FACTORS AFFECTING RESTING-STATE FUNCTIONAL CONNECTIVITY ACROSS THREE INTRINSICALLY CONNECTED NETWORKS IN TRAUMATIC BRAIN INJURY

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DEDICATION

To my wife, Jenny, and to our daughter, Emily.

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by

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THE RELATIONSHIP BETWEEN COGNITIVE FACTORS AND RESTING-STATE FUNCTIONAL CONNECTIVITY IN THREE INTRINSICALLY CONNECTED NETWORKS AFTER TRAUMATIC BRAIN INJURY

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This study investigated the factors that influence post-TBI functional connectivity within three intrinsically connected networks; the default mode network (DMN), central executive network (CEN), and salience network (SN). The aim was to develop a predictive model for each network, based off a combination of cognitive performance, brain volumetric factors, aging/demographic factors, and TBI-related factors. A secondary aim was to examine the relationship between the SN and the anticorrelation (i.e., between-network BOLD signal

correlation) between the DMN and CEN. Participants (n=63) sustained a mild-to-moderate TBI within six-months of participating in the study. They completed a cognitive assessment battery consisting of measures of executive functioning, language, memory, reasoning, and intelligence estimates. They also underwent structural MRI, resting-state fMRI, and completed mood symptom questionnaires. A seed-based, resting-state functional connectivity analysis was conducted for the DMN, CEN, and SN. Measures of brain volumetrics were calculated from the structural MRI. Stepwise multiple linear regressions using cognitive factors, demographic and injury factors, functional outcomes, brain volumetric factors, and symptoms of depression were preformed in order to develop predictive models of DMN, CEN, and SN functional connectivity. A Pearson correlation was used to examine the relationship between SN functional connectivity and DMN/CEN anticorrelation.

The predictive model for the DMN accounted for approximately 50% of the variance within the network, and was comprised of factors which included TBI severity, age at assessment, volumetric factors, and cognitive factors (including attention and abstract verbal reasoning). The predictive model for the CEN accounted for 37% of the network's variance, and was comprised solely of cognitive factors, including verbal ability, attention, and inhibition. The SN model accounted for 45% of the variance, and was comprised of factors that included gender, functional outcomes, volumetric factors, and cognitive factors (including attention and cognitive switching). The functional connectivity within the SN had a trending positive correlation with the degree of anticorrelation between the DMN and CEN. These results not only reveal the factors that contribute to functional connectivity, but they

also highlight the differences between networks, including that the DMN may be more sensitive to volumetric changes and TBI severity than the CEN or SN.

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Default Mode Network (DMN) – A resting-state network that increases in activation in absence of an externally imposed task, and decreases in activation during an externally imposed task. The DMN is typically considered to be composed of the ventral-medial prefrontal cortex (VmPFC), left lateral parietal cortex (LLPC), right lateral parietal cortex (RLPC), bilateral hippocampi, and posterior cingulate cortex (PCC).

Salience Network (SN) – A neural network composed of the anterior insula (AI) and the anterior cingulate cortex (ACC), believed to play a role in activation/deactivation of relevant neural networks and detection of salient external stimuli.

Central Executive Network (CEN) -- A network comprised of the bilateral dorsolateral prefrontal cortex (DLPFC) and the posterior parietal cortex (PPC), believed to play a role in judgment, decision making, working memory, and executive functions.

Blood oxygen level-dependent (BOLD) – A measurement derived from levels of oxygenation in blood, based on the concept that increased neuronal activity will require the bloodstream to deliver greater amounts of oxygen. BOLD is commonly used as a proxy measurement for neural activity used in fMRI.

Resting-state - An imaging modality involving measuring the BOLD response in fMRI while the subject is awake, but at rest, in absence of an externally imposed task.

Functional Connectivity - The degree of correlation between the fluctuations in the BOLD signal in disparate neural areas. Areas that have high degrees of BOLD synchrony are said to have functional connectivity or to be functionally connected.

Cohesiveness: For the purposes of this study, cohesiveness describes whole-network connectedness. The greater the overall functional connectivity within a network, the greater the network cohesiveness. It can also be used to describe the relationship between networks, as the greater the functional connectivity between networks, the greater the internetwork cohesiveness.

Anticorrelation- In the context of functional connectivity, anticorrelation refers to distal neural regions that have a strong negative correlation in BOLD signal fluctuation.

CHAPTER ONE

Introduction

Approximately 1.7 million people suffer a traumatic brain injury (TBI) in the United States each year. Brain injury is one of the leading causes of emergency room visits, and can have drastic impacts on an individual's life (Faul, Xu, Wald, & Coronado, 2010). For example, TBI commonly results in cognitive deficits, including difficulties with memory, cognition, language, adaptive abilities, and other cognitive functions (Arciniegas, Frey, Newman, & Wortzel, 2010; Dikmen, Machamer, Powell, & Temin, 2003). This can lead to social deficits, adaptive skill deficits, and diminished opportunities for employment. However, changes to cognitive ability are not the only sources of disability following TBI. Post-TBI psychiatric issues are increasingly recognized as contributing to functional deficits (O'Donnell et al., 2013). Mood symptoms, anxiety symptoms, and symptoms of PTSD have been reported post-TBI (Zatzick et al., 2007). From where do these deficits and changes arise? What happens in the brain to cause these post-TBI alterations in cognition, emotion, and functional status? One potential answer to these questions may lie in changes to neural networks in the brain. The last decade has seen an increase in research on intrinsically connected networks, identified not by physical neural connections or by cortical geography, but rather by correlations in activity. These correlations in activity are even seen in so-called "resting scans"; neuroimaging conducted while participants are awake, but resting in a scanner. Three such networks are the default mode network (DMN), the central executive network (CEN), and the salience network (SN). Each of these networks is believed to play a role in various aspects of cognition and emotional processes, and all three are believed to be altered by TBI.

Investigating these networks post-TBI, and their relationship with cognitive measures, functional outcomes, depressive symptoms, and demographic factors may shed light into their functioning.

CHAPTER TWO

Review of the Literature

Imaging Modalities

The brain is the ultimate "black box" of the human body. For millennia, mankind understood rudimentary associations between the brain and behavior. Ancient Egyptians, who in antiquity were regarded as having relatively advanced knowledge of anatomy and medicine, recognized that injuries to the head could affect cognitive and motor functioning. Centuries later, the ancient Greeks similarly regarded the brain as the seat of intelligence, though competing theories at the time implied that the brain simply helped cool the blood. Yet, despite thousands of years of behavioral observations, battle injuries, and dissections, the detailed functioning of a live, healthy brain remained a mystery.

In the latter half of the 20th century, several methods emerged that allowed for in-vivo study of the central nervous system. In the 1970s, computed tomography (CT) allowed for the first three-dimensional views of a living brain. In the 1980s, Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) provided a glimpse into the metabolism and function of cerebral architecture. Though initially introduced in the 1970s, improvements in magnetic resonance imaging (MRI) throughout the 1980s resulted in clearer structural images than CT. Furthermore, the risks associated with exposing an individual to the radiation levels associated with CT were avoided with MRI, since MRI measured the response of water-based hydrogen atoms to a strong magnetic field. MRI was also discovered to be sensitive to the paramagnetic properties of blood, including the ferromagnetic differences between oxygenated and deoxygenated blood. This led to the

development of functional magnetic resonance imaging (fMRI) paradigm in the 1990s, which allowed us to overlap functional information onto structural information, further refining the ability to examine in-vivo neural activity. Within the fMRI modality, a marker for brain activity was developed: the blood-oxygen level dependent (BOLD) response. Briefly, this indicator makes use of the paramagnetic properties of blood to measure the rate at which oxygen is released from the bloodstream to nearby neurons, which hypothetically require increasing amounts of oxygen with greater activity. This hemodynamic response to the increased neuronal oxygen demand is theoretically considered to be a marker for neural activity (Ogawa, Lee, Kay, & Tank, 1990). This discovery allowed researchers to examine which areas of the brain required greater amounts of oxygen during particular tasks by observing regional increases in BOLD signal while the patient participated in a cognitively demanding in-scanner task.

One more recent development in neuroimaging is recognition of the utility of resting-state imaging. In contrast to active imaging, participants undergo imaging while they are resting, but awake, in the scanner. Typical instructions to participants in these studies include statements to fixate their gaze on a target cross on a neutral screen, or to close their eyes but remain awake. This method captures the brain's naturally occurring BOLD fluctuations in absence of an externally imposed task. Though once considered to be statistical "noise", these fluctuations are now believed to reveal significant information about the brain and its cognitive abilities. Resting-state imaging, though possessing shortcomings of its own, avoids some of the pitfalls associated with active imaging. For example, a participant's engagement or effort in a task are no longer a concern, nor is the delay in BOLD response that can build

up during repeated trials or blocks of an in-scanner task. Furthermore, the brain does not operate like a simple on-off switch. Though areas of the brain are often considered to be “on” or “activating” in response to a specific stimuli, in reality, the changes in BOLD signal following task engagement are usually relatively small, i.e., less than 5% of the basal rate during rest (Raichle & Mintun, 2006). This represents only a small change in the brain’s overall energy consumption. Thus, even the brain’s “resting” metabolism represents a significant portion of its “active” metabolism, approximately 95%. Since the metabolism of the brain at rest is relatively high, resting-state provides a glimpse into the brain at the state in which it uses most of its energy, and spends a majority of its time. At the same time, the naturally occurring fluctuations in the BOLD signal typically represent a 2-3% signal change, comparable to task-induced changes (Damoiseaux et al., 2006). Furthermore, resting-state analyses offer a greater signal-to-noise ratio than active analyses, as eloquently explained by Fox and Greicius (2010). Therefore, resting-state imaging research provides important information about the inner workings of the brain, and is a valid line of exploration for modern imaging methods.

Functional Connectivity

Within neuroimaging, several different methods exist for examining neural activity. A common technique is simply to measure levels of brain activity via the BOLD response. Since higher levels of BOLD signal are believed to be indicative of greater levels of brain activation, differences in neural activity can be measured between various brain regions, across different time points, and during different tasks. Building on BOLD-inferred neural

activity, a more recent imaging paradigm is to examine the degree to which brain regions display a synchrony of BOLD fluctuation. This is known as functional connectivity, and it can be calculated by correlating BOLD signal change in one area of the brain with BOLD signal change in another area of the brain. Areas of the brain that display a high correlation in their BOLD fluctuation are considered to have "functional connectivity," or to be functionally connected. Studying areas of the brain that are functionally connected has lead to the identification of previously unstudied neural networks (Raichle et al., 2001; Seeley et al., 2007; Sridharan, Levitin, & Menon, 2008), allowed for new ways to examine the relationship between neural regions (Raichle, 2011), and provided new insights into disease (Zhang & Raichle, 2010). Coherent, neural network-related BOLD fluctuations are believed to account for much of the inter-trial variability in signal that, as mentioned before, was once regarded as noise, and may play a role in the variability in human behavior (Fox, Snyder, Zacks, & Raichle, 2006). For example, spontaneous fluctuations in the BOLD signal in the somatomotor cortex have also been related to variability in performance on a simple motor task (Fox, Snyder, Vincent, & Raichle, 2007).

Functional connectivity has been a useful tool for studying the relationship between bilateral brain structures, and exploring regions that have been traditionally difficult to image. For example, Roy et al. (2009) found the bilateral amygdala to have a high degree of functional connectivity in healthy individuals, and could be divided into three distinct sub-networks, based on each network's unique functional connectivity pattern. Resting-state functional connectivity was used to identify bilateral motor neural circuits (the rostral, ventral, and dorsal cingulate motor areas) that had only been hypothesized to exist in

humans, based on research on monkeys (Habas, 2010). Functional connectivity analyses have been useful for verifying theoretical in-vivo connections that were too small to capture with DTI or fMRI resolution. For example, Nioche, Cabanas, and Habas (2009) were able to provide further evidence for neural circuits involving the red nucleus and the substantia nigra, which were too small to accurately image using other in-vivo techniques, by measuring their functional connectivity. Functional connectivity analyses have also been used to study changes in patterns of activation. Hampson, Olson, Leung, Skudlarski, and Gore (2004) were able to study task-related changes in the visual system in response to stimuli, by tracking functional connectivity changes. Functional connectivity has also been used on a larger scale to investigate changes in global, whole-brain connectivity. Balthazar, de Campos, Franco, Damasceno, and Cendes (2013) noted significant differences in whole-brain functional connectivity between healthy controls and patients with Alzheimer's disease, while Bohr et al. (2012) found increased whole-brain functional connectivity in older adults with depression. Skudlarski et al. (2008) used whole-brain functional connectivity maps to demonstrate parity between fMRI and DTI methodology.

Functional connectivity is believed to relate to underlying structural connectivity by the way of white matter connections between brain regions (Quigley et al., 2003). One opportunity to investigate this theory arises from patients with white matter damage, like that which results from traumatic axonal injury (TAI). TAI is essentially a fracturing or shearing of axons following strong rotational and/or acceleration/deceleration forces (Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). Disruption in white matter between functionally connected areas has been shown to correlate with impairments in functional connectivity

between those regions. For example, Sharp et al. (2011) found a significant, large negative correlation between white matter integrity in the corpus callosum (as measured by mean diffusivity from a DTI scan) and functional connectivity in the default mode network following TBI. When examining a sample of TAI patients, Marquez de la Plata et al. (2011) noted a significant decline in interhemispheric functional connectivity between the hippocampi, compared to healthy controls. In a more drastic example, Johnston et al. (2008) studied interhemispheric functional connectivity in an individual with intractable epilepsy, before and after a complete callosotomy. They predicted a sharp decline in interhemispheric functional connectivity, as the corpus callosum represents the major white matter structure that connects the hemispheres. Their hypothesis was confirmed, and the patient displayed a significant decline (88.5%) in functional connectivity acutely post-surgery. Of note, *intra*hemispheric functional connectivity, which was not predicted to be affected by the callosotomy, was preserved. However, the relationship between functional and structural connectivity may more complex than a simple measure of white matter volume and integrity. In a study of the effects of a callosotomy in monkeys, O'Reilly et al. (2013) found significant reductions in interhemispheric functional connectivity post-callosotomy. However, when the researchers failed to sever the anterior commisure, a relatively small interhemispheric white matter connection, the decline in functional connectivity was significantly reduced. The authors theorized that perhaps non-callosoal commisures and indirect structural connections may be enough to maintain functional connectivity in following a callosotomy. Of note, this study was conducted eight months post-surgery, allowing time for reorganization, in contrast to Johnston et al. (2008), who examined a human callosotomy patient acutely post-surgery,

with minimal time for reorganization. As commented on by Uddin (2013), subcortical inputs and neurotransmitter systems may play a role in functional connectivity as well. Honey et al. (2009) noted that regions of the brain lacking strong anatomical connections can still show functional connectivity. However, they hypothesized this may be due to subcortical connections (e.g., thalamic or limbic), signal noise, or the inherently flexible nature of a functionally connected network when compared to a structurally connected network.

While functional connectivity is based on strong positive correlations in BOLD fluctuation, there is also value in examining strong negative correlations. The degree to which the BOLD signal is negatively correlated between two brain regions or networks is known as anticorrelation (Fox et al., 2005). Just as a strong positive correlation and high functional connectivity imply a relationship between two regions or networks, so does strong anticorrelation. Both anticorrelation and strong positive correlation imply the existence of some degree of underlying neurophysiologic structure, which influences positive BOLD synchrony in one situation, and negative BOLD synchrony in the other. Though anticorrelation has been viewed as relating to competition between neural networks (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008), it may also represent inhibitory responses (and cooperation) shared between networks (Liang, King, & Zhang, 2012). However, there is some thought that anticorrelation may simply be a set of spurious negative correlations artificially introduced by preprocessing methods. Murphy, Birn, Handwerker, Jones, and Bandettini (2009) and Weissenbacher et al. (2009) argued that anticorrelation findings may be an artifact of the global signal regression (a form of statistical analysis) commonly used in preprocessing. Subsequent research demonstrated that anticorrelation could be discovered

through methods that did not involve global signal regression; however, and that the results from global signal regression and non-global signal regression methods were similar (Chai, Castanon, Ongur, & Whitfield-Gabrieli, 2012; Liang, et al., 2012). Of note, anticorrelation is not to be confused with an overall lack of correlation, where there is neither positive nor negative correlations of BOLD signal between two brain regions. Lack of correlation does not imply the strong relationship assumed in strong positive correlations or in anticorrelations (Fox, et al., 2005). Rather, it implies an overall lack of relationship between the two areas. However, as noted by Honey et al. (2009), functional connections are more flexible than structural ones. Though two regions may have a lack of functional connectivity at a given time point, they may display functional connectivity or anticorrelation under different circumstances.

Resting-State Network Measurement

Areas of the brain that share strong functional connectivity are increasingly being recognized as belonging to discrete, intrinsic, neural networks. Such networks cannot be located simply by means of an examination of the physical anatomy of the brain, or by tracing the white matter pathways. They become visible when constructed via functional connectivity maps. There are two basic and generally accepted methods for evoking and measuring large-scale resting-state neural networks (Fox & Raichle, 2007). The first is known as independent component analysis (ICA), and the second is known as a seed-based approach. There are several variations on these two methodologies, including some methods that combine aspects of each. With ICA, the BOLD signal for all the voxels in the brain are

analyzed, and statistically separated into spatial areas of high correlation that may represent functionally connected networks (Calhoun, Adali, Stevens, Kiehl, & Pekar, 2005; Calhoun, Liu, & Adali, 2009; Fox & Raichle, 2007). One advantage of this method is that the statistical processes used in the creation of the maps minimize noise intrusions into the signal. This method is useful for finding and identifying multiple networks, regardless of their relation to one another, which makes finding and quantifying anticorrelated networks easier. No *a priori* selection of networks occurs before the analysis, which some ICA practitioners claim reduces researcher bias. However, this approach does have disadvantages. An ICA has the potential to identify a high number of potential networks throughout the brain. The researcher must decide, post-hoc, which network (or networks) best represent their network of interest. Alternatively, if no networks meet the researcher's criteria, an ICA may need to be re-run with changes to the statistical parameters. Additionally, there can be a degree of guesswork when initially setting up an ICA, as the researcher will often have to specify the number of networks the ICA analysis should discover. If set too low, this can lead to a conglomeration of mildly related networks. If set too high, this can lead to a fractioning of coherent networks into smaller, seemingly nonsensical sub-networks.

An alternative to the ICA approach is the seed-based approach, which allows a researcher to identify *a priori* which networks should be analyzed, based on their goals (Fox & Raichle, 2007). A region of interest (ROI) from each network is selected to serve as a "seed" for the network. Statistical programs determine which areas of the brain display significant levels of BOLD signal synchrony with selected voxels within these ROIs. The resulting correlation map (also known as a z-value map) reveals the extent of the desired

network. This method is considered to be a good choice when a research question specifically involves a particular network, as it results in precise, researcher-chosen networks. Though not as strongly robust to noise as an ICA, seed-based approaches have been shown to be sufficiently resistant to noise effects (Z. Li, Kadivar, Pluta, Dunlop, & Wang, 2012). This method is also not without its limits. First, it is difficult to study multiple networks without running multiple calculations, one for each network (Fox & Raichle, 2007). Second, the results from seed-based approaches are highly dependent on the placement of the ROI, and small changes in the location of the network seed can have significant changes on the resulting evoked network, as observed by Margulies et al. (2007). Overall, both methods can produce similar results through significantly different methodology (Joel, Caffo, van Zijl, & Pekar, 2011), and both methods have proven sufficiently reliable in test-retest conditions (C. C. Guo et al., 2012).

The Default Mode Network

One resting-state neural network is the default mode network (DMN). The DMN displays increased activation in absence of an externally imposed task, and is less active during increased cognitive demand, such as while completing externally imposed tasks (Raichle, et al., 2001; Shulman et al., 1997). The regions involved in the DMN were first identified by Shulman et al. (1997) during a meta-analysis of task-induced brain deactivations in PET studies. Mazoyer et al. (2001) noted the self-referential, autobiographical thinking that occurred during these resting-states. Raichle et al. (Gusnard & Raichle, 2001; Raichle, et al., 2001) were the first to use the term “default network” and

outline the generally accepted neuroanatomy of the DMN, which is typically considered to be comprised of the posterior cingulate cortex (PCC), ventromedial prefrontal cortex (VmPFC), and can be expanded to include the bilateral hippocampi, and the bilateral inferior parietal cortexes (LLPL and RLPL) (Buckner, Andrews-Hanna, & Schacter, 2008; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle, et al., 2001). These regions show strong functional connectivity during resting and active states. There exists a degree of controversy as to the inclusion of the bilateral hippocampus with the DMN, with some studies intentionally excluding it from analysis (Arenivas et al., 2012) while other studies make no mention of its involvement (Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011).

Various explanations have been proposed for the function of the DMN, including roles in planning and imagination, consolidation and stabilization of memories, setting the context for future information processing, maintaining activation in frequently used neural pathways, and maintaining episodic memory (Buckner & Vincent, 2007; Greicius & Menon, 2004). Functional connectivity within the DMN, and also between the DMN and areas associated with visual processing, have been associated with greater emotional intelligence traits (Takeuchi et al., 2013). Another hypothesis about the DMN is that it serves to maintain a competitive balance between excitation and inhibition that helps the brain respond quickly to environmental changes, with minimal effort. Essentially, DMN activity keeps the brain in a balanced state where relatively little external stimulus is needed to activate and stabilize other neural networks as needed (Deco, Jirsa, McIntosh, Sporns, & Kotter, 2009), much like a well-balanced scale where little weight is needed to shift the balance in one direction or the

other. One somewhat contrarian view to the role of the DMN is posited by Boly et al. (2008; 2009) who note the existence of the DMN in studies of comatose, anesthetized, or sleeping individuals, and postulate that DMN fluctuations may not reflect conscious thought, but may reflect a deeper, more basic level of brain functioning, though likely not so basic as to be a statistical artifact of respiration, cerebral blood flow, or neurometabolism.

With regards to a role in cognition, diminished deactivation of the DMN (compared to its activation level during rest) during tasks requiring focus has been associated with poorer cognitive performance (Singh & Fawcett, 2008). For example, increased DMN activation during mentally challenging tasks is believed to be related to distractibility (Fassbender et al., 2009) as well as poor performance on tasks of attention (Bonnelle et al., 2011), working memory (Anticevic, Repovs, Shulman, & Barch, 2010) and overall executive function (Damoiseaux et al., 2007). Essentially, DMN deactivation is needed during tasks requiring increased focus. However, the DMN may remain active without measurable impact on performance on simpler tasks. As task difficulty increases, activity level in the DMN decreases (Singh & Fawcett, 2008). In contrast to studies of activation levels, DMN functional connectivity has been shown to positively correlate with performance on working memory tasks; specifically, functional connectivity between the medial frontal gyrus/anterior cingulate cortex and the PCC (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006). Greater levels of functional connectivity were associated with better cognitive performance, indicating that strong cohesiveness within the DMN may be a marker of healthy cognition or cognitive functioning. Activation changes in the DMN have been shown to relate to subsequent changes in activation in other areas of the brain. For example, the degree to

which the DMN is suppressed during a simple sensory task correlates positively with the degree of increase in activation in the somatosensory cortex needed for the task (Greicius & Menon, 2004), which may be indicative of competition between networks, or possibly that a larger, overreaching network has a role in coordinating network activity.

Though the DMN thus far has been discussed as if it were a solitary whole, there is evidence that the DMN may be best conceptualized as cooperating, but dissociable, subsystems. Leech, Kamourieh, Beckmann, and Sharp (2011) examined the differences between the dorsal and ventral PCC. Each displayed a different pattern of functional connectivity during cognitively demanding tasks, with the ventral PCC becoming less integrated with the DMN and more functionally connected with task-positive networks. In contrast, the dorsal PCC became more integrated with the DMN and showed greater anticorrelation with task-positive networks. The researchers theorized that this was due to the PCC's role as a coupling station between the DMN and task-positive networks. This may provide evidence that the DMN is part of a larger neural network comprised of smaller, resting state and task-positive networks. If so, these patterns of connectivity displayed by the PCC may be a potential mechanism by which discrete neural networks could "cooperate" and function together as a larger network. This also reinforces the idea that functional connectivity between networks (internetwork) may be as important as functional connectivity within networks (intranetwork), and a suitable target for further research.

Susceptibility to change within the DMN following TBI

The DMN has been shown to be sensitive to disruption following TBI, though there is disagreement in the literature as to the nature of those changes. Zhou et al. (2012) examined mild TBI patents at two months post-injury, and found declines in functional connectivity between posterior regions of the DMN (namely, the PCC and parietal regions) and increased functional connectivity in the frontal regions (the VmPFC). The authors noted that the posterior decline may explain post-TBI cognitive problems, while anterior increase may relate to symptoms of depression, fatigue, and anxiety that are often reported post-TBI. These findings are somewhat contrary to Mayer, Mannell, Ling, Gasparovic, and Yeo (2011), who found decreased functional connectivity within the DMN and increased functional connectivity between the DMN and right anterior cingulate cortex and lateral prefrontal cortexes in patients with mild TBI, compared to healthy controls. These scans were conducted within three weeks of sustaining a mild TBI, during the acute phases of recovery. A follow-up scan three to five months post-TBI found no significant changes in functional connectivity from the acute stage; the differences from controls observed acutely in functional connectivity persisted into the chronic stages of recovery. Even in this "radiologically normal" sample, reduced connectivity within the DMN, and increased connectivity between the DMN and areas associated with attention control, may represent attempts to compensate for declines in attention abilities. Several possible explanations exist for the discrepancy in findings between Zhou et al. (2012) and Mayer et al (2011). First, Zhou's sample had a mean age of 37.8, while Mayer's sample's mean age was one decade younger, at 27.15. Second, while Zhou and Mayer both examined mild TBI, they defined it

differently. Zhou reported GCS scores ranging from 12-15, and required participants to have experienced at least a 10-second loss of consciousness. Mayer's sample's GCS score ranged from 13-15, and had no requirement for loss of consciousness, indicating that this sample may have been less severely injured. Third, the methods employed for evoking and measuring the DMN were different, with Zhou using an ICA, and Mayer employing a seed-based approach. Zhou et al. noted that this may explain, albeit slightly, the difference in findings between the two studies. In addition, both groups had slightly different post-TBI recovery timeframes during which patients were examined. Meyer et al.'s patients were likely still in the acute phases of recovery during the first scan, though symptoms of a mild-TBI should have resolved by the time of their three to five month follow-up scans.

Stevens et al. (2012) used ICA to examine a sample of mild-TBI patients two to twenty weeks post-injury. They found decreases in functional connectivity within the DMN, and between the DMN and the medial frontal gyrus, parahippocampal gyrus, and right inferior frontal/premotor cortex area. In a sample of moderate-to-severe TBI patients at three to six months post-injury, Hillary et al. (2011) found that patients had lower functional connectivity between the anterior and posterior nodes of the DMN. However, they also found changes in the DMN and other networks during follow-up scans, which will be discussed in greater detail in following sections. Sharp et al. (2011) studied a group of patients with mild-to-severe TBI, and found increased DMN functional connectivity (specifically, the PCC) compared to controls. Of note, the time since injury for this group ranged from six months to eighty months, a much greater range than other studies. The researchers also found that TBI patients with higher resting DMN functional connectivity did better on cognitive tasks than

patients with lower functional connectivity. Additionally, patients with more white matter damage displayed lower functional connectivity, and thus, poorer cognitive task performance. Patients also showed greater DMN deactivation during a working-memory task, potentially due to increased cognitive load. This was interpreted by the authors to mean that the brain requires greater DMN deactivation for difficult tasks, but would not need to deactivate as much for less demanding tasks.

A similar set of findings was reported by Tang et al. (2012), who found increased DMN functional connectivity in a group of mild-to-severe TBI patients, compared to controls, though no mention was made of the time since injury. The authors also reported a global decline in white matter integrity, which they hypothesized likely made it more difficult for the nodes of the DMN to communicate effectively, resulting in increased functional connectivity as an attempt at compensation. Palacios et al. (2013) examined individuals with severe TBI at four years post-injury. They noted increases in functional connectivity within the anterior node of the DMN compared to healthy controls. This increase was viewed as a compensatory measure, due to a decline in structural integrity in the cingulate tract, which connects the anterior and posterior regions of the DMN. The researchers also observed that individuals with higher functional connectivity in the anterior regions of the DMN did better on cognitive testing. This relationship was not found among the healthy controls. Vanhaudenhuyse et al. (2010) used an ICA to examine severely injured patients who were in minimally conscious states, ranging from locked-in syndrome (brain activity and likely conscious thought, but complete bodily paralysis) to vegetative coma. When compared to healthy controls, they found decreases in functional connectivity within

the DMN. Furthermore, functional connectivity within the DMN correlated positively with level of consciousness, with the most severely comatose patients displaying the lowest DMN functional connectivity. Boly et al. (2009) found the DMN to be preserved in comatose patients, though with significantly less functional connectivity than healthy controls. However, in a patient who was clinically "brain-dead" but physically alive, no evidence of DMN functional connectivity was discovered, indicative that the DMN is more than simply an artifact of respiration, blood flow, or other neurometabolic processes.

From the wide variation in results when studying the DMN in a TBI population, a conclusion can be drawn that demographic information about the sample, including type and severity of injury, and time since injury, must be taken into consideration when examining results. Sample demographics likely play a large role in post-TBI DMN results. When considering the breadth of results reported, it may be possible that there exists an optimal amount of DMN functional connectivity post-TBI. Very high functional connectivity and very low functional connectivity could both be indicators of abnormality.

Though the DMN is sensitive to disruption, it has also been shown to be responsive to intervention. For example, studies have revealed alterations in DMN activation patterns due to psychiatric medication (Marquand et al., 2011; Posner et al., 2013; Sambataro et al., 2010). Lewis, Baldassarre, Committeri, Romani, and Corbetta (2009) documented decreases in DMN deactivation during a visual search task in healthy controls, after intensive training on the task. They also observed increases in functional connectivity in the visual cortex associated with the visual search, and changes in connectivity between networks following training. Meditation's impact on the DMN has also been explored (Taylor et al., 2013), with

experienced mediators displaying greater functional connectivity among nodes of the DMN during non-meditative rest when compared to novice meditators. After four weeks of intensive memory training, Takeuchi et al. (2012) found an increase in functional connectivity in the external attention system and the DMN in healthy controls, after working memory training. They noted increases in functional connectivity between the VmPFC and the PCC, and decreased functional connectivity between nodes of the DMN and nodes of task-positive networks.

As mentioned earlier, Hillary et al. (2011) studied predominantly severe TBI at three and six months post-injury. They found declines in functional connectivity within the DMN at three months and increases in DMN functional connectivity at six months. At six months, both the PCC to middle frontal and PCC to medial/temporal functional connectivity in TBI patients were greater than healthy controls. Sharp et al. (2011) found DMN functional connectivity in both controls and TBI patients was negatively correlated with performance on measures of processing speed. In the patient group, individuals with the highest DMN functional connectivity also had the least cognitive impairment. The authors explained these changes as compensatory increases in functional connectivity, due to patients being in the chronic phase of their injury, and thus having developed compensatory adaptive changes. Overall, while the DMN is sensitive to disruption post-TBI, it is also sensitive to recovery effects, including medication, meditation, and cognitive rehabilitation. Even in a sample of chronic-stage TBI patients, one might expect to see changes within the DMN, and between the DMN and other networks, as a result of cognitive training.

The Central Executive Network

In contrast to resting-state networks like the DMN, the brain also possesses task-positive networks. These networks activate in the presence of externally imposed tasks that require focus, and deactivate in absence of such tasks. One task-positive network is the central executive network (CEN), which is comprised of the bilateral dorsolateral prefrontal cortex (DLPFC) and the bilateral posterior parietal cortex (PPC) (Dosenbach et al., 2007; Seeley, et al., 2007; Sridharan, et al., 2008). The CEN is believed to play a role in judgment, decision making, working memory, and executive functions (Dosenbach, et al., 2007; Seeley, et al., 2007); processes which have been shown to be commonly impaired in individuals with TBI (Ponsford, Olver, & Curran, 1995; Spitz, Ponsford, Rudzki, & Maller, 2012). The DLPFC has been shown to be active during inhibition, such as during go no-go tasks (Menon, Adleman, White, Glover, & Reiss, 2001). Functional connectivity within the CEN has been shown to correlate with executive functions in healthy individuals (Seeley, et al., 2007).

To date, little research has been conducted to examine the effects of TBI on the CEN. However, the pattern of common cognitive deficits following TBI suggests that the CEN may be vulnerable to disruption. Stevens et al. (2012) studied a mild-TBI population at 13-136 days post-TBI using ICA. Though they did not explicitly examine the CEN, they noted post-injury increases in functional connectivity in areas usually associated with the CEN. Similarly, Hillary et al. (2011) found increases in CEN functional connectivity in predominantly severe TBI patients between the DLPFC and the parietal lobes at three months post-injury. However, at a six-month follow-up scan, functional connectivity within the CEN

had dropped to a level lower than healthy controls. The increased CEN functional connectivity at the earlier scan may have represented a degree of compensation for reduced abilities, which faded as the patients continued to recover skills. The lower-than-control functional connectivity at the six-month scan may be the result of structural damage to the white matter connections within the CEN, only evident after the initial higher, compensatory functional connectivity faded. In an EEG study of individuals with mild TBI due to blast injury, lateral frontal areas (consistent with the nodes of the CEN) were found to be less synchronous with each other in TBI patients than in healthy controls (Sponheim et al., 2011). Similar to findings reported in earlier sections, this may represent damage to the commisural fibers that connect the left and right hemispheres, resulting in impaired functional connectivity in bilateral structures. Though not a direct investigation of the CEN, Marquez et al. (2011) found no differences in bilateral DLPFC (a node of the CEN) functional connectivity between controls and mild-to severe TBI patients at seven months post-TBI.

When examining activation levels, several studies have noted increased post-TBI activation in the nodes of the CEN, or increased activation in the cortex around the nodes of the CEN (Christodoulou et al., 2001; Dettwiler et al., 2013). Interestingly, similar patterns have been noted in multiple sclerosis patients, indicating that this pattern may be attributable to alterations in white matter, or perhaps general mild cognitive dysfunction, as opposed to specifically related to TBI (Chiaravalloti et al., 2005). This increased activation in additional areas of the prefrontal cortex may indicate some form of neural recruitment or compensation for reduced performance ability (Reuter-Lorenz & Park, 2010). As commented on by Hillary (2008), there is thought that post-TBI increased frontal involvement during cognitively

demanding tasks may be related to plasticity or compensation. However, Hillary alternatively proposed that this increased prefrontal activation may be related to a natural mechanism of effortful “top-down” cognitive control by the individual. Along a similar line of thought, Turner, McIntosh, and Levine (2011) examined patterns of frontal activation in three groups: a sample of TBI patients, a sample of healthy older adults, and a sample of younger adults undergoing a cognitively difficult task. They found similar patterns of frontal activation across all three samples. They concluded that what others may view as “recruited” cortical areas are actually a natural part of the frontal network that becomes activated during difficult tasks or with aging. In TBI patients, this area is activated during less-demanding cognitive tasks. An alternative explanation for this phenomenon was proposed by Hillary and Biswal (2007), who hypothesized that some post-TBI changes in neural activation may be due to changes in cerebral blood flow, especially if the vasculature in the brain has been compromised.

In sum, research into the effects of TBI on the CEN have revealed varied results, similar to the range of findings on the effects of TBI on the DMN, possibly as a result of varied patient demographics. The field lacks a clear, generally accepted theory as to the mechanisms or reasons for these changes, or the long-term implications. Like other neural systems, there may be an optimal amount of post-TBI CEN functional connectivity with regards to cognitive performance, with levels too high or to low signaling inefficiency and impairment.

Compared to the DMN, less is known about the effects of intervention in the CEN. Though the cognitive skills associated with the CEN have been shown to improve with

cognitive training (Spikman, Boelen, Lamberts, Brouwer, & Fasotti, 2010; Vas, Chapman, Cook, Elliott, & Keebler, 2011), few studies have specifically examined the CEN bas a whole, post-intervention. Strangman et al. (2009) trained patients with TBI-related memory difficulties and healthy controls to use a semantic memory strategy as part of cognitive rehabilitation program, which is generally accepted as an effective strategy for list-learning. While using the semantic strategy to learn a list of words, TBI patients displayed less functional connectivity between the left DLPFC and the angular gyrus (AG), compared to healthy controls, and performed worse on the task. When free to use any strategy to perform the memory task except the semantic strategy, TBI patients displayed increased activity in the DLPFC, compared to controls, and no significant difference in the AG. Thus, in TBI patients, when the DLPFC should have displayed increased functional connectivity with the AG during the semantic-recall trial, it did not. When the DLPFC should have been less active during the non-directed recall trial, it was more active. The authors concluded that these patterns may be due TBI patients having to use different neural mechanisms to complete the same tasks as healthy controls, possibly due to diminished neural resources or altered neural connections. The authors noted that similar “same strategy, different pathway” changes are seen in cognitively normal healthy adults when performing the same task using the same strategy as younger adults. To extrapolate the results from this study and apply them to the current study, individuals with TBI may display altered patterns of functional connectivity compared to healthy controls, which may results in a different overall pattern of connectivity within the CEN, and between the CEN and other networks.

Cognitive rehabilitation programs and retraining programs are not the only methods for affecting functional connectivity within the CEN. Other interventions have been shown to have an impact on behavioral outcomes, as well as functional connectivity. For example, neurofeedback as a treatment for anxiety has been demonstrated to increase functional connectivity in the DLPFC (Scheinost et al., 2013). Electroconvulsive therapy for depression has been shown to "normalize" hyper-activation in the orbitofrontal cortex and increase the functional connectivity between the DLPFC, PCC, and ACC (Beall et al., 2012). Children with ADHD who displayed lower bilateral DLPFC activation during a working memory task displayed normalized activation following administration of atomoxetine, a medication used in ADHD treatment (Cubillo et al., 2013). In other ADHD studies, decreased activation in the DLPFC and the ACC has been shown to become normalized with long-term medication use (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Similar to the conclusions about the DMN, these studies indicate that the CEN is capable of change post-TBI in response to rehabilitative efforts.

The Salience Network

Like the DMN and CEN, the salience network (SN) is another neural network that has been identified by functional connectivity. It is comprised of the anterior insula (AI) and the anterior cingulate cortex (ACC) (Seeley, et al., 2007; Sridharan, et al., 2008). Though this network has been associated with a variety of cognitive processes, one of its primary functions may be to filter stimuli that come through the senses to detect relevant stimuli, then activate regions of the brain necessary for higher order cognitive tasks, such as the CEN, and

simultaneously deactivate resting-state networks, such as the DMN (Menon & Uddin, 2010; Seeley, et al., 2007; Sridharan, et al., 2008). In this way, the SN may act as a switching network in the brain, responsible for activating and de-activating neural networks in response to external stimuli. Within the SN, the right anterior insula (rAI) has been hypothesized to serve as a "cortical outflow hub", receiving information from a wide range of brain regions and regulating activity in other areas of the brain (Ham, Leff, de Boissezon, Joffe, & Sharp, 2013; Menon & Uddin, 2010; Sridharan, et al., 2008).

Compromise to the SN may alter the activation patterns and functional connectivity "downstream" areas that have connectivity with the SN, such as the DMN and CEN. For example, in TBI patients, white matter integrity across the SN has been shown to predict DMN deactivation during cognitively demanding tasks (Bonnelle et al., 2012). On a larger level, this finding suggests that alterations in activity and functional connectivity in a given network may be due to influences from outside the network, possibly from other intrinsic, functionally connected networks. On a more specific level, this interaction between the DMN and SN hints at a larger, possibly hierarchically-organized network, composed of discrete intrinsic networks that simultaneously influence and are influenced by each other.

Additional evidence of a relationship between the SN and other intrinsic networks was reported by Sridharan, Levitin, and Mennon (2008). They reported event-related fMRI signal activity in the SN started earlier than in the CEN and DMN, indicating that the SN (in particular, the right fronto-insular cortex) plays a causal role in activation/deactivation of the DMN and CEN. The authors further noted that the SN, with its rich structural connections across the cortex, is neuroanatomically positioned to generate control signals to the CEN and

DMN. Chen et al. (2013) investigated this concept by using transcrainal magnetic stimulation (TMS) to explore directionality and causality between these networks. When stimulating the DLPFC node of the CEN with TMS, they observed a subsequent decline in DMN functional connectivity with the CEN and SN. Conversely, when applying an inhibitory TMS pulse to the DLPFC, they found a shift in signal frequency of the DMN consistent with disinhibition (i.e., increased activity) of the network. However, activating the only node of the SN accessible to TMS (due to neuroanatomical restrictions) resulted in no significant changes to the DMN or CEN. The authors concluded that this indicates a causal relationship between this node of the CEN and the DMN, and is possibly evidence against the view of the SN as a switching station for the DMN and CEN. However the authors further noted that activating other areas of the SN, which they were not able to reach with TMS, may reveal different effects on the DMN or CEN. Additionally, the relationship between the SN, CEN, and DMN may not be accurately captured by TMS impulses. Taken together, this set of studies may point to a relationship between the DMN, CEN, and SN, that is more complex than the notion that they are three competing, yet discrete, intrinsic neural networks. They may actually be part of a larger, more complex, unifying network that plays a large role in cognition.

In addition to widespread neural connections and effects on other neural networks, the SN also seems to be involved in a variety of cognitive processes, as mentioned earlier. The SN seems play a role in social cognition, as functional connectivity within the SN has been related to greater interpersonal emotional intelligence trait scores (Takeuchi, et al., 2013). Activation in the SN has been shown to relate to the likelihood of an individual

helping another individual (Greening et al., 2013), while lesions in the SN have been related to decreased empathy (Leigh et al., 2013). In a study of social responsibility, activation in the ACC was associated with reinforcement of behaviors related to personal gain (P. Li et al., 2013). The SN has also been shown to play a role in resiliency after childhood abuse (van der Werff et al., 2013) and in moral reasoning (Chiong et al., 2013). In addition to its role in social process, the SN seems to play a role in error detection. The ACC has been shown to activate when an individual perceives that they have made an error (Menon, et al., 2001) or when the outcomes of an action are unexpected (Greening, et al., 2013). Activation in the ACC increases steadily throughout adolescence and into adulthood, which may play some role in social maturation and increased self-inhibition (Ordaz, Foran, Velanova, & Luna, 2013). As noted earlier, the SN is believed to play a role in detecting salience of stimuli. Listening to distorted speech has been noted to increase activation in the nodes of the SN, possibly due to the increased effort to screen the speech for relevant information. However, activation levels are reduced as the listener adapts to the distorted speech, and requires less effort to screen (Erb, Henry, Eisner, & Obleser, 2013). One of the nodes of the SN, the AI, has also been associated with saliency and reward related to food consumption (Oberndorfer et al., 2013). Baseline SN functional connectivity before a painful stimulus has been associated with perception of pain post-stimulus (Wiech et al., 2010). Similarly, pre-scanner ratings of anxiety have been found to correlate positively with functional connectivity within the SN, particularly the ACC (Seeley, et al., 2007).

The SN is also believed to play a role in memory. For example, in a study comparing patients with Alzheimer disease to healthy controls, Alzheimer patients displayed decreased

functional connectivity within areas of the SN, This reduced functional connectivity was associated with poorer performance on a complex-figure memory task and a list-learning task in the Alzheimer patients, but not in healthy controls (Xie et al., 2012). In a study of working memory training in healthy adults, the ACC showed increased functional connectivity with the medial frontal gyrus after six weeks of training. There was a positive relationship between degree of functional connectivity change and increase in working memory performance (Jolles, van Buchem, Crone, & Rombouts, 2013). Nodes of the SN are also believed to play a role in working memory performance. Krawczyk and D'Esposito (2013) noted increased functional connectivity between the left insula and the left prefrontal cortex during specific reward-related working memory tasks, while Lenartowicz and McIntosh (2005) observed that different patterns of ACC functional connectivity were related to performance on an n-back task. One potential reason may be due to the relationship between salience/relevance of information and probability of recall (Fine & Minnery, 2009). If the SN does play a role in detection and evaluation of salient information, perhaps its strong anatomical connections with areas on the temporal and frontal lobes assist with working memory and episodic memory. In summary, the SN has been associated with a wide variety of cognitive and emotional processes, and it shares rich anatomic connections and strong functional connections with other networks (most notably the DMN and CEN). Taken together, this may indicate that the SN has a role in integrating or coordinating interactions between networks, or itself may be a node of a larger group of networks.

Little is known about the effects of TBI on the functional connectivity within the SN. To date, research has primarily examined post-TBI changes in functional connectivity

between the SN and other networks, not within the SN itself. In a study of patients under sedation, the SN displayed significant declines in functional connectivity (Guldenmund et al., 2013). Altered functional connectivity within the SN, and between the SN and other networks, has been noted in several psychiatric disorders, which will be discussed in later sections. Thus, changes in the SN post-TBI, following rehabilitation, maybe a rich area for research.

Compared to the research on the DMN and CEN, less is known on the potential changes that occur in the SN in response to training or intervention. In a study examining the effects of exercise on the DMN and SN in obese adults, exercise and weight loss were associated with declines in DMN activity, but no change in SN activity was observed (McFadden, Cornier, Melanson, Bechtell, & Tregellas, 2013). Increased functional connectivity between the DMN and SN has been noted following a few minutes of meditation in experienced meditators (Froeliger et al., 2012), though this may reflect a transitory shift as opposed to lasting alterations. In a similar study, experienced meditators displayed higher resting functional connectivity within the SN, and between the SN and nodes of the DMN and CEN than novice meditators (Hasenkamp & Barsalou, 2012). Individuals who were trained to increase rAI BOLD signal via biofeedback displayed higher activation post-training, compared to controls or a placebo sham-training group (Lawrence et al., 2013). Following successful treatment of joint pain, the degree of pain reduction correlated significantly with decline in AI activation (Lickteig, Lotze, & Kordass, 2013). Taken together, these studies indicate that the SN may be responsive to medication and non-medicinal interventions, much like the DMN and CEN. Alterations in the SN have been

noted after undergoing training, such as meditation. However, on the whole, evidence for lasting changes in the SN is relatively weak, and more research would be needed before definitive conclusions could be reached.

Anticorrelation Between Networks

Thus far, intrinsically connected networks have been discussed in light of positive correlations between nodes and networks. However, some networks also possess opposite patterns of activation, resulting in significant negative correlations between networks. The degree and strength of these negative correlations, known as anticorrelations, has become a topic for research, especially between the DMN and CEN. One study by Kelly, Uddin, Biswal, Castellanos, and Milham (2008) observed the degree of anticorrelation between the DMN and various task-positive networks during at rest. Stronger levels of anticorrelation (i.e., greater negative correlation) between the DMN and task-positive networks predicted better performance on a later task of attention and processing speed. Sours et al. (2013) noted a decrease in the level of anticorrelation between the DMN and CEN in a mild-TBI population with memory complaints, compared to a mild-TBI population without memory complaints, or healthy controls. However, one weakness of this study is that no measure of attention was included in their cognitive battery, meaning that attention difficulties (which could lead to poor performance on memory tests) could not be ruled out in the sample. This is especially relevant in light of the previously mentioned relationship between anticorrelation and attention. In their study of resting-state networks and social cognition, Takeuchi et al. (2013) found greater anticorrelation between the DMN and CEN to be related

to higher emotional intelligence interpersonal traits. However, they also found a relationship between connectivity between the nodes of the SN and DMN and traits of emotional intelligence. The researchers theorized that these findings may indicate that greater anticorrelation between the DMN and CEN allows for better self-referential processing and better attention to external stimuli. Individuals with these traits are likely to score better on measures of emotional intelligence, as they are attentive to others, and aware of their own emotional processes. Thus, DMN-CEN anticorrelation may relate, via its role in attention, to emotional intelligence. Further evidence for the role of DMN-CEN anticorrelation in attention was found in a medication study of children with ADHD. Methylphenidate was shown to decrease activation of the DMN during working memory tasks, while increasing activation in nodes of the CEN, thus having the effect of increasing anticorrelation (Cubillo, et al., 2013). Taken together, these studies indicate that there may be an optimal balance of anticorrelation between task-positive networks and task-negative networks, and the DMN-CEN anticorrelation appears to play a role in attention. Though anticorrelation could be viewed as an indicator of competition between networks, it can alternatively be viewed as an indicator of internetwork cooperation and resource sharing. Strong anticorrelation could also be a sign that the DMN and CEN are part of a larger network, or that a third network influences and coordinates activity in both networks.

The DMN, CEN, SN, and Psychiatric Disorders

Changes within and between the DMN, CEN, and SN have been found in a variety of psychiatric conditions. In a study of individuals with schizophrenia, patients displayed more

variability in their DMN spatial maps, which were significantly different compared to controls. Patients also displayed correlations between reported positive symptoms of schizophrenia and increased deactivation in the medial frontal gyrus, PCC, and left middle temporal gyrus (Garrity et al., 2007). Compared to healthy controls, patients with post-traumatic stress disorder (PTSD) displayed greater functional connectivity within the DMN (Bluhm et al., 2009) and weaker functional connectivity within the CEN (Daniels et al., 2010). Patients with depression have been found to have increased DMN activity while reevaluating negatively-charged emotionally-related stimuli (Sheline et al., 2009). Alterations in DMN functional connectivity have also been noted in depression, including between the DMN and the dorsal medial prefrontal cortex (Sheline, Price, Yan, & Mintun, 2010), which shows increased functional connectivity with several networks in depressed individuals.

Given its high degree of connectivity with other cortical regions, it is not surprising that the SN has been implicated in a variety of psychiatric conditions. A review of the literature reveals a role of the SN, or nodes of the SN, in nearly every class of psychiatric disorder. Hyperconnectivity within the SN has been associated with autism, which is not surprising, given its aforementioned role in social processing (Uddin & Menon, 2009; Uddin et al., 2013). In aging, resting-state SN functional connectivity has been used to distinguish patients with fronto-temporal dementia from patients with Alzheimer disease, and from healthy controls (Day et al., 2013; X. He et al., 2013). Similar to findings in the DMN, dysregulation within SN has been noted in schizophrenia (Orliac et al., 2013; White, Joseph, Francis, & Liddle, 2010). More specifically, Zhou et al. (2010) found decreased SN

functional connectivity in frontotemporal dementia, but increased functional connectivity in Alzheimer disease. Furthermore, lower rAI activation has been found in patients with schizophrenia, and has been associated with increased intensity of hallucinations (Manoliu et al., 2013). Aberrant patterns of functional connectivity have also been found in PTSD, including deficits in switching between the DMN and other networks (Daniels, Frewen, McKinnon, & Lanius, 2011; Daniels, et al., 2010). Areas of the SN have been implicated in obsessive-compulsive disorder, as volumetric studies have shown reduced volume in the bilateral AI and the ACC (de Wit et al., 2013). Methamphetamine addicts have displayed decreased SN activation in response to pleasant stimuli, compared to healthy controls (May, Stewart, Migliorini, Tapert, & Paulus, 2013). In response to the perception of sweet flavors, women who had recovered from anorexia displayed decreased AI activation, while women who had recovered from bulimia had increased AI activation, compared to controls (Oberndorfer, et al., 2013). While performing self-identity and social knowledge tasks, individuals with anorexia displayed lower activation in the ACC than individuals with bulimia, and both groups displayed less activation than healthy controls (McAdams & Krawczyk, 2013). Considering the wide range of psychiatric literature that reveals some degree of SN involvement in various disorders, the SN may play a role in emotional and cognitive processes. It also indicates that any model that would attempt to tie together various discrete neural networks would likely need to include the SN, due to its apparently crucial role in daily experiences.

Though changes within the DMN, CEN, and SN have been discussed as individual networks, changes in the relationship between pairs of these networks have also been

identified in psychiatric conditions. The CEN and DMN have both been implicated in schizophrenia, as patients with schizophrenia have been shown to display hyperconnectivity compared to controls in both networks at rest (Unschuld et al., 2013). The DLPFC within the CEN has also been shown to display decreased functional connectivity with other brain regions in patients with schizophrenia, as well as their first degree relatives. Furthermore, the decline in functional connectivity had a positive correlation with decline in scores on executive function tasks in patients and their relatives (Su et al., 2013). Less anticorrelation (i.e., increased functional connectivity) between the DMN and CEN has been found in schizophrenia, and is believed to correlate with the severity of hallucinations (Manoliu, et al., 2013; Williamson, 2007). Increased resting functional connectivity between the left DLPFC and the DMN has been found in medication-naive adults with ADHD. This suggests the CEN plays a role in ADHD, in addition to the DMN, which displays decreased deactivation in ADHD (Hoekzema et al., 2013). Furthermore, individuals with ADHD display decreased activation in the ACC and DLPFC, which have been linked to poor inhibition and deficits in attention. (Hart, et al., 2013). Compared to healthy controls, patients with frontotemporal dementia displayed increased functional connectivity between the DMN and SN, while patients with Alzheimer's displayed decreased functional connectivity between the DMN and SN (J. Zhou, et al., 2010). Taken together, these results indicate a role for interactions between networks, not just within networks, in a wide range of conditions, from psychiatric disorders to aging to TBI. Conversely, this also indicates that interactions between networks also play a role in healthy functioning, and that there might exist an optimal, healthy relationship between the DMN, CEN and SN which may serve as a biomarker for treatment

and recovery. Thus, understanding these three networks is clearly important to understanding cognitive processes and adaptive functioning.

Neural Networks and Aging

The DMN and CEN have been shown to be temporally and spatially consistent in healthy controls across relatively short periods of time (Damoiseaux, et al., 2006). On a larger timescale, functional connectivity in the brain is known to change across the lifespan. Between the ages of 18-89, the brain experiences a gradual decline in functional connectivity in the large networks that are characterized by low-frequency correlations (Schlee et al., 2012). In the SN, activation in response to empathy (i.e., viewing another in pain) has been found to decrease with age (Y. C. Chen, Chen, Decety, & Cheng, 2013). Healthy older adults display less intrinsic activity in the anterior regions of the DMN at rest than younger adults (Damoiseaux et al., 2008). When studying changes within specific components of the DMN, one study of healthy seniors found an increase in activity in the medial temporal lobes and decreases in activity in the PCC, which overlap with areas of the DMN (Schlee, Leirer, Kolassa, Weisz, & Elbert, 2012). Older adults have also been found to show less recovery at one-year post-TBI than younger adults, which may be a reflection of age-related diminished cognitive reserve, or greater physiological susceptibility to injury with age (Rothweiler, Temkin, & Dikmen, 1998).

The term “cognitive reserve” has been used to refer to the concept that the brain has a “reserve” that somehow protects it from functional decline in the light of neurological insult (Stern, 2002). Theories as to what contributes reserve have included factors such as brain

volume, volumetric differences, genetic factors, level of education, verbal abilities, intelligence, and age (Stern, 2009). Cognitive reserve (measured by education and verbal intelligence) was found to negatively correlate with resting-state activity in the DMN, among healthy seniors (Bastin et al., 2012). Additionally, the same study found memory and executive function performance positively correlated with cognitive reserve and negatively correlated with cerebral activation. In healthy and cognitively normal elderly, amyloid buildup has been associated with a decline in functional connectivity among select nodes of the DMN (Sheline et al., 2010). The authors related increased amyloid to disruption in the connective pathways between nodes. Amyloid, as measured by distribution volume ratio as measured by Pittsburg Compound B on PET, has also been related to aberrant DMN activity in cognitively normal older and mildly impaired older adults when compared to healthy young controls (Sperling et al., 2009). Strong evidence exists for changes within the DMN in Alzheimer disease, including lowered glucose metabolism in the PCC (Minoshima et al., 1997), atrophy in the medial temporal lobe and PCC which accelerates with disease progression (Buckner et al., 2005), amyloid deposits throughout the areas of the DMN (Buckner, et al., 2005), and decreased functional connectivity in the DMN (including declines between the DMN and the PCC) (Cha et al., 2013).

In a sample of older adults with amnestic mild cognitive impairment, increases in DMN activity were found during resting-state in the middle cingulate cortex, middle prefrontal cortex, and left inferior parietal cortex, while decreases were noted in the lateral prefrontal cortex, medial temporal lobe, right angular gyrus, and the PCC. Correlations were found between activation patterns in some of these areas (left prefrontal, left medial temporal

gurus, and right angular gyrus) and memory, with lower levels of activation associated with poorer memory performance (Jin, Pelak, & Cordes, 2012). Taken together, this indicates that a study investigating intrinsic, functionally connected networks should be mindful of the effect that aging may have on functional connectivity. When exploring the factors that contribute to functional connectivity, age should not be ignored. As noted above, even non-symptomatic older adults may experience alterations in their network profiles.

Changes in Networks During Recovery from Brain Injury

Since the DMN, CEN, and SN are all believed to undergo some degree of alteration after TBI, it stands to reason that they may continue to undergo changes during recovery from injury. Previous research on a sample of post-stroke aphasic patients who made a strong recovery with regard to speech skills revealed higher functional connectivity in the semantic processing network during a language processing task, compared to healthy controls (Sharp, Turkheimer, Bose, Scott, & Wise, 2010). Furthermore, a similar increase in functional connectivity in healthy controls was found when a language processing task became more difficult, leading to the conclusion that the increased functional connectivity displayed in the aphasic patients was likely due to the effects of inefficient language processing. To generalize these findings to other networks, increased frontoparietal functional connectivity may be associated with recovery of cognitive skills post-TBI.

Functional connectivity within the DMN (specifically, between the PCC to middle frontal and the PCC to medial temporal/hippocampal) has been shown to increase across the first six months of recovery following severe TBI (Hillary, et al., 2011). This same study also

found a decrease in functional connectivity (ACC to parietal and DLPFC to PCC) in goal-directed networks (similar to the CEN) in a patient group during the same timeframe. Notably, and perhaps significantly, the functional connectivity between the insula (recognized as part of the SN) and the DLPFC (part of the CEN) increased between during rehabilitation. Mayer et al. (2011) examined the DMN at the acute state of TBI recovery (3 weeks post-injury) and again at a later, post-acute state of recovery (3-5 months post-injury). Like Hillary et al., they found a decrease in functional connectivity within the DMN at the acute stage, compared to healthy controls. However, they also found increased functional connectivity with nodes of the DMN and areas associated with effortful, top-down processing (between the rACC and lateral prefrontal cortex, and between the right prefrontal cortex and PCC) at the acute stage. They found no significant changes in functional connectivity in the TBI sample between the acute and post-acute scans.

Post-TBI functional connectivity in the DMN during resting-state has been used to predict impairment in sustained attention (Bonnelle, et al., 2011). Patients displayed increasing DMN activation levels as in-scanner tasks progressed (ie, the longer they performed a task, the greater the level of DMN activation at the end of the task), though it remained consistent in controls. Impairments in sustained attention were associated with higher DMN functional connectivity in patients, but not in controls. Higher levels of functional connectivity were associated with white matter compromise and poorer performance on measures of sustained attention in patients. When examining more severely injured patients, Nakamura, Biswal, and Hillary (2009) used graph theory to note changes in large-scale resting networks during recovery from TBI. Between three and six months post-

injury, networks displayed increased path length, improvements in local efficiency and global efficiency, and a decline in networks strength, which the authors noted had the result of making the patient's networks appear more like the networks of healthy controls.

Section Summary

The DMN, CEN, and SN are three intrinsically connected networks that may be vulnerable to disruption following TBI. Though studies have related these three networks to various cognitive outcomes, volumetric change, and psychiatric symptoms, no study to date has attempted to predict post-TBI network functional connectivity cohesiveness from these factors. Furthermore, relatively little attention has been focused on how these networks interact with each other, and the factors that may influence inter-network connectivity.

CHAPTER THREE

Study Goals and Aims

Overall Aim

This study examined three intrinsic functionally connected networks (the DMN, CEN, and SN) in a population of individuals who suffered a TBI. The relationships between resting-state network cohesiveness, cognitive performance, and demographic factors were assessed. Furthermore, the relationship between networks, including the relationship between the cohesiveness of the SN and the degree of anticorrelation between the DMN and CEN, were assessed.

Hypotheses

Hypothesis 1: Combining neuropsychological measures of executive functioning, depressive symptoms, demographic factors, and injury data will result in a significant model that will predict default mode network functional connectivity in mild-to-moderate TBI.

Rationale: Individually, age, severity of TBI, gender, time since injury, working memory, sustained attention, episodic memory, white matter volume, and depressive symptoms have all been associated with the DMN. In some cases, DMN functional connectivity has been used to attempt to classify individuals into various disease categories (i.e., controls vs. TBI). However, no study has examined combinations of these factors in an attempt to develop a model of the factors that feed into DMN functional connectivity, including the amount of variability that each factor accounts for. Functional connectivity is likely multi-faceted and

complex, and is likely influenced by a variety of factors, to varying degrees. This study provided a unique opportunity to examine combinations of these factors, as a wide range of cognitive measures were included as potential predictor variables. This allowed for a wider range of variables to be assessed for their relationship with the DMN.

Hypothesis 2: Combining neuropsychological measures of executive functioning, depressive symptoms, demographic factors, and injury data will result in a significant model that will predict CEN functional connectivity in mild-to-moderate TBI.

Rationale: Similar to the rationale for Hypothesis 1, age, severity of TBI, gender, time since injury, working memory, sustained attention, cognitive flexibility ("switching"), planning, white matter volume, and depressive symptoms have all been associated with CEN functional connectivity. However, no study has clarified the factors that feed into CEN functional connectivity, which is likely multi-faceted and complex. This study provided a involved a wider range of cognitive and functional measures than is typical of most resting-state functional studies, allowing for the development of a more complex model to explain CEN functional connectivity.

Hypothesis 3: The relationship between the DMN and measures of attention will be stronger than the relationship between the SN and measures of attention.

Rationale: The DMN, CEN, and (to a lesser degree) SN have all been broadly associated with executive functions. One crucial component of executive functioning is attention, which has been associated with the DMN and SN. To date, no study has compared the relative strengths of these associations, especially in light of the theory that the SN is responsible for the level of activation/deactivation of the DMN and CEN. Thus, understanding the relationship that each of these networks have with attention may help elucidate the relationship between the networks, which will be explored further in a subsequent hypothesis. Since the SN is hypothesized to function as a switching network, it would have an influence on the activity level and functional connectivity of the DMN and CEN. Therefore, the SN would still display a relationship with attention, albeit a weaker relationship than the DMN. Evidence of a relationship between the SN and attention, though at a lower level of significance than the relationship between the DMN and attention, would lend evidence to concept that the SN is a switching network.

Hypothesis 4: The relationship between the CEN and measures of cognitive flexibility will be stronger than the relationship between the SN and measures of cognitive flexibility.

Rationale: Similar to the rationale for Hypothesis 3, the SN will have a relationship with cognitive flexibility, albeit weaker than the relationship between the CEN and cognitive flexibility, due to the influence of the SN on the activity level, and possible functional connectivity, of the CEN. Therefore, the SN will display a relationship with cognitive flexibility, albeit weaker than the relationship between the CEN and cognitive flexibility.

Exploratory Hypothesis 5: The degree of anticorrelation between the DMN and CEN will be significantly and positively correlated with the coherence of the SN.

Rationale: One theoretical function of the SN is to activate and deactivate neural regions as needed, to respond to environmental stimuli. As explored in previous hypotheses, the SN has been proposed to play a significant role in the activation/deactivation of the DMN and CEN. Furthermore, previous research has linked structural integrity of the SN to the degree of anticorrelation between the DMN and CEN. To expand on this idea, it is proposed that a SN with stronger functional connectivity will result in stronger anticorrelation between the DMN and CEN.

CHAPTER FOUR

Methodology

MATERIALS AND METHODS

Participants

Data were collected as part of a study to evaluate the effectiveness of reasoning training in military and civilian chronic TBI patients. This sample was composed of soldiers and civilians, age 19-65, who have sustained a mild to moderate TBI, and are at least six months post-injury. Inclusion criteria included the ability to safely have an MRI, tolerate at least two hours of intervention sessions at a time, and participate in tasks involving motor abilities, as some of the neuropsychological measures require a motor response. Participants must have been able to speak, read, and comprehend English well enough to participate in the testing. Exclusion criteria included a history of cerebral palsy, mental retardation, autism, epilepsy, schizophrenia, pervasive developmental disorder, other neurological disorders, or psychosis. Individuals with a history of previous TBI were allowed in the study, and data was gathered as to the number of previous TBI, age at previous TBI, and severity of previous TBI. Medical information was obtained from the available medical records of potential participants. Informed consent was obtained from all individuals. Those included in the study underwent neuropsychological testing and neuroimaging, which included a resting-state fMRI and a structural T1-weighted image.

Outcome Measures

A variety of tests and measures were chosen for inclusion in this study, based on their accepted validity in the field of neuropsychology. See Appendix A for further information on these measures. Briefly, they included the GOS-E, GCS, BDI-II, VSLT, Daneman-Carpenterm, Digit Vigilance, WAIS-III Digit Span, and selected subtests of the WASI, WTAR, WMS-IV, and D-KEFS.

Functional and Structural Magnetic Resonance Image Acquisition and Processing

Image Acquisition: Functional and anatomical magnetic resonance images were obtained for each participant using a Philips 3-Tesla Scanner (Philips MR systems Achieva Release 2.5.3.0). Functional images were acquired with an echo-planar image sequence sensitive to BOLD-contrast (TE 30ms, TR 2s, flip angle 70°). The volume covered the whole brain with a 64x64 matrix and 37 transverse slices (4 mm thickness with no gap, voxel size 3.44x3.44x4 mm). Resting-stated data consisted of two runs, each consisting of 205 volumes. Structural images of individual subjects were acquired to serve as template images onto which the functional data were mapped and for volumetric assessment. The structural scans included a T1-weighted spin echo image sequence with 36 transverse slices and a Magnetization Prepared Rapid Access Gradient Echo (MPRAGE) image sequence with 160 sagittal slices.

Image Processing: Functional images were processed using the Data Processing Assistant for Resting-State fMRI (DPARSF) (Chao-Gan & Yu-Feng, 2010), run through SPM 8 in MATLAB 2012a. Preprocessing consisted of the following steps, which represent

commonly accepted practices in the literature: slice timing correction, motion correction and realignment to the T1 image, removal of the linear trend, transformation to standard Talairach space (matrix = 61 x 73 x 61, resolution = 3 x 3 x 3 mms), and smoothing by a Gaussian filter with a full width at half maximum (FWHM) of 4 mm. Appropriate low-frequency fluctuations was isolated and kept using band-pass filtering (0.01-0.1 Hz). White matter and cerebrospinal fluid signals were regressed out using averaged signals from the white matter and the ventricles for each ROI. Six head-motion parameters were similarly regressed out of the signal. Of note, the global mean signal was *not* regressed out.

A motion-correction toolbox, known as McFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002) was operated through FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012) in order to assess the mean and maximum level of motion for each participant. Individuals with relative mean motion greater than .25 mm were removed from further analysis, as were individuals with maximum instances of motion greater than 3.5mm.

Brain tissue volume, normalized for subject head size, was estimated with SIENAX (Smith et al., 2002), a toolbox operated through FSL. SIENAX starts by extracting brain and skull images from the structural T1 image. The brain image was then affine-registered to MNI152 space, using the skull image to determine the registration scaling. This is done primarily to obtain the volumetric scaling factor, used as normalization for head size. Next, tissue-type segmentation with partial volume estimation was carried out in order to calculate total volume of brain tissue (including separate estimates of volumes of grey matter, white matter, peripheral grey matter and ventricular CSF).

As mentioned earlier, a seed-based approach was used to create functional connectivity maps for each network. For the DMN, the bilateral posterior cingulate cortex was seeded using the accepted MNI coordinates of (±10 -56 12). The CEN was seeded using the dorsolateral prefrontal cortex, MNI coordinates of (±45 +16 +45). For the SN, the bilateral fronto-insular cortex was seeded using coordinates of (+37 +25 -4) and (-32 +24 -6) (Sridharan, et al., 2008). An ROI toolkit that functions within SPM, MARSbar v0.43(Brett, Anton, Valabregue, & Poline, 2002), was used to create spheres with a 4mm radius at the voxel coordinates for each network, which served as network seeds. Using DPARSF, the cross-correlation coefficient between these seed voxels and all other voxels were calculated to generate a correlation map, which was transformed to a z-score map. Next, an ROI analysis was performed, based on four known CEN regions (bilateral DLPFC and bilateral inferior parietal cortexes), four DMN regions (PCC, VmPFC, LLPC, RLPC), and three SN regions (ACC and the bilateral AI). To obtain these ROIs, all participants' functional connectivity z-maps were combined to create an averaged functional connectivity z-map for each network. These maps were examined in order to identify the voxels with the highest z-score (representing the greatest connectivity) in each network node. For example, the averaged DMN map was used to find the coordinates of the peak voxels in the PCC, VMPFC, RLPC, and LLPC. Next, between-node functional connectivity was calculated for each network, using DPARSF. This was accomplished by defining an ROI (i.e., a sphere with a 5mm radius) at the coordinates of each peak voxel (one in each network node). The functional connectivity analysis was performed between each ROI for the main nodes of the

DMN. Due to inconsistencies in the literature, the bilateral hippocampi were not included as part of the DMN, nor was the anterior cingulate cortex included as part of the CEN.

Once the cross-ROI functional connectivity had been calculated for each network, a statistical method known as the function of the determinant was used to conceptualize and quantify the networks. This method has been used in previous studies of resting-state networks before, most notably by Arenivas et al. (2012). The same procedure was used for each network. First, the functional connectivity was calculated between each node of a network (for example, the DMN) with every other node in the network. For example, in the DMN, this resulted in six between-node correlations (i.e., VMPFC to PCC, VMPFC to LLPC, VMPFC to RLPC, PCC to LLPC, PCC to RLPC, and LLPC to RLPC). The resulting six correlation coefficients were then entered into a square correlation matrix (see Figure 1). The degree of cohesiveness between the nodes within the network was represented by a determinant statistic, which was obtained by computing the function of the square matrix containing the correlations. This function of the determinant was then statistically corrected for symmetry and variance using a negative logarithm and square root of the determinant, which allowed for comparisons between networks. The resulting single numerical value represented whole-network connectedness, and higher values indicated greater levels of network cohesiveness. This assessment was completed for the DMN, CEN, and SN. Next, a pooled map was created for each network. To do this, the functional connectivity z-value maps for each individual participant were combined and averaged, using a custom script run through MATLAB 2012a. This was done to create an average map of the DMN, CEN, and SN (Figures 3, 4, and 5, respectively).

Figure 1

Within network Correlation Matrix

	MFC	PCC	LLPL	RLPL
MFC	**1**	*r*	*r*	*r*
PCC	*r*	**1**	*r*	*r*
LLPL	*r*	*r*	**1**	*r*
RLPL	*r*	*r*	*r*	**1**

r = the value of the correlation between nodes

Anticorrelation Between the DMN and CEN:

In order to measure the degree of anticorrelation between the DMN and CEN, the degree of functional connectivity between each node of the CEN and each node of the DMN was calculated using a Pearson correlation (represented by the top right quadrant of Figure 2). This was done using each individual's unique DMN and CEN node coordinates, and each individual's resting-state fMRI data. The resulting Pearson correlations were then transformed z-values, using a Fisher's z transformation. Next the mean and standard deviation of the between-network z-values was calculated, which was used to represent the degree of anticorrelation between the DMN and CEN.

Figure 2

Between-network Anticorrelation Matrix

	DMN node 1	DMN node 2	DMN node 3	DMN node 4	CEN node 1	CEN node 2	CEN node 3	CEN node 4
DMN node 1	**1**	*r*	*r*	*r*	*r*	*r*	*r*	*r*
DMN node 2	*r*	**1**	*r*	*r*	*r*	*r*	*r*	*r*
DMN node 3	*r*	*r*	**1**	*r*	*r*	*r*	*r*	*r*
DMN node 4	*r*	*r*	*r*	**1**	*r*	*r*	*r*	*r*
CEN node 1	*r*	*r*	*r*	*r*	**1**	*r*	*r*	*r*
CEN node 2	*r*	*r*	*r*	*r*	*r*	**1**	*r*	*r*
CEN node 3	*r*	*r*	*r*	*r*	*r*	*r*	**1**	*r*
CEN node 4	*r*	*r*	*r*	*r*	*r*	*r*	*r*	**1**

r = the value of the between-node correlation

Hypothesis-Specific Methods and Statistics

The relationship between network cohesiveness and predictive factors was investigated using multiple regressions. Descriptive results were produced for all variables, and statistical assumptions were checked before conducting analyses. When available, standardized scores were used from the cognitive measures in order to minimize the impact of demographic factors such as age, gender, and education level.

The following steps were followed in order to conduct each multiple regression. In step one, an initial stepwise forward multiple regression was conducted, and variables were added if alpha <0.25 and removed if alpha >0.26. This provided a list of potential predictors. In step two, this list was then entered into a backward multiple regression. Variables were entered into the model if alpha <0.05, and were removed from the model if alpha >0.1.

Variance inflation factor (VIF) statistics were run to assess the degree to which any significant predictor variable exhibited significant multicollinearity with any other significant predictor variable. The same group of factors were included as potential predictors for the DMN, CEN, and SN, and are listed as follows: Cognitive tests: D-KEFS Card Sorting condition 1, D-KEFS Card Sorting condition 2, D-KEFS Verbal Fluency condition 1, D-KEFS Verbal Fluency condition 2, D-KEFS Verbal Fluency condition 3, Verbal Fluency total set-loss errors, Verbal Fluency total repetition errors, D-KEFS Color Word Interference condition 1, D-KEFS Color Word Interference condition 2, D-KEFS Color Word Interference condition 3, D-KEFS Color Word Interference condition 4, Digit Vigilance Total Time, Digit Vigilance Total Errors, Daneman-Carpenter Reading Span Test Total score, D-KEFS Trail Making Test condition 1, D-KEFS Trail Making Test condition 2, D-KEFS Trail Making Test condition 3, D-KEFS Trail Making Test condition 4, D-KEFS Trail Making Test condition 5, WMS-IV Logical Memory Immediate Recall, WMS-IV Logical Memory Delayed Recall, WASI Similarities, WASI Vocabulary, WASI Matrix Reasoning, WASI Estimated FSIQ, WTAR estimated premorbid FSIQ, Digit Span Forward Total, Digit Span Backward Total, Digit Span Combined Total, and VSLT Total Score. Measures of depression: BDI-II Cognitive Subscale, BDI-II Non-cognitive subscale, and BDI-II Total Score. Volumetric measures: normalized grey matter volume, normalized peripheral grey matter volume, normalized ventricular CSF volume, normalized white matter volume, normalized total brain volume. Demographic and injury factors: age at first TBI, number of previous TBIs, age at most recent TBI, age at assessment, time between injury and assessment, TBI severity, GOS-E, years of education, gender, and civilian/military status.

The factors that survived the initial step of the multiple regression for each network are listed in the subsection regarding their respective hypotheses.

Hypothesis 1: After entering all of the aforementioned predictors for DMN cohesiveness into the stepwise multiple regression, the following factors met criteria for inclusion into the second step and were entered into the stepwise backward multiple regression: age at first TBI, age at assessment, Daneman-Carpenter, D-KEFS Card Sort condition 2, Digit Span Total, normalized global grey volume, normalized global ventricular CSF volume, TBI severity, time since injury, D-KEFS Trail Making Test condition 1, D-KEFS Trail Making Test condition 2, D-KEFS Trail Making Test condition 3, D-KEFS Trail Making Test condition 4, normalized total brain volume, WASI Similarities, and WMS Logical Memory Delayed Recall.

Hypothesis 2: After entering all of the aforementioned predictors of CEN cohesiveness into the stepwise multiple regression, the following factors met criteria for inclusion into the second step and were entered into the stepwise backward multiple regression: Age at injury, Digit Vigilance Total Errors, D-KEFS Card Sort condition 2, D-KEFS Color Word Inhibition condition 1, D-KEFS Color Word Inhibition condition 2, D-KEFS Color Word Inhibition condition 3, D-KEFS Trail Making Test condition 1, D-KEFS Verbal Fluency condition 1, D-KEFS Verbal Fluency Total Set-Loss Errors, Digit Span Forward, normalized global ventricular CSF, D-KEFS Trail Making Test Condition 2, VSLT Total Score, WASI Vocabulary, WMS Logical Memory Immediate Recall.

Hypothesis 3: After entering all of the aforementioned predictors of SN cohesiveness into the stepwise multiple regression, the following factors met criteria for inclusion into the second step and were entered into the stepwise backward multiple regression: Age at assessment, D-KEFS Card Sort condition 1, D-KEFS Card Sort condition 2, D-KEFS Color Word Inhibition condition 1, D-KEFS Color Word Inhibition condition 3, D-KEFS Color Word Inhibition condition 4, D-KEFS Verbal Fluency condition 1, Digit Span Backwards, Digit Span Forwards, Digit Span Total, gender, normalized ventricular CSF volume, GOS-E, TBI severity, D-KEFS Trail Making Test condition 2, D-KEFS Trail making Test condition 5, normalized total brain volume, and VSLT Total Score.

Of note, the DMN multiple regression results from the analysis of hypothesis one were used again when assessing this hypothesis. The portion of the variance accounted for by measures of attention in the SN were compared the same metrics on the DMN. To do this, the standardized beta (represented by "*ß*") was examined for each variable, which represents the degree to which each predictor affects the outcome of the effects if all other predictors are held constant.

Hypothesis 4: To assess hypothesis four, the results from the multiple regression performed on the CEN while assessing hypothesis two were compared with the results of the linear regression performed on the SN while assessing hypothesis three. The portion of variance explained on the linear regression by measures of cognitive flexibility in the SN was compared to that explained by the same tests on the CEN by examining the standardized beta

(represented by a "*ß*") of each variable, which represents the degree to which each predictor affects the outcome of the effects of all other predictors are held constant.

Exploratory Hypothesis 5: To assess exploratory hypothesis five (the relationship between the SN and the degree of anticorrelation between the DMN and CEN), a Pearson's correlation was used to examine the relationship between the cohesiveness of the SN and the anticorrelation between the DMN and CEN. As mentioned earlier, z-scores will be used to represent the degree of anticorrelation. Due to methodological concerns with correlating z-scores with a determinant scores (due to score distributions), SN cohesiveness for this hypothesis will be represented z-scores. These will be calculated by transforming the between-node correlations (obtained in an earlier step of calculating the determinant) into z-scores using a Fisher's z transformation. The z-scores will then be averaged, with the mean z-score representing the network connectivity. As a secondary analysis, the relationship between DMN cohesiveness, CEN cohesiveness, SN cohesiveness, and degree of anticorrelation were explored with a Pearson's correlation.

CHAPTER FOUR

RESULTS

Descriptive Statistics: A total of 63 participants were included in the study. Demographic features and clinical characteristics for the participants are shown in Table 1. The means, standard deviations, ranges, and frequencies of all cognitive measures are listed in Table 2. For the most part, participants' mean scores were in the average range on cognitive measures, with the exception of Digit Span, which was below average. Of note, the mean BDI-II total score was 17.56, which is indicative of mild symptoms of depression. Two individuals reported more scores over 40, indicative of more severe symptoms. Details on the volumetric measures are listed in Table 3, and the results of the network cohesiveness analysis are in Table 4. The mean GOS-E score was 6.43, which falls between the "upper moderate disability" and "lower good recovery" ranges.

Table 1

Sample Demographic Characteristics

Characteristic	Mean (SD)	Range
Age at Assessment	40.05 (12.05)	19 - 65
Age at Injury	32.97 (13.36)	16 - 64
Age at 1st TBI	20.59 (11.82)	3 - 48
Years since Injury	7.29 (6.73)	0.5 - 25
Education (yrs)	16.13 (2.58)	12 - 20+
Est. Current IQ	108.82 (11.84)	83 - 141
Est. Premorbid IQ	111.20 (8.23)	90 - 123
	Percent	
TBI Severity	90.5% mild, 9.5% moderate	
Number of Previous TBIs	0: 61%; 1: 29%; 2: 8%; 3: 2%	
Civilian/Military	66% civilian, 34% military	
Gender	62% male, 38% female	
Ethnicity	84% Caucasian, 13% African American, 3% Hispanic	

Table 2

Mean, SD, and Range of Neuropsychological Scores

Measure	Mean (SD)	Median	Range
GOS-E	6.43 (0.67)	7	5 - 7
BDI-II Total	17.56 (10.79)	16.5	0 - 50
BDI-II Cognitive Subscale	5.89 (4.73)	5	0 - 18
BDI-II Non-Cognitive Subscale	11.68 (7.13)	10	0 - 32
WASI Estimated Current IQ (standard score)	108.82 (11.84)	110	83 - 141
WTAR Premorbid IQ Estimate (standard score)	111.20 (8.23)	112.5	90 - 123
Daneman-Carpenter Reading Span Task (raw)	2.82 (0.85)	2.5	1.5 - 4.5
Digit Vigilance Total Time (t-score)	50.57 (10.93)	51	31 - 79
Digit Vigilance Total Errors (t-score)	47.97 (10.70)	48	26 - 71
D-KEFS Card Sort Condition 1 (SS)	10.64 (2.57)	11	5 - 17
D-KEFS Card Sort Condition 2 Description (SS)	9.92 (3.44)	10	1 - 17
D-KEFS Color Word Condition 1 (SS)	9.05 (3.34)	10	1 - 14
D-KEFS Color Word Condition 2 (SS)	9.52 (3.24)	11	1 - 14
D-KEFS Color Word Condition 3 (SS)	9.38 (3.25)	10	1 - 15
D-KEFS Color Word Condition 4 (SS)	9.59 (3.16)	11	1 - 14
D-KEFS Trail Making Test Condition 1 (SS)	11.60 (2.55)	12	1 - 15
D-KEFS Trail Making Test Condition 2 (SS)	10.87 (3.19)	12	1 - 16
D-KEFS Trail Making Test Condition 3 (SS)	10.79 (3.36)	12	1 - 15
D-KEFS Trail Making Test Condition 4 (SS)	10.82 (2.83)	12	1 - 15
D-KEFS Trail Making Test Condition 5 (SS)	11.87 (2.04)	12	1 - 15
D-KEFS Verbal Fluency Condition 1 (SS)	10.98 (2.85)	11	3 - 18
D-KEFS Verbal Fluency Condition 2 (SS)	10.79 (3.77)	11	2 - 19
D-KEFS Verbal Fluency Condition 3 (SS)	11.11 (3.55)	11	4 - 18
D-KEFS Verbal Fluency Total Set Loss Errors (raw)	1.08 (1.57)	1	0 - 8
D-KEFS Verbal Fluency Total Repetition Errors (raw)	2.40 (3.01)	2	0 - 17

Visual Selective Learning Task, Total (Standard Score)	114.67 (38.12)	114	29 - 200
WAIS-III Digit Span Forward Total (SS)	10.48 (2.26)	10	6 - 16
WAIS-III Digit Span Backward Total (SS)	7.19 (2.24)	7	3 - 13
WAIS-III Digit Span Total (SS)	10.48 (2.67)	10	5 - 18
WASI Similarities (t-score)	54.51 (6.34)	56	39 - 68
WASI Matrix Reasoning (t-score)	59.08 (6.74)	60	39 - 70
WASI Vocabulary (t-score)	59.97 (9.50)	53	24 - 80
WMS-IV Logical Memory Immediate (SS)	13.14 (4.14)	13.5	4 - 22
WMS-IV Logical Memory Delayed (SS)	11.27 (4.66)	12	1 - 20

Note: SS= Scaled Score

Table 3

Volumetric Measures Descriptive Statistics

Volumetric Measure ($mm^{3)}$	Mean (SD)	Range
Normalized Peripheral Grey	642,620 (45,194)	549,629 - 791,057
Normalized Ventricular CSF	41,808 (20,621)	9,682 - 110,565
Normalized Global Grey	811,445 (55,935)	710,119 - 991,835
Normalized Global White	734,617 (41,894)	647,781 - 827,798
Normalized Total Volume	1,546,062 (77,101)	1,371,948 - 1,723,987

Note: CSF= Cerebral Spinal Fluid

As a whole, the sample was relatively well educated, and the average participant was approximately 40 years of age. A vast majority received a mild TBI, with the remainder receiving a moderate TBI. They were well into the chronic stages of recovery, and reported to fall in to the lower end of what would be considered “good” recovery. On average, the sample was reporting mild symptoms of depression.

With regard to network functional connectivity, the pooled connectivity maps for the DMN, CEN, and SN are presented in Figures 3, 4, and 5, respectively. With regard to network cohesiveness, histograms of the distribution of the determinant statistic values for the DMN, CEN, and SN are displayed in Figures 6, 7, and 8, respectively. Figure 9 displays a histogram of the distribution of z-values for the DMN/CEN anticorrelation.

Table 4

Network Cohesiveness Descriptive Statistics

Network Cohesiveness	Mean (SD)	Range
DMN (determinant)	1.37 (.25)	0.93 - 1.94
CEN (determinant)	1.62 (0.25)	1.00 - 2.14
SN (determinant)	1.13 (0.23)	0.65 - 1.67
Anticorrelation (z-value)	0.35 (0.23)	-0.16 - 1.02

Note: DMN= Default Mode Network, SN= Salience Network, CEN=Central Executive Network

Research Hypotheses

Hypothesis 1: Predictors of DMN network cohesiveness. It was postulated in hypothesis 1 that the cohesiveness of the DMN could be predicted from a combination of cognitive test scores, volumetric data, outcome measures, depressive symptoms, and demographic and injury data. The hypothesis was supported. When all of these factors were entered into a stepwise linear regression and then eliminated using a backward stepwise procedure, it was found that a model consisting of age at assessment, D-KEFS Card Sorting condition 2, Digit

Span Total Score, normalized global grey matter volume, normalized ventricular CSF volume, TBI severity, D-KEFS Trails Making Test condition 2, D-KEFS Trail Making Test condition 3, normalized total brain volume, and WASI Similarities significantly predicted DMN cohesiveness (Table 5). The results indicate that these predictors explained 50% of the variance (R^2 = .449, F(10, 57)=3.83, p<.001). A histogram of the DMN cohesiveness (determinant statistic) values is displayed in Figure 6.

Hypothesis 2: Predictors of CEN network cohesiveness. It was postulated in hypothesis 2 that CEN cohesiveness could be predicted from a combination of cognitive test scores, volumetric data, outcome measures, depressive symptoms, and demographic and injury data. This hypothesis was supported. When all of the aforementioned factors were entered into a stepwise linear regression and then eliminated using a backward stepwise procedure (Table 6), it was found that a model consisting of D-KEFS Color Word Inhibition condition 3, D-KEFS Verbal Fluency condition1, D-KEFS Verbal Fluency Total Set-Loss Errors, Digit Span Forward, D-KEFS Trail Making Test condition 1, and WASI Vocabulary explained 37% of the variance (R^2= .370, F (6,57)=4.99, p<.001). A histogram of the CEN cohesiveness values (determinant statistic) is displayed in Figure 7.

Hypothesis 3: The DMN, SN, and attention. It was proposed in hypothesis 3 that the relationship between the DMN and measures attention would be stronger than the relationship between the SN and measures of attention. This hypothesis was not supported. A backwards stepwise multiple regression was performed to examine the effect of cognitive test

scores, volumetric data, outcome measures, depressive symptoms, and demographic and injury data on SN cohesiveness. The results (Table 7) indicated that a model consisting of D-KEFS Card Sorting condition 2, D-KEFS Color Word Inhibition condition 1, D-KEFS Color Word Inhibition condition 4, Digit Span Backwards, Digit Span Total, gender, normalized ventricular CSF volume, GOS-E, and normalized total brain volume explained 45% of the variance in the cohesiveness of the SN (R^2=.45, $F(9,60) = 4.65$, $p<.001$). A histogram of the SN cohesiveness values (determinant statistic) is displayed in Figure 8. As mentioned earlier, age at assessment, D-KEFS Card Sorting condition 2, Digit Span Total Score, normalized global grey matter volume, normalized ventricular CSF volume, TBI severity, D-KEFS Trails Making Test condition 2, D-KEFS Trail Making Test condition3, normalized total brain volume, and WASI Similarities significantly predicted DMN cohesiveness and explained a significant portion of cohesiveness in the DMN.

Hypothesis 4: The CEN, SN, and cognitive flexibility. Hypothesis 4 stated that the relationship between the CEN and cognitive flexibility would be stronger than the relationship between the SN and cognitive flexibility. This hypothesis was not supported. As mentioned above, significant predictive factors for the CEN were D-KEFS Color Word Inhibition condition3, D-KEFS Verbal Fluency condition1, D-KEFS Verbal Fluency Total Set-Loss Errors, Digit Span Forward, D-KEFS Trail Making Test condition 1, and WASI Vocabulary. Predictive factors for the SN were found to be D-KEFS Card Sorting condition2, D-KEFS Color Word Inhibition condition 1, D-KEFS Color Word Inhibition condition 4, Digit Span Backwards, Digit Span Total, gender, normalized ventricular CSF

volume, GOS-E, and normalized total brain volume. No measures of cognitive flexibility were included in the predictive model for the CEN; perhaps the closest measure was one of inhibition, the D-KEFS Color Word Inhibition condition 3 (ß= -0.435). One measure of cognitive flexibility included in the predictive model for the SN, D-KEFS Color Word Inhibition condition 4 (ß=-0.301).

Exploratory Hypothesis 5: The SN and Anticorrelation: Exploratory Hypothesis 5 postulated that the degree of anticorrelation between the DMN and CEN would be significantly and positively correlated with the coherence of the SN. This hypothesis was partially supported. A Pearson's correlation revealed a moderate correlation approaching significance between SN cohesiveness and DMN/CEN anticorrelation (r= .220, p=.084). In addition, significant relationships were found between DMN and CEN cohesiveness (r=.292, p<.02) and between CEN and SN cohesiveness (r=.295, p=.019). Degree of anticorrelation had a positive correlation with DMN cohesiveness (r=.373, p=.003) and CEN cohesiveness (r=.865, p<.001). However, no significant relationship was found between DMN and SN cohesiveness (r=.135, p=.291). A histogram of the anticorrelation z-values is displayed in Figure 9.

CHAPTER FIVE
Conclusions and Discussion

This study examined the factors influencing the resting-state functional connectivity (i.e., network cohesiveness) of three intrinsically-connected networks in a population of individuals with mild to moderate TBI. Multiple linear regressions were used to develop a predictive model for the default mode network (DMN), central executive network (CEN), and the salience network (SN). Predictive factors entered into the models included demographic factors, injury factors, volumetric data, and results from a cognitive assessment battery. Furthermore, the interaction between networks, specifically between the SN and the anticorrelation between the DMN and CEN, was evaluated.

With regard to the cognitive aspects of the assessment battery, mean test scores appeared to fall within the average range. This included estimates of pre-morbid and current IQ, as well as verbal fluency, verbal reasoning, immediate and delayed memory, nonverbal reasoning, processing speed, and cognitive switching. However, a measure of working memory, Digit Span Backwards, was below the expected population mean. These results indicate that, as a whole, the sample was relatively cognitively intact, with average scores largely falling within one SD of the mean. The exception to this was Digit Span Backwards, which was one SD below the expected mean. Overall, the sample was middle aged, mildly injured, experiencing few cognitive difficulties as measured by testing, in the chronic stages of recovery, of average intelligence, and reporting mild symptoms of depression.

Hypothesis 1: Hypothesis 1 posited that a combination of neuropsychological measures of executive functioning, depressive symptoms, demographic data, and injury data would predict default mode network functional connectivity in mild-to-moderate TBI. This hypothesis was supported, as a combination of volumetric measures (grey, ventricular CSF, and total brain volumes), measures of simple attention (Digit Span), measures of complex attention (D-KEFS Trail Making Test conditions 2 and 3), verbal reasoning (WASI Similarities), reasoning and concept formation (D-KEFS Card Sorting condition 2), demographic factors (age at assessment), and injury factors (TBI severity), when entered into a multiple linear regression, resulted in a significant predictive model (Table 5). This was found to predict approximately 50% of DMN cohesiveness variance.

Table 5

Multiple Linear Regression Results, DMN

Domain	Variables Entered	ß	Sig	VIF
Demographic/Injury	**Age at Assessment***	0.46	.002	1.75
	TBI Severity*	0.24	.046	1.15
	Age at 1st TBI			
	Time since injury			
Cognitive	**D-KEFS Trail Making Test 2***	0.51	.005	2.51
	Digit Span Total*	0.44	.002	1.55
	D-KEFS Trail Making Test 3*	-0.37	.034	2.42
	WASI Similarities *	-0.33	.022	1.67
	D-KEFS Card Sort Condition 2*	-0.32	.02	1.52
	Daneman Carpenter			
	D-KEFS Trail Making Test 1			
	D-KEFS Trail Making Test 4			
Volumetric	**Normalized Global Grey Volume***	0.88	.001	4.97
	Normalized Total Brain Volume*	-0.74	.002	4.28
	Normalized VCSF Volume*	-0.34	.013	1.52

*included in final predictive model

Cognitive Factors: Attention

As noted earlier, relationships have been reported between DMN functional connectivity and performance on tasks of attention (Bonnelle, et al., 2011), working memory (Anticevic, et al., 2010) and overall executive functions (Damoiseaux, et al., 2007). Therefore, the inclusion of a measure of attention in the factor model was expected. One explanation may be the special position that attention plays in executive functioning. For example, in the D-KEFS, attention is considered to be a “fundamental” basic cognitive skill that is essential in order to perform more advanced, “higher-order” cognitive skills (Delis, Kaplan, & Kramer, 2001). Though the D-KEFS Trail Making Test condition 2 and 3 are not

explicitly considered to be attention tests, they have a great deal of similarity to the classic Tail Making Test A, which is considered to have a significant attention component (Strauss, Sherman, & Spreen, 2006). The inclusion of several measures that rely heavily on fundamental cognitive skills, and the lesser role of tests that strongly involve higher-order executive function skills (such as planning, problem solving, switching, inhibition, etc.) lends evidence to the view that the DMN represents some degree of "basic" brain functioning. As discussed earlier, the DMN has been theorized to perhaps represent a neural "holding pattern," allowing the brain to remain in a state of readiness to more quickly respond to environmental demands (Deco, et al., 2009). This view of the DMN as a more base-level network is further supported by the relatively heavy weight given to volumetric measures, age, and (to a lesser degree) TBI severity in this model. This would seem to indicate that the DMN is more sensitive to these factors as opposed to the CEN (which will be discussed later), and alterations to the DMN the fundamental cognitive skills associated with it may underlie changes in higher-order skills seen with age, illness, and injury. This is also somewhat in-line with research from Boly et al. (2008; 2009), who reported declines in DMN functional connectivity that corresponded with deepening levels of unconsciousness, and concluded that the DMN reflected a basic level of brain functioning (though more than simply an artifact of respiration or blood flow).

Cognitive Factors: Verbal

When examining the factors included in the DMN model, two measures stood out as representing domains not typically associated with the DMN; WAIS Similarities, an

assessment of abstract verbal reasoning, and the D-KEFS Card Sorting condition 2, an assessment of reasoning and concept formation. Though verbal reasoning ability was not traditionally associated with the DMN, recent research has noted strong anticorrelation at rest between pre-supplementary motor areas associated with language and the DMN (Ter Minassian et al., 2014), though research relying on anticorrelation may be problematic in itself (which is discussed further in the context of hypothesis 4). Another study examined the resting-state functionally connected network that resulted from seeding Broca's Area, and noted significant overlap with nodes of the DMN (Muller & Meyer, 2014). This burgeoning idea of a relationship between language and the DMN may again relate to the more established view of the DMN's relationship with attention; a more cohesive DMN may use fewer resources during cognitively demanding tasks, thus allowing more efficient utilization by other neural networks, such as language networks or the CEN. If the DMN is less cohesive, then perhaps the resulting increased variability in neural activity would result in an inefficient use of neural resources, thus disrupting attention, concentration, and higher-order cognitive skills. Therefore, individuals with better DMN cohesiveness may have better attention, and may be better able to concentrate while attempting to answer abstract verbal reasoning questions. On the other hand, there is thought that the DMN plays a role in maintaining activation in frequently used neural pathways (Buckner & Vincent, 2007; Greicius & Menon, 2004). If true, then perhaps the DMN has a role in maintaining some degree of "readiness" in pathways associated with verbal abilities.

A similar line of reasoning may underlie the inclusion of the D-KEFS Card Sorting condition 2 in the predictive model for the DMN. The pattern identification, classification,

cognitive flexibility, and reasoning skills involved in identifying the pattern another individual is following during a card sort task are likely skills that require attention and concentration—skills associated with the DMN. Alterations in the DMN could result in poorer attention and concentration, which, in turn, have a negative impact on verbal ability and reasoning skills. However, this explanation is likely too simplistic. If a simple relationship with attention and concentration were enough to include a test into the predictive model for the DMN, then nearly all tests in the battery would be included. The explanation for the inclusion of D-KEFS Card Sorting must involve other factors. Breaking down the tasks involved in the card sorting test reveals that one key component is conceptualization. Resent research into the neural processes involved during the process of solving a math problem examined neural activity during each step of the problem solving process. During an early phase in the process, when individuals were simply defining the problem, increased activity was noted in regions associated with the DMN (J. R. Anderson, Lee, & Fincham, 2014). Activation in nodes of the DMN was not observed during other steps in problem solving, such as computing or encoding. The researchers hypothesized that this activation was related to aspects of visual attention and search during the time when participants are attempting to conceptualize the problem to be solved. This is similar to the card sorting descriptive task, during which participants have to visually examine the cards in order to deduce the sorting pattern that the examiner is following, as they try to conceptualize the pattern and verbally explain it. This raises the question as to why D-KEFS Card Sort condition 1 was included, but not D-KEFS Card Sort Condition 2. Though there is a lot of similarity between these tasks, there is one fundamental difference. In D-KEFS Card Sort

condition 1, the individual taking the test has to come up with the categories by which to sort the cards. Though this is speculation, perhaps the process of developing one's own sort strategy does not have as strong of a relationship with the DMN as trying to conceptualize someone else's sort strategy.

The D-KEFS Card Sorting condition 2 also involves a task that is relatively unique in the battery. The participant must observe another individual and deduce their intentions and motives, and transform these into coherent verbal explanations. This hints at the possibility of some involvement of social processing, mirroring, theory of mind, or perspective taking. Though the relationship between these variables and performance on the card sort descriptive task is likely not strong, there is evidence of a relationship between the DMN, social cognition, and understanding others (W. Li, Mai, & Liu, 2014; Molnar-Szakacs & Uddin, 2013). Perhaps this card sorting task involved significant degrees of attention, conceptualization, and predicting/understanding the actions of another person to allow its inclusion into the DMN predictive model.

Volumetric and Age Factors

Further examination of the weight of the different cognitive factors included in the model reveals information about the DMN. As mentioned earlier, two of the factors with the greatest *ß* were volumetric factors, one of which is normalized volume of grey matter. There is evidence in the literature tying grey matter volume to functional connectivity. For example, grey matter loss has been associated with attenuated DMN functional connectivity in multiple sclerosis (Bonavita et al., 2011), epilepsy (Voets et al., 2012), and dementia

(Bozzali, Padovani, Caltagirone, & Borroni, 2011). The second heaviest weighted factor in the model was normalized ventricular CSF, which had a large negative *ß.* This indicates that increases in ventricular CSF were related to declines in DMN cohesiveness. Taken together, these two findings make intuitive sense. Increased ventricular space is often considered to be a sign of atrophy or injury, and declines in grey matter are associated with poorer cognitive and motor performance. However, the third volumetric measure included in the model was normalized total brain volume, which had a negative *ß.* This indicates that lower brain volumes are associated with higher DMN functional connectivity. Typically, declines in brain volume are associated with aging or disease (Scahill et al., 2003; Takao, Hayashi, & Ohtomo, 2012). Similarly, the factor of age at the time of assessment was a significant part of the predictive model, and itself had a positive *ß,* indicating that increases in age are associated with increases in DMN cohesiveness. These two findings appear to be contrary to the other research on age and functional connectivity, which typically finds a decline in functional connectivity with age (Schlee, Leirer, Kolassa, Weisz, et al., 2012). This finding seems to imply that age is associated with *increased* DMN cohesiveness. There is some support for this idea in literature, with one study finding a mixture of increases and decreases with age in various DMN sub-networks (Campbell, Grigg, Saverino, Churchill, & Grady, 2013), and another finding that shorter-range connections are less sensitive to aging effects than longer range connections (Tomasi & Volkow, 2012a).

A possible explanation rests in the method used to conduct the multiple linear regression. Factors in a multiple linear regression that have a strong correlation with each other, but do not violate multicollinearity assumptions, may appear in the predictive model

with opposite ß signs. In the DMN model, none of the factors were significantly collinear. However, some of them were likely correlated, to some degree. For example, the DMN predictive model contained both D-KEFS Trail Making Test condition 2 and D-KEFS Trail Making Test condition 3. These tests are similar enough that there likely exists a degree of positive correlation between the scores, yet the multicollinearity analysis revealed that neither one was significantly collinear. Both appear in the predictive model, yet D-KEFS Trail Making Test condition 2 had a positive ß, while D-KEFS Trail Making Test condition 3 had a negative ß. This same concept may affect other factors in the model which are likely correlated, yet not significantly collinear, such as age at assessment and the volumetric measures, which (as mentioned earlier) are believed to be sensitive to aging effects. Therefore, interpretation of the direction (sign of the ß) of various factors in the model should be interpreted with caution.

With the aforementioned methodological caveat in mind, several possible alternative explanations exist for unexpected direction of factors included in the model. However, these are speculative at this time. First, it has been theorized that there exists an optimal amount of functional connectivity for the intrinsically-connected networks, and levels of functional connectivity above this amount may reflect compensatory, yet inefficient changes in the network (Turner, et al., 2011) or vascular changes (Hillary & Biswal, 2007). This is especially relevant given the population of the present study, who suffered a mild to moderate TBI, and thus, may be slightly less efficient at some tasks but accurate nonetheless. The combination of age and the changes in brain volume as a result of TBI may have resulted in less processing efficiency which results in increases to functional connectivity with age.

Perhaps greater functional connectivity is required in order for these older participants to maintain cognitive scores that fall in the average range. Furthermore, as discussed earlier, there is equipoise in the field as to the effects of mild to moderate TBI on functional connectivity in general, with some studies finding an increase (hyperconnectivity), while others finding a decrease (hypoconnectivity). Lastly, another potential explanation for these findings may be found in a recent meta-analysis, which examined the effect of variations in tests used in a cognitive battery on task-based functional connectivity. The results suggested that different tests that are believed to assess the same cognitive domain (for example, the various tests that purport to study working memory), can result in significantly different patterns of task-based functional connectivity, with some studies reported hypoconnectivity and other reporting hyperconnectivity (Bryer, Medaglia, Rostami, & Hillary, 2013). Though the present study is a resting-state study, this does indicate that different tests related to the same domain may have different relationships with intrinsically connected networks, and may contribute to some of the findings that are seemingly contradictory to other resting-state findings.

An alternative to this explanation may involve changes to the size and shape of the DMN following injury or age. A recent study revealed that the DMN, during a heavy cognitive load, spatially decreases in size in healthy older adults, compared to young controls (Prakash, Heo, Voss, Patterson, & Kramer, 2012). Certain networks (such as the CEN) are believed to “recruit” nearby cortical areas in healthy aging, resulting in alterations in the spatial size of the network as well (Allard & Kensinger, 2014; Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006). Though there is debate on the cause of this change,

one line of thought is that this process helps the brain compensate for reduced efficiency. This same effect has been observed in asymptomatic individuals with mild TBI, when under heavy cognitive load (Sinopoli et al., 2014). This recruitment of nearby neural areas post-TBI may be akin to the brain accessing these areas that it would normally access with increased age. In the context of a TBI, these areas are recruited at a younger age, due to the effects of the TBI (Hillary, et al., 2006).

Taken together, perhaps the positive relationship between age and DMN cohesiveness and the negative relationship between brain volume and DMN may be a reflection of a geographically altered DMN. The method of generating ROIs in the present study created a unique set of coordinates for each ROI, for each individual. This method for evoking the DMN, while accepted in the field, likely results in increased accuracy and ability to accommodate geographic changes in the DMN present in each individual. Instead of examining the network with a one-size-fits-all approach, the method used in the current study allows for a functional connectivity map tailored to each individual's unique pattern. Thus, age-related changes in DMN geography (which may affect the location of the voxels with peak functional connectivity) may not have such a strong effect on the data as in other studies. Using a one-size-fits-all map will miss individual variations in the locations of peak functional connectivity, and potentially result in artificially lowered levels of functional connectivity in individuals whose functional connectivity maps differ from the average map, or from a map generated from healthy controls. Therefore, the seeming aberrant relationships between total brain volume, age, and DMN cohesiveness may actually reflect an increased accuracy in mapping the DMN due to the aforementioned method, as well as increased DMN

functional connectivity related to group-level poorer performance on neuropsychological measures, potentially as a result of the participant's history of TBI. Again, caution is urged when interpreting these findings, due to the aforementioned artifacts of the multiple linear regression.

TBI Severity

On a similar note, the predictive model returned a positive *ß* for TBI severity. The inclusion of TBI severity in the predictive model was interesting, given the limited range of TBI severity included in the sample. This may be an indication of the relatively strong impact that TBI can have on the DMN, if this relatively small variance in TBI severity in the sample was still influential enough to warrant inclusion in the model. There is disagreement in the literature as to the effect that mild-to-moderate TBI has on DMN functional connectivity, including the direction of any potential change in DMN functional connectivity (Mayer et al., (2011) and Zhou et al., (2012), for example). The method used in this paper may again have resulted in a more accurate representation of each individual's DMN. This may have decreased inaccurate results that may have arisen in other research as a result of individual variability in the location of the areas of peak activation in each DMN node, or alterations in size of the nodes in the DMN as a result of injury. Thus, the current method may have more accurately captured the effects of mild TBI on intrinsically-connected networks.

Excluded and Other Factors

Also worth examining are those measures which were not included in the model. Most notable, no measures of depression or functional status survived the second analysis. This may indicate that there is no significant relationship between the DMN and depression. However, there is evidence of alterations to the DMN in depressed individuals (W. Guo et al., 2013; Nixon et al., 2014; Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2013). It is worth noting in the present study that even though the mean score on the BDI-II was indicative of mild symptoms of depression, the participants in the study were not diagnosed with depression, per se. Therefore, the lack of depressive symptoms in the predictive model may reflect the lack of clinical depression in the sample. On the other hand, specific symptoms of depression could be related to DMN cohesiveness, and perhaps the total and categorical totals from the BDI-II (which were the only data from the BDI-II included in the first step) were not sensitive enough to theses specific symptoms. On a similar note, the GOS-E may not be sensitive enough to capture the effects of changes in DMN cohesiveness, which perhaps does not have a significant effect on functional abilities.

Though the current model explained approximately 50% of the variance, leaving 50% still unaccounted. One possible contributing factor to post-TBI DMN cohesiveness could be sustained attention, like that which would be assessed using a sustained attention task such as the Connors Continuous Performance Task. There is evidence to suggest that alterations in DMN cohesiveness are more noticeable during tasks that require longer period of attention (Bonnelle, et al., 2011). Another potential source of variance is intra-individual differences in functional connectivity. This study did not capture pre-TBI DMN cohesiveness, which could

potentially have a strong relationship to post-TBI cohesiveness, since functional connectivity has been found to be relatively consistent in healthy controls, even when assessments are separated by as much as six years (Persson, Pudas, Nilsson, & Nyberg, 2014). Premorbid factors are often powerful predictors of post-TBI functioning (Dikmen et al., 1994), so it may stand to reason that pre-TBI functional connectivity may be a significant predictor of post-TBI functional connectivity, especially considering the inter-individual variability in functional connectivity patterns.

Hypothesis 2: Hypothesis two posited that a combination of neuropsychological measures of executive functioning, depressive symptoms, demographic data, and injury data will predict CEN functional connectivity in mild-to-moderate TBI. This hypothesis was supported, as a combination of cognitive inhibition (D-KEFS Color Word Inhibition condition 3), simple attention (Digit Span Forward), visual attention/vigilance (D-KEFS Trail Making Test condition 1), and verbal ability (D-KEFS Verbal Fluency condition 1, D-KEFS Verbal Fluency Total Set-Loss Errors, and WASI Vocabulary), when entered into a multiple linear regression, resulted in a significant model (Table 6). This predicted 37% of CEN cohesiveness.

Table 6

Multiple Linear Regression Results, CEN

Domain	Variables Entered	ß	Sig	VIF
Demographic	Age at most recent Injury			
Cognitive	**D-KEFS Trail Making Test 1***	0.50	<.001	1.27
	Digit Span Forward	0.46	.001	1.40
	D-KEFS Color Word Condition 3*	-0.44	.006	1.87
	D-KEFS Verbal Fluency Condition 1*	0.30	.022	1.30
	WASI Vocabulary*	0.27	.033	1.18
	D-KEFS Verb. Fluency Total Set-loss Errors*	0.20	.08	1.05
	Digit Vigilance Total Errors			
	D-KEFS Card Sort Condition 2			
	D-KEFS Color Word Condition 1			
	D-KEFS Color Word Condition 2			
	D-KEFS Trail Making Test 2			
	VSLT Total			
	WMS Logical Memory Immediate Recall			
Volumetric	Normalized Global VCSF Volume			

*included in final predictive model

Role of Inhibition in the Model

Overall, the inclusion of D-KEFS Color Word Inhibition condition 3, which is similar to the classic Stroop Test, was generally expected. Inhibition is strongly associated with the prefrontal cortex (Blasi et al., 2006), which overlaps with a significant portion of the CEN. The direction of the relationship is worth noting, as the ß for this factor was moderate in size and negative, indicating that better performance on this measure was associated with mild decreases in CEN cohesiveness. However, no other factors that contributed to CEN cohesiveness had negative ß. As noted earlier, caution should be used when interpreting the

sign (positive vs. negative) of the ß in the predictive model. Though none of the variables had significant multicollinearity, they may correlate with each other, which can influence the sign of the ß.

With that caveat in mind, one potential explanation for this may be found through an examination of the cognitive domains encompassed by the other measures in the model with positive associations with CEN; verbal fluency, simple attention, verbal reasoning, and visual attention/vigilance. Of all of these domains, only inhibition has been strongly associated with the CEN, and inhibition is considered to be a higher-order, more complex skill. As discussed in the previous section, levels of functional connectivity that are too high may signal inefficiency in the network, and have been related to poorer performance on cognitive tasks. For example, in one study, individuals who experienced more difficulty on a working memory task (and were assumed to experience a heavier cognitive load because of their poor performance) actually displayed increased CEN functional connectivity, as well as increased CEN activity (Engstrom, Landtblom, & Karlsson, 2013). To extrapolate those findings to the current study, perhaps individuals who performed better on D-KEFS Color Word Inhibition had more efficient, effective CEN, and thus, had slightly lower functional connectivity than less efficient performers. Thus, better performances on this task may be associated with small declines in CEN cohesiveness. On a similar note, post-TBI individuals who had a chance to practice a working memory task displayed decreased BOLD activation in the frontal lobes when performing that task at a later time (Medaglia et al., 2012), which suggests that increased activation may be associated with less familiarity and poorer performance on a task.

It is also worth noting that D-KEFS Color Word Inhibition condition 3 was the only measure of inhibition to show up in the predictive model. Though not detailed in the hypothesis, it was expected that more measures of higher-level executive functioning would be included in the CEN model. It is indeed curious that other measures involving higher-level executive functions were not included, and raises the question if the inclusion of this measure is perhaps a spurious finding. This may indicate that the association between higher-level executive functions and the CEN is not as strong as originally believed. This also could indicate that the relationship between the CEN and higher-level executive functions is secondary to the relationship between the CEN and lower-level executive functions.

Attention and Verbal Factors

As noted above, two of the factors included in the CEN model were Digit Span Forward and D-KEFS Trail Making Test condition 1. Digit Span Forward is considered to be a measure of simple attention. The D-KEFS Trail Making Test condition 1 involves some degree of attention, but also is believed to involve degrees of vigilance and processing speed (Delis, et al., 2001). Three other factors included in the model were D-KEFS Verbal Fluency condition 1, D-KEFS Verbal Fluency Set-loss errors, and WASI Vocabulary. These three measures are typically considered to assess verbal fluency, monitoring during a verbal fluency task, and verbal knowledge. These three skills are not typically associated with the CEN. However, one view of the CEN is that it is an externally focused, goal-directed, task positive network, which plays a significant role in engaging executive functions on a task. The relationship between these factors and cohesiveness may reflective of better externally-

directed goal-monitoring abilities, inhibition of competing responses, and increased cognitive focus. While the CEN may not directly relate to the aforementioned skill domains, it may help facilitate their performance.

Excluded and Other Factors

Also worth noting are the factors that were not included in the model. No measures of demographics, injury-related aspects, or volumetrics were included in this model. This is quite different from the DMN model (and the SN model, which will be explored later), which featured such variables quite prominently. One reason for this may lie in the fundamental difference between networks. The CEN is a task-positive state network, while the DMN is a resting-state network. The predictive model for the DMN involved resting-state data, ostensibly capturing the network at its peak. However, the CEN was imaged at rest, when it is least likely to be active. Though resting state functional connectivity of the CEN is believed to strongly relate to task-based functional connectivity, surprising little research has been conducted into this concept. On a global level, changes in functional connectivity patterns and strengths were noted between rest and task-based imaging (Di, Gohel, Kim, & Biswal, 2013). Perhaps some aspect of this difference is responsible for the disparity, and repeating the current study with a task-based fMRI may yield different results for the CEN.

Finally, this model predicted 37% of CEN cohesiveness variance, which means that 63% of variance was unaccounted for. Similar to the discussion for the DMN, perhaps pre-morbid factors play some role CEN cohesiveness. Alternatively, perhaps the battery used, which was primarily reliant on the D-KEFS, contributed to this finding. As mentioned

earlier, variations in assessment tools that are designed to assess the same neuropsychological construct can result in differences in correlation between functional connectivity and test performance (Bryer, et al., 2013). Perhaps using a different assessment battery would result in model that predicts more of the CEN variance. Finally, the present study did not account for structural integrity within the brain. A model that included measures of structural connectivity, or of white matter integrity, may more fully explain CEN cohesiveness.

Hypothesis 3: Hypothesis three stated that the relationship between the DMN and attention will be stronger than the relationship between the SN and attention. This hypothesis was not supported, as Digit Span was responsible for a fairly equal amount of variance in both predictive models.

SN Predictive Model

Overall, the model for the SN accounted for 45% of the variance (Table 7). The remaining 55% of variance may be accounted for in part by social factors, which this study was not designed to evaluate. For example, the SN has been associated with feelings of anxiety (Seeley, et al., 2007), social behavior (Takeuchi, et al., 2013), and identifying potential salient stimuli that could become targets for cognitive focus (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). No measures addressing these functions were included in the cognitive battery in the present study. As discussed earlier, the sign (positive vs. negative) of the *ß* in the SN predictive model should be interpreted with caution, as this can

be influenced by the inclusion of factors in the model that are not significantly multicollinear, but do have a degree of correlation with each other. For example, in the SN model, Digit Span Backward has a negative *ß*, while Digit Span Total has a positive *ß*. Though neither of these factors violated the assumption of multicollinearity, they likely are positively correlated with each other, and thus, have opposing *ß* signs in the predictive model.

Table 7

Multiple Linear Regression Results, SN

Domain	Variables Entered, SN	*ß*	Sig	VIF
Demographic/Injury	**Gender***	-0.39	.001	1.07
	GOS-E*	0.20	.067	1.02
	Age at Assessment			
	TBI Severity			
Cognitive	**D-KEFS Color Word Condition 1***	0.54	.001	2.02
	Digit Span Total*	0.44	.047	4.40
	Digit Span Backward*	-0.35	.083	3.64
	D-KEFS Color Word Condition 4*	-0.30	.07	2.47
	D-KEFS Card Sort Condition 2*	-0.28	.033	1.55
	Digit Span Forward			
	D-KEFS Card Sort Condition 1			
	D-KEFS Color Word Condition 3			
	D-KEFS Trail Making Test 2			
	D-KEFS Trail Making Test 5			
	D-KEFS Verbal Fluency Condition 1			
	VSLT Total Score			
Volumetric	**Normalized Total Brain Volume***	0.35	.008	1.49
	Normalized Global Ventricular CSF*	0.25	.049	1.44

*included in final predictive model

Examining the factors that were included in the SN model reveals an overlap with some factors included in the DMN model, as well as several factors unique to the SN. For example, the SN model included D-KEFS Card Sorting Condition 2, Digit Span Total, normalized ventricular CSF, and normalized total brain volume, all of which were included in the DMN model. Digit Span, a measure of simple attention, had nearly identical *ß* in both models. However, the DMN model revealed inclusion of D-KEFS Trail Making Test 2 and 3, which are more complex measures of attention, both involving visual scanning, motor planning, as well as attention abilities (Delis, et al., 2001). The SN model included Digit Span Backwards, considered to be a measure of working memory (Lezak, Howieson, & Lowing, 2004; Strauss, et al., 2006). A previous study found a similar link between working memory and SN activation (Engstrom, et al., 2013).

The SN and Gender

In addition to normalized brain volume and normalized ventricular CSF, gender was also present in the SN model. The *ß* associated with this finding revealed that being male had a slightly positive effect on SN cohesiveness. There is disagreement as to the potential effect of gender on functional connectivity. One study found no significant difference between genders in DMN, CEN, or SN connectivity (Weissman-Fogel, Moayedi, Taylor, Pope, & Davis, 2010). An examination of global functional connectivity similarly found no significant gender differences (Nielsen, Zielinski, Ferguson, Lainhart, & Anderson, 2013). On the other hand, investigations into non-network specific gender and interhemispheric functional connectivity have revealed significant gender effects: Tomasi and Volkow (2012b)

studied global functional connectivity and network path length differences between genders, and noted that males had greater lateralization (right-sided) and more shorter-range connections than females, who had greater long-range connections. Alternatively, the presence of gender in the SN predictive model may simply reflect demographic differences that were not measured as part of this study, such as mechanism of injury (Hoppe, Kordahi, Paik, Lee, & Granick, 2014), the effect of sex hormones on recovery from TBI (Davis et al., 2006), gender differences in response to trauma and injury (Holbrook et al., 2005), or perhaps the differential effects of gender on appraisals of salience (Grose-Fifer, Migliaccio, & Zottoli, 2014; Hahn, Xiao, Sprengelmeyer, & Perrett, 2013; Kana, Murdaugh, Wolfe, & Kumar, 2012).

SN and Functional Outcomes

Finally, the SN predictive model was the only network predictive model in the current study to include a measure of adaptive functioning, the GOS-E. However, interpretation of this factor in the model is limited, due to the small range of GOS-E scores in the sample. Furthermore, the GOS-E is somewhat of a coarse estimate of adaptive functioning. Therefore, interpretation of this factor's inclusion in the predictive model should proceed with caution. Additionally, the sub-items of multi-item scales (such as the GOS-E and the BDI-II) were not included in the regression analysis, as there was concern that their inclusion would result in a model that was too specific to the population and "over-fit" the data. Thus, the specific items of the GOS-E that may feed into the SN model are currently unknown. With those caveats in mind, an examination of the *ß* revealed that higher GOS-E scores,

indicating a better functional recovery, were associated with increased SN cohesiveness. Though the present study did not examine the different functional areas assessed in the GOS-E, potential reasons for the GOS-E to predict SN connectivity may include the role that the SN is believed to play in error monitoring, social abilities, emotional intelligence, and salience detection. All of these skills would likely be vital to an individual who is successfully returning to work, engaging appropriately in social and leisure activities, and maintaining healthy relationships with family and friends; all of which are components of the GOS-E.

The findings from the present study (including a strong overlap between DMN and SN predictive factors) may indicate that the SN plays a larger role in basic cognitive processes than previously thought. This is in addition to its theorized role in monitoring the environment and activating/deactivating ("switching") networks. Perhaps the association between the SN cohesiveness and working memory indicates that this executive function is important for switching networks, or for monitoring incoming stimuli for salient information.

Hypothesis 4: The relationship between the CEN and cognitive flexibility will be stronger than the relationship between the SN and cognitive flexibility. This hypothesis was inconclusive; as mentioned earlier, no measure of cognitive flexibility was included in the predictive model for the CEN, though D-KEFS Color Word Inhibition condition 4 was included in the model for the SN. Though the SN is not considered to be a strict resting-state network like the DMN, it is also likely not strictly a task-positive network like the CEN. The SN has been conceptualized in the present study as a monitoring switching network, playing

a significant role in activating/deactivating networks, in response to salient environmental stimuli. Perhaps the predictive models for the CEN and the SN would change if the participants were imaged as they performed a task that required the detection of salient stimuli, or as they performed a task of cognitive flexibility, switching, or inhibition.

SN and Inhibition/Switching

Though the factors included in the SN model were previously discussed, one significant factor in the SN model was the D-KEFS Color Word Inhibition condition 4. This is a higher-order cognitive inhibition/switching task, and was initially hypothesized to factor in the CEN model. Its inclusion in the SN model was predicted, consistent with the view that cognitive skills associated with the DMN and CEN would also relate, to a lesser degree, to the SN. However, the current results (e.g., the lack of a measure of switching in the CEN model) call that hypothesis into question, and instead push for the development of alternative explanations. One potential alternative theory behind the inclusion of an inhibition/switching task may have less to do with network switching, and more to do with the cognitive functions associated with the SN itself. As mentioned earlier, error detection has been associated with the SN (Menon, et al., 2001). Error detection may play an important role in a test such as D-KEFS Color Word Inhibition condition 4, which requires participants to follow specific rules when performing a Stroop-like task. Awareness of errors one has committed could help participants avoid committing such errors again.

Exploratory Hypothesis 5: Hypothesis 5 stated that the degree of anticorrelation between the DMN and CEN would be significantly and positively correlated with the coherence of the SN. This hypothesis was partially supported, as a trending positive correlation was found between mean DMN/CEN anticorrelation and SN cohesiveness. However, the relationship between the DMN and the SN, and between the CEN and the SN were also examined. The CEN and DMN had moderate positive correlations with each other, and the CEN and a similar moderate positive correlation with the SN. Both the DMN and CEN had a positive correlation with the degree of anticorrelation, though the correlation between degree of anticorrelation and the CEN was much stronger.

Anticorrelation and Regression of the Mean Signal

It was initially predicted that a strong degree of anticorrelation would be found between the DMN and the CEN. This was anticipated to take the form of a strong negative correlation between the DMN and CEN nodes. However, the results of this study revealed an overall small positive correlative relationship, contrary to expectations and much of the literature. Only four individuals in the sample had a negative mean anticorrelation (of note, a review of the medical history of these four individuals revealed nothing to mark them as outstanding from the rest of the sample, nor did their scores on the assessment battery set them apart). In this sample of predominantly mild TBI, it seems unlikely that injury severity alone would be responsible for this finding. One potential explanation for this may lay in the preprocessing methods employed for this study; the mean global signal was not regressed out of the data prior to conducting the functional connectivity analysis. This was done to avoid

over-inflating the degree of anticorrelation between the DMN and CEN, but instead it seems to have nearly removed it altogether. This would be consistent with the work of Anderson et al. (2011), who concluded that large-scale intrinsic network anticorrelation is an artifact of global signal regression. Additionally, the researchers reported that larger intrinsically connected networks, such as the ones examined in the present study, are more influenced by this artifact than smaller networks. Murphy, Birn, Handwerker, Jones, and Bandettini (2009) came to a similar conclusion after examining global signal regression. They note that the process of global signal regression results in a bell-shaped distribution of correlation values, with a mean of zero, and half of the correlations falling into the negative range. The process of removal of the global signal artificially creates these negative correlations, so that the sum of all correlations is equivalent to the mean of zero. As further noted by Murphy et al. (2009), inclusion of the global signal does not remove the positive correlations associated with the functional connectivity within the DMN. However, task-positive networks (such as the CEN) are not visible on a seed-based functional connectivity map of the DMN unless the global signal is removed. Similarly, they add that regressing out movement, white matter signal, and CSF signal can result in similar decreases in anticorrelation.

DMN, CEN, and Anticorrelation

As noted earlier, the CEN and DMN had moderate positive correlations with each other, and the CEN had a similar moderate positive correlation with the SN. Both the DMN and CEN had a positive correlation with the degree of anticorrelation between them, though the correlation between degree of anticorrelation and the CEN was much stronger than for

the DMN. This may suggest that all three networks are affected by similar underlying conditions. For example, diffuse and traumatic axonal injury is known to disrupt functional connectivity within and across networks (Arenivas, et al., 2012; Sharp, Scott, & Leech, 2014). Taken together, this may be an indication that the CEN plays some role in anticorrelation, or that the factors that govern anticorrelation also have a strong effect on the CEN. This would also seem to be evidence against the idea that the SN is strongly involved in maintaining the level of anticorrelation between the DMN and CEN (though the possibility exists that the SN modulates anticorrelation via influencing the CEN). Instead, this would indicate that the CEN exerts some degree of control over the DMN, which has some support in the literature.

SN and DMN/CEN Anticorrelation

The current study is limited in its ability to extrapolate causality, due to the fact that correlations were used. However, the work by Chen et al. (2013) examined causality in relationship between the DMN, SN and CEN, via transcrainal magnetic stimulation. They were able to alter DMN functional connectivity by stimulating or inhibiting the DLPFC on the CEN, though no effect on the DMN was found by stimulating or inhibiting the SN. The positive correlation between CEN cohesiveness and anticorrelation may lend further evidence for role of the CEN in activating or deactivating the DMN.

In light of a general lack of “negative” anticorrelation, the SN-anticorrelation relationship is probably not as meaningful, especially in light of the very strong positive correlation between CEN cohesiveness and anticorrelation. The results of the present study

would seem to indicate that the CEN plays a larger role in maintaining the relationship between itself and the DMN. This would delegate the SN to a role of activating/deactivation networks, not maintaining the level of activation/deactivation, as proposed in the current hypotheses. This view of the SN is consistent with recent research, which further adds to the view that the SN plays a role in activating/deactivating the DMN and CEN (Goulden et al., 2014).

Regardless of positive or negative "anticorrelation," the relationship between the DMN and CEN is likely a worth topic of study. Carbonell, Bellec, and Shmuel (2014) studied the effect of global signal regression, and found that while regressing out the mean signal does indeed reduce anticorrelation, there is still evidence that anticorrelation between the DMN and CEN is more than statistical anomaly. They proposed mathematical correctional procedures that would allow for the discovery of truly anticorrelated regions, even within the context of global signal regression. Other research has proposed similar ideas, albeit through alternative correction methods (Carbonell, Bellec, & Shmuel, 2011; H. He & Liu, 2012). Furthermore, there is evidence that the relationship between the DMN and CEN may be fluid and able to change with regard to task demand. That is, researchers found that anticorrelation was not static or fixed, but rather, flexible and variable, depending on the demands of a given activity (Popa, Popescu, & Pare, 2009). If so, a resting-state paradigm, without regression of the global signal, may not be the best setting to capture this important relationship. Instead, imaging during a task, including shifts from rest to active and changes in type and difficulty of task, may provide relevant insight into the correlates of anticorrelation.

Difference Between Models

One notable finding was in the differences between predictive network models, with the difference between the DMN and the CEN models the most striking. For example, the DMN model featured volumetric measurements with relatively large ß values. However, the CEN model was comprised solely of cognitive factors. The SN model seemed to include a combination of factors from the DMN and CEN models. When considering the DMN model, it seems that the DMN is affected by things that physically affect the brain, such as volumetric alterations, age, and TBI factors. Furthermore, the DMN was associated with more basic cognitive processes in this study. This would indicate that the DMN seems to represent a basic level of "health" in the brain. This may be also why alterations in the DMN have been implicated in a wide range of disorders. Perhaps healthier brains have "better" DMN functional connectivity, which relates to better cognitive performance on basic cognitive skills (such as attention, focus, and concentration).

In contrast to the predictive model for the DMN, the model for the CEN did not include any volumetric, demographic, or injury factors; it was composed solely of cognitive factors. Perhaps this is indicative of a network that is less sensitive to structural changes in the brain, unlike the DMN. In fact, the predictive model of the CEN would suggest that it is influenced more by aspects of crystallized intelligence, schooling, and higher-level cognitive skills—though it is still reliant on lower-level skills, such as attention. While the DMN could hypothetically represent the "health" or the "base level" of the brain, the CEN could represent advanced specialized function, and therefore would serve as less of a barometer of brain health than the DMN.

Along these lines, the SN appeared to contain a blend of factors from the DMN and CEN models. Earlier, it was hypothesized that this may be related to the SN's role in switching/activating/deactivating the DMN and CEN. The SN model contains demographic and volumetric factors, like the DMN, but also contains a higher-level executive function factor, like the CEN. Alternatively, the SN has been associated with complex skills, such as social abilities and emotional intelligence (Takeuchi, et al., 2013). Successfully performing these complex tasks likely requires the coordination of several different neural areas, as well as the integration of several different skill sets. This may be responsible for some of the variety of factors involved in the SN model.

One way of conceptualizing these results may be to consider the degree to which various factors are important to each network. Though no factor analysis was performed as part of this study, the factors included in the model could theoretically be conceptualized as factors related to structural integrity, factors related to intelligence, factors related to basic attention and awareness, and factors related to phasic attention. Each of these factors likely has different relevance for each network; the DMN was shown to be more sensitive to factors related to structural integrity, the CEN less so. Perhaps one way these networks may be conceptualized, categorized, or compared in future research is by the weight of their contributing factors.

Future Directions

Several concepts from this study warrant further exploration, including methodological variations, the relationship between networks, and exploring other factors for

inclusion in the predictive models. First, the methods used in generating the networks have been mentioned several times during the discussion. It would be interesting to compare popular methods for network generation head to head, perhaps analyzing for differences in network cohesiveness and relationship with cognitive, volumetric, and demographic factors. Another topic for further exploration is the relationship between the DMN and the CEN. Though traditionally considered to be one of negative anticorrelation, the present study found a mostly positive "anticorrelation" between these two networks. One reason for this may be the inclusion of the global mean signal, which is traditionally removed during preprocessing. However, since there is thought that anticorrelation is merely an artifact of the process of removing the global mean signal, future research may further compare and contrast preprocessing methods for significant differences.

An additional direction for future research may be to perform a study similar to the present one, but during active executive function tasks in the scanner, instead of resting-state. This may allow for a better conceptualization of the CEN and the SN, as well for additional information as to the deactivation of the DMN during task. This could also help clarify the relationship between resting-state functional connectivity and task-state functional connectivity in task-positive networks. Additionally, the inclusion of a measure of structural integrity, such as an analysis of diffusion-weighted imaging, could potentially increase the amount of variance explained by the predictive models.

Further studies could involve conceptualizing or profiling individuals who performed better on the test battery compared to those who performed more poorly, or comparing individuals with strong network cohesiveness to those with weak network cohesiveness.

Finally, the inclusion of control groups may be illuminating, as it would allow for direct comparison of cohesiveness levels to healthy individuals, as well as allowing for comparisons of volumetrics, demographics, and performance on the assessment battery.

Limitations

First, the study lacked a group of healthy controls, which would allow for comparisons of performance on the assessment battery, comparisons of network profiles, and comparisons of predictive models. Second, a decision was made to not regress out the mean global signal. This procedure may have lead to falsely high levels of DMN/CEN anticorrelation in the past. The anticorrelation in the present study was much more positive, and less negative, than expected. This may make it difficult to compare the anticorrelation findings in the current paper with anticorrelation findings in other papers which regressed out the mean global signal. Third, there were some limitations due to demographic factors. For example, data on method of injury was not consistent enough for inclusion in the study, though it potentially could have made for stronger predictive models. There was large variability in the time since TBI, as well as variability in the number of previous TBI. As with most neuroimaging studies, inclusion a larger sample size would have been beneficial. With regard to the assessment battery, a large number of variables were included in the predictive models, and some of them were likely correlated. This had the potential to induce increased levels of error into the data. The use of a more focused cognitive assessment battery, based off the predictive models in this study, could reduce those levels of error. Furthermore, careful selection of a test battery to eliminate multicollinearity between test

measures (or strong correlations between test measures) may help clarify the roles of different factors in future predictive models, and reduce the chances of negative ß values arising from methodological artifacts. Finally, inclusion of a measure of white matter integrity (such as diffusion tensor imaging) may have further contributed to the predictive models.

Summary and Conclusions

The present study investigated factors that influenced the cohesiveness of the DMN, CEN, and SN in a sample of relatively well-functioning of adults with a history of mild to moderate TBI. Previous studies had investigated the effects of TBI on functional connectivity in these networks, as well as the relationship between these networks and various cognitive functions. However, these factors were previously analyzed in isolation; this study combined demographic data, injury data, performance on a cognitive assessment battery, volumetric data, symptoms of depression, and functional outcomes in order to develop a more holistic model of network functioning. Furthermore, this study was conducted in a population of predominantly mild TBI, so that the participants in the study would have networks that were not normal, but only mildly impaired.

The first two hypotheses predicted that the cohesiveness of DMN and CEN could be predicted from the aforementioned factors. The predictive model for the DMN included a combination of volumetric factors, age at assessment, TBI severity, measures of complex attention, and abstract verbal reasoning. Results indicated that the DMN is indeed impacted by TBI, and functional connectivity has a relationship with cognitive factors. The CEN

predictive model was composed primarily of cognitive measures, and included indices of simple attention, cognitive inhibition, verbal fluency, and verbal knowledge. The predictive model for the SN included measures of brain volume, as well as gender, functional outcome, simple attention, working memory, and cognitive flexibility. Hypothesis three, which stated that the degree of variance accounted for by measures of simple attention in the DMN would be greater than the degree of variance accounted for by the same measures in the SN, was not supported. Hypothesis four, which stated that the percent of CEN cohesiveness variance accounted by measures of cognitive switching would be greater than the percent of variance accounted for by the same measures on the SN, was inconclusive. Exploratory hypothesis 5, which stated that the degree of anticorrelation between the DMN and SN would correlated with the cohesiveness of the SN, was partially supported.

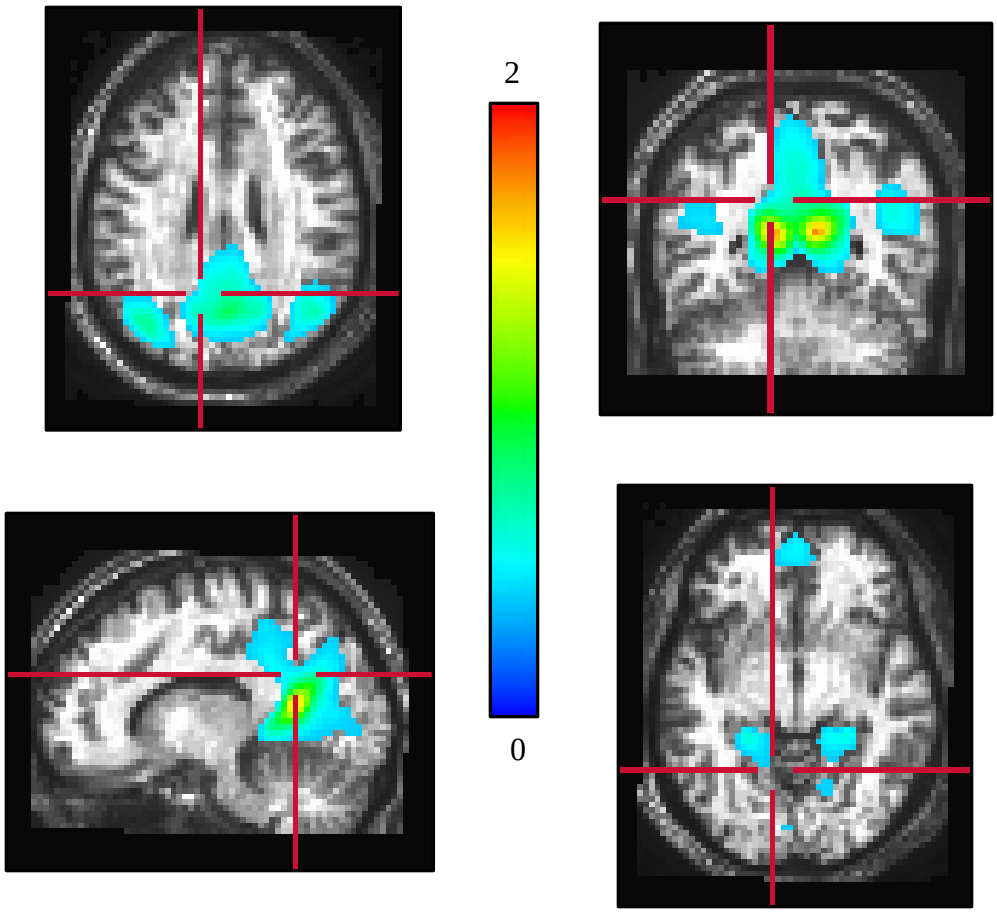
Of note is the difference between the predictive models for each network, and what these differences indicate about the networks themselves. Aspects related to brain structure and integrity (age, volumetrics, TBI severity) were featured prominently in the DMN model, while the CEN model only included cognitive measures. This may be indicative of fundamental differences between the networks, with the DMN perhaps more related to the overall health and basic functioning of the brain, and the CEN more related to intelligence and experience. The SN model appeared to be a combination of factors from the DMN model and the CEN model. This may be due to its role as a switching network, or it may relate to the SN's association with the process of assigning saliency to environmental stimuli. Furthermore, the SN has been strongly associated with social and emotional processes, which likely require the integration of complex cognitive factors.

In light of the controversy as to the inclusion of the global mean signal and its impact on anticorrelated networks, the current findings would indicate that perhaps the relationship between networks may be more complex than previously believed. For example, there may be more subtleties to the relationship between the DMN and the CEN than mere anticorrelation. Furthermore, while the results of the present study do allow for commentary on the role of the SN as a switching or monitoring network, they would seem to indicate that the SN may not play a role in maintaining network functional connectivity, once a network has been activated. However, a study of activation levels at rest and during task may be better able to address this concept.

Figures

Figure 3

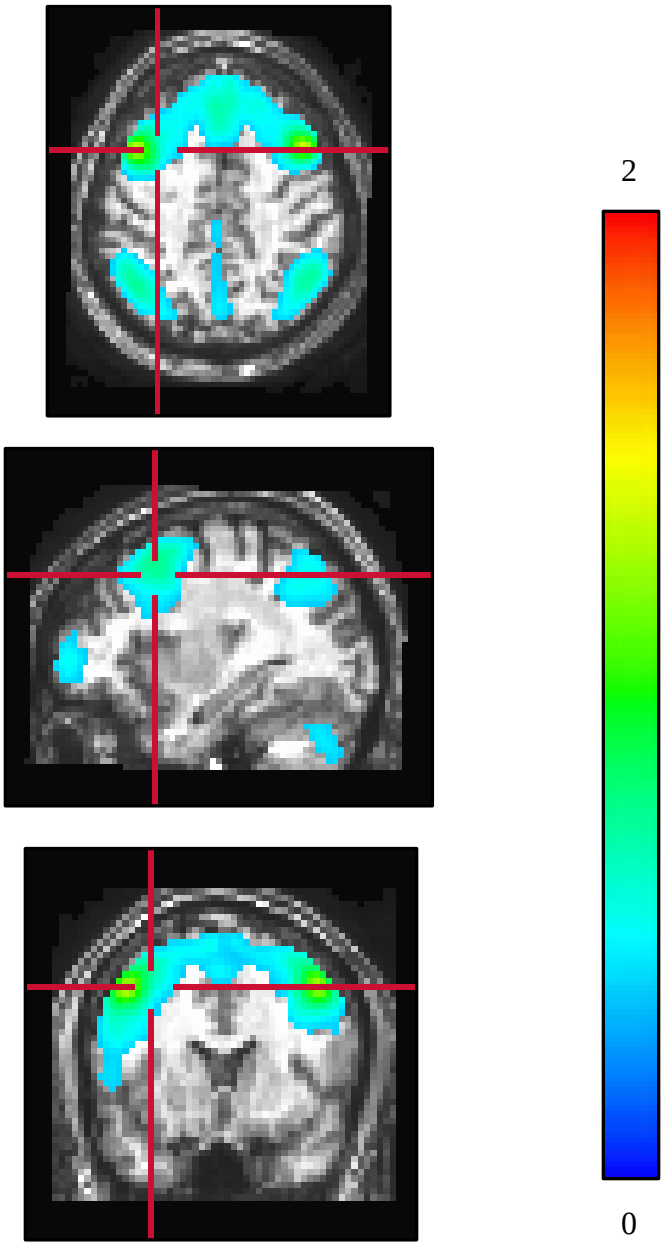
DMN Pooled Functional Connectivity Map



note: images were thresholded at 0.4 with a cluster size of 150.

Figure 4

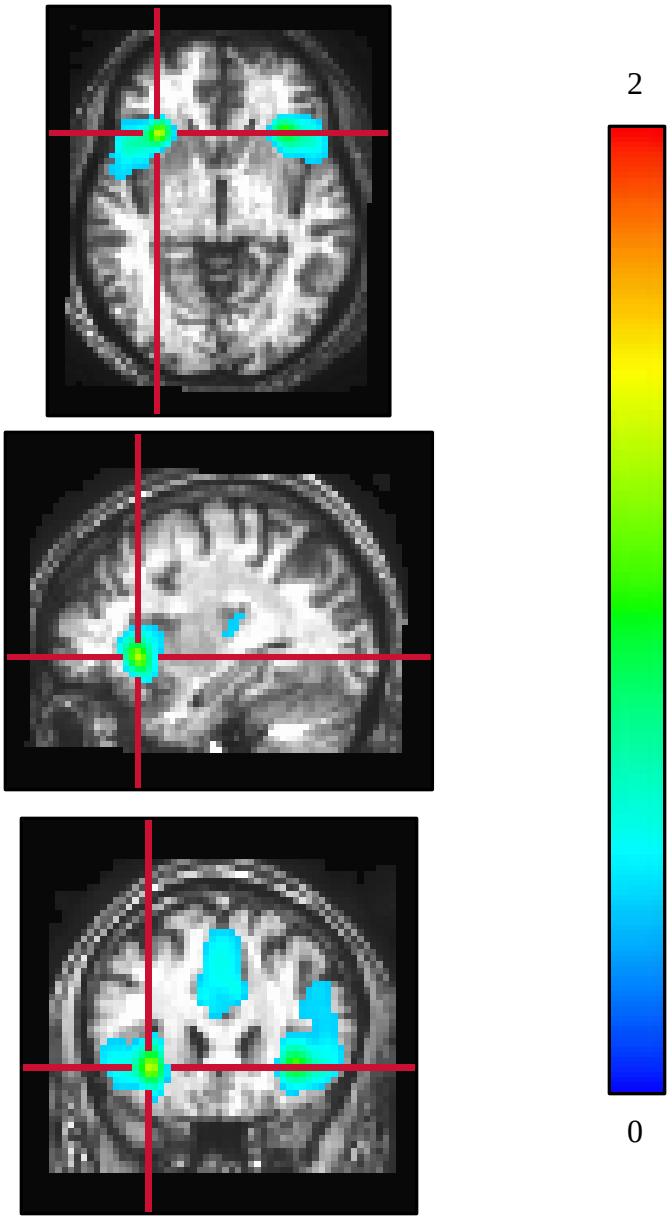
CEN Pooled Functional Connectivity Map



note: images were thresholded at 0.4 with a cluster size of 150.

Figure 5

SN Pooled Functional Connectivity Map



note: images were thresholded at 0.4 with a cluster size of 150.

Figure 6

DMN Cohesiveness Histogram

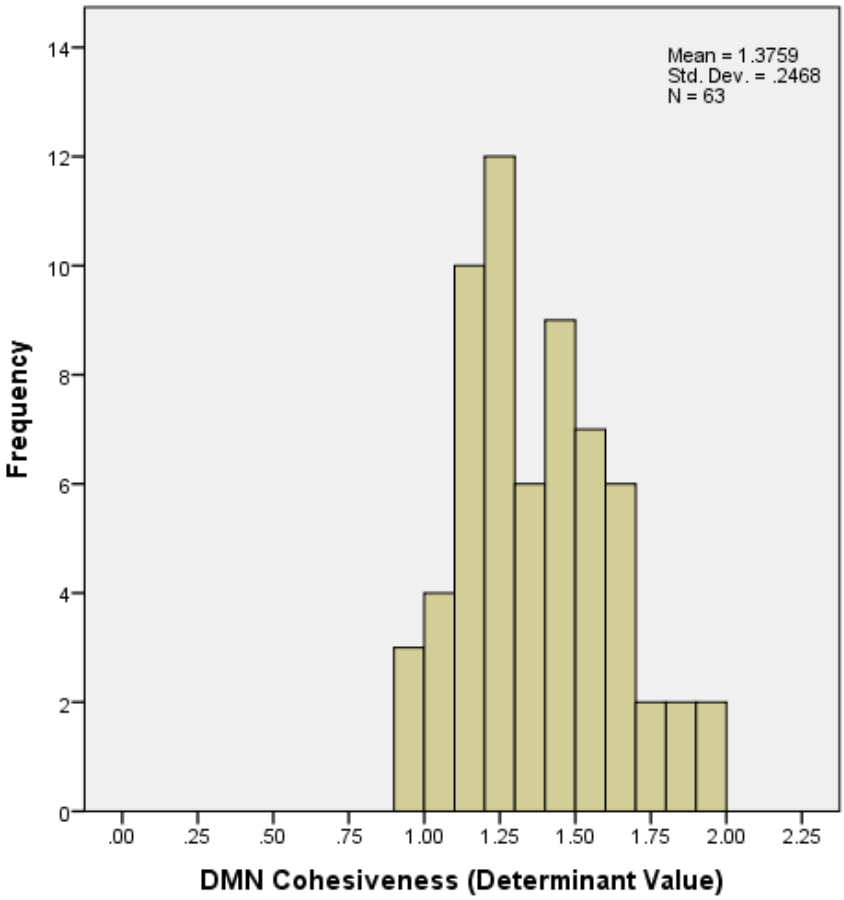


Figure 7

CEN Cohesiveness Histogram

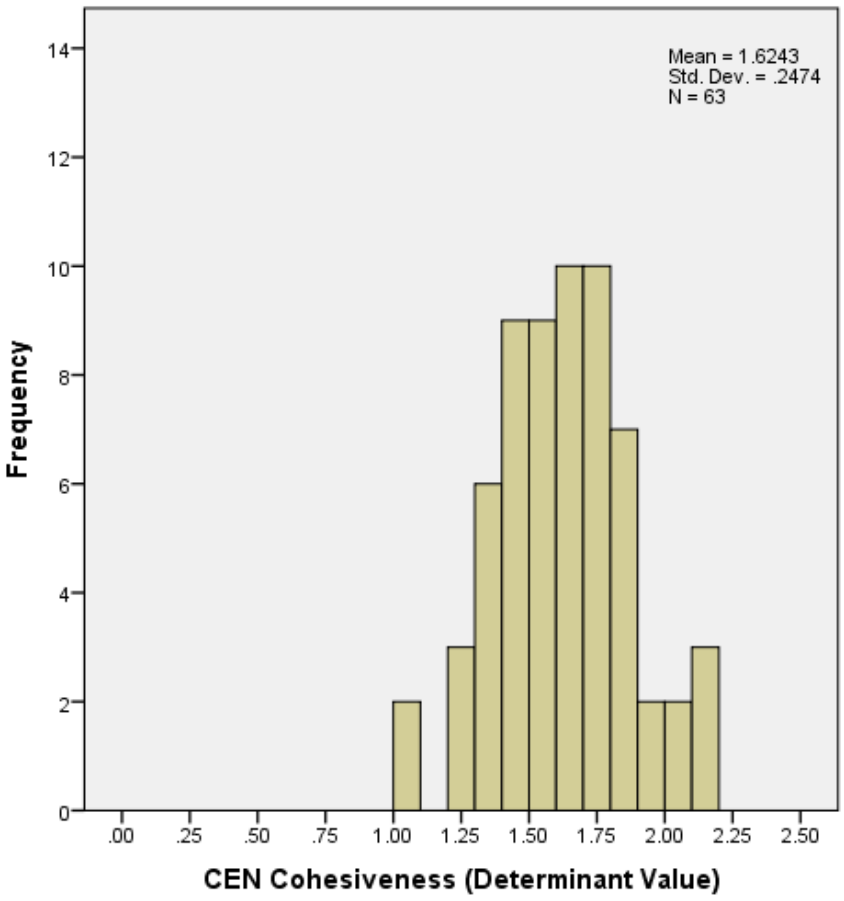


Figure 8

SN Cohesiveness Histogram

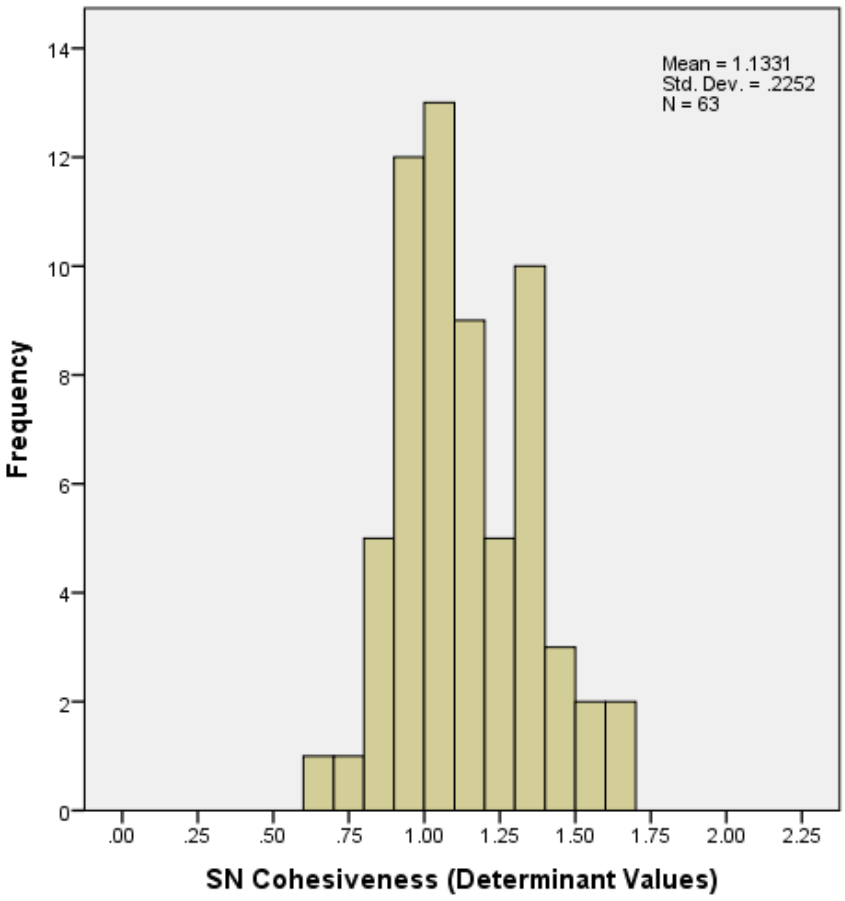
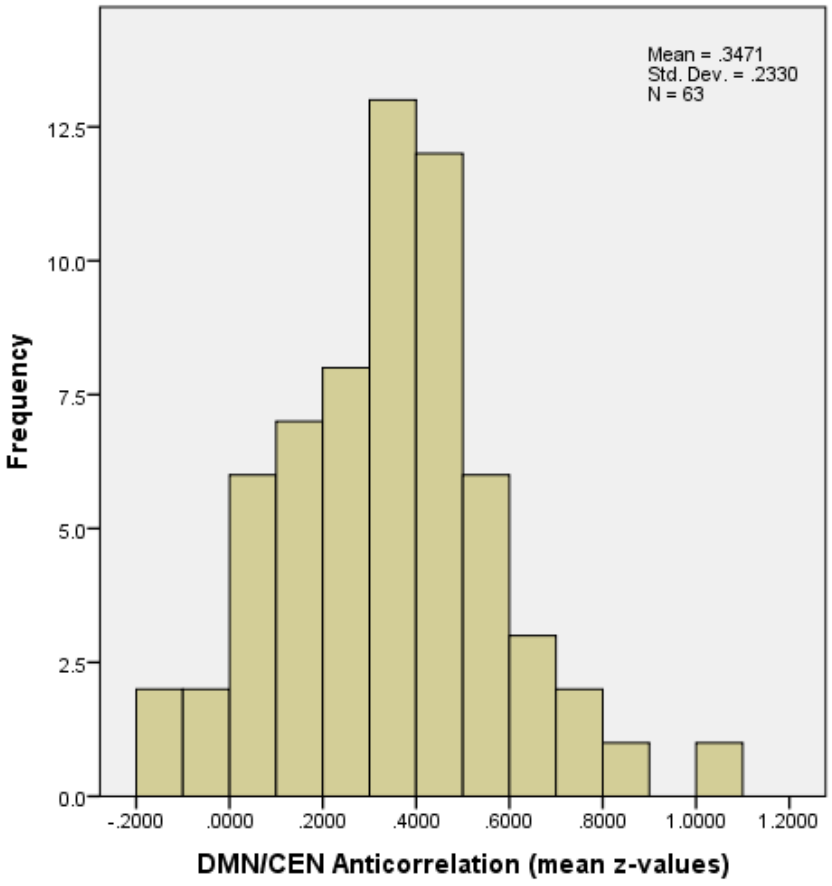


Figure 9

Anticorrelation Histogram



APPENDIX A

Functional Outcomes:

Glasgow Outcome Scale-Extended (GOS-E): The GOS-E is a structured clinical interview that assesses changes in multiple functional domains following a TBI. However, the GOS-E is less more general than other measures of post-TBI functioning, and higher scores are associated with better outcomes (Wilson, Pettigrew, & Teasdale, 1998).

TBI Severity:

Glasgow Coma Scale (GCS): The GCS is a way of measuring immediate and subsequent levels of TBI, based off of eye, motor, and verbal response. Scores range from 3-13, with lower scores indicating more severe levels of TBI severity and impairment (Lezak, et al., 2004; Strauss, et al., 2006). When available, scores were obtained from participant medical records. When unavailable, scores were estimated from participant functional levels.

Emotional Outcomes:

Beck Depression Inventory-II (BDI-II): The BDI-II is a self-report measure for assessing the presence and severity of depressive symptoms. It contains 21 items divided into a four-point Likert scales which pertain to symptoms of depression, such as sadness, loss of pleasure, feelings of guilt, crying, agitation, etc. A total score can

be calculated, as well as cognitive and non-cognitive subscales, and a fast-screen subscale, which focuses on reported symptoms of sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticalness, and suicidal thoughts. Higher scores on the BDI-II and the subscales are related to greater severity of depressive symptoms (Beck, Steer, Ball, & Brown, 1996; Strauss, et al., 2006).

Cognitive Outcomes: General Cognitive Functioning

Wechsler Abbreviated Scale of Intelligence (WASI): The WASI is a brief estimate of intelligence. An estimated full-scale IQ (FSIQ) can be derived from four or two of its subtests, which consist of Vocabulary, Matrix Reasoning, Similarities, and Block Design. For this project, only Vocabulary, Matrix Reasoning, and Similarities were administered (and are described in further detail in subsequent sections). An estimated FSIQ was derived from Vocabulary and Matrix Reasoning, from norms published in the WASI manual (Strauss, et al., 2006; Wechsler, 1999).

Cognitive Outcomes: Premorbid Estimate

Wechsler Test of Adult Reading (WTAR): The WTAR requires participants to read out loud 50 irregularly spelled words. Word reading is believed to be a skill that correlates well with intelligence, and is also fairly resilient to decline after neurological insult. Because of this, premorbid intellectual functioning can be estimated from tests that assess word reading ability, like the WTAR, which has

been shown to be an accurate assessment tool for assessing premorbid intelligence in the TBI population. The WTAR will be used to estimate premorbid FSIQ for the purposes of this study (Green et al., 2008; Strauss, et al., 2006).

Cognitive Outcomes: Executive Function

Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (TMT): Overall, the D-KEFS TMT is similar to the classic Trail Making Test, though it includes additional tasks (compared to the classic "A" and "B" trials of the classic TMT). The D-KEFS TMT consists of five sub-trials. On condition one, subjects are asked to perform a visual-scanning task by searching a field of numbers, and marking the number three. On condition two, participants are asked connect numbers in sequential order. On condition three, participants are asked to connect letters in alphabetical order. On condition four, participants are asked to alternate between connecting letters and numbers, in sequential order. On condition five, participants are asked to trace a series of lines as quickly as possible. The various TMT conditions are related to several cognitive domains. Condition one is a visual search task, conditions two and three are processing speed tasks, condition four is a cognitive flexibility task, while condition five is a motor speed task (Delis, et al., 2001; Strauss, et al., 2006).

D-KEFS Color Word Interference: This D-KEFS subtest is a variant on the Stroop procedure, and has four conditions. In condition one, participants are presented

with a sheet with squares of color organized into rows, and they have to say the name of each color as quickly as they can, going across the rows and down the page. In condition two, the participants are presented with names of colors printed in black ink in lowercase font, and they have to read the words as quickly as they can. In condition three, participants are again presented with words of colors, but they are printed color. The participant has to say aloud the color of ink while not saying the written name of the color. On condition four, the participant is provided a set of rules to follow as to when to say the color of ink, and when to read the written word, and must follow the rules and read the word/say the ink color as quickly as possible. Conditions three and four assess the individual's ability to inhibit an over-learned response (e.g., reading), as well as their cognitive flexibility (Delis, et al., 2001; Strauss, et al., 2006).

D-KEFS Card Sorting: This subtest involves two conditions. On condition one, the participant is provided with a set of six cards, which they are asked to sort into two groups, according to as many rules as they can think of (for example, the participant may sort by color, by content, etc). On condition two, the examiner sorts the cards into piles, and the participant has to describe the sorting rule that the examiner is following. This test, similar in concept to the Wisconsin Card Sorting Task, assesses problem solving, verbal and non-verbal concept formation, and cognitive flexibility (Delis, et al., 2001; Strauss, et al., 2006).

D-KEFS Verbal Fluency: This test is similar to the classic FAS test. In condition one, participants are asked to say as many words as they can think of that begin with a specific letter in 60 seconds. In condition two, participants name as many words as they can think of that belong to a specific category (for example, pets) in 60 seconds. On the condition three, participants are asked to alternate between naming items from two different semantic categories, again in 60 seconds. The first two conditions of this test asses verbal fluency, while the third condition assesses verbal fluency and cognitive flexibility (Delis, et al., 2001; Strauss, et al., 2006)

Cognitive Outcomes: Language

WASI Vocabulary: The Vocabulary subtest of the WASI asks participants to provide definition for words, and assess lexical knowledge (Strauss, et al., 2006; Wechsler, 1999).

WASI Similarities: In this subtest, the examiner presents the participant with two words and asks them to describe how they are alike. This test assess verbal reasoning and, to a lesser degree, lexical knowledge (Strauss, et al., 2006; Wechsler, 1999).

Cognitive Outcomes: Nonverbal Reasoning

WASI Matrix Reasoning: This WASI subtest asks participants to examine incomplete matrices of images or designs and to select the image or design that would

complete the matrix. The participant is provided six items from which to choose the correct answer. This test assesses nonverbal reasoning, and to a lesser degree, perceptual organization skills (Strauss, et al., 2006; Wechsler, 1999).

Cognitive Outcomes: Memory

Wechsler Memory Scale-IV (WMS-IV) Logical Memory: The participant is read two paragraphs by the examiner, and asked to recall details of the paragraphs under two conditions. In the "immediate" condition, they are asked to recall as many details of the paragraph immediately after hearing it. In the "delayed" condition, they are asked to recall details of the paragraphs again, after a delay of 20-30 minutes, during which time other non-verbal tests are administered. This test assesses immediate and delayed verbal memory (Strauss, et al., 2006; Wechsler, 2008).

The Visual Selective Learning Task (VSLT): This test is a visual list-learning task that places different values on different stimuli. For example, words in uppercase may be assigned a value of one "point", while lowercase words maybe worth ten "points. Participants are provided these point values, and informed that they will be presented with a list of words on a screen, one at a time, and at the end of the list, they are to earn as many "points" as they can by recalling words. However, since different categories are worth different point values, participants need to strategize and place priority on higher-value words, while focusing less on lower-

value words. This task combines executive function and planning skills, as well as salience detection and working memory skills (Hanten et al., 2004).

Cognitive Outcomes: Working Memory

Daneman-Carpenter Reading Span Task: This test requires participants to read aloud a series of sentences. As they progress, the sentences increase in length and complexity. The sentences are presented in sets, and at the end of each set, participants are then asked to recall the last word of each sentence in the set. They are scored on the number of words they could remember, and the length/complexity of the sentences whose last word they could recall. This test purports to examine the interaction working memory, memory storage, and reading comprehension. Specifically, it is theorized that increased demands on comprehension and processing will affect working memory and short-term memory storage, requiring participants to trade-off between processing and storage; a deeper reading and understanding of the sentence will likely improve the chances that the last word will be recalled, but at theoretical cost to the other words that the participant is attempting to hold in their working memory (Barrett, Tugade, & Engle, 2004; Daneman & Carpenter, 1980).

Cognitive Outcomes: Attention

Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Span: The WAIS-III Digit Span consists of a “forward” and a “reverse” condition. In the forward condition, the

participant is read a series of numbers, and asked to repeat them back exactly as they were read. In the reverse condition, the participants are asked to repeat a string of digits in the reverse order than they were read by the examiner. Scores are calculated for both conditions individually, as well as a combined total score. Digit Span is considered to be a measure of simple attention and working memory (Strauss, et al., 2006; Wechsler, 1999).

Digit Vigilance: The Digit Vigilance test presents participants with a page containing 59 rows of 35 single-digit numbers, and asks them to mark all instances of a target number (for example, 6) as quickly as they can. Norms are provided for number of errors, as well as completion time. This test examines simple attention (i.e., vigilance), while minimizing demands on other executive functions (such as cognitive flexibility) or memory (R. Lewis & Rennick, 1979).

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