285	-0.137	-0.197	-0.342	-0.357
	TMTB	0.115	0.330	-0.325	-0.159	**-0.448***
	Stroop II	0.148	0.138	-0.338	-0.231	**-0.536***
Learning & Memory	CVLT-II Total	-0.083	0.047	-0.072	-0.259	0.163
	CVLT-II SD	0.074	0.072	-0.177	-0.248	0.149
	CVLT-II LD	0.174	0.181	-0.108	-0.252	0.044
Processing Speed	DSC	-0.175	0.369	-0.344	-0.165	-0.096
	Stroop I	-0.141	-0.165	**-0.458***	**-0.694****	**-0.579****
	SS	0.163	0.425	-0.200	-0.129	-0.415
	TMTA	-0.266	-0.050	-0.310	-0.261	-0.299

Note. Significant associations prior to False Discovery Rate correction: * = $p<0.05$, ** $p<0.01$. All correlated cognitive outcome scores are T-Scores. n varies by edge (i.e., MFC & LLPC n =20 ; MFC & RLPC n = 21; MFC & PCC n = 22; PCC & LLPC n =21 ; PCC & RLPC n = 20). LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex. FSE = Functional Status Exam; GOSE = Glasgow Outcome Scale-Extended; DSB = Digit Span Backward; 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.

Prior to correction for multiple comparisons, associations with MD were significant for structural edges, which included the RLPC. For example, both edges including the RLPC were positively and significantly associated with processing speed (i.e., TMTA). The MD value of the PCC and RLPC structural connectivity was positively associated with performance on a test of executive functioning (i.e., TMBT).

Table 4

Correlations between Mean Diffusivity and Outcome in TAI

		MD				
Outcome Measure		MFC & LLPC	MFC & RLPC	MFC & PCC	PCC & LLPC	PCC & RLPC
Functional	FSE	0.151	-0.040	0.064	-0.039	-0.247
	GOSE	-0.362	-0.162	-0.035	-0.040	0.312
Executive Function	DSB	0.245	0.073	0.069	0.124	0.211
	COWAT	0.231	0.110	-0.103	0.242	0.220
	TMTB	-0.045	-0.018	0.046	0.299	**0.462***
	Stroop II	0.317	-0.398	0.154	0.420	0.362
Learning & Memory	CVLT-II Total	0.061	-0.042	-0.245	-0.155	-0.359
	CVLT-II SD	0.068	-0.106	-0.076	-0.108	-0.187
	CVLT-II LD	0.144	-0.133	0.070	0.024	-0.151
Processing Speed	DSC	-0.148	0.010	0.197	0.059	0.173
	Stroop I	0.393	-0.165	0.104	-0.015	0.127
	SS	0.018	0.009	0.197	0.237	0.360
	TMTA	0.160	**0.443***	0.296	0.416	**0.481***

Note. Significant associations prior to False Discovery Rate correction: * = $p<0.05$, ** $p<0.01$. All correlated cognitive outcome scores are T-Scores. *n* varies by edge (i.e., MFC & LLPC *n* = 20; MFC & RLPC *n* =21 ; MFC & PCC *n* =22 ; PCC & LLPC *n* = 21; PCC & RLPC *n* = 20). LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex. FSE = Functional Status Exam; GOSE = Glasgow Outcome Scale-Extended; DSB = Digit Span Backward; 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.

Additional analyses were carried out among all participants and separately by controls and patients to examine the correlation among functional and structural connectivity. The entire group of participants showed a positive and significant association between functional and structural (FA) connectivity of the PCC and RLPC. Negative and significant associations existed between MD and FC of the MFC and LLPC and PCC and LLPC. In the control group only, no associations were significant (Table 5).

Table 5

Correlations Between Functional & Structural Connectivity: Combined Groups

DTI Metric	FC				
	MFC & LLPC	MFC & RLPC	MFC & PCC	PCC & LLPC	PCC & RLPC
FA					
MFC & LLPC	0.140	0.187	0.142	-0.019	0.125
MFC & RLPC	0.403*	0.315	0.379*	0.199	0.162
MFC & PCC	0.089	0.172	0.240	0.141	0.134
PCC & LLPC	0.290	0.152	0.272	0.119	0.109
PCC & RLPC	0.363*	0.309	0.431*	0.559*	0.496*
MD					
MFC & LLPC	-0.378*	-0.204	-0.595**	-0.375*	-0.194
MFC & RLPC	-0.232	-0.247	-0.505**	-0.277	-0.254
MFC & PCC	-0.078	-0.118	-0.278	-0.363*	-0.176
PCC & LLPC	-0.285	-0.125	-0.517**	-0.499*	-0.297
PCC & RLPC	-0.044	0.001	-0.315	-0.307	-0.225

Note. *Significant at 0.05 FDR. Enclosed values indicate the correlations of interest (i.e., correlation between and edge's functional and structural integrity). FA = Fractional Anisotropy; FC = Functional Connectivity; MD = Mean Diffusivity; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex. FA *n* varies by edge (i.e., MFC & LLPC *n* =37; MFC & RLPC *n* =37; MFC & PCC n =39; PCC & LLPC *n* =37; PCC & RLPC *n* =34). MD *n* varies by edge (i.e., MFC & LLPC *n* =37; MFC & RLPC *n* =36; MFC & PCC *n* =38; PCC & LLPC *n* =37; PCC & RLPC *n* =35).

Table 6

Correlations Between Functional & Structural Connectivity in Controls

DTI Metric	FC				
	MFC & LLPC	MFC & RLPC	MFC & PCC	PCC & LLPC	PCC & RLPC
FA					
MFC & LLPC	0.008	0.041	-0.229	-0.274	-0.141
MFC & RLPC	0.267	0.237	0.025	0.049	-0.043
MFC & PCC	-0.051	0.136	-0.165	-0.113	-0.134
PCC & LLPC	0.375	0.148	0.034	0.111	-0.099
PCC & RLPC	-0.133	-0.024	-0.042	-0.204	0.071
MD					
MFC & LLPC	-0.249	-0.095	-0.197	-0.478	-0.136
MFC & RLPC	0.277	0.098	0.153	0.148	0.258
MFC & PCC	-0.201	-0.145	-0.248	-0.148	0.063
PCC & LLPC	-0.415	-0.064	-0.260	-0.465	-0.110
PCC & RLPC	0.157	0.191	0.132	-0.064	0.131

Note. No significant associations. Enclosed values indicate the correlations of interest (i.e., correlation between and edge's functional and structural integrity). FA = Fractional Anisotropy; FC = Functional Connectivity; MD = Mean Diffusivity; LLPC = Left Lateral Parietal Cortex; RLPC = Right Lateral Parietal Cortex; MFC = Medial Frontal Cortex; PCC = Posterior Cingulate Cortex. *n* varies by edge. (i.e., MFC & LLPC *n* = 17; MFC & RLPC *n* = 17; MFC & PCC *n* = 17; PCC & LLPC *n* = 16; PCC & RLPC *n* = 15).

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