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Changes in resting connectivity during recovery from severe traumatic brain injury

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ABSTRACT

In the present study we investigate neural network changes after moderate and severe traumatic brain injury (TBI) through the use of resting state functional connectivity (RSFC) methods. Using blood oxygen level dependent functional MRI, we examined RSFC at 3 and 6 months following resolution of posttraumatic amnesia. The goal of this study was to examine how regional off-task connectivity changes during a critical period of recovery from significant neurological disruption. This was achieved by examining regional changes in the intrinsic, or “resting”, BOLD fMRI signal in separate networks: 1) regions linked to goal-directed (or external-state) networks and 2) default mode (or internal-state) networks. Findings here demonstrate significantly increased resting connectivity internal-state networks in the TBI sample during the first 6 months following recovery. The most consistent finding was increased connectivity in both internal and external state networks to the insula and medial temporal regions during recovery. These findings were dissociable from repeat measurements in a matched healthy control sample.

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1. Introduction

There is growing interest in the use of functional neuroimaging, and in particular blood oxygen level dependent functional magnetic resonance imaging (BOLD fMRI), to document brain changes associated with traumatic brain injury (TBI). This developing literature has focused primarily on the task-induced changes that differentiate clinical and healthy samples during cognitive, motor and sensory tasks. In one specific literature examining working memory (WM; or the ability to maintain a small amount of information “in mind” for online use) deficits after TBI, several consistent findings have emerged. Investigators have almost universally observed increased involvement of the regions critical for WM, including prefrontal cortex (PFC) and anterior cingulate cortex (ACC) and occasionally parietal regions in TBI (Christodoulou et al., 2001; Hillary et al., 2010, 2011; McAllister et al., 1999, 2001; Medaglia et al., 2011; Newsome et al., 2007; Scheibel et al., 2007). There is also rich literature examining the role of frontal systems disruption and the critical contribution of

cognitive control to deficit after TBI (McDowell et al., 1997; Hillary et al., 2010; Perlstein et al., 2004; Larson et al., 2006, 2007; Scheibel et al., 2007, 2009). These studies offer heuristics as for how large-scale neuronal activity might adapt to TBI, including the potentially critical role of anterior networks and those involved in cognitive (or attentional) control.

While early studies of TBI have helped clarify some of the basic “activation” changes associated with injury and afford the opportunity to link specific cognitive deficits to brain activation changes, there are a number of important future directions for this literature. First, a majority of the studies to date have been cross-sectional observations which pose significant methodological challenges for investigators (e.g., differential task performance between groups) (Price et al., 2006; Price and Friston, 2002) and often do not permit the examination of critical within-subject dynamics. As a remedy to this, the current study makes use of a longitudinal design during a critical window of recovery (i.e., between 3 and 6 months post injury) in order to examine within-subject brain changes.

Second, most studies to date using functional imaging methods to examine the consequences associated with TBI have focused on task-related brain activation. The study of task “activation” offers the opportunity to examine task-specific alterations in neural networks after TBI, but such approaches limit the scope of study (focusing on task induced regions of interest (ROIs), instead of whole brain function) and are burdened by design challenges that are often difficult to resolve. For example, examining task-related activation

Abbreviations: TBI, traumatic brain injury; fMRI, functional magnetic resonance imaging; WM, working memory.

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requires the creation of appropriate control tasks and the need to guarantee equivalent task performance between groups [e.g., task accuracy in TBI vs. healthy control (HC)]. Moreover, the work to date has focused almost solely on the magnitude of the signal (i.e., topographical activation differences) as opposed to communication within the network or covariance in (and between) ROIs.

In pioneering work conducted over 15 years ago, Biswal et al. demonstrated that covariance in voxels comprising the primary motor cortex during rest showed spatial overlap with the observable change in the BOLD response during motor stimulation. These influential findings were the foundation to an intriguing method for investigating brain function through the use of “resting” BOLD data to understand underlying neural connectivity, or “resting state functional connectivity” (RSFC) throughout the brain (Biswal et al., 1995). In fMRI work, RSFC methods often focus on isolating the covariance in very low frequency (~0.1 Hz) fluctuations in the BOLD signal, thus permitting analysis of non-task related brain activity which likely plays a non-trivial role in both on-task and off-task functioning.

This early work was extended by Lowe et al. (1997) by demonstrating similar effects in larger regions of sensorimotor cortex (i.e., across multiple slices) and other examiners used these methods to examine relationships between motor and association cortex (Xiong et al., 1998, 1999). Of critical importance in this literature is the demonstration that task-induced activation maps underestimate the size and number of functionally connected regions and that functional networks are more fully revealed by RSC analysis (Biswal et al., 1995; Xiong et al., 1998, 1999). These studies established the foundation for “resting-state functional connectivity studies” using fMRI (Biswal et al., 1995; Greicius and Menon, 2004; Gusnard and Raichle, 2001; Hampson et al., 2002; Lowe et al., 1997) and a literature examining task negative or “default mode” networks (Fox et al., 2005; Raichle et al., 2001; Raichle and Snyder, 2007). In the case of the latter, examiners identified distinct “off-task” networks operating in concert as one transitions in and out of goal-directed behavior.

One general interpretation differentiating task-on and task-off networks is that they are reciprocal so that at moments where goal-directed behavior is necessary, the “inward” or self-reflective default mode network remits, giving way to neural activity relevant to task. However, interpreting this relationship as an opponent process may oversimplify this relationship; separate investigations have demonstrated that the default mode activity plays a role in task and the magnitude of deactivation in default mode regions contribute to task performance (Cole et al., 2010; Hampson et al., 2010). These findings offer guiding principles for understanding the role of resting states in healthy neural systems, but questions remain regarding how significant neural network disruption, such as that observed in TBI, might influence the interplay between task-related positive and negative brain activation.

The examination of both RSFC and default-mode networks in clinical samples remains novel, but there are already several findings that provide a framework for understanding how neurological disruption influences the resting signal and for developing expectations in TBI. To date, resting connectivity has been used to examine network changes in a number of clinical disorders including schizophrenia (Camchong et al., 2009; Rotarska-Jagiela et al., 2010; B. Zhou et al., 2010), normal aging (Koch et al., 2010), stroke (Carter et al., 2010), mood disorders (Chepenik et al., 2010; Hamilton et al., 2010; Sheline et al., 2010), multiple sclerosis (Rocca et al., 2010) and dementias (J. Zhou et al., 2010). There have also been whole brain analyses using resting data to examine alterations in cerebral blood flow (Kim et al., 2010) and we recently applied graph theory to examine “small-worldness” in networks after TBI (Nakamura et al., 2009). In one of the more intriguing applications of resting connectivity to date, Vanhaudenhuyse et al. (2010) used baseline BOLD measures to differentiate cognitively intact and comatose non-communicative brain injured patients. Not surprisingly, the outcome of these studies has varied and this is likely due as much to meth-

odological differences as the effects of distinct pathophysiology in the clinical samples represented. Even so, two important findings emerge from this literature that may be relevant for TBI in the current study. The first is that neurological compromise has been demonstrated to influence resting connectivity (broadly defined). Second, one consequence for global brain connectivity is that connections between critical nodes may be greatly diminished or even unobservable after neurological disruption (see Ongur et al., 2010; Skudlarski et al., 2010; Vanhaudenhuyse et al., 2010).

We anticipate that network disruption results in less coherence in resting connectivity during periods of goal-directed behavior and, therefore, we should observe increased connectivity in internal-state networks during recovery. That is, significant neurological disruption of frontal systems (often observed in TBI), may result in a failure to effectively transition between self-reflective processing and outward goal-directed behavior.

1.1. Study purpose

The goal of this study is to examine resting state connectivity to determine if there are systematic changes in whole-brain connectivity during recovery from TBI. We aim to examine the changes in resting fMRI connectivity during the first 6 months following injury when behavioral recovery is known to occur (Millis et al., 2001; Pagulayan et al., 2006). The use of resting fMRI circumvents the methodological dilemmas that arise when using fMRI in clinical samples including difficulty guaranteeing task compliance and assumptions surrounding cognitive subtraction and pure insertion, where contributing components to a task are presumed to be linear and/or additive (Hillary, 2008; Price et al., 2006; Price and Friston, 2002). Moreover, the influences of diffuse neurological disruption (like that observed in TBI) on whole-brain neural networks remain essentially unknown. Traditional fMRI studies in TBI have excluded much of the operating brain in order to isolate specific task-related networks. While this approach offers advantages for examining discrete cognitive deficits, it offers very little information about global brain changes secondary to injury. Consequently, there is very little work documenting how large-scale neural networks adapt to neural disruption and resting connectivity offers one approach to address this issue. For these reasons, resting connectivity is ideal for identifying alterations in the BOLD signal in the recovering brain. This approach may provide additional insight into how neural plasticity is expressed in the injured brain and offer context for findings in cross-sectional activation studies to date, including determining the meaning of increased neural involvement repeatedly observed in activation studies (for review see Hillary, 2008).

Of note, RSFC and the DMN and even the notion of the brain at “rest” have contextual meanings. For the purpose of this study, we will focus on the intrinsic, or resting, BOLD signal during off-task blocks that flank a visual working memory task. In this sense, we are not isolating the off-task “deactivations” that are often the focus in traditional studies of the DMN. Instead, we focus on covariance between four seeded ROIs and the intrinsic BOLD signal during these off-task blocks.

2. Materials and methods

2.1. Subjects

Ten participants with moderate and severe TBI between the ages of 19 and 56 years and ten healthy adults of comparable age underwent MRI scanning at separate time points for this study. Individuals with TBI underwent MRI data acquisition at 3 and 6 months after emerging from posttraumatic amnesia (PTA). These study participants were included from an original sample of 15 subjects. The data from five subjects were not included in the current study due to attrition ($n=1$), an inability to adequately perform the cognitive task at

3 months post PTA ($n = 3$), and claustrophobia ($n = 1$). Because it was a primary goal in this study to examine alterations in PFC following disruption to frontal systems, subjects with small identified areas of contusion or hemorrhage in the frontal regions were included (7/10 subjects in this study sustained injuries to frontal regions). TBI severity was defined using the Glasgow Coma Scale (GCS) in the first 24 h after injury (Teasdale and Jennett, 1974) and GCS scores from 3 to 8 were considered “severe” and scores from 9 to 12 were considered moderate. One individual with a GCS score of 13 was included because acute neuroimaging findings were positive. During recruitment for either group, potential study participants were excluded if they had a history of previous neurological disorder such as seizure disorder, significant neurodevelopmental psychiatric history (such as schizophrenia or bipolar disorder), or had a history of substance abuse requiring inpatient treatment. To control for potential resting connectivity changes with repeated exposure to the MRI environment, a HC sample of comparable age was enrolled in the study and underwent two MRI scans separated by approximately 3 months (mean = 90.2 days, SD = 23.8).

2.2. TBI and focal lesions

There is accumulating evidence that, following moderate and severe TBI, even cases that appear to result in isolated injury (e.g., subdural hematoma), there are likely whole-brain consequences (Büki and Povlishock, 2006; Fujiwara et al., 2008). Findings from these and other studies indicate that diffuse axonal injury is a nearly universal finding (Wu et al., 2004). While there have been laudable efforts to examine diffuse injury in the absence of conspicuous focal lesions (Sanchez-Carrion et al., 2008a, 2008b), the samples examined in these instances may not often represent what is commonly observed in TBI which is most often represented by mixed pathophysiology. For this reason, focal injury was not an exclusionary criteria in the current study, unless the injury necessitated neurosurgical intervention and/or removal of tissue.

2.3. MRI procedure and data acquisition

Data were acquired using a Philips Achieva 3.0 T system (Philips Medical Systems, The Netherlands) with a 6-channel head coil and a Siemens Magnetom Trio 3.0 T system (Siemens Medical Solutions, Germany) with an 8-channel head coil both housed in the Department of Radiology, Hershey Medical Center, Hershey, PA. Subjects were made aware of the importance of minimizing head movement during all MRI scanning and any trials where motion was recognized were discontinued or repeated. For all subjects, high resolution brain anatomical images with isotropic spatial resolution of $1.2 \text{ mm} \times 1.2 \text{ mm} \times 1.2 \text{ mm}$ were acquired using the MPRAGE sequence. Other imaging parameters for the MPRAGE sequence consisted of: 468.45 ms/16.1 ms/18°, repetition time (TR)/echo time (TE)/flip angle (FA), a $250 \times 200 \text{ mm}^2$ field of view (FOV), and a 256×180 acquisition matrix. Echo planar imaging (EPI) was used for functional imaging. Imaging parameters for EPI were 2000 ms/30 ms/89°, TR/TE/FA, a $230 \times 230 \text{ mm}^2$ FOV and a 128×128 acquisition matrix.

2.3.1. fMRI WM paradigm and off-task blocks

While the current study focuses on non-task related covariance in the BOLD fMRI signal, the resting connectivity observed here is influenced by task (we focus on the “resting” blocks flanked by a WM task), so a brief description of this visual working memory task is provided here. This study used a visual WM paradigm requiring rehearsal and memory of face stimuli. The task included exposure to two pictures of male and female Caucasian faces presented in black and white adapted from a standardized dataset (Beaupre and Hess, 2005). This paradigm requires the subject to match the identity and location of two face stimuli. For example, the subject views a box

divided into quadrants and within two quadrants are two faces which appear for 3000 ms. After a delay of 3000 ms requiring focus on a fixation point, the subject is provided a target stimulus, or two face stimuli, presented in two of the four quadrants. At the time of presentation of the target, the subject is required to make a yes/no decision about the identity (match/no match) and the location of a single face presented in one of the four quadrants. This non-verbal working memory paradigm is initiated with a 20-second baseline followed by individual 42-second experimental trials (blocks) alternating with 20-second baseline measurements (i.e., fixation stimulus). The current study focuses on covariance in the BOLD fMRI signal during the 20-second baseline periods (between periods of task), including a mean of 165.3 (SD = 5.23) volumes per run (after eliminating volumes with movement, poor signal-to-noise ratio) across two runs ($n = 19$; data for 1 subject included 1 run at 1 time point).

2.3.2. fMRI resting connectivity: ROI determination and analytic procedure

2.3.2.1. Regions of interest. It was a focus here to examine RSFC in two separate classes of networks previously examined in this literature: 1) a network posited to have reciprocal interaction while engaging in goal-directed behavior or external stimulation and 2) a network believed to play a role in self-reflection or internal-states (Sheline et al., 2010). Almost universally, medial PFC (MedPFC) and posterior cingulate cortex (PCC) have been identified as central to the network organized around “internal-states” (Raichle and Snyder, 2007; Zou et al., 2009). In addition, because TBI most commonly disrupts frontal systems (and therefore, executive control processes) (Hillary et al., 2002; Whyte et al., 1998), we also aimed to examine fluctuation in the BOLD signal in regions believed to be directly involved in cognitive control and volitional behavior. Thus, we examined resting connectivity in dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) and related regions during rest that might be best conceptualized as a “goal directed” network. These two networks will henceforth be referred to as the “internal-state” and “goal-directed” networks. The internal-state network was examined by correlating activity in each voxel in the brain with two “seeds”: one in PCC ($[X Y Z] = [-6 -50 38]$) and one in MedPFC ($[X Y Z] = [0 48 -2]$). In all cases, the seeds were the average time-series of a sphere with a radius of 3 mm. The PCC and MedPFC seeds were derived from a review of the literature on the “Default Mode Network” (e.g., Sumowski et al., 2010; Greicius et al., 2003). The goal-directed network was examined in the same way, but with seeds placed in the DLPFC (Brodmann's areas 9/46/10; $[X Y Z] = [-36 31 13]$) and ACC (Brodmann's areas 6/32; $[X Y Z] = [-1 7 55]$). The placement of these seeds was based on prior work summarizing attentional control networks (Wager and Smith, 2003). Overall, this approach permits the observation of networks reciprocal to those that are directly related to task. Fig. 1A and B illustrate the four distinct seeding locations.

2.3.2.2. Procedure for determining covariance in resting signal. For BOLD time series analyses, data were preprocessed using both Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) and FSL (Smith et al., 2004). In data preprocessing, the first 5 images of each time-series were removed to ensure that magnetization had reached a steady state. The data from both runs were then realigned with the first image of the first run in the remaining time-series. The data were then smoothed, using a Gaussian smoothing kernel (FWHM = $6 \times 6 \times 6 \text{ mm}$), scaled to the mean intensity across the entire time-series, band-pass filtered (high-pass = 0.005 Hz; low-pass = 0.1 Hz), and detrended (to remove any linear drifts remaining in the data). The data were then deconvolved with a boxcar function representing the time spent on the working memory task (described above) and signal

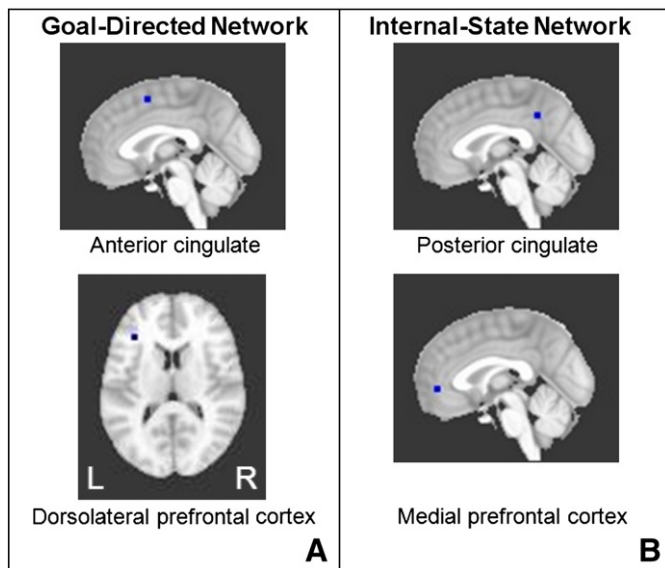


Fig. 1. A and B illustrate the “seed” placement for determining the four networks examined in this study. A shows the seed for goal-directed networks (ACC and DLPFC) and B displays the seed placements for the internal-state networks (PCC and MedPFC). Note: only 1 “seed” placed for each region, any asymmetry in connectivity results are not interpreted as true hemispheric differences.

attributable to physiological parameters, signals from cerebrospinal fluid and white matter, mean BOLD and signal six motion parameters were included as regressors of no interest. The residuals from the deconvolution were saved, and used as the resting-state data (see Biswal et al., 2010 for a similar approach). Regressing the global signal out of the data in this way has drawn some comment in relation to anticorrelations in the networks that show correlated activity (Murphy et al., 2009). However, because this is a commonly used preprocessing step (see Kelly et al., 2009; Di Martino et al., 2008), and because we do not specifically investigate anticorrelated activity in the present article, we elected to remove the global signal (particularly since the effect of gross differences in signal between groups on patterns of connectivity is unknown).

Resting data were then demeaned and resampled into standard (i.e., Montreal Neurologic Institute) space. Finally, correlations were calculated between each seed time-series and each voxel in the brain, resulting in 4 volumes per subject (the correlations between each of our 4 seed regions and every voxel in the brain). To determine statistical significance and in order to correct for multiple comparisons, we used a cluster-level threshold of 598 contiguous voxels that was determined using Monte Carlo simulations (using the AlphaSim program, available at <http://afni.nimh.nih.gov>). Because these are the first serial data to examine significant neurological disruption, we also employed an inclusive threshold in order to permit exploration of more subtle findings or those from spatially smaller regions (cluster size = 550, or the equivalent of correcting to $p < 0.10$). Two significant findings with this second threshold are indicated as such in Table 3. To ensure that the resulting r -values were normally distributed, Fisher's r -to- z transformation was applied to the data.

The resulting z' scores were used for two types of analyses: 1) group-level ANOVAs for each of the four seeded regions with the factors Group (HC vs. TBI) and Time (Time 1 vs. Time 2) and 2) within-group influence of time on connectivity in the four ROIs (Time 2 – Time 1 connectivity). The purpose of the ANOVAs was to comprehensively investigate the patterns of connectivity change using a voxelwise approach (for each of the four seeds). Because we were primarily interested in those regions that changed across time differentially in the two groups, we will focus on the interaction between Group and Time in the Results section. Moreover, because we were primarily interested in the change across time in the TBI

group, we further limited the regions to those in which there was no statistically significant change across time in the HC group. The purpose of this second analysis was to examine subthreshold effects not observed in the ANOVA and to capture within-group effects, with specific interest in change during this window of recovery in TBI.

3. Results

3.1. Demographic, clinical descriptors

The groups were well-matched for age and gender, but there were significant between-group differences in education (see Table 1).

3.2. fMRI results: behavioral data

The current study does not focus on task-related BOLD signal change, however, task performance is a reasonable indicator of cognitive improvement from 3 to 6 months and here we compared the second run of each time point (to permit task acclimation during the first run and minimize the influence of early task practice effects). Compared to the HC sample, accuracy was significantly reduced in the TBI sample at Time 1 [TBI mean (SD) = 0.81 (0.15), HC mean = 0.95 (0.05); $t(17) = 2.38$; $p = 0.039$] and this difference diminished at Time 2 [TBI mean = 0.89 (0.1), HC mean = 0.95(0.07); $t(17) = 1.50$; $p = 0.15$]. Similar change was evident in RT for the task at Time 1 [in ms: TBI mean (SD) = 1454 (282), HC mean = 1205 (214); $t(17) = -2.15$; $p = 0.048$] compared to Time 2 [in ms: TBI mean (SD) = 1288 (253), HC mean = 1106 (202); $t(17) = -1.71$; $p = 0.107$]. Thus, these findings indicate that the improvements in performance observed in the TBI sample are greater than what was observed in the HC sample and cannot be attributed to task practice alone. Note: behavioral data at both time points were not available for one subject with TBI.

3.3. fMRI results: BOLD signal change during WM task

In order to provide context for understanding the current resting connectivity results, it is noted that the “on-task” period of the current paradigm elicits BOLD signal change primarily in PFC, parietal areas, and the cerebellum. These findings are consistent with other studies of non-verbal WM (Glahn et al., 2002).

3.4. Examining resting connectivity

It was a goal in the current study to examine both internal-state and goal-directed networks in off-task resting BOLD fMRI data. The current findings are separated into results for within-group change for the TBI sample from the first to the second time point for both networks (e.g., internal-state and goal-directed networks).

Table 1

Demographic characteristics for both groups and injury information for the TBI sample.

Demographic variables	TBI mean (SD)	HC mean (SD)	Group comparison
Age	29.4 (11.0)	27.5 (12.1)	$p = 0.71$
Education	12.2 (0.63)	14.6 (1.6)	$p = 0.001^*$
Gender	7 m, 3 f	4 m, 6 f	$p > 0.05$
Clinical variable	TBI sample		
GCS score	Mean = 5.4; SD = 3.5; range = 3–14		
Acute hospital days	Mean = 18.3; SD = 8.1; range = 5–32		
Acute CT/MRI result (n)	F (7); T (7); DAI (4); IVH (3); shift (3); P (1); P/O (1); Thal (1); BG (1); cerebellum (1)		

F = frontal lobe, T = temporal lobe, IVH = intraventricular hemorrhage; shift = ventricular compression; P = parietal; P/O = parietal-occipital; Thal = thalamus; BG = basal ganglia.

* = statistical significant.

3.4.1. Resting connectivity results: Group \times Time interaction

There were a number of regions demonstrating significant Group \times Time interaction effects. One important distinction between groups was the separation between internal state and external state networks in this analysis. That is, Group \times Time effects dissociated the groups along the “internal” and “external” network divisions. Individuals with TBI demonstrated decreased connectivity in external state networks while the HC sample showed increased connectivity in these areas. By contrast, individuals with TBI demonstrated increased internal state connectivity between time points and the HC sample showed the opposite effect. Table 2 and Fig. 2 summarize the findings that differentiated the groups when considering change over time.

3.4.2. Resting connectivity results – within-group

As noted, it was also a goal to examine the greatest connectivity changes within the TBI sample from Time 1 to Time 2. In order to examine the gross influence of time on connectivity results within TBI (irrespective of the effect in HCs), the residual BOLD time series was analyzed by placing a “seed” in each of the four ROIs (i.e., ACC, PCC, MedPFC, and DLPFC) and comparing results between time points. When considering only effects within the TBI sample we again observed primarily increases in internal state networks and decreases in goal-directed networks (see Figs. 3–5). The one exception to this finding was increased connectivity observed between the DLPFC seed and the insula. This increased connectivity is consistent with that observed within the MedPFC seed (see Table 3).

3.4.3. Connectivity and performance change

While the current study does not focus on task-related BOLD signal change, there are certainly findings in the literature demonstrating that the relationship between internal and external-state networks has implications for task performance. To examine those relationships here, we conducted a Pearson correlational analysis for RT change scores and 8 connectivity change scores for the primary regions showing differences in Table 1 (ACC to BA40; DLPFC to thalamus/parietal; PCC to BA6; PCC to BA37) and Table 2 (ACC to parietal/precuneus; DLPFC to BA13; MedPFC to BA13; PCC to BA37). No analyses here revealed statistically significant results, although small effects were noted between change in RT and change in DLPFC to insula connections ($r = -0.44$; $p = 0.23$) and MedPFC to insula connections ($r = 0.43$; $p = 0.25$).

Table 2

Sites of significant connectivity change during Group \times Time interaction analysis (mixed effects ANOVA).

	BA	X	Y	Z	Cluster	Direction
ACC seed						
Postcentral gyrus	3	30	-30	48	1267	+HC/TBI-
Postcentral gyrus (into inferior parietal lobule)	40	-22	-36	60	999	+HC/TBI-
DLPFC seed						
Thalamus [extending to parietal (precuneus/cuneus) and occipital areas]	-	-24	-20	0	963	+HC/TBI-
Medial frontal seed						
Inferior occipital gyrus	18	40	-88	-16	789	-HC/TBI+
PCC seed						
Middle frontal gyrus	6	-24	4	60	720	-HC/TBI+
Middle temporal gyrus	37	-54	-60	0	686	-HC/TBI+
Precuneus	31	10	-66	22	826	-HC/TBI+

Key: BA refers to Brodmann's Areas; XYZ refers to the location of the voxel with the strongest connection to the seed, across the group; cluster refers to the number of voxels in the cluster (voxel size = $2 \times 2 \times 2$ mm); direction refers to the direction of the difference in each group: “+” sign indicates that the relationship with the seed was stronger at Time 2 than Time 1, “-” sign indicates that the relationship with the seed was weaker at Time 2 than Time 1. Note: all findings here were statistically significant at a corrected cluster size of 598 voxels ($p < .05$).

4. Discussion

The current study aimed to examine intrinsic, or “resting” brain connectivity during a period known to be of critical importance for recovery following moderate and severe TBI. The approach used here in a group of individuals sustaining moderate and severe TBI used BOLD fMRI to examine fluctuations in the “off-task” BOLD signal. Primary findings reveal increased involvement of internal-state networks during recovery from TBI (elaborated below). We arrived at this finding by examining two theoretically distinct resting networks: an internal-state network thought to be involved in self-reflective processes and a goal-directed network, that is thought to be associated with engaging external stimuli.

The clinical context for these findings must be emphasized. This is a sample of individuals with predominantly severe TBI where there was known disruption in neural functioning corroborated by clinical MRI (see Table 1) and we anticipate that these injuries have a direct consequence on neural connectivity. It is essentially unknown how large-scale neural networks adapt to significant neural disruption, in particular during the first 6 months following moderate to severe injury. While the findings clearly indicate changes in both internal and goal-directed networks during this period of recovery, these data should be interpreted only for the period of recovery measured here. That is, the increases observed in connectivity are quite different compared to the response in HCs and may be indicative of short or long-term changes in connectivity and therefore the long-term trajectory of these network connections remains uncertain. Of note, individuals with TBI demonstrated significantly improved performance from Time 1 to Time 2 and this is unlikely an improvement that can be accounted for by practice alone. Inasmuch as improvements in working memory function represent one metric of improvements in brain function, the changes in connectivity reported here occur in the context of recovery from TBI.

The following discussion outlines two specific observations permitted by the findings presented here. First when examining the regions that dissociated groups over time (i.e., mixed-effects ANOVA), the two groups were separated along the lines of “internal” and “goal-directed” networks between time points. Second, there were consistent increases in connectivity in several regions including the middle temporal lobe and insula; these findings are consistent with the literature and may have implications for transition between internal and goal-directed states and learning and task proceduralization.

4.1. Group by Time interactions

A Group \times Time ANOVA revealed that, in multiple network regions (see Table 2), there was a Group by Time interaction so that the groups showed clear dissociations along the two networks (i.e., internal-state and goal-directed). For those findings that dissociate the groups over time, primary findings reveal down-regulation of goal-directed attentional networks (ACC and DLPFC to parietal regions) and increased connectivity in regions associated with internal-state responsivity (i.e., MedPFC and PCC).

The reason for this shift in goal-directed and internal state networks shift is not entirely clear. Increased connectivity in similar networks has also been observed in clinical samples, such as substance abuse (Ma et al., 2011) and may be indicative of a period of recalibration between internal and goal-directed inputs permitting sufficient “release” from volitional on-task processing. The importance of this release has been documented previously, as the interplay between internal and external-state networks has been determined to predict task performance (Fox et al., 2007; Kelly et al., 2008). Finally, we do not anticipate that what is observed here is directly attributable to distinct task load issues between the groups. While there is some evidence that task “load” immediately preceding the “rest” period may influence internal-state connectivity (see Pyka et al., 2009; van Dijk et al.,

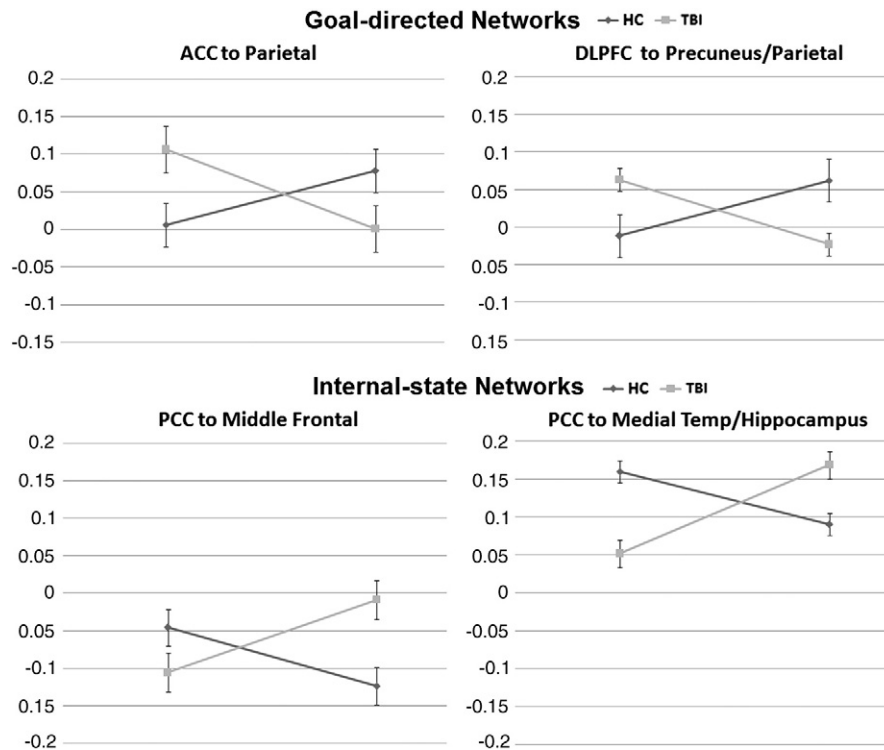


Fig. 2. TBI sample plotted for z' values (y-axis) vs. Time 1 and Time 2 (x-axis) to demonstrate the findings differentiating groups over time (i.e., mixed effects ANOVA findings in Table 1). Error bars are averaged standard error for group for each seeded network. Note: mean standard z -scores summarize each set of scores (all interactions significant, $p < 0.05$).

2010), the PCC and MedPFC connections observed here are increasing over time and occur in the context of improving performance.

Unfortunately, there were no statistically significant relationships between RT change and resting connectivity change for either analyses (i.e., ANOVA and between-time comparison). Nevertheless, it does appear that DLPFC down-regulation may have at least some modest influence on RT change; analysis of connectivity change that

dissociated these groups over time revealed a negative, but non-significant correlation between RT change and DLPFC change ($r = -0.44$). Moreover, increased connectivity in MedPFC was positively associated with RT albeit non-significantly ($r = 0.43$). Thus, if permitted to interpret these data, the diminished DLPFC to parietal connections (referred to elsewhere as the “frontoparietal control network”, see Spreng et al., 2010) coupled with increased MedPFC to insula connectivity may be an indicator of improving neural efficiency. That is, greater connectivity to internal-state connections, may operate to integrate demands from “internal” and “external” environments, providing greater continuity between these environments over time; the insula has been posited to play a critical role in developing and updating the “representations” of external demands (Mennes et al., 2010).

What is unclear is why change during a period of recovery would trend in the opposite direction with the network connections observed in the HC sample? While provisional, we might infer this trend to be a necessary, but temporary, release from control and “re-syncing” of external and internal states from 3 to 6 months post PTA. A follow-up observation noting trends in these networks at 12–18 months post injury might provide information about the relative permanence of this down-regulation of DLPFC to parietal (i.e., “attentional control”) connections.

In contrast with the diminished DLPFC connectivity observed over time, one of the most consistent findings dissociating these two groups was the increased involvement of PCC connectivity in the TBI sample. Certainly there is data demonstrating that these two networks (DLPFC and PCC) are dissociable and have often been observed to be negatively correlated (see Greicus et al., 2003), so the reciprocal findings here are consistent with a larger literature. However, analyses in separate seeding findings for PCC to medial temporal/hippocampus (i.e., BA37) and PCC to middle frontal areas (BA6) revealed no significant correlations with RT ($r = -0.01$, $r = -0.9$ and $r = -0.03$ respectively). Thus, connectivity change between PCC and medial temporal and anterior regions may have less direct consequence for behavior compared to the changes observed in

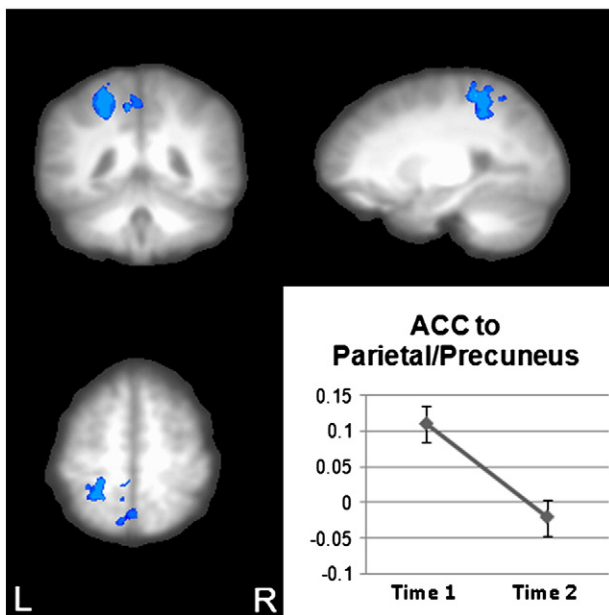


Fig. 3. Connectivity for the Time 2 – Time 1 findings in the TBI sample. Data here display the change in connectivity between the ACC seed and inferior parietal lobe and precuneus. Error bars are standard error averaged over time. Note: only 1 “seed” placed for each region, any asymmetry in connectivity results are not interpreted as true hemispheric differences.

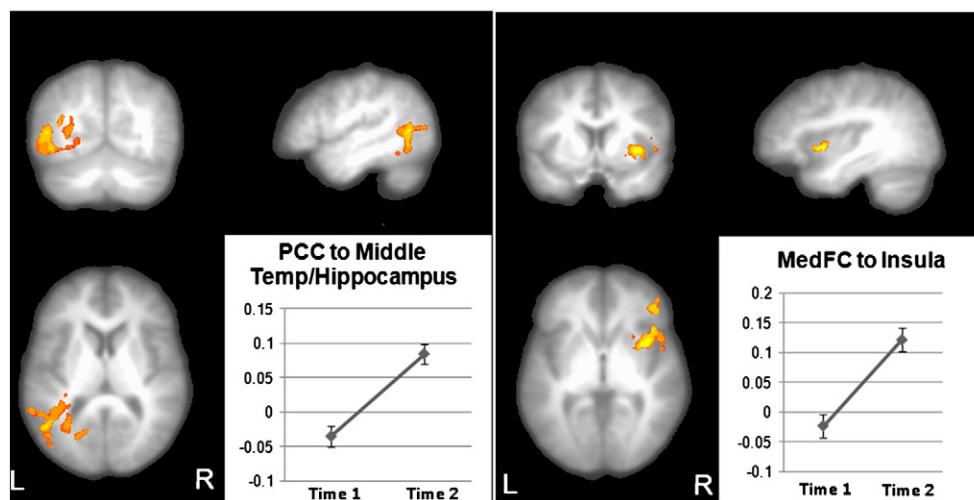


Fig. 4. Connectivity for the Time 2 – Time 1 findings in the TBI sample in “internal-state” networks. Data here display the change in connectivity between the PCC seed and middle temporal lobe and the MedPFC seed and the insula. For convenience, these views are presented together. Error bars are standard error averaged over time. Note: only 1 “seed” placed for each region, any asymmetry in connectivity results are not interpreted as true hemispheric differences.

DLPFC and MedPFC. In order to clarify the consequences large-scale connectivity changes have for behavior, future work should include larger samples observed at similar time points to isolate the clinical and performance factors that might influence the timing and magnitude of these network shifts.

4.2. Within-group change over time

While the interaction results reveal distinctions between groups, it was also a primary goal to observe those effects occurring over time within the TBI sample that may have been either consistent with or distinct from the HC sample, but did not rise to the level of statistical significance during ANOVA analysis. For this reason, we also conducted an analysis permitting observation of significant changes within the network observed within the TBI sample (see Figs. 3–5). This analysis of the direct effect of time (which we treat here as a surrogate for recovery) with performance reveals overlapping effects with the between-group comparison; internal-state networks demonstrated increased connectivity and external-state networks showed decreased connectivity. One important exception here was in a connection between DLPFC and the insula. This finding was

unexpected, but converges with other connectivity data summarized above (i.e., between-group analysis) and is interpreted below.

Overall, Fig. 2 illustrates the change in connectivity over time for both groups and indicates that the internal state networks are more highly connected within the TBI sample over time and dissociable from the effects observed in the HC sample. The first 6 months represent a critical window of recovery following TBI, but certainly recovery can occur for several years following injury (Millis et al., 2001). Given this, what is unknown in TBI is if this result is maintained or if this is a nonlinear effect that later returns to approximate what is observed in HCs once greater recovery has occurred. We anticipate that the latter is an accurate depiction of this trajectory, but additional analyses with a more protracted time line would be necessary to confirm this.

4.3. Connectivity change and limbic system

The most consistent finding in these results is between seeded regions and changes in connectivity to the insula and middle temporal regions, including hippocampus. In all cases, connections to these regions are increasing from Time 1 to Time 2 and these findings are dissociable from the HC sample (see Table 1 and Fig. 2).

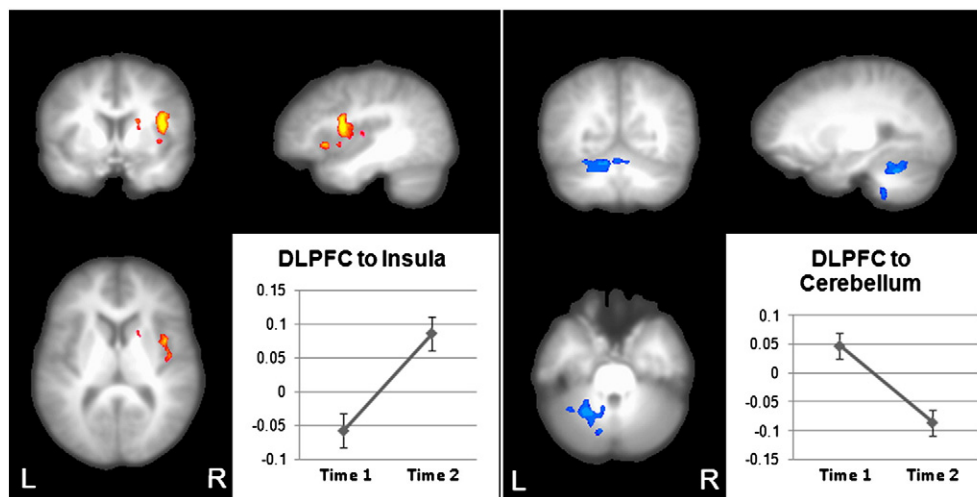


Fig. 5. Connectivity for the Time 2 – Time 1 findings in the TBI sample. Data here display the change in connectivity between the DLPFC seed and the insula and cerebellum. For convenience, these views are presented together. Error bars are standard error averaged over time. Note: only 1 “seed” placed for each region, any asymmetry in connectivity results are not interpreted as true hemispheric differences.

Table 3
Sites of significant connectivity change during Time 2 minus Time 1 analysis in the TBI sample.

	BA	X	Y	Z	Cluster	Direction
ACC seed						
Postcentral gyrus (extending back into parietal (precuneus) areas)	3/4	−4	−38	62	1380	TBI−
DLPFC seed						
Insula ^a	13	42	6	14	563	TBI+
Culmen (extending up into occipital areas (fusiform gyrus))	−	−24	−52	−26	767	TBI−
Tail of the caudate ^a	−	−32	−42	12	554	TBI−
Medial frontal seed						
Insula (extending forward into inferior frontal areas)	13	36	8	−2	1038	TBI+
PCC seed						
Middle temporal gyrus (extending into hippocampus)	37	−50	−60	8	1636	TBI+

Note: In no case was this contrast significant for the HC group.

^a These areas were significant at a lower threshold, cluster size = 550, $p < 0.10$; all other findings were statistically significant at a corrected cluster size of 598 ($p < 0.05$).

We offer here two interpretations of these primary shifts in the data. First, the movement in these data from anterior “attentional control” regions (e.g., DLPFC to parietal connections) to increased connectivity in posterior and medial temporal regions (e.g., PCC to hippocampus connections) likely reflects greater task proceduralization and formal integration of the task into memory. That is, at 6 months post PTA, individuals with TBI may be better able to incorporate memorial systems and consolidate the constraints and demands of the task. This interpretation is consistent with the reductions in time-on-task (i.e., RT), as formal “representations” of the task permit more rapid processing and reduce demand on attentional control networks for effortful task processing.

Second, the increased connectivity from the insula to PCC and DLPFC is the only finding that does not dissociate the internal and goal-directed networks. In all statistically significant observations here, connectivity with the insula increased from 3 to 6 months post PTA. The insula has been linked to a number of functions during task perturbation including emotion, task saliency, and monitoring internal states (for review see Kurth et al., 2010). In the examination of large-scale connections, there is recent evidence that the insula plays a critical role in “salience processing” and permits negotiation and shifting between internal-state and attentional control processes (Menon and Uddin, 2010). Other examiners have noted the unique topographical location of the insula placing it at the boundary between “cognitive, homeostatic, and affective systems of the human brain” serving as a conduit between external demands and the internal milieu (Craig, 2009). With this literature as context, the current data indicate that from 3 to 6 months post PTA, increased connectivity to the insula may play a critical role in recovery by increasing interoception and permitting appropriate transitions between the sub-networks examined in this study.

5. Study limitations and future directions

The current study holds the advantage of examining TBI during a known window of recovery at separate time points and it is the first to do so using resting connectivity methods. Even so, there are several limitations to this study that require mention. The most significant shortcoming to this study is the small sample size for each of the groups; certainly to conduct sub-group analyses (e.g., injuries to right vs. left hemisphere), additional subjects would be required. In addition, the control group was significantly more educated than the TBI sample. However, it is unclear that a 2-year difference in education observed here could account for fundamental differences in

internal and goal-directed networks examined. While there was almost no variance in the TBI sample with regard to education, a correlational analysis between education and connectivity change for each of the four change scores revealed no relationships (the highest correlation was $r = 0.19$ in ACC). Also, any between group differences in connectivity attributable to education should be at least partially ameliorated by the current emphasis on within-subject change over time. As noted, direct comparisons between connectivity change and task performance revealed only modest, non-significant relationships between connectivity change and RT change; a larger sample is required to determine if connectivity change observed here does indeed have direct implications for performance. Even given these concerns, the current data are unique and offer a preliminary look at how large-scale networks change during recovery from significant neurological disruption.

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