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CHRONOLOGY AND CHRONICITY OF ALTERED RESTING-STATE FUNCTIONAL CONNECTIVITY AFTER TRAUMATIC BRAIN INJURY

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Umesh M. Venkatesan

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The thesis of Umesh M. Venkatesan was approved* by the following:

Frank G. Hillary
Associate Professor of Psychology, Clinical
Thesis Advisor

Peter A. Arnett
Professor of Psychology, Clinical
Director of Clinical Training

Nancy A. Dennis
Assistant Professor of Psychology, Cognitive

Stephen J. Wilson
Assistant Professor of Psychology, Clinical

Melvin M. Mark
Professor of Psychology
Psychology Department Head

*Signatures are on file in the Graduate School.

ABSTRACT

While traumatic brain injury (TBI) results in widespread disruption of neural networks, changes in regional resting-state functional connectivity patterns after insult remain unclear. Specifically, little is known about the chronology of emergent connectivity alterations and whether they persist after a critical recovery window. In the current study, resting-state fMRI and seed-voxel correlational analyses were utilized in both cross-sectional and longitudinal designs to probe intrinsic connectivity patterns involving the posterior cingulate cortex (PCC) and hippocampi, regions shown to be important in the default mode network (DMN) and vulnerable to neuropathology. A total of 22 participants in the chronic phase of moderate-severe TBI and 18 healthy controls were included for cross-sectional study. Longitudinal analyses included 13 individuals in the TBI group for whom data approximately three months after injury (subacute) were available. Overall, results indicated dissociable connectivity trajectories of the PCC and hippocampi during recovery from TBI, with PCC alterations characterized by early hypersynchrony with the anterior DMN that is gradually reduced, and hippocampal changes marked by increasing synchrony with proximal cortex and subcortex. The PCC also showed increasing antiphase synchrony with posterior attentional regions, and the hippocampi showed decreasing antiphase synchrony with frontal attentional regions. Antiphase synchrony of the hippocampus and dorsolateral prefrontal cortex at the subacute stage of TBI was positively associated with attentional performance on neuropsychological tests at both the subacute and chronic stages. These findings highlight the heterogeneity of regional-whole brain connectivity changes after TBI, and suggest that residual connectivity alterations exist in the clinically stable phase of TBI. Parallels between the chronicity of the observed effects and findings in other

neurologic conditions (e.g., Alzheimer's disease) are discussed in the context of neurodegenerative potential after TBI.

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saTBI relative to cTBI, there is increased negative connectivity between right hippocampus and bilateral superior and middle frontal gyri (dorsolateral prefrontal cortex).

Introduction

A major worldwide health concern, traumatic brain injury (TBI) affects children and adults of virtually all ethnic and socioeconomic backgrounds. In the United States alone, approximately 1.7 million sustain a TBI annually, and the condition accounts for almost one-third of injury related deaths (Faul et al., 2010). Populations in which TBI is most commonly found include children and men (Faul et al., 2010; Rutland-Brown et al., 2006), and its incidence follows a trimodal distribution, with children below the age of 5, adolescents 15-19 years old, and adults over 65 being at highest risk (Faul et al, 2010). While not traditionally considered a progressive disorder, TBI— particularly moderate or severe— can leave survivors with chronic impairments in a host of functional domains. Estimates have placed the U.S. civilian prevalence of long-term disability due to TBI at 3.2 million (Zaloshnja et al., 2008). Such figures call for continued research in TBI outcomes, both functional and neurological, and emphasize the need to view the disorder as a life-long condition, one that potentially may present new challenges not only within the acute recovery period, but also through to advanced age.

Historically, research in TBI has advanced a fixed injury-deficit model in which isolated brain insult is followed acutely by neurological and functional recovery that eventually reach a plateau. Such a conceptualization is useful for understanding readily manifest cognitive effects of injury and functional implications such as those for occupational and community reintegration. It does not, however, address the course of chronic neurological deficits, and it disregards the dynamic nature of complex neural systems throughout the lifespan. In contrast, the current study argues against fixed post-injury effects, positing that cognitive impairments (and their associated neuropathology) are not static, and that injury may accelerate the decline of cognitive function with age. A major goal of this thesis is to outline the connection between TBI

and Alzheimer's disease (AD) established in previous literature, and to demonstrate how neurological aberrances in TBI during a supposedly stable phase may foreshadow neurodegeneration later in life. Specifically, disrupted neural network function is offered as a possible precursor to the emergence of neurodegenerative processes several years after initial trauma.

TBI pathophysiology

TBI is an umbrella term encompassing several distinct types of force-induced brain trauma, each with its own causal mechanisms— for example, motor vehicle accidents, falls, and physical abuse— and neuropathologic profile. Before reviewing basic pathophysiological features of TBI, it is important to note that provision of acute care and prediction of subacute complications and long-term outcomes depend largely on the severity of the injury sustained. Severity may be defined by level of consciousness responsiveness, commonly assessed by the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), loss of consciousness (LOC) duration, and the duration of post-traumatic amnesia (PTA), a temporary state of confusion and disorientation following trauma. The current proposal focuses on moderate to severe forms of non-penetrating (i.e., closed-head) brain injury, which are distinguished from milder injury such as concussion, and typically involve a prolonged PTA or loss of consciousness, and/or abnormalities on structural neuroimaging.

Among the most common features of moderate to severe brain injuries are cerebral contusions, hemorrhages, and diffuse or traumatic axonal injury (DAI/TAI) (Maas et al., 2008); these abnormalities may occur in isolation, or together in more global forms of trauma. While contusions and hemorrhages are usually due to impact of the head with a foreign body, and thus

constitute focal injuries, DAI involves the mechanistic stretching and subsequent degeneration of neuronal axons in several areas, resulting from rapid accelerative-decelerative and/or rotational forces on the brain (Gennarelli & Graham, 1998; McIntosh et al., 1996). In many cases of TBI, however, blunt and non-impact forces may act synergistically to produce a combination of focal and diffuse pathology (Hammeke & Gennarelli, 2003; Povlishock et al., 2005). For example, rotational forces and simultaneous impact with either an external object or the skull during a vehicular crash may result in both axonal stretching and/or shearing and intracranial bleeding.

TBI is associated with subsequent brain damage in the days and weeks following initial insult, a phenomenon known as secondary injury (Hammeke & Gennarelli, 2003). Secondary consequences of TBI commonly include ischemia, hypoxia, edema, as well as biochemical alterations (for a review, see Werner & Engelhard, 2007). In addition, brain insult initiates a complex process of electrochemical alterations, axolemma deformation, and axonal swelling that contribute to axonal degeneration and disconnection even months after injury (see Maxwell et al., 1997, for a review in animal and human models). These events have been found to occur in both mild (Povlishock et al., 1983) and severe (Erb & Povlishock, 1988) head injury in the cat, suggesting that the actual transection of axons is rarely a direct consequence of TBI (Maxwell et al., 1997). Hence, secondary effects of TBI may exacerbate or compound immediate, or primary, injury, leading to devastating outcomes.

While it is yet to be determined exactly how secondary events relate to the persistent cognitive impairment observed long after TBI, there is substantial evidence to suggest that post-injury disturbances in cerebral blood flow and tissue oxygenation negatively influence long-term functional outcome (e.g., Chestnut et al., 1993; Davis et al., 2009; Jaggi et al., 1990; van den Brink et al., 2000). Furthermore, it has been noted that even putatively focal brain injuries

include some amount of DAI (Gentleman et al., 1995; Shigemori et al., 1992), and that such diffuse pathology initiates a number of neurometabolic and immunologic cascades (see Hovda et al., 2009; Stahel et al., 1998). These cascades result in, among a host of other anomalies, disruption of the blood-brain barrier, generation of free radicals, and neurochemical dysregulation (Hammeke & Gennarelli, 2003). Because elevated levels of the excitatory neurotransmitter, glutamate, are found acutely after TBI, glutamate excitotoxicity is thought to be a critical factor in the development of secondary cascades (Yi & Hazell, 2006). Severe brain injury is also associated with increased glucose metabolism (i.e., hyperglycolysis; Bergsneider et al., 1997) acutely, followed by a protracted period of hypoglycolysis (Bergsneider et al., 2001). Accordingly, glycolytic processes have been the target of some early therapeutic interventions such as hypothermia (Zhao et al. 2011) and insulin administration (Van den Berghe et al., 2005). Furthermore, hypermetabolism has also been noted in the upregulation of beta-amyloid precursor protein (Graham et al., 1996), signifying a possible link to the pathogenesis of AD, discussed later.

Cognitive symptomatology of TBI

TBI traditionally has been referred to as a disorder of frontal lobe functioning, as bony ridges of the skull portion surrounding the pre-frontal and frontal cortices make these regions especially vulnerable to both tissue and axonal damage. Accordingly, deficits in executive functioning (including inhibitory control), working memory, attention, and information processing speed— all of which are thought to rely on the integrity of structures within the frontal lobes— are among the most consistently reported post-traumatic symptoms (Mattson & Levin, 1990; McAllister, 2011; McDonald, Flashman, & Saykin, 2002). Residual cognitive deficits are apparent several years after injury and past recovery plateau (Dikmen et al., 2009;

Draper & Ponsford, 2008; Millis et al., 2001; Schretlen & Shapiro, 2003), indicating that cognitive impairments proceed into later life and interact with natural cognitive aging processes. However, little is known about the effect of brain injury on age-related cognitive decline and vice-versa. As in TBI, normal aging evidences degradation in frontal cortical pathways supporting efficient information processing and executive functions. More posteriorly located brain pathology, primarily hippocampal atrophy, has also been observed to a variable extent both in injury and with increasing age (Bigler et al., 1997; 2002; Driscoll et al., 2003; Tate & Bigler, 2000). Despite this concordance, dysfunction in episodic memory, a principal function of the medial temporal lobe (MTL, encompassing hippocampal formation), has received far more attention in the aging versus TBI literature. This is likely because, as mentioned before, the primary deficits in TBI involve those cognitive abilities typically associated with frontal systems.

While marked episodic memory impairment may not manifest acutely or even a few years after injury, it is plausible that it emerges in older age. It is also important to note that this type of memory is dependent on interactions of MTL regions with other cortex, particularly the prefrontal cortex (Gabrieli et al., 1998), and damage to the axons of multiple cortical and subcortical circuits can negatively impact memory function (Lockhart et al., 2012). Given this knowledge, a case may be made for the diffuse axonal and specific frontal pathologies of TBI as key contributors to the breakdown of memory systems seen in normal cognitive aging. This notion implies that axonal disruption constitutes network deficiencies that lead to *premature* aging processes, both at the neurophysiological and neurocognitive levels. The concept of accelerated aging is helpful in understanding how TBI may initiate neurodegeneration, and forms a backdrop for the current proposal.

Neurobehavioral outcome research in TBI

Because TBI often occurs relatively early in life, the accurate prediction and characterization of long-term functional outcomes is important in early rehabilitation efforts and management of the condition. Outcome research has been conducted in a wide variety of domains. Several studies have found significant mental health disturbances following TBI that may be related to both premorbid psychiatric history and organic effects of injury; these include mood, anxiety, and personality disorders (Bombardier et al., 2010; Dikmen et al., 2004; Rapoport, 2012) as well as general impairments in social and occupational functioning (Temkin et al., 2009). Psychological deficits have been found to persist decades after TBI (Hoofien et al., 2001; Koponen et al., 2002), and are likely lifelong problems. TBI may also lead to medical complications such as sepsis, respiratory dysfunction, and hypotension, among others, though it is unclear how these conditions influence mortality (Corral et al., 2012). Moreover, secondary neurological deficits in language (Safaz et al., 2008), vision (Rutner et al., 2006), and motor function (Walker & Pickett, 2007) are common after TBI, as is the development of seizure disorder in individuals with moderate to severe brain trauma (Bazarian et al., 2009).

Neuropsychological sequelae, while the most pervasive and extensively studied effects, are heterogeneous in TBI (Millis et al., 2001; Salmond & Sahakian, 2005), presumably due to a variety of possible injury mechanisms and differing capacities for resilience across individuals. Previous neuropsychological outcome work in TBI has centered on the chronic nature of its diverse cognitive symptom constellation. In a smaller literature, it has been observed that a subset of those who sustain TBI exhibit signs of dementia of the Alzheimer's type (DAT) and Parkinsonism, suggesting that TBI may be associated with neurodegenerative disease processes (Bazarian et al., 2009). However, the mechanisms by which brain injury or its sequelae may

initiate such processes are largely unknown. The section that follows provides an overview of the epidemiological and neurobiological evidence for a link between TBI and AD, a condition involving widespread cognitive decline. Focus is then placed on a relatively recent theoretical model implicating specific neural network dysfunction in AD and its risk populations, and how this line of investigation may inform the conceptualization of long-term neurological consequences of brain trauma. The study proposed thereafter operates within this framework to investigate network change in TBI.

Traumatic brain injury as a risk factor for Alzheimer's disease

The idea that TBI and AD may somehow be related emerged from clinical case reports documenting autopsy-confirmed AD in head trauma patients (Heyman, 1998). The first empirical study examining TBI as a potential risk factor for AD found that those diagnosed with AD were 5.31 times more likely to have had sustained a head injury than healthy individuals, while results from several epidemiological investigations since have offered varying degrees of support for this relationship (see Lye & Shores, 2000, for original studies). For example, in a meta-analytic review of seven case-control studies, Mortimer and colleagues (1991) observed that the probability of previous head injury in individuals with AD was 1.82 times greater than in a community-based sample; this association was stronger for males and, counterintuitively, in the absence of a family history of dementia. The former finding was later replicated by Fleminger et al. (2003) using 15 studies. In contrast, data from other research indicate that mild TBI may only augment susceptibility introduced by the APOEε4 allele, an established genetic risk factor for AD (Mayeux et al., 1995).

More recent work has found neuropathological support for Mortimer et al.'s (1991) conclusions. The first retrospective autopsy study examining TBI, APOEε4, and AD reported that of 58 cases of closed-head injury, 12.1% exhibited definite Alzheimer's pathology upon autopsy, and 10.3% were deemed probable AD (Jellinger et al., 2001). Evidence of TBI was seen in 7% of 57 individuals with AD. Overall, those who displayed signs of both TBI and AD were not more likely to be positive for the APOEε4 allele, supporting a previous hypothesis that TBI might pose a risk for AD in the absence of a genetic predisposition (Rasmusson et al., 1995).

The differential relationships between varying mechanisms of injury and AD risk have not been studied in detail. However, moderate to severe head trauma seems to be more closely associated with AD than mild brain injury (Plassman et al., 2000). A study by Mehta et al. (1999) found no relationship between mild TBI and AD, and no moderational effects of injury-related or genetic variables. On the other hand, repetitive concussive trauma, such as those encountered in contact sports, may contribute to an increased chance of AD development (Guskiewicz et al., 2005) or the manifestation of another dementing disorder known as chronic traumatic encephalopathy (CTE; McKee et al., 2009). Like AD, CTE is a condition involving proteinopathies (protein malformations), but characterized primarily by excessive aggregation of the tau protein into neurofibrillary tangles in mostly frontal, parietal, and insular cortices (see Baugh et al., 2012, for a review). While appearing similar to other dementias in advanced stages, early CTE is clinically distinct from AD, encompassing notable mood, personality, and behavioral changes in addition to memory and cognitive impairment (for a review, see Gavett et al., 2011).

Some epidemiological research suggests that compared to what is observed in the general population, brain insult may lead to an earlier onset of dementia (Gedye et al., 1989; Nemetz et

al., 1999; Schofield et al., 1997). Nemetz and colleagues (1999) found that although the incidence of AD in their TBI sample was comparable to that in the community, the time from injury to presentation of AD symptomatology was reduced from an expected mean of 18 years—based on population incidence estimates of AD— to 10 years. An explanation for this finding offered by these authors and others is that brain injury may interact with other factors, perhaps constituting preexisting susceptibility, to accelerate the onset of DAT (Lye & Shores, 2000; Starkstein & Jorge, 2005). Despite uncertainty regarding the causal role of TBI in the development of AD, however, studies of pathophysiology have revealed cogent connections between the two conditions.

The physiological hallmarks of AD include extracellular neuritic (senile) amyloid plaques formed by excessive deposition of the beta-amyloid protein, as well as intracellular neurofibrillary tangles, which result from aggregation of the tau protein (Hyman et al., 2012). Over time, abnormal protein accumulation leads to progressive neurodegeneration and cell death. This is the central argument of the widely studied amyloid cascade hypothesis, which forms the basis of many investigations in AD, and posits that neuritic plaques are etiologically paramount in the pathogenesis of AD (Hardy & Higgins, 1992). While the mere presence of plaques does not confirm dementia, elevated levels indicate a risk for DAT in cognitively normal individuals (Villemagne et al., 2011). Apolipoprotein E (APOE) has been implicated in AD because of its role in the degradation of beta-amyloid (Jiang et al., 2008). A specific isoform, APOEε4, is relatively ineffective in this clearance process, and therefore, possession of an APOEε4 allele is thought to be a risk factor for the formation of senile plaques (Jiang et al., 2008).

The significance that plaque pathology has in neurodegeneration makes it a prime candidate for a mediating role in the relationship between head trauma and AD. Accordingly,

several studies in the brain injury literature have reported post-traumatic beta-amyloid deposition and formation of plaques resembling those found in AD. A comprehensive review of these findings in human and animal models is found in Johnson et al. (2010), but briefly, amyloid in the form of diffuse plaques has been detected within hours of severe brain injury (Ikonomovic et al., 2004) and in patients as young as 10 years old (Roberts et al., 1991; 1994). The latter also found neuritic plaques in adults over the age of 70 with TBI. In contrast, plaques of any kind were primarily found in old vs. young control participants, suggesting that amyloid pathology in brain injury is specific to trauma and not merely an artifact of aging (Roberts et al., 1994). In addition, a recent study by Johnson et al. (2012) revealed that a single brain injury earlier in life is associated with increased plaque burden upon autopsy decades later.

The exact mechanisms by which post-traumatic plaques are deposited are yet to be elucidated. However, the observation that beta-amyloid is present in the axons of inflamed cells acutely after brain insult suggests that plaque formation might be a direct consequence of axonal injury (Chen et al., 2009; Smith et al., 2003). Furthermore, amyloid precursor protein (APP), the peptide from which beta-amyloid is cleaved, and enzymes involved in this cleavage have been identified in damaged axons following injury (Chen et al., 2009; Smith et al., 2003; Uryu et al., 2007). These findings have led some to propose that trauma creates special metabolic circumstances that render brain tissue susceptible to protein aggregation and plaque burden (Johnson et al., 2010).

Arriving at network dysfunction in AD

With substantial support for the initiation of Alzheimer's-like disease processes early after injury, it is necessary to consider the regions of the brain in which plaques typically

develop. Although most work in both AD and TBI has examined several anatomical areas without making explicit reference to differential plaque burden, a few specific findings in the aging and dementia literature merit discussion. In elderly with and without dementia, PET tracer imaging studies have revealed plaque pathology mostly in widespread neocortex (Morris et al., 1996; Price et al., 1993) including, but not limited to, prefrontal (PFC), mediolateral temporal, lateral parietal, and posterior cingulate (PCC) cortices as well as the precuneus (Ikonomovic et al., 2004; Mintun et al., 2006; Price et al., 1991; Rowe et al., 2007). Notably, there is indication that the PFC and precuneus/PCC areas may be the first and most prominent sites of plaques in normal cognitive aging or preclinical dementia (Mintun et al., 2006; Rowe et al., 2007) and might exhibit more rapid progressive plaque pathology than other regions (Rodrigue et al., 2012). The finding of topographically dispersed beta-amyloid plaques is consistent with the stages of AD's pathophysiological progression outlined in Braak & Braak (1991) and its update (Thal et al., 2002); here, formation occurs in a top-down fashion, with plaque deposition beginning in all four neocortices before progressing to cingulate and other limbic areas, and then to subcortical and brainstem regions.

The selective regional accumulation of plaques is related to findings in the functional brain imaging of AD. In their landmark paper, Buckner and colleagues (2005) examined pooled data from individuals in the early stages of AD to create unified maps of amyloid plaque deposition, cortical atrophy, glucose metabolism, retrieval success (episodic memory), and default mode activity, and found striking spatial convergence. Using PET tracer imaging, they found plaque pathology distributed predominantly along the midline frontal and parietal regions, extending laterally, as well as in posterior regions including the precuneus, PCC, and retrospenial cortex; this is consistent with findings from earlier PET work discussed above. In addition, they

noted reduced glucose metabolism and greater atrophy also in the precuneus, posterior cingulate, and posterior parietal regions across levels of amyloid burden. Remarkably, despite known atrophy of the MTL early in AD, amyloid and metabolic aberrances were not marked here.

Two more findings from Buckner et al. (2005) concern an intrinsic resting-state network (RSN; Raichle et al., 2001) that is detected by analysis of functional connectivity when an individual is at rest, a technique known as resting-state functional connectivity (RSFC; Biswal et al., 1995). Functional connectivity refers to temporal correlations between low frequency fluctuations (LFFs) of the BOLD fMRI signal in spatially remote brain regions (Friston et al., 1996), and has been used during resting-state MRI to identify this network, which Raichle and colleagues have termed the *default mode network* (DMN). The DMN comprises highly correlated, spatially distinct brain regions (Greicius et al., 2003) that exhibit greater neuronal activity during passive rest than when performing a cognitively effortful task, with PCC, medial prefrontal, lateral parietal, and parahippocampal regions as its primary components (Fox et al., 2005; Raichle et al., 2001). It has therefore been referred to as a task-anticorrelated, or "task-negative", network that is distinct from a "task-positive" network (TPN) containing regions commonly activated during a variety of cognitive tasks (notably, dlPFC, inferior parietal lobule, intraparietal sulcus, and frontal eye fields; Fox et al., 2005). In addition, the DMN has been found to support attentionally demanding task performance and predict on-task activation (Hampson et al., 2006; Kelly et al., 2008; Raichle, 2010; Weissman et al., 2006). It is also hypothesized to play a unique role in internally focused tasks such as autobiographical memory retrieval and self-referential thought (Buckner et al., 2008).

When comparing the pattern of DMN activity (e.g., during passive viewing or stimulus-devoid rest) with the topography of amyloid pathology, Buckner et al. (2005) discovered a

notable overlap in the precuneus, PCC, and retrosplenial cortex. DMN activity was also detected in bilateral MTL. Moreover, in event-related data, the precuneus, PCC, and retrosplenial and lateral parietal cortices were associated with successful retrieval of episodic information (Buckner et al., 2005).

The DMN possesses a unique metabolic profile (Raichle et al., 2001), and its nodes—the precuneus/PCC area, in particular— are thought to be critical neuronal "hubs", in that they exhibit a relatively high density of connections with brain regions of other distinct functional systems (Buckner et al., 2009; Fransson & Marrelec, 2008; Hagmann et al., 2008). Buckner et al. (2005) modeled the development of AD as a metabolic cascade in which the DMN's metabolic properties make it vulnerable to amyloid deposition and plaque pathology. Atrophy and further metabolic disruption of default mode regions ensue and eventually lead to memory impairment. Hence, the DMN, particularly its posterior cortical nodes as well as the hippocampal formation, seems to be implicated in a memory network that is selectively targeted in early AD pathophysiology (Buckner et al., 2005; 2008; Greicius et al., 2004; see Sperling et al., 2010, for a review).

Exactly how the DMN is dysfunctional in AD and in groups at risk for Alzheimer's dementia is a topic that has received much attention in the past decade. However, TBI has not been examined in this literature, a surprising observation given that brain injury has been characterized as a disruption of distributed neural networks (Hillary et al., 2011a; Nakamura et al., 2009). Before proposing an investigation in TBI, it is important to review the existing evidence for DMN dysfunction in those with or predisposed to AD to appreciate how neural network dynamics may precipitate neurodegenerative processes. In the next section, resting-state

functional connectivity (RSFC) studies of the DMN in AD and populations at risk for AD are taken up for discussion.

Functional connectivity of DMN in AD

The seminal work in DMN functioning in AD was conducted by Greicius and colleagues (2004), who were the first to propose that the DMN might be impaired in AD. Their hypothesis was based on previous studies that obtained support for connectivity between PCC and MTL and for hypometabolism of the PCC in early AD (for original citations, see Greicius et al., 2004). When comparing maps of the putative resting-state DMN (obtained through independent components analysis [ICA]) between healthy young and elderly participants as well as individuals with mild AD, Greicius et al. (2004) detected bilateral hippocampal and entorhinal cortex coactivation within the DMN in both healthy samples. Only the right hemisphere showed such coactivation in those with mild AD. In contrast, those with AD showed significantly reduced hippocampal involvement in the DMN in the left hemisphere. Although they did not directly examine connectivity between PCC and MTL, the authors concluded that their results offer support for reduced connectivity between PCC and MTL, which may in part explain metabolic anomalies in the PCC early in AD and represent a biomarker of latent or incipient AD. Furthermore, this work suggested a prominent role of the DMN in episodic memory processing, traditionally the domain of the MTL.

The findings of Greicius et al. (2004) have been corroborated by a number of groups demonstrating diminished functional connectivity in AD between PCC and specific regions (Hafkemeijer et al., 2011; Mevel et al., 2011). Interestingly, nearly all of these studies have also found separate patterns of increased connectivity between PCC and other brain regions or

between regions outside the PCC in patients. For example, a resting-state ROI correlation analysis in amnestic mild cognitive impairment (aMCI), revealed decreased functional connectivity of the PCC with areas in temporal cortex, but increased connectivity between PCC and widespread frontal cortex compared to healthy elderly (Bai et al., 2009). This group also employed ICA to obtain maps (components) of coactivated regions during rest. Their approach revealed PCC hyperconnectivity with the rest of the DMN component in aMCI patients at baseline, but hypoconnectivity of these regions and hyperconnectivity of frontal areas at follow-up 20 months later (Bai et al., 2011). Likewise, there is evidence showing that when PCC is defined as a seed ROI, PCC-dorsal medial prefrontal cortex (dmPFC) and PCC-dlPFC connectivity are increased and more bilaterally distributed, relative to controls, from early to advanced AD (Zhang et al., 2008; 2010). Using the hippocampus as a seed, Wang et al. (2006) noted significant reductions in right hippocampal connectivity with dmPFC, ventral anterior cingulate cortex (vACC), and the right PCC, but increases between the left hippocampus and right dorsolateral prefrontal cortex, in their AD sample.

Support for aberrant functional connectivity patterns in prodromal or mild AD has also been garnered from studies examining multiple RSFC maps (Sorg et al., 2007; Qi et al., 2010) or interregion correlations throughout the entire brain during rest (Bai et al., 2010; Wang et al., 2007). These studies have revealed more global network differences between affected and healthy individuals (i.e., not limited to the posterior DMN and MTL). An analysis of RSNs in aMCI and healthy controls revealed eight networks, of which only the DMN and the executive attention network— encompassing prefrontal and superior parietal regions— exhibited reduced connectivity in patients (Sorg et al., 2007). In addition, PCC-hippocampal connectivity was detected only in the healthy sample (Sorg et al., 2007).

In a different approach, Wang et al. (2007) investigated changes in magnitude of both positive and negative correlations across the brain in early AD, and determined that during rest, the weight of positive correlations are decreased between frontal and parietal regions, but increased within prefrontal, parietal, and occipital areas. Decreased negative correlations were also notable, and occurred between regions of the DMN and "task-positive" network (TPN), identified in earlier literature as intrinsically anti-correlated networks (Fox et al., 2005). Post-hoc analysis revealed that in both the AD and control groups, the PCC was negatively correlated with regions that overlap with the TPN and positively correlated with regions included in the task-negative network. Decreases in both positive and negative correlations involving the PCC were found in the AD sample. This led to the speculation that an effect of AD pathophysiology might be a disruption of the balance, or interplay, between on-task and off-task networks (Wang et al., 2007; Zhang et al., 2010). Indeed, several studies of task-related deactivation in AD have supported such a change in network dynamics (Hafkemeijer et al., 2011; Sperling et al., 2010).

Aberrant RSFC implicating the DMN has also been found in those at risk for the AD, including individuals with MCI (discussed previously), carriers of an APOEε4 allele, and cognitively normal elderly with high amyloid burden, (for a review of all, see: Hafkemeijer et al., 2011; of APOEε4: Mevel et al., 2011). As in the case of AD, some of these studies have found support for both increased and decreased connectivity patterns, generally referring to decreases in posterior DMN-related connectivity and increases involving frontal regions (APOEε4: Filippini et al., 2009; Dennis et al., 2007; amyloid burden: Mormino et al., 2011). A particularly strong case for increased connectivity has been made in younger individuals possessing APOEε4, with independent investigators reporting increased connectivity between DMN regions, namely, PCC and MTL (Filippini et al., 2009; Dennis et al., 2009; Westlye et al., 2011).

Dennis et al. (2009) also found decreased connectivity between anterior and posterior cortical areas, consistent with results from work in AD discussed previously.

The presence of both increased and decreased functional connectivity in AD and its risk populations is in line with the conceptualization of AD as a functional disconnectivity syndrome (Delbeuck et al., 2001). A growing number of studies from the literature of AD point to an anterior to posterior disconnection, referring to disrupted connectivity primarily between frontal and temporoparietal cortices, originally described by Grady et al. (2001) in a memory task. Wang et al. (2007) were among the first to demonstrate this phenomenon while considering whole-brain connectivity during rest. More recently, Sanz-Arigita et al. (2010) implemented a graph theoretical approach to demonstrate increased disorganization of whole-brain networks and a disruption of long-distance connections (frontal to parieto-occipital cortices) in AD, lending further support to anterior-posterior disconnection theory. Due to the heterogeneity of pathology and symptom presentation in early AD, however, regions implicated in this pattern of disconnection have varied across studies. Moreover, several authors have hypothesized that simultaneous increased and decreased connectivity represent anterior compensatory mechanisms for the breakdown of posterior processes (Bai et al., 2011; Qi et al., 2010; Wang et al., 2007; Wang et al., 2006; Zhang et al., 2008; 2010). In this view, increased connectivity vis-à-vis regions of frontal cortex, for example, may indicate that these regions lend extra resources to maintain cognitive performance in the face of neurological compromise. However, in light of the limited evidence for relationships between behavior and connectivity measures in early or preclinical AD, such inferences presently are not tenable. For example, it may be that seemingly compensatory increases in connectivity are in fact signs of excitotoxicity, and foreshadow cell death (Sperling et al., 2010). Nonetheless, taken together, connectivity differences between those

at risk for AD (cognitively, genetically, or pathophysiologically) and their healthy counterparts indicate possible biomarkers of latent or incipient AD that are currently imprecise, but one day may have clinical utility for the timely detection of AD (Damoiseaux, 2012).

The resting-state DMN in TBI

There are currently only a handful of studies that have examined resting-state DMN activity in TBI. Interestingly, a majority of them have found support for both a critical role of the PCC and an anterior-posterior disconnection. Kim et al. (2010) were the first to report on resting-state perturbations in regions of the default mode. They measured absolute cerebral blood flow (CBF) in moderate to severe TBI, and found reductions, compared to controls, most notably in bilateral PCC, bilateral thalamus, and more rostral areas such as bilateral anterior cingulate and middle frontal cortices. In TBI, relative hypoperfusion was also seen in posterior cingulate and thalami, but there was evidence of relative hyperperfusion in right temporal gyri and insula (Kim et al., 2010). Although no neuropsychological data were presented, hypoperfusion in DMN regions, principally the PCC, was thought to be related to cognitive impairment (Kim et al., 2010). Subsequently, in an analysis of "rest" intervals from a working memory task, Hillary et al. (2011[b]) demonstrated decreased functional connectivity of ACC and dlPFC with parietal lobe as well as increased connectivity of PCC with middle frontal and middle temporal areas during injury recovery (from 3-6 months post-injury). Each of these trends was opposite from what was observed in healthy controls during a 3-month period.

Other work exploring the DMN in moderate-severe TBI has reported increased intranetwork functional connectivity, featuring prominently the PCC and precuneus regions, using ICA and dual regression techniques (Bonnelle et al., 2011; Sharp et al., 2011; review of

basic method in Zuo et al., 2009). These investigations have attempted to elucidate the relationship between resting connectivity and task performance. For example, Sharp et al. (2011) noted greater connectivity of the posterior cingulate to the rest of the DMN in TBI relative to healthy participants. Because faster reaction times were associated with greater connectivity in the patient sample, an adaptive, or compensatory, role for this increased connectivity was proposed (Sharp et al., 2011). Furthermore, functional connectivity of precuneus to remaining DMN at the beginning of a choice reaction time (CRT) task was negatively associated with change in reaction time (RT) during that task, suggesting that higher connectivity supports better and more stable performance (Bonnelle et al., 2011). These authors also found that the magnitude of precuneus-DMN connectivity correctly classified a subgroup of individuals with TBI demonstrating deficits in sustained attention compared to both controls and brain-injured individuals with intact sustained attention. However, as the low-sustained attention TBI group was defined based on greater increase in RT between time-points, it is unclear whether what the authors referred to as a "vigilance decrement" is truly attention-related or an artifact of cognitive fatigue. Moreover, neither Sharp et al. (2011) nor Bonnelle et al. (2011) examined relationships between DMN and regions of other RSNs.

The DMN has also been researched in mild TBI (mTBI), where it has been observed that similar to AD, connectivity within the DMN and DMN-TPN anticorrelations are reduced, while connectivity in frontal regions is increased (Johnson et al., 2012; Mayer et al., 2011). Specifically, seed ROIs placed in either PCC or rostral ACC (rACC, a node of the DMN) showed reduced connectivity with each other in patients versus controls in Mayer et al. (2011). Like Wang et al. (2009), this study also examined negative correlations, and found reduced strength of anticorrelations in mTBI between rACC and inferior parietal lobule (IPL) of the TPN.

Anticorrelations between IPL and mPFC were also reduced, as was the positive correlation between IPL and middle frontal gyrus seen in controls. However, increased connectivity in mTBI was detected in posterior parietal areas with IPL and in frontotemporal regions (including hippocampal formation), superior parietal lobule, and striatum with right lateral prefrontal cortex. In a recent analysis, Johnson et al. (2012) also demonstrated reduced connectivity strength and number of connections associated with PCC and lateral parietal cortices, but increased connectivity of mPFC.

Overall, RSFC work in TBI has revealed prominent PCC abnormalities, increased connectivity in more frontally located regions, disruption of anterior-posterior connections and reduced opposing synchrony of the DMN and TPN. This is in line with findings in AD and its risk groups. However, no studies to date have explicitly compared resting-state data in TBI to patterns of findings in AD, nor have regional intercorrelations throughout the entire brain been examined in TBI during "pure" rest, that is, not derived from rest periods of tasks, as was done in previous papers (Hillary et al., 2011[b]; Nakamura et al., 2009). Further, using strictly seed-based approaches (as in Hillary et al., 2011[b]; Johnson et al., 2012; Mayer et al., 2011) may result in biased observations, as they require a priori specification of regions of interest (ROIs). Studies employing ICA techniques (e.g., Bonnelle, et al. 2011; Sharp et al., 2011), on the other hand, force data into orthogonal or semi-orthogonal components, and limit analyses between regions of different components. Because relationships between DMN and non-DMN regions exist and might be altered after neurological insult, it is important that investigations of this network consider the context in which it operates.

The current proposal endeavors to examine task-independent, resting state functional connectivity in TBI and control groups as well as within a critical window of TBI recovery. To

address methodological pitfalls in existing TBI literature as well as to extend previous findings, this study will adopt a whole-brain interregion correlational approach. Such a technique obviates the need for ROI selection, and thus provides unbiased measures of connectivity. It is also befitting to exploratory analyses, allowing for the detection of effects in regions of many different networks, including but not limited to the DMN. Because of the importance of PCC in both TBI and AD, subsequent analyses will employ a seed-voxel approach to directly investigate connectivity associated with this region.

Study Rationale

Given compelling evidence for neural network impairment, especially in the DMN, as an early marker of AD and integral to its pathophysiology, it is critical to examine network function in all populations with established risk for the disease. Doing so would allow for a better characterization of the functional disturbances associated with neurodegenerative processes. Work in this area has begun in some risk groups, but brain injury research remains relatively distant from the dementia literature. Because TBI traditionally has been viewed as a disorder of frontal systems, posterior brain regions largely, albeit inadvertently, have been overlooked or deemphasized. Considering that many cognitive impairments following head trauma (e.g., reduced processing speed and working memory) are attributed primarily to areas of the prefrontal cortex, this regional focus is perhaps expected to some degree. However, deepening epidemiological and cellular/molecular links between TBI and dementia signify a need for research inquiries in TBI to parallel those being pursued actively in neurodegenerative disease and at-risk populations. A better understanding of functional connectivity alterations following TBI, particularly in the PCC and hippocampi, may help to uncover potential mechanisms of both neurorecovery and neurodegeneration in this population.

The current study focuses on the whole-brain functional connectivity patterns revealed by resting-state fMRI (rs-fMRI) of two principal regions of interest: the PCC and the hippocampi. These regions are targeted due to their importance in cognitive and memory functioning, their eminence in resting connectivity studies of neurologic— particularly, neurodegenerative— disorders, and the fact that their specific whole-brain connectivity profiles have been investigated much less frequently than those of other areas (e.g., in frontal cortex) in TBI. In addition, to the author's knowledge, the current study is the first in brain injury to investigate quantitative

between-group differences in hippocampal-whole brain connectivity. Informed by previous work in TBI, the study hypothesizes that individuals in the chronic phase of TBI (approx. 1-5 years post-injury) will exhibit increased integration within the DMN, represented by greater positive connectivity between the PCC or hippocampi and other DMN regions compared to healthy controls (HCs). It further predicts that there would be decreased interplay between DMN and task-positive regions, quantified by diminished negative connectivity between the PCC or hippocampi and regions outside the DMN.

Given the potential impact of functional connectivity on behavior and ongoing intervention efforts, a second goal of the current study concerns the temporal characteristics, or chronology, of connectivity alterations after TBI. At present, there exists only one study in moderate to severe TBI that tracked the trajectory of connectivity patterns of DMN nodes during a recovery period: in an analysis of "rest" intervals from a working memory task, Hillary and colleagues demonstrated decreased functional connectivity between goal-directed (or task-positive) regions and increased functional connectivity between the PCC and temporal lobe during injury recovery (from 3-6 months post injury)(Hillary et al., 2011). These findings signify that network function after TBI is highly dynamic in the months following trauma. However, the point at which connectivity profiles are stabilized is yet to be identified, and it is plausible that connectivity alterations evident early after injury might endure beyond critical early windows of clinical recovery, typically regarded as the first year post-injury (Jourdan et al., 2013; Ketchum et al., 2012; Radford et al., 2013; Whyte et al., 2013). The present investigation probes longitudinal connectivity changes in a subset of individuals from the TBI group, comparing connectivity profiles derived from rs-fMRI in the subacute phase (approx. 3 months post-injury) to those in the chronic phase. The aim here is to outline the developmental trajectory of any

identified changes between the TBI and HC groups, and to examine whether functional connectivity changes during the chronic phase are gradually evolving phenomena or if they are relatively more immediate effects of brain injury.

In light of previous work speculating that DMN-associated connectivity changes may constitute a biomarker for latent or incipient AD, a principal goal of the proposed study is to determine if such changes are present in TBI. If supported, they may illuminate a neuropathological relationship between TBI and neurodegenerative disease that is yet to be delineated. To this end, the specific aims of this thesis study are:

1. To investigate the functional connectivity of the PCC and hippocampi with the rest of the brain in individuals with chronic-stage moderate to severe TBI and healthy controls. In addition, focus will be placed on altered connectivity of the PCC and hippocampi to regions in the TPN, which might indicate disruption of intrinsic connectivity related to cognitive processes. Specific hypotheses include:
    a. Elevated connectivity magnitude (increased positive correlations) between the PCC or hippocampi and other DMN regions in TBI
    b. Diminished strength of negative connectivity (decreased negative correlations) between the PCC or hippocampi to regions in the TPN in TBI
2. To examine, within-subjects, changes in the functional connectivity of the PCC and hippocampi with the rest of the brain from subacute- to chronic-stage TBI. Of special interest is the presence or absence of effects identified in Aim #1, which may to help characterize how chronic connectivity alterations develop and are either resolved or maintained. It is predicted that:

   a. TBI results in early hyperconnectivity (increase positive correlations in subacute vs. chronic stage) between DMN nodes.

3. To examine, longitudinally, the relationship between measures of functional connectivity and attentional performance on neuropsychological tests. The following is hypothesized for the TBI group:
   a. Reduced negative correlation of DMN and TPN regions is associated with cognitive impairments in attention.
   b. Increased within-DMN connectivity is associated with better performance.
4. To determine whether demographic factors, such as age at injury (i.e., the age at which an individual sustained the TBI) and time post-injury (i.e., the amount of time that has elapsed since sustaining the TBI), are related to seed-voxel connectivity strength. As advanced age is typically associated with worse outcome, and longer post-injury time may permit greater recovery, the following is expected:
   a. Advanced age is associated with a greater magnitude of functional connectivity alterations.
   b. Longer post-injury time is associated with a smaller magnitude of functional connectivity alterations.

Methods

Participants

The current study included both cross-sectional and longitudinal components. Cross-sectional analyses included 23 individuals with moderate to severe TBI and 18 healthy controls (HCs). One individual's data in the clinical group was discarded due to excessive head motion to yield a final cross-sectional sample of 22 participants with TBI (ages 19-69; $\bar{x}$ = 34.05, sd = 15.04) and 18 HCs (ages 19-61; $\bar{x}$ = 29.83, sd = 12.57). The groups did not differ significantly in age or years of education. TBI severity was defined using the Glasgow Coma Scale (GCS) in the first 24 hours after injury (Teasdale and Jennett, 1974). Only individuals with either a GCS score less than 13, loss of consciousness for 30 minutes or more, or with positive neuropathologic findings upon structural neuroimaging were eligible for participation. Individuals with TBI sustained their injury, on average, 2.50 years (sd = 1.70) prior to scanning, with a mean GCS of 6.65 (sd = 3.88). The goal of examining this chronic sample was to first establish the connectivity effects observable in chronic-phase moderate to severe TBI in rs-fMRI data. In order to gain insight into the evolution of these effects, a subset of the chronic sample (n = 13) where data were available at approximately 3 months after the resolution of post-traumatic amnesia (herein referred to as the subacute stage) was studied in a separate longitudinal analysis. Participants in this subsample ranged in age from 19 to 54 (at the chronic stage: $\bar{x}$ = 28.54; sd = 9.51) and had a mean GCS of 6.25 (sd = 4.12). Demographic and clinical characteristics of all participant groups are found in Tables 1A and 1B.

Table 1A: Cross-sectional sample characteristics (n = 40)			
	TBI	**HC**	**p-value[2]**
Gender	14 M, 8 F	11 M, 7 F	--
Age	34.00 ± 15.08	29.83 ± 12.57	0.355
Education	12.82 ± 1.47	13.28 ± 1.90	0.394
GCS[1]	6.65 ± 3.88	--	--
Years post-injury	2.50 ± 1.70	--	--

Table 1B: Longitudinal sample characteristics (n = 13)[3]		
	Subacute stage	**Chronic stage**
Gender	9 M, 4 F	
Age	27.08 ± 9.61	28.46 ± 9.58
Education	12.69 ± 1.70	
GCS	6.25 ± 4.11	
Years post-injury	0.25 ± 0.07	1.36 ± 0.53

Table 1: A & B) GCS=Glasgow Coma Scale. A) [1]GCS not available for 2 participants- injury severity was confirmed by loss of consciousness time or positive neuroimaging findings for these individuals; [2]p-value obtained from two-sample t-test for group differences. B) [3]Data reported for identical set of subjects at two time points.

Candidates for either the TBI group or the HC group were excluded if they had a history of neurologic disorder such as prior TBI, stroke, seizure disorder, or significant history of serious psychiatric illness (e.g., schizophrenia or bipolar disorder). Individuals were also excluded if they had a history of inpatient treatment for substance abuse. These exclusions were assessed via medical chart review, covered in the institutional review board-approved consent form, and communicated to the study participant and/or the family member(s) of each participant prior to enrollment.

Neuropsychological Testing

Participants in the longitudinal arm of the study were administered a neuropsychological test battery to assess cognitive functioning at both time points. Testing was targeted towards the domains of attention and working memory, as these are most commonly encountered types of

deficits following TBI. To standardize all measures on the same normative group, z-scores were created for each participant using the mean and standard deviation of test results from 12 normal-performing healthy control participants. To explore the potential relationship between functional connectivity and cognition, an attentional composite score was constructed for each individual and consisted of the sum of the z-scores for the Trail Making Test - Part A (Army Individual Test Battery, 1944), WAIS-III Digit Span (Wechsler, 1997), and the Visual Search and Attention Test (VSAT; (Trenerry, Crosson, DeBoe, & Lieber, 1990). Composite scores were used in regression analyses with connectivity results.

Scan Protocol and Preprocessing

All included participants underwent MRI and fMRI scanning and completed multiple runs of working memory tasks. After completion of these tasks, they were instructed to stare at a fixation cross and stay as motionless as possible during a 5- to 6-minute rs-fMRI scan. For the purposes of the current paper, data analyses on the rs-fMRI time series are discussed.

Imaging data were acquired for each participant using either a Philips (Ph) 3T system and a 6-channel SENSE head coil (Philips Medical Systems, Best) or a Siemens (Si) 3T Magnetom Trio (Siemens, New York City, USA).[1] Data collection was parameterized to maximize consistency between magnets. 3D high resolution T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) image sequences were optimized across scanners and acquired for each participant to provide high resolution underlays for functional brain activation. Echo planar imaging (EPI) was used for resting-state functional imaging. EPI sequences were acquired with a 2000 ms repetition time (TR); 30(Si) or 34(Ph) ms echo time (TE); 90^{o} flip angle

[1] The difficulties in recruiting and testing TBI patients as well as the longitudinal aspects of the current work necessitated the use of two different scanners.

(FA); 230 x 230(Si) or 240 x 240(Ph) mm^2 field of view (FOV); 80x80 acquisition matrix; and 34 or 35 4-mm-thick axial slices with no gap between slices. Between 150 and 180 functional volumes were collected for each participant.

Preprocessing of fMRI data was performed using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm8). To control for initial signal instability, the first five volumes (10 s) were removed from analyses for all participants. The following 145 volumes were subject to analyses; participants with sequences beyond 150 volumes had these extra volumes excluded from analyses. Preprocessing steps included realignment of functional volumes to the first functional image of the series via affine transformation (Ashburner, Neelin, Collins, Evans, & Friston, 1997; Friston et al., 1995). Each participant's functional images were then coregistered to their respective T1 MPRAGE, and all data were normalized using a standardized T1 template from the Montreal Neurological Institute (MNI) using a 12-parameter affine approach and trilinear interpolation. Normalized time series data were smoothed with a Gaussian kernel of 6 x 6 x 8 mm^3 to minimize anatomical differences and to increase signal-to-noise ratio.

Statistical Analyses

Hypotheses 1 and 2: In TBI versus healthy individuals, connectivity magnitude between the PCC or hippocampi and other DMN regions is increased (increased positive correlations)(Hyp. 1). The strength of negative correlations between the PCC and hippocampi to regions in the TPN is diminished (reduced negative correlations) in TBI (Hyp. 1). Longitudinally, there is hyperconnectivity within the DMN in the subacute vs. chronic stage of TBI (Hyp. 2).

Connectivity patterns associated specifically with the PCC and hippocampi were investigated through a seed-voxel correlational approach. Briefly, BOLD signal time courses were extracted from specified regions of interest (ROIs, or "seeds"). Whole-brain connectivity maps associated with each seed were entered into statistical analyses to determine between-group differences in positive and negative seed-voxel connectivity. Seed-based analyses were identical in the cross-sectional and longitudinal arms of the study, and details of this analytic procedure are provided below.

Seed Placement: Based upon a literature examining network connectivity after moderate and severe TBI, analyses were focused on connectivity of the PCC, left hippocampus, and right hippocampus. To do so, seed regions of interest (ROIs) were selected within the CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). This toolbox provides coordinates for the PCC (-6, -52, 40; 10 mm radius) identified in Fox, et al. (Fox et al., 2005) and derived from a previous meta-analysis of deactivated regions during passive vs. active tasks.(Shulman et al., 1997) Hippocampal seeds were defined as analogous regions in each hemisphere and extracted as ROI masks from the widely used Automatic Anatomic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), also available in CONN. This approach to hippocampal seeding has been employed previously in resting-state studies of neurodegenerative disease (Bai et al., 2011; Wang et al., 2007).

fMRI Data Analyses: Preparation and extraction of seed time series for functional connectivity analyses were performed using the CONN Toolbox. This toolbox employs the aCompCor technique for noise correction (Behzadi, Restom, Liau, & Liu, 2007), a method that avoids the spurious introduction or magnification of negative correlations between voxels associated with global mean signal regression (Murphy, Birn, Handwerker, Jones, & Bandettini,

2009). The toolbox performed segmentation of individual structural volumes into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) maps. WM and CSF maps along with six motion regressors obtained from data preprocessing in SPM were entered as confounds in accordance with aCompCor procedures. A temporal band pass filter of 0.008 to 0.09 Hz was applied to isolate the frequency window of interest.

First- and second-level connectivity analyses followed similar processing streams in the cross-sectional and longitudinal arms of the study. For both seeds and in each individual, using CONN, bivariate correlations (Pearson's *r*) were computed between the average BOLD value in the seed (i.e., across all voxels in the seed) and every other voxel in the brain as measures of functional connectivity. Correlation values were Fisher (z)-transformed to normalize their distribution and to facilitate later analyses with neuropsychological variables. Because of the current study's aim to investigate both positive and negative connectivity profiles, for each group (or time point) of interest, a map of all areas significantly positively connected to a specified seed was constructed using a voxel (height) significance threshold of $p < 0.005$ and an appropriate cluster-defining (extent) threshold corrected for multiple comparisons at $p < 0.05$. Cluster sizes were determined by Monte Carlo simulations in the 3DClustSim program of AFNI (http://afni.nimh.nih.gov). Simulations were conducted with explicit whole-brain masks and a Gaussian filter width of 10 x 10 x 12 to account for intrinsic smoothness of the data. Positive connectivity maps from the two groups were added together using the ImCalc function in SPM to create a combined sample-wide positive connectivity mask, which was used in t-tests (paired t-tests in the longitudinal data) for group differences. Thus, second-level comparisons were restricted to functional connections that were significant for at least one group. Between-groups t-tests were performed employing a more liberal voxel threshold of $p < 0.01$ with an extent

threshold corrected at $p < 0.05$ and determined by simulations on the combined mask; this was based on previous studies similarly employing masking for connectivity analyses (Dennis et al., 2008; Dew, Buchler, Dobbins, & Cabeza, 2012). An identical procedure was utilized to examine group differences in negative seed-voxel connectivity.

Anatomical locations of clusters were identified using the xjView toolbox (http://www.alivelearn.net/xjview) in SPM. Connectivity results were visualized in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/index.html), and these images are presented herein.

Hypothesis 3: Greater disturbances in functional connectivity are related to neuropsychological deficits in patients with TBI. Specifically, reduced negative correlation of DMN and TPN regions is associated with attentional deficits.

To explore whether functional connectivity is related to cognition, positive and negative Fisher-transformed correlation values of the three seeds were regressed on attentional composite scores within each time point of the longitudinal analysis. Connectivity at the subacute stage was also correlated with attention scores at the chronic stage to determine whether there is an association between early connectivity alterations and later performance. Positive and negative connectivity masks obtained above for each time point of interest were used to restrict connectivity-behavior correlations to areas showing significant seed-voxel connectivity at that time point. For all regressions, a voxel threshold of $p < 0.01$ with an extent threshold corrected at $p < 0.05$ (determined using 3dClustSim) was implemented.

Hypothesis 4: The magnitude of functional connectivity is related to age at injury and time post-injury. Greater age at injury and shorter time elapsed since injury are

independently associated with increased positive connectivity within the DMN and decreased negative connectivity between DMN and TPN regions.

For the cross-sectional chronic TBI group, the relationship between age at injury and time post-injury and seed-voxel connectivity was examined through regression analysis similar to the analysis of cognitive performance and connectivity above. Positive and negative Fisher-transformed correlation values of the three seeds were regressed on either age at injury or time post-injury for the cross-sectional TBI group. Positive and negative connectivity masks obtained above for each time point of interest were used to restrict connectivity-demographic correlations to areas showing significant seed-voxel connectivity at that time point. For all regressions, a voxel threshold of $p < 0.01$ with an extent threshold corrected at $p < 0.05$ (determined using 3dClustSim) was implemented.

Results

Neuropsychology

Neuropsychological testing results from longitudinal analyses are presented in Table 2 (see following page). Participants at the subacute stage of TBI performed significantly worse than the comparison group on Trails A, VSAT, and the attentional composite at $p < 0.05$; differences in Digit Span and Trails B performance were not significant. Participants at the chronic stage were not significantly different from the comparison group, and these individuals improved significantly for all test measures from the subacute to chronic stage, suggesting good neurocognitive recovery. Attentional composite scores were also significantly different between time points, with an average improvement in z-score of 2.77. Practice effects may account for some variance in performance improvement over time, but given that the first year following TBI is a critical recovery period, performance gains can be at least partially attributed to positive change in neurological status.

Between-group differences in seed-voxel functional connectivity (cross-sectional)

Table 3 outlines PCC connectivity findings in each group. Compared to the control group, the TBI sample demonstrated increased positive connectivity of the PCC to a cluster in the right ventromedial prefrontal cortex (vmPFC) extending into the adjacent rostral anterior cingulate cortex (Figure 1A). This was the only cluster that survived both height and extent thresholds. Increased positive connectivity of the PCC in controls compared to TBI patients was detected for a smaller cluster in the left supramarginal gyrus.

Table 2: Neuropsychological test performance								
	Subacute TBI raw (sd)	Subacute TBI z-score	Chronic TBI raw (sd)	Chronic TBI z-score	Controls (n = 12) raw (sd)	Paired t-tests within TBI groups	Indep. samples t-tests (HC vs. subacute)	Indep. samples t-tests (HC vs. chronic)
Trails A[1]	31.54 (12.17)	-1.40	24.23 (7.88)	-0.39	21.42 (7.25)	p = 0.036	p = 0.020	p = 0.364
Trails B[1]	66.46 (25.67)	-0.77	52.77 (14.74)	0.21	55.75 (13.93)	p = 0.047	p = 0.214	p = 0.608
Digit Span Total[2]	16.38 (3.28)	-0.42	18.54 (3.50)	0.11	18.08 (4.01)	p = 0.019	p = 0.257	p = 0.766
VSAT Total[3]	102.08 (19.12)	-1.81	120.77 (13.67)	-0.58	129.58 (15.20)	p = 0.000	p = 0.001	p = 0.140
Attentional Composite	--	-3.63	--	-0.85	--	p = 0.000	p = 0.001	p = 0.291

Table 2: Trails=Trail Making Test; VSAT=Visual Search and Attention Test; Attentional Composite=z-score sum of Trails A, Digit Span Total, and VSAT Total. Data provided for the same 13 individuals at the subacute and chronic stages of TBI. See text for references for neuropsychological tests administered.

Table 3: Cross-sectional differences in PCC connectivity			
	Location	Cluster size (vox)	Peak (MNI coordinates)
Positive connectivity			
HC > cTBI	L Supramarginal G. (IPL)	52	-60, 52, 34
cTBI > HC	R vmPFC	94	12, 50, -6
Negative connectivity			
cTBI > HC	R Supramarginal G. (IPL)	96	57, -28, 26

Table 3: HC=healthy control; cTBI=chronic TBI; L=left; R=right; G=gyrus; IPL=inferior parietal lobule; vmPFC=ventromedial prefrontal cortex

The TBI sample demonstrated greater negative connectivity between the PCC and the right supramarginal gyrus in the inferior parietal lobule (IPL; Fig. 1B). There were no significant regions of greater negative connectivity with the PCC in the HC group.

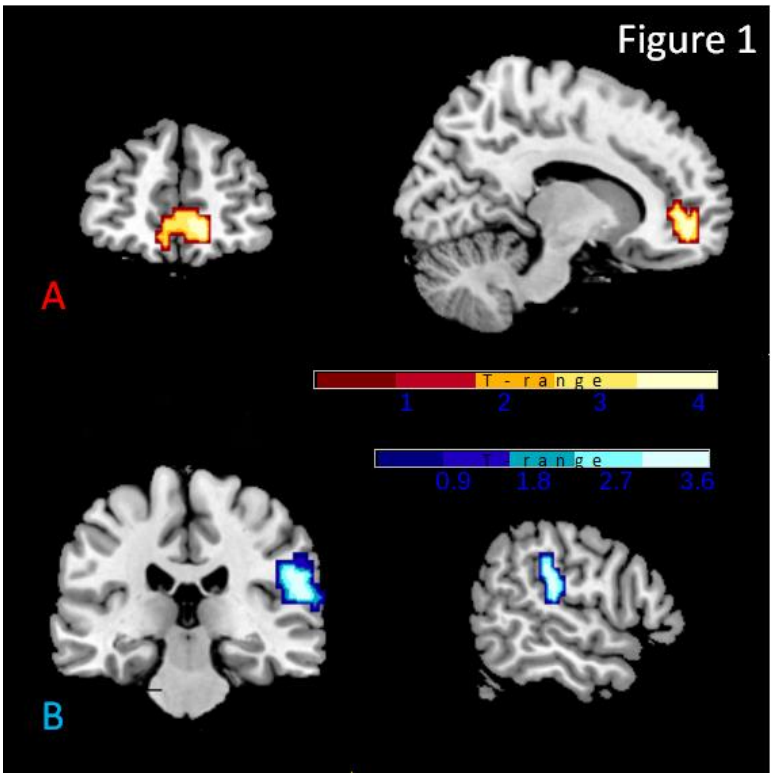

Figure 1: Functional connectivity results for the PCC seed in chronic TBI > healthy control contrasts in coronal (left) and sagittal (right) slices. Images depict, in TBI, A) increased positive connectivity between posterior cingulate cortex and ventromedial prefrontal cortex and B) increased negative connectivity between posterior cingulate cortex and inferior parietal lobule.

Table 4 displays results of group-level comparisons for both hippocampal seeds. Increased positive connectivity of both hippocampi in TBI was significant for clusters in proximal temporal lobe areas, including the parahippocampal gyri and temporal poles; significant clusters for the two seeds overlapped substantially (see Fig 2C). Additionally, the left hippocampus showed greater positive connectivity to brainstem regions, and the right hippocampus showed greater positive connectivity to the right superior temporal gyrus, insula,

and subcortical structures, including the putamen. All of these effects, including those for the left hippocampal seed, were predominantly right-lateralized (Fig. 2A, B, C). For controls, increased positive connectivity of the left hippocampus was observed with the right middle and left inferior temporal gyri, with the latter cluster extending into the occipital lobe.

Increased negative hippocampal connectivity in the patient vs. control groups for the left seed was observed in significant clusters mostly spanning midline white matter; these clusters were excluded from interpretation. TBI patients also demonstrated greater negative connectivity between the right hippocampus and a cluster of voxels in the left cerebellum. Controls exhibited greater negative connectivity between the left hippocampus seed and the right angular gyrus extending into the superior parietal lobule, the left dorsolateral prefrontal cortex, and the right inferior temporal gyrus extending into the fusiform gyrus.

Table 4: Cross-sectional differences in hippocampal connectivity			
	Location	**Cluster size (vox)**	**Peak (MNI coordinates)**
Positive connectivity			
		Left hippocampus	
HC > cTBI	L Inf. Temporal G. (BA 20)	127	-54, -46, -18
	R Mid. Temporal G.	55	57, -40, -10
cTBI > HC	R Sup. Temporal G. (Pole) R Parahippocampal G.	172	33, 11, -38
	R Midbrain R Brainstem R Cerebellum	140	12, -25, 22
		Right hippocampus	
cTBI > HC	R Sup. Temporal G. R Insula	87	48, -13, -22
	R Mid. Temporal Pole R Parahippocampal G.	54	27, 8, -42
Negative connectivity			
		Left hippocampus	
HC > cTBI	R Angular G. R Sup. Parietal Lobule	61	33, -58, 38
	L Inf. Frontal G. (BA 9) L Mid. Frontal G.	42	-54, 8, 38
	R Inf. Temporal G. (BA 37)	36	51, -61, -18
cTBI > HC	Corpus callosum	54	3, -22, 26
	Midline white matter	31	18, -40, 34
		Right hippocampus	
cTBI > HC	L Cerebellum	63	-36, -46, -54

Table 4: HC=healthy control; cTBI=chronic TBI; L=left; R=right; G=gyrus; Sup=superior; Mid=middle; Inf=inferior; BA=Brodmann Area

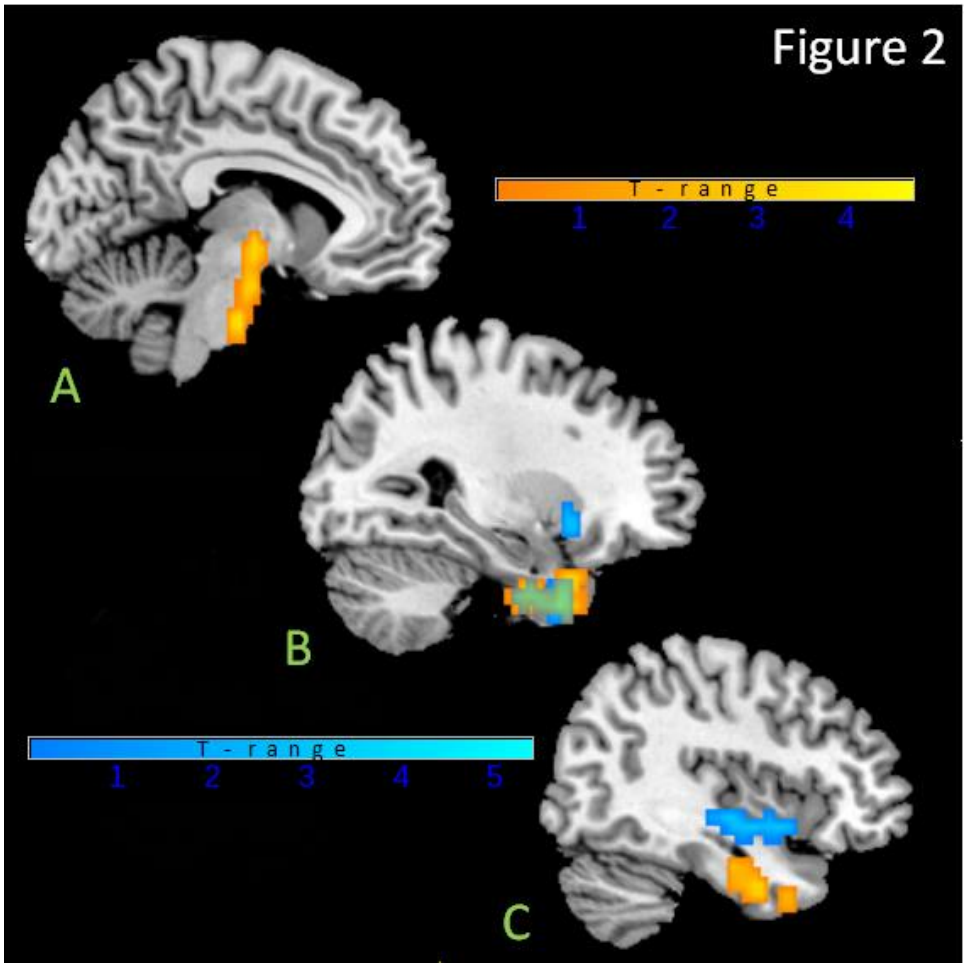

Figure 2: Positive functional connectivity results for the hippocampal seeds in chronic TBI > healthy control contrasts, shown in sagittal slices. Results for the left seed are shown in warm color and results for the right seed are shown in cool color. Images depict, in TBI, A) increased connectivity of left hippocampus to brainstem; B) overlap of significant clusters for each seed (right temporopolar regions); and C) increased connectivity between left hippocampus and right temporal lobe, and between right hippocampus and right superior temporal gyrus and insular cortex.

Longitudinal investigation of seed-voxel connectivity

As individuals progressed from the subacute to chronic post-injury stages, a robust decrease in positive connectivity was observed from the PCC to frontal areas, notably involving regions covering the mPFC and extending laterally (Table 5; Fig. 3A). Connectivity loss between the PCC and prefrontal cortex was significant for a large cluster of voxels in the medial superior

frontal gyrus (dorsomedial prefrontal cortex). Chronic-stage TBI showed some increased positive connectivity to a cluster of voxels in lateral and superior portions of the temporal lobe compared to subacute-stage TBI. Increased negative PCC connectivity from subacute to chronic stages were found in a region encompassing the anterior insula and frontoparietal operculum and in the right supramarginal gyrus of the IPL (Table 5; Fig. 3B).

Table 5: Longitudinal differences in PCC connectivity

	Location	Cluster size (vox)	Peak (MNI coordinates)
Positive connectivity			
saTBI > cTBI	L Sup. Frontal G. L Med. Frontal G.	215	-18, 32, 50
cTBI > saTBI	R Sup. Temporal G. (BA 22) R Mid. Temporal G.	54	66, -49, 14
Negative connectivity			
cTBI > saTBI	R Frontopar. Operculum R Sup. Temporal G. R Insula	200	54, 5, 2
	R Supramarginal G. (IPL; BA 40)	146	66, -40, 34

Table 5: saTBI=subacute TBI; cTBI=chronic TBI; L=left; R=right; G=gyrus; Sup=superior; Med=medial; Mid=middle; BA=Brodmann Area; Frontopar=frontoparietal; IPL=inferior parietal lobule

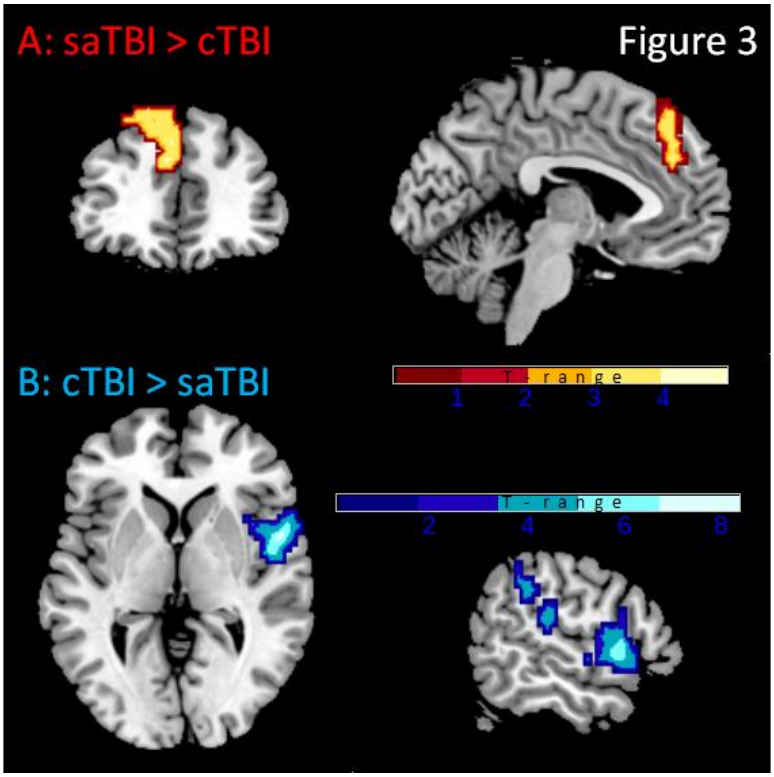

Figure 3: Functional connectivity results for the PCC seed in longitudinal analyses. A) In subacute TBI (saTBI) relative to chronic TBI (cTBI), there is increased positive connectivity between posterior cingulate cortex and dorsomedial prefrontal cortex. B) In cTBI relative to saTBI, there is increased negative connectivity between posterior cingulate cortex and the frontoparietal operculum and inferior parietal lobule.

From subacute- to chronic-stage TBI, positive connectivity increased from the right hippocampus to primarily parahippocampal and proximal subcortical (thalamic, brainstem) regions (Table 6; Fig. 4A). There were no findings of greater positive connectivity in the subacute stage. Negative connectivity was increased in the subacute stage between left hippocampus and a portion of the right precuneus, and between the right hippocampus and clusters located in the middle and superior frontal gyri (Table 6; Fig. 4B).

Table 6: Longitudinal differences in hippocampal connectivity			
	Location	**Cluster size (vox)**	**Peak (MNI coordinates)**
Positive connectivity			
		Right hippocampus	
cTBI > saTBI	L Thalamus	50	-6, -28, 6
	L Midbrain		
	L Brainstem		
	R Uncus (BA 28)	42	24, -10, -34
	R Parahippocampal G.		
Negative connectivity			
		Left hippocampus	
saTBI > cTBI	R Precuneus (BA 7)	35	3, -64, 46
		Right hippocampus	
saTBI > cTBI	L Mid. Frontal G.	104	-33, 50, 22
	L Sup. Frontal G.		
	R Mid. Frontal G.	30	36, 41, 34
	R Sup. Frontal G.		

Table 6: saTBI=subacute TBI; cTBI=chronic TBI; L=left; R=right; BA=Brodmann Area; Mid=middle; Sup=superior; G=gyrus

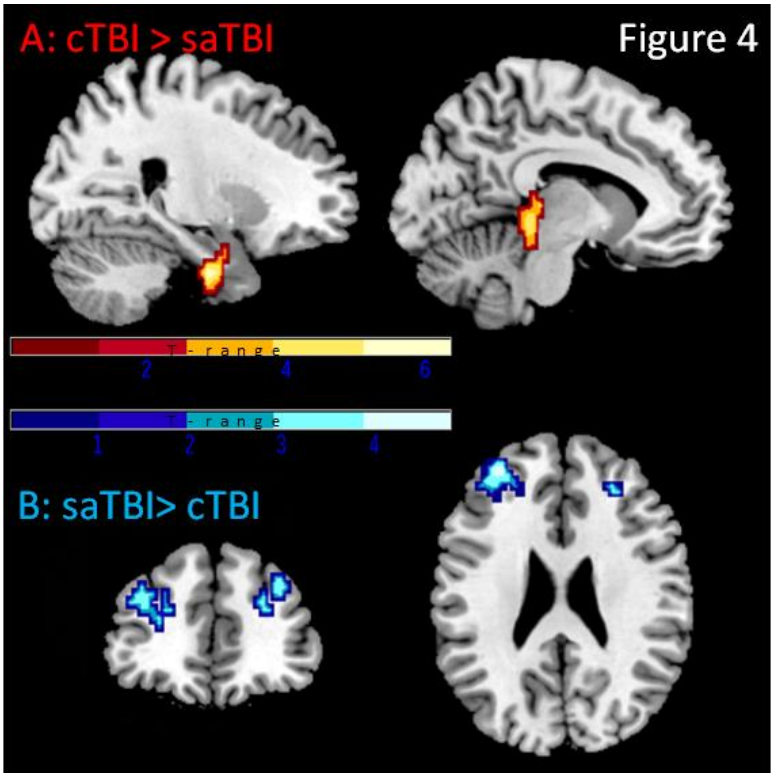

Figure 4: Functional connectivity results for the right hippocampal seed in longitudinal analyses. A) In chronic TBI (cTBI) relative to subacute TBI (saTBI), there is increased positive connectivity between right hippocampus and proximal right temporal lobe and brainstem. B) In saTBI relative to cTBI, there is increased negative connectivity between right hippocampus and bilateral superior and middle frontal gyri (dorsolateral prefrontal cortex).

Functional connectivity and behavior

In the subacute stage of TBI, negative connectivity between the left hippocampus and the right middle frontal gyrus (dorsolateral prefrontal cortex) was positively correlated with attentional composite scores (peak MNIxyz = 45,32,26; T = 4.05; 21 voxels). A nearly identical pattern of subacute negative hippocampal-prefrontal connectivity was positively correlated with attentional performance in the chronic stage, and this was significant for two clusters in the dorsolateral prefrontal cortex (peak = 42,35,22; T = 6.02; 32 voxels; and peak = 27,47,14; T = 4.69; 13 voxels). In the subacute stage, there was a subthreshold trend toward contemporaneous attentional scores positively predicting positive PCC connectivity with the left precuneus.

However, subacute positive connectivity between the posterior cingulate and the precuneus was significantly negatively correlated with attentional performance at the chronic stage, that is, greater subacute positive connectivity was associated with poorer performance later (peak = 9, -40, 38; T = 5.69; 120 voxels). There were no significant relationships between chronic-stage connectivity and performance.

Functional connectivity and demographics

In the cross-sectional sample, age at injury predicted PCC-precuneus connectivity such that increased age at injury was associated with greater positive connectivity between these regions (peak = 3, -70, 46; T = 4.47; 49 voxels). Time post-injury was not a significant predictor of connectivity strength.

Discussion

The current study interrogated whole-brain resting-state functional connectivity associated with the PCC and hippocampi in order to determine whether moderate-severe TBI results in significant connectivity alterations of these regions and how these alterations may develop over a recovery window. Importantly, the study investigated the development of effects from relatively early after injury to the chronic phase to identify enduring connectivity changes that may have prognostic value. It was hypothesized that the TBI group would show increased within-DMN positive connectivity (synchrony) and reduced negative connectivity (antiphase synchrony) between DMN and task-positive network (TPN) regions (Hypothesis 1).

Consistent with predictions, the TBI sample in cross-sectional analyses exhibited greater synchrony of the PCC with another principal DMN node, the ventromedial prefrontal cortex, compared to controls. Greater synchrony in TBI was noted between the hippocampi with other medial temporal as well subcortical and brainstem regions. There was also evidence of decreased antiphase synchrony between the left hippocampus and distributed task-related regions in TBI. In contrast to hypotheses, however, the TBI group exhibited increased antiphase synchrony between the PCC and posterior attentional network areas compared to controls. These findings indicate that in the clinically stable phase of TBI, functional connectivity both within and between critical networks are altered from those observed in healthy individuals and that the nature of these alterations is not uniform, but region-specific.

The longitudinal analysis with a subset of the original TBI sample revealed a remarkable dissociation between the chronologies of both positive and negative connectivity profiles within seeds and these profiles between seeds. Considered alongside cross-sectional analyses with

controls, longitudinal TBI data suggest that synchrony between the hippocampi and proximal temporal and subcortical areas is an early consequence of trauma (Hypothesis 2) that continues to intensify into the chronic phase, at which time substantial hypersynchrony is evident. Conversely, there are losses in the antiphase synchrony of the hippocampi with dorsolateral prefrontal cortex, and these changes have implications for behavior (discussed below). On the other hand, the PCC showed diminishing synchrony with the anterior DMN and increasing antiphase synchrony with TPN regions from subacute to chronic stages. While consistent with the expected recovery trajectory, these results also support the chronicity of PCC alterations. PCC connectivity changes are not fully resolved in the chronic stage, at which time they comprise significant residual elevations in both DMN synchrony and TPN antiphase synchrony (Hypothesis 2).

In addition to hypothesized group differences in network connectivity, the current study also predicted that connectivity alterations would be associated with attentional functioning in the longitudinal TBI sample (Hypothesis 3). While no significant relationships between chronic-stage connectivity and behavior emerged, subacute-stage antiphase synchrony between the left hippocampus and right dorsolateral prefrontal cortex positively predicted attentional performance at both time points. This finding is concordant with the hypothesis that cognitive performance is supported by the reciprocity between the DMN and TPN. However, it was also revealed that synchrony between the PCC and precuneus at the subacute stage is negatively associated with performance at the chronic stage, a result that suggests hyperconnectivity within the DMN is not a compensatory effect, but perhaps a marker of network inefficiency.

The final hypothesis of the present work involved the prediction that connectivity alterations in chronic TBI would be related to age at the time of injury and the amount of time

elapsed since injury (Hypothesis 4). The cross-sectional (chronic) TBI sample showed greater positive connectivity between the PCC and precuneus, principal nodes of the DMN, as age at time of injury increased. Given that younger age is thought to afford better long-term clinical outcomes, and taken together with the current finding that greater synchrony between the PCC and precuneus is associated with more impaired cognitive performance later, this effect suggests that hypersynchrony within the DMN is both a response to and a reflection of greater premorbid network vulnerability.

Incomplete resolution of PCC connectivity patterns

The current study's observation of increased connectivity of the PCC and ventromedial prefrontal cortex in the cross-sectional TBI sample is likely a reflection of the PCC's central role in the DMN and its susceptibility to pathology (Buckner et al., 2005; Greicius, Srivastava, Reiss, & Menon, 2004; Leech & Sharp, 2013). In particular, the vulnerability of the PCC to connectivity alterations is borne out of the fact that it is a rich neural hub, endowed with a relatively large number of connections to several functional brain systems in widespread areas of cortex (van den Heuvel & Sporns, 2011, 2013). PCC findings here also resonate with previous work in moderate or severe TBI during various phases of recovery. Using independent components analysis to map the DMN, Sharp and colleagues reported increased functional connectivity of the PCC and precuneus with the rest of the DMN during rest (Sharp et al., 2011) and during the course of a task (Bonnelle et al., 2011) in a mixed group of patients ranging from three months up to over six years after injury. It has also been found that severe forms of TBI impact the integrity of the PCC as an influential receiver and director of neural information (Pandit et al., 2013). Thus, increased synchronization of PCC with the rest of the DMN may reflect a modulatory mechanism vis-à-vis disruption in distributed networks (Leech & Sharp,

2013). This is consistent with the view of hyperconnectivity as a generalized response to neural compromise, whether traumatic or insidious in nature (Hillary et al., manuscript in review).

In the current study, the idea of such "reactive" hyperconnectivity is extended to suggest that during the course of recovery, the need for PCC synchronization with the rest of the DMN, especially areas in the mPFC, may be lessened as widespread networks reach a more "healthy" equilibrium (Nakamura, Hillary, & Biswal, 2009). However, it should also be noted that multiple distinct patterns of PCC synchrony may develop or attenuate with recovery. As revealed by the current longitudinal analyses, the target regions of PCC synchrony are dissociable between time points. When comparing subacute- and chronic-stage TBI, the study observed greater PCC synchrony with medial prefrontal regions at the subacute stage, but greater PCC synchrony with superior and middle temporal gyri at the chronic stage. This latter finding is consistent with earlier data (Hillary et al., 2011), and suggests that decreasing synchrony of the PCC with the DMN is accompanied by increasing synchrony of this region with structures outside the DMN, possibly indicating a restoration of synchronous patterns lost acutely to insult.

The current findings in the PCC are contrasted with those from Arenivas et al. (2012), who computed the similarity between TBI and control PCC connectivity maps to an average control map, and noted that the TBI group showed less concordance with the comparison map; they interpreted this finding as decreased PCC-DMN connectivity in TBI (Arenivas et al., 2012). However, their approach makes it difficult to assess between-group differences in connectivity magnitude, which was a principal endeavor in the current study. Further, the increased connectivity within the DMN observed in the current study has been interpreted by some as a compensatory response to trauma (Bonnelle et al., 2011; Sharp et al., 2011). For example, Sharp and colleagues found that faster performance on an attentional task was associated with greater

within-DMN connectivity at rest (Sharp et al., 2011). These investigators also found that precuneus-DMN functional connectivity at the beginning of a task resulted in less variable reaction times during the task, and concluded that elevated functional connectivity supports performance (Bonnelle et al., 2011). However, the present data suggest that elevated functional connectivity may not always represent a supportive mechanism, and that what might seem to facilitate behavior at one point in recovery (an ostensibly compensatory process) could in fact be an early sign of systemic and chronic disruption. Illustrating this idea is the fact that, in the current study, there was a marginal effect for PCC-precuneus connectivity predicting attentional ability; this effect was only present in the subacute group. On the other hand, subacute connectivity between the PCC and a large portion of the precuneus was significantly and *negatively* associated with behavioral performance at the chronic time point, signifying that early hyperconnectivity may actually be detrimental to long-term functioning. Furthermore, performance at the chronic time point improved significantly from the subacute to chronic stages. Taken together, these data do not support the theory that increased PCC functional connectivity represents a compensatory mechanism, and instead suggest that cognitive performance improves as synchrony with this region decreases over time.

If hypersynchrony of the PCC and anterior DMN occurs acutely after TBI and is lessened with time, the question remaining is whether or not it subsides completely to a "normal" level. Previous literature does not offer explanations for residual connectivity increases, such as the increased synchrony observed in the current study between the PCC and another classic default mode node, the vMPFC, in the comparison of chronic TBI and controls. To shed light on these findings, the reader is oriented to results involving the antiphase synchrony of the PCC.

The present investigation found, in those with chronic TBI, strong antiphase synchrony between the PCC and posterior regions of the TPN, involving especially the right supramarginal gyrus in the inferior parietal lobule (IPL). In both cross-sectional and longitudinal analyses, the chronic TBI group emerged as exhibiting more pronounced antiphase synchrony between these regions than subacute TBI and controls. Chronic- vs. subacute-stage individuals also demonstrated increased connectivity between the PCC and the insula and frontoparietal operculum. The IPL is involved in a number of cognitive functions, including both episodic and working memory (Berryhill, 2012), executive functioning (Niendam et al., 2012), and bottom-up attentional processes (Behrmann, Geng, & Shomstein, 2004; Corbetta & Shulman, 2002; Corbetta, Patel, & Shulman, 2008; Shomstein, 2012). Similarly, the anterior insula and frontoparietal operculum have been implicated extensively in a network important for selecting salient stimuli and guiding behavior in coordination with multiple other brain systems (Dosenbach et al., 2006; Eckert et al., 2009; Menon & Uddin, 2010), and the structural integrity of this network has been found to be crucial for DMN functioning in severe TBI (Bonnelle et al., 2012). Moreover, given that concurrent modulations of the DMN and task-positive regions have been found to support task performance in healthy individuals (Arsalidou, Pascual-Leone, Johnson, Morris, & Taylor, 2013; Hampson, Driesen, Roth, Gore, & Constable, 2010; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008; Weissman, Roberts, Visscher, & Woldorff, 2006), an increase in antiphase synchrony during the clinical recovery period may signify a restoration of balanced network function necessary for efficient cognitive processing. Specifically, in the case of PCC-insula connectivity, research has shown that the insula is involved in diverse functions during task perturbation (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010) and resides at the crossroads of cognitive, affective, and homeostatic systems (Craig, 2009). Thus, this region

may be instrumental in negotiating activity between default and task-related networks (Hillary et al., 2011).

Taken together, previous functional characterizations of specific regions within the frontal and parietal cortices suggest that antiphase synchrony between these regions and the PCC may represent behaviorally relevant restoration of network function. However, what is puzzling is the apparent overshoot of this reinstatement, with chronic-stage TBI evincing more antiphase synchrony with the right IPL than even controls. In keeping with the view of the DMN and TPN as reciprocal networks, co-occurring internetwork (PCC-TPN) antiphase synchrony and residual intranetwork (PCC-DMN) synchrony as described above may be two parts of a larger effect involving the modulation of distributed networks. In other words, greater antiphase synchrony of the PCC with the right IPL or regions of other networks essential for goal-directed activity (e.g., frontal "salience" regions) in chronic TBI may complement increased within-DMN synchrony, allowing for an optimal balance between DMN and TPN activity. Exactly when this pattern of network interplay begins to shift so that it resembles more closely the dynamics of healthy brain networks— or if such a shift occurs at all— is an important question for future work.

Development of hippocampal connectivity alterations

The probing of hippocampal functional connectivity in the present investigation adds to the characterization of DMN changes following injury and is especially important given that connectivity of the hippocampi has not been well defined in the TBI literature. A previous study performed whole-brain connectivity analyses with bilateral hippocampi as seeds, but only visually compared group averaged maps of whole-brain connectivity, precluding inferences from being made about group differences in connectivity magnitude (Marquez de la Plata et al., 2011).

In the current investigation, it was shown that TBI results in increased synchrony of the hippocampi with relatively proximal regions (e.g., in parts of the anterior MTL, parahippocampal gyrus, insula, and brainstem) and a reduction in antiphase synchrony between hippocampus and task-positive regions, particularly the prefrontal cortex, compared to controls. Further, longitudinal results indicate that both of these effects emerge relatively early after injury, with hypersynchrony progressing from a unilateral to a bilateral phenomenon. These findings fit with previous literature documenting structural hippocampal anomalies (Bigler, Anderson, & Blatter, 2002; Tate & Bigler, 2000) and episodic memory impairment (Millis & Ricker, 1994; Wiegner & Donders, 1999; Wright, Schmitter-Edgecombe, & Woo, 2010) after brain trauma. Critically, the current results show that the connectivity profiles of the hippocampi do not seem to "recover" with greater time post-injury. That is, hippocampal synchrony grows stronger during the clinical recovery period, and is in fact hypersynchronous with nearby regions in the chronic phase, while antiphase synchrony is eventually lost.

One interpretation of hippocampal hypersynchrony is that it is a marker of connectivity loss or dysregulation in other parts of the cortex. The extent to which it represents a compensatory mechanism requires further clarification, but at present is a plausible explanation. For example, Yoo et al. (2007) studied sleep-deprived (but otherwise healthy) individuals and found that activation in unique regions of the frontal lobe in this group predicted memory encoding, which was worse overall compared to controls (Yoo, Hu, Gujar, Jolesz, & Walker, 2007). Interestingly, the specificity of frontal activity in the sleep-deprived group was accompanied by hypersychronous patterns between left hippocampus and brainstem, and right hippocampus and subcortical structures (thalamus, putamen). These findings bear notable resemblance to observations in the longitudinal TBI sample, where attentional performance at

both time points was significantly and positively associated with antiphase synchrony between left hippocampus and right dorsolateral prefrontal cortex at the subacute stage. The same relationship did not hold at the chronic time point, and in the larger analyses between chronic TBI and controls, antiphase synchrony between left hippocampus and diffuse task-positive areas in both hemispheres was decreased in TBI. Thus, these findings suggest that interplay between the hippocampi and frontal cortex may be essential for basic attentional abilities that are often impaired secondary to TBI. As this relationship is attenuated, hypersynchronous patterns may emerge in a compensatory fashion. Furthermore, compensatory processes may not be linear, as there were no direct correlations between hippocampal synchrony and behavioral scores, but hypersynchrony with a variety of functionally distinct cortical and subcortical regions was observed.

Potential markers of neurorecovery and neurodegeneration

Although there exists a relatively small literature in moderate-severe TBI with which to compare the current findings, the current results show striking similarities with those obtained in several studies of neurodegenerative disease, particularly Alzheimer's disease (AD) and related conditions. For example, it has been found that resting-state antiphase synchrony between regions of different networks is impaired in AD (Brier et al., 2012; Sorg et al., 2007; Wang et al., 2007; Zhang et al., 2010), and the loss of antiphase synchrony between posterior regions and frontal cortex in AD-risk populations may be especially relevant to the development of AD (Bai et al., 2011). Hippocampal hypersynchrony with proximal regions and/or other regions of the DMN has been noted in risk groups for AD, including APOEe4 positive individuals (Dennis et al., 2010; Filippini et al., 2009; Westlye, Lundervold, Rootwelt, Lundervold, & Westlye, 2011) and MCI (Das et al., 2013; Wang et al., 2011) as well as in early AD itself (Wang et al., 2007).

Similarly, increased resting-state connectivity between the PCC and other DMN regions has been noted in elderly individuals with elevated regional brain atrophy and memory complaints (Hafkemeijer et al., 2013), in MCI (Bai et al., 2009; Bai et al., 2011; Esposito et al., 2013), and in the very early stages of AD (Damoiseaux, Prater, Miller, & Greicius, 2012; Zhang et al., 2009; Zhang et al., 2010). Increased synchronization of vulnerable cortical regions such as the PCC and hippocampi has recently become an important part of the disconnection hypothesis prominently featured in literature on AD and other neurodegenerative dementias (Delbeuck, Van der Linden, & Collette, 2003; Pievani, de Haan, Wu, Seeley, & Frisoni, 2011). Much like the compensatory hypothesis in TBI, this model proposes that network hyperconnectivity in the very early stages of Alzheimer's pathology represents a compensatory response to high neurometabolic demands, and that these hyperconnections eventually turn into hypoconnections— consistent with neurodegeneration— when compared to healthy elderly (Damoiseaux, 2012; Hafkemeijer, van der Grond, & Rombouts, 2012; Mevel, Chetelat, Eustache, & Desgranges, 2011).

The results of the current study in TBI suggest that there may exist parallels between neural changes observed after brain injury and those present in MCI and AD. Specifically, the current study found that the hyperconnectivity patterns associated with PCC that seem to be most extensive in the months immediately following injury are still present to a significant extent in the chronic phase. In addition, there is a marked increase in both local and more diffuse (but still proximal) connectivity of the hippocampi. The determination of whether this generally increased within-DMN coherence continues to attenuate (in the case of PCC-anterior DMN) or gains more strength (in the case of the hippocampi) with time and what these phenomena might represent behaviorally requires tracking individuals several years post injury. Nonetheless, the current data

bring to light the possibility of enduring connectivity alterations in some individuals with TBI. Considering that similar changes have in observed in AD-related literatures, it is reasonable to posit that connectivity alterations in TBI may be maintained or exacerbated with time (i.e., superimposed on age-related decline) and thereby foreshadow neurodegenerative processes.

It is intriguing that the courses of PCC and hippocampal connectivity patterns after injury do not mirror one another. Whole-brain functional connectivity analyses, naïve of any seed definitions, have suggested that individuals advance towards a more "healthy" state in the months following injury (Nakamura et al., 2009), corresponding to significant clinical recovery in the first year. However, the current finding of progressive hippocampal hypersynchrony does not fit readily into this narrative. The current results instead support the functional heterogeneity of nodes within distributed networks (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Leech, Kamourieh, Beckmann, & Sharp, 2011; Uddin, Kelly, Biswal, Castellanos, & Milham, 2009; Whitfield-Gabrieli et al., 2011) as well as their plasticity potential. Furthermore, the present study found other network effects evident at both stages of injury, such as those involving antiphase synchrony of the hippocampi with frontal areas, which seem to show unique developmental courses. As such, the present study underscores the importance for future work to investigate specifically compromised network nodes, as they may provide a more nuanced view of connectivity changes after trauma and challenge the "back to normal" assumption. What if, indeed, functional systems never return to typical patterns? While substantive predictions about how chronic connectivity alterations affect remote functional outcomes are beyond the scope of this discussion, the concordance between the current results and those in neurodegenerative disease offers a preliminary working hypothesis for the consequences of TBI-induced network changes on long-term neurological status.

Limitations and Conclusion

This study was not without limitations. Although the sample size may be considered comparable to those in other studies of TBI, it remains modest, especially in longitudinal analyses, and findings should be interpreted with caution. Relatedly, brain injury by nature is extremely heterogeneous, and the effect of this heterogeneity in the current sample is unknown. Additionally, while seed-voxel connectivity analysis offers a relatively straightforward way to examine and interpret widespread connectivity associated with specific hubs, brain networks comprise spatially remote regions that may exhibit divergent connectivity patterns. It is conceded that while the current study depicts important gross effects associated with two crucial nodes, it does not capture the inevitable complexity of changes induced by trauma. In addition, because limited behavioral data was available, such variables should be implicated in future work to directly examine the relationship between network connectivity and behavioral outcome in the chronic phase. Despite these limitations, however, the current study demonstrated notable effects with all seeds in both cross-sectional and longitudinal analyses as well as relationships between connectivity and cognition. These effects are consistent with previous literature in both TBI and MCI/AD and therefore deserving of continued attention.

Probing of resting-state network connectivity in TBI is a relatively recent endeavor. While there has been some support for altered resting-state default mode function after TBI, the connectivity profiles of critical nodes in this network require further delineation as to their nature and evolution. The present data offer novel insights into the chronology of resting-state connectivity alterations after major head trauma. In particular, they represent the first data in TBI characterizing the connectivity profiles of major network regions over a critical recovery period, as well as the only data identifying quantifiable group differences in hippocampal-whole brain

connectivity. Furthermore, a novel hypothesis has been offered about the meaning of chronic connectivity alterations and its potential impact on the long-term functional integrity of neural systems, based on strikingly similar findings in AD and related conditions. Because head injury poses an increased risk for degenerative pathology, it is imperative for network connectivity changes that may be indicative of neurodegeneration to be surveyed in TBI. With continued longitudinal work, the connectivity changes observed within the first few years of injury should be followed to better elucidate how they may combine with natural aging processes. Tracking of these patterns may lead to better prediction of long-term outcome of devastating head injury and thus inform timely delivery of behavioral and pharmacological interventions (Ham & Sharp, 2012). Because there now exists converging evidence that trauma results in mutability at the network level, the notion of TBI as representing a non-progressive pathology is no longer tenable. Future research should proceed in the framework of TBI as a disorder that interacts with complex and dynamic neural systems throughout the lifespan, potentially creating further complications and thus necessitating long-term monitoring and rehabilitation efforts.

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