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Chronology and Chronicity of Altered Resting-State Functional Connectivity after Traumatic Brain Injury

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Abstract

Whereas 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. We used resting-state functional magnetic resonance imaging and seed-voxel correlational analyses 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 stage of moderate-to-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 3 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. Our 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 neurodegenerative disease are discussed in the context of potential long-term outcomes of TBI.

Key words: default mode; dementia; functional connectivity; resting state; traumatic brain injury

Introduction

In the past decade, functional neuroimaging research has seen advances in what is now known as resting-state functional connectivity, or the temporal correlation between neural activity in spatially distinct brain regions[1] while the brain is ''at rest.''[2] At the forefront of these techniques is resting-state functional magnetic resonance imaging (rs-fMRI). Investigations using rs-fMRI have centered on the default mode network (DMN),[3] a constellation of brain regions exhibiting greater activity at rest than in the face of cognitive challenge,[4,5] with a unique metabolic profile that may be particularly susceptible to pathophysiological processes.[6–9] Though functional connectivity of the DMN has been studied widely in a variety of clinical populations, a relatively small literature base exists in moderate or severe traumatic brain injury (TBI), for which long-term neuropsychological outcomes are heterogeneous and therefore difficult to predict.[10,11] The delineation of intrinsic connectivity alterations after TBI may shed light on enduring functional changes affecting cognitive status in the remote future.

Although there has been some investigation of resting-state, or intrinsic, network alterations after TBI, such changes remain poorly defined at the level of specific brain regions. To date, most rs-fMRI studies in this population have taken a whole-brain *a priori* approach to investigating the DMN.[12,13] However, recent work has suggested that pathology in specific nodes, such as the posterior cingulate cortex (PCC), may have important implications for neurorecovery after trauma. Studies of TBI have reported increased within-DMN functional connectivity during task performance, featuring prominently the PCC and precuneus regions.[14,15] In addition, graph theoretical approaches have found support for a breakdown of the PCC as a central DMN ''hub'' after injury, resulting in a more disorganized connectivity profile, when compared to healthy individuals.[16]

Despite evidence for the relative vulnerability of the PCC to neurological insult in a whole-brain context, few studies have targeted specifically this region for functional connectivity analyses in a hypothesis-driven manner. Work in both clinical and healthy populations has supported the idea that the PCC is densely

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functionally connected to a number of distinct and distributed brain systems,[17–19] and this region shows alterations in functional connectivity in a number of patient samples, compared to matched controls.[20] In moderate-to-severe TBI, it has been proposed that altered connectivity patterns involving the PCC may be related to neurocognitive impairment.[12,14,15] Therefore, delineation of this region's unique connectivity profile may provide insight into neural mechanisms underlying cognitive sequelae after trauma.

The examination of PCC connectivity is strongly supported by existing literature in neurological conditions, but targeted investigation of other DMN nodes may reveal additional information about aberrant network activity and behavior. A notable region for which there exists little research on functional connectivity patterns after TBI is the hippocampus. Though not included in the original conceptualization of the DMN, subsequent research has implicated the medial temporal lobes (MTLs) in the DMN, demonstrating intrinsic functional connectivity between, especially, the hippocampus and posterior parietal default regions.[8,21,22] More recent models of the DMN have shown that the MTLs are both structurally and functionally connected to other default regions,[23,24] and converging evidence from several studies indicates that the MTLs and posterior DMN together play a major role in episodic memory functioning.[7,25–27] Despite the fact that TBI frequently results in episodic memory impairment,[28] hippocampal functioning, in relation to large-scale brain networks after injury, remains poorly understood. Further, research from literature in other disorders suggests that characterization of both PCC and hippocampal functional connectivity profiles after neurotrauma may have clinically predictive value.[29–32]

The current study focused on the whole-brain functional connectivity patterns revealed by rs-fMRI of two principal regions of interest: the PCC and the hippocampi. We targeted these regions because of their importance in cognitive and memory functioning, evidence of their involvement in neural and cognitive sequelae of TBI, and their eminence in resting connectivity studies of neurological disorders. In addition, to our 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, we hypothesized that individuals in the chronic phase of TBI (approximately 1–5 years postinjury) would 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). We further predicted 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, by extension, ongoing intervention efforts, a second aim of our study concerned the temporal characteristics—or chronology—of connectivity alterations after TBI. There currently exists only one study in moderate-to-severe TBI that tracked the trajectory of connectivity patterns of DMN nodes during an early recovery period.[33] However, the point at which connectivity profiles are stabilized has yet to be identified, and it is plausible that connectivity alterations evident early after injury might endure beyond a critical early window of clinical recovery, typically regarded as the first year postinjury.[34–37] In the present investigation, we probed longitudinal connectivity changes in a subset of individuals from our TBI group, comparing connectivity profiles derived from rs-fMRI in the subacute phase (approximately 3 months postinjury) to those in the chronic phase. Our aim was to outline the developmental trajectory of any identified changes between the TBI and HC groups, as well as 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.

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 HCs. One individual's data in the clinical group were discarded because of excessive head motion to yield a final cross-sectional sample of 22 participants with TBI (ages 19–69; x = 34.05; standard deviation [SD] = 15.04) and 18 HCs (ages 19–61; 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)[38] obtained on admission to the trauma unit. Individuals with either a GCS score less than 13, loss of consciousness for 30 min or more, or with positive neuropathological findings upon structural neuroimaging were eligible for participation. Individuals with chronic TBI sustained their injury a median of 2 years before scanning. The goal of examining this chronic sample was to first establish the connectivity effects observable in chronic-phase TBI in rs-fMRI data. In order to gain insight into the evolution of these effects, we also studied a subset of the chronic sample ($n = 13$), where data were available at approximately 3 months after the resolution of posttraumatic amnesia, herein referred to as the subacute stage. There was no temporal overlap in latest subacute and earliest chronic scans acquired. Demographic and clinical characteristics of all participant groups are found in Table 1A,B. Where available, acute clinical neuroimaging findings are presented in Supplementary Table 1 (see online supplementary material at http://www.liebertpub.com).

Table 1A. Cross-Sectional Sample Characteristics (N = 40)

	TBI	*HC*	p *value*[b]
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[a]	med = 6 rg = 3–14	—	—
Years postinjury	med = 2 rg = 0.5–5.67	—	—

Table 1B. Longitudinal Sample Characteristics (N = 13)[c]

	Subacute stage	*Chronic stage*
Gender	9 M, 4 F	
Age	27.08 ± 9.61	28.46 ± 9.58
Education	12.69 ± 1.70	
GCS	med = 5; rg = 3–14	
Years postinjury	med = 0.25 rg = 0.17–0.33	med = 1.08 rg = 0.5–2.42

[a]GCS not available for 2 participants; injury severity was confirmed by loss of consciousness time or positive neuroimaging findings for these individuals.

[b]*p* value obtained from two-sample *t*-test for group differences: med = median; rg = range.

[c]Data reported for identical set of subjects at two time points.

GCS, Glasgow Coma Scale; TBI traumatic brain injury; HC, healthy controls; M, male; F, female.

Candidates for either the TBI group or the HC group were excluded if they had a history of neurological disorder, such as earlier 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 by medical chart review, covered in the institutional review board–approved consent form, and communicated to the study participant and/or family member(s) of each participant before 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 toward the domains of attention and working memory, given that these are the most commonly encountered types of deficits after TBI. To standardize all measures on the same normative group, *z*-scores were created for each participant using the mean and SD of test results from 12 normal-performing HC participants. Cognitive and connectivity measures were included in post-hoc exploratory analyses to investigate potential brain-behavior relationships. To avoid individually correlating multiple test scores without *a priori* hypotheses, an attentional composite score was constructed for each individual by summing *z*-scores of tests sensitive to TBI. Comprising this composite score were the Trail Making Test–Part A,[39] Wechsler Adult Intelligence Scale-III Digit Span,[40] and the Visual Search and Attention Test (VSAT).[41] Composite scores for each participant 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-min rs-fMRI scan. For the purposes of the current article, we discuss data analyses on the rs-fMRI time series.

Imaging data were acquired for each participant using either a Philips (Ph) 3T system and a six-channel SENSE head coil (Philips Medical Systems, Best, The Netherlands) or a Siemens (Si) 3T Magnetom Trio (Siemens, New York, NY).* Data collection was parameterized to maximize consistency between magnets. Three-dimensional (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, 30(Si) or 34(Ph) ms echo time, 90-degree flip angle, 230×230(Si) or 240×240(Ph) mm^2 field of view, 80×80 acquisition matrix, and 34 or 35 axial slices (4 mm thick) 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 sec) 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 by affine transformation.[42,43] 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 $6\times6\times8\ mm^3$ to minimize anatomical differences and increase signal-to-noise ratio.

Region of interest ("seed") determination

Based upon a literature article examining network connectivity after moderate and severe TBI, we focused analyses on connectivity of the PCC, left hippocampus, and right hippocampus. To do so, we selected seed regions of interest (ROIs) within the CONN Toolbox.[44] For the PCC, we selected a well-established spherical ROI (–6, –52, 40; 10 mm radius) frequently used in DMN investigations. This ROI was originally identified in the seminal article by Fox and colleagues[4] and derived from a previous meta-analysis of deactivated regions during passive versus active tasks.[45] In contrast, the hippocampus has more recently been implicated in the DMN, and a reliable functional ROI has not yet been established for this region. Therefore, hippocampal seeds were defined as analogous anatomical regions in each hemisphere and extracted as ROI masks from the widely used Automatic Anatomic Labeling atlas,[46] also available in CONN. This approach to hippocampal seeding has been employed previously in resting-state studies of neurodegenerative disease.[47,48]

Functional magnetic resonance imaging 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,[49] a method that avoids the spurious introduction or magnification of negative correlations between voxels associated with global mean signal regression.[50] The toolbox performed segmentation of individual structural volumes into gray matter, 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 bandpass 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 blood-oxygen-level–dependent 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.

Analyses of group differences in positive and negative connectivity profiles were carried out in a two-step procedure, with correction for multiple comparisons at both levels. For simplicity, we discuss here the analytic stream for positive connectivity, while noting that an identical procedure was followed for investigating negative connectivity. In each group (or time point) of interest, we first identified regions showing significant positive connectivity to a specified seed by constructing a seed-voxel connectivity map corrected for the family-wise error (FWE) rate at $p<0.05$. This was achieved using an individual voxel threshold of $p<0.005$ and a corresponding cluster size threshold determined by Monte Carlo simulations in the 3DClustSim program of AFNI (http://afni.nimh.nih.gov).[51–55] Research has shown that this threshold provides optimal balance between type I and II errors.[56] Simulations were conducted on explicit whole-brain masks with 10,000 iterations and a Gaussian filter width of $10\times10\times12$ to account for intrinsic smoothness of the data.

*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. Additional analyses were undertaken to assess the potential impact of scanner confounds, and these provided results consistent with our original findings. Therefore, we present results from the full sample below.

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*	*Independent samples t-tests (HC vs. subacute)*	*Independent 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	—	$p = 0.000$	$p = 0.001$	$p = 0.291$

Data provided for the same 13 individuals at the subacute and chronic stages of TBI. See text for references for neuropsychological tests administered. Attentional Composite = *z*-score sum of Trails A, Digit Span Total, and VSAT Total.

Trails, Trail Making Test; VSAT, Visual Search and Attention Test; TBI, traumatic brain injury; SD, standard deviation.

In the second step, positive connectivity maps from the two groups were added together using the ImCalc function in SPM to create a combined sample-wide positive connectivity map. This map was used as an inclusive mask in subsequent *t*-tests for group differences, again at a corrected threshold of $p < 0.05$ (using an uncorrected voxel threshold of $p < 0.01$ and a cluster size determined by simulations on the mask). Thus, second-level comparisons were restricted to functional connections that were significant for at least one group. This approach is based on previous studies using similar thresholds and masking techniques together in connectivity analyses[57–60] and has two important advantages. First, it permits differences in positive and negative connectivity to be examined separately, which was a major goal of this study. Second, it ensures that observed group differences

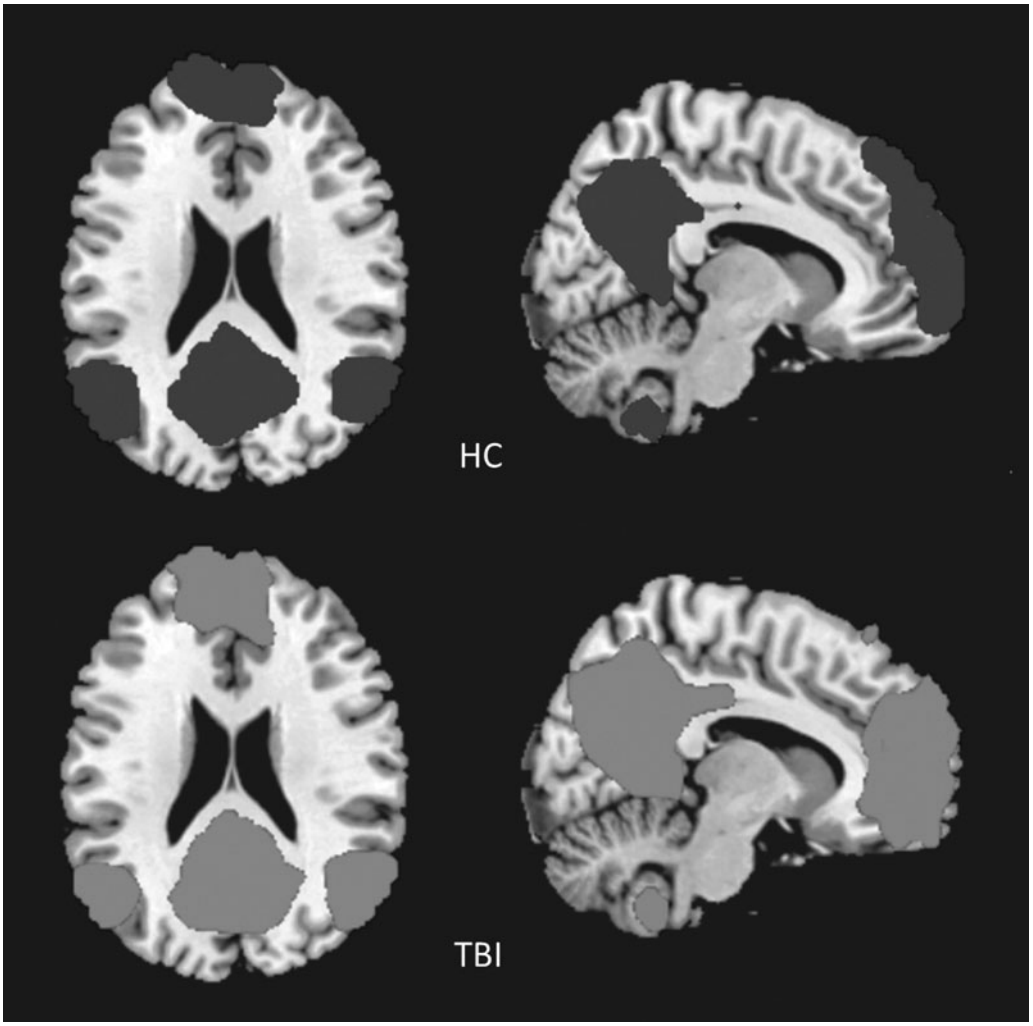

FIG. 1. Whole-brain functional connectivity with the posterior cingulate cortex (PCC) seed in HCs (top) and TBI participants (bottom) in identical axial and sagittal sections. Images reflect family-wise error correction at $p < 0.05$ (uncorrected voxel threshold of $p < 0.005$; minimum cluster size = 64). The canonical default mode network is readily identified by PCC seeding in both groups. HC, healthy controls; TBI, traumatic brain injury.

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

PCC, posterior cingulate cortex; HC, healthy control; cTBI, chronic traumatic brain injury; L, left; R, right; G, gyrus; IPL, inferior parietal lobule; vmPFC, ventromedial prefrontal cortex; MNI, Montreal Neurological Institute.

are meaningful in that they reflect effects that are also of primary significance within groups.

To explore whether functional connectivity is related to cognition, we regressed positive and negative Fisher-transformed correlation values of our three seeds on attentional composite scores within each time point of the longitudinal analysis. We also investigated whether connectivity in the subacute stage is associated with behavior in the chronic stage. 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, we implemented a FWE-corrected threshold of $p < 0.05$ using a voxel threshold of $p < 0.01$ and a corresponding cluster threshold determined by simulations on these masks.

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.

Results

Neuropsychology

Neuropsychological testing results from longitudinal analyses are presented in Table 2. Participants in the subacute stage of TBI performed significantly worse than the comparison group on Trails A, VSAT, and the attentional composite. These individuals improved significantly for all cognitive measures from the subacute to chronic

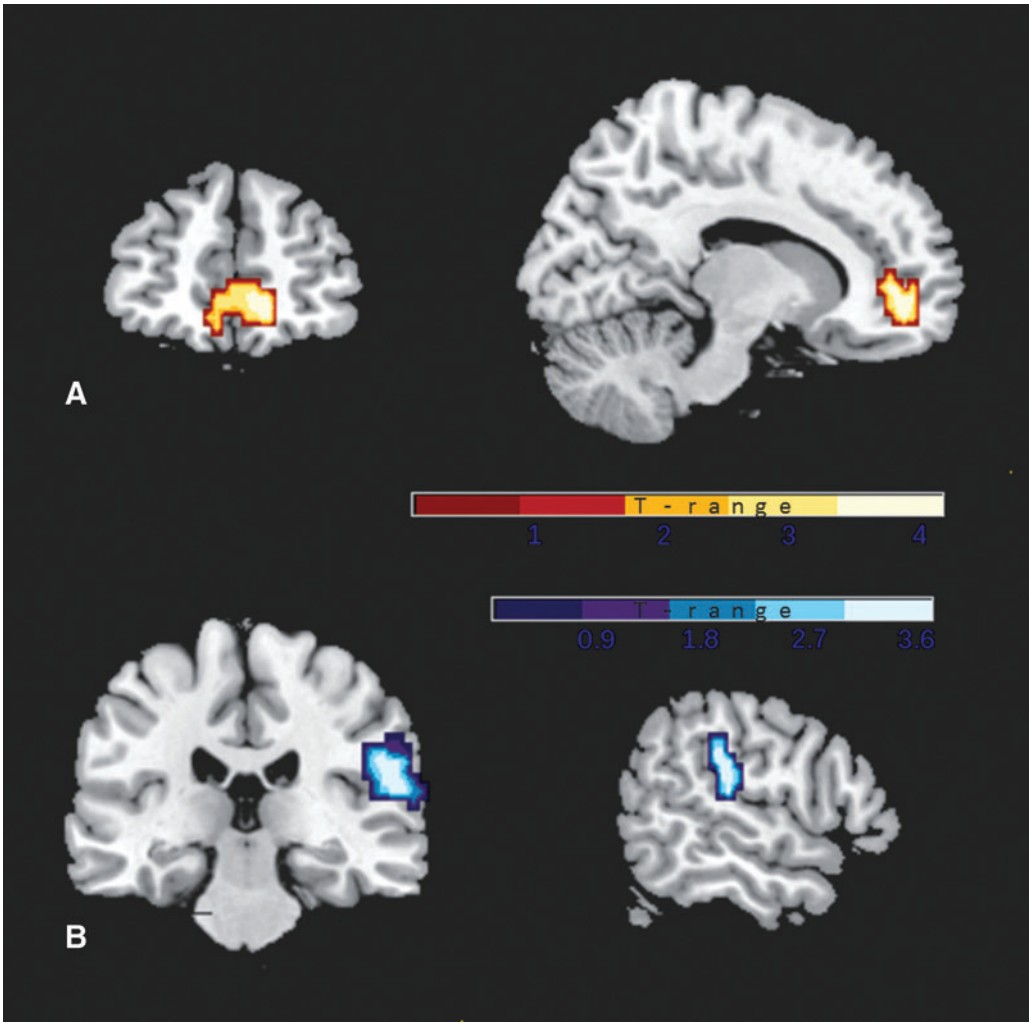

FIG. 2. Functional connectivity results for the posterior cingulate cortex seed in chronic TBI > healthy control contrasts in coronal (left) and sagittal (right) slices. Images depict, in TBI, (**A**) increased positive connectivity between posterior cingulate cortex and ventromedial prefrontal cortex and (**B**) increased negative connectivity between posterior cingulate cortex and inferior parietal lobule. TBI, traumatic brain injury. Color image is available online at www.liebertpub.com/neu

stage, suggesting good neurocognitive recovery. Practice effects may account for some variance in performance improvement over time, but given that the first year after TBI is a critical recovery period, performance gains are largely attributable to positive change in neurological status.

Cross-sectional investigation of seed-voxel functional connectivity

As an integral node of the DMN, seeding of the PCC should reveal connectivity to canonical DMN regions. To confirm that our analyses represent functional connectivity related to the network of interest, we present results of PCC seeding within the HC and TBI groups in Figure 1. These correlation maps reveal robust connectivity of the PCC with the rest of the DMN, including both medial prefrontal cortex and lateral parietal cortices. They further validate our approach to investigating DMN-related PCC connectivity in the current sample.

Table 3 outlines findings for group differences in PCC connectivity. Compared to the control group, the TBI group demonstrated increased positive connectivity of the PCC to a cluster in the right ventromedial prefrontal cortex (vmPFC; Fig. 2A) and greater negative connectivity between the PCC and the right supramarginal gyrus in the inferior parietal lobule (IPL; Fig. 2B). Controls showed greater positive PCC connectivity with a small cluster in the left supramarginal gyrus.

Table 4 displays results of group-level comparisons for both hippocampal seeds. The TBI group predominantly demonstrated increased positive connectivity of both hippocampi with right-lateralized cortical and subcortical regions (Fig. 3A–C). These included proximal temporal lobe areas (parahippocampal gyri and temporal poles) as well as the insular cortex and brainstem; significant clusters for the two seeds overlapped substantially (see Fig 3B). In contrast, controls exhibited greater negative connectivity between the left hippocampus seed and the regions in the posterior parietal cortex, the left dorsolateral prefrontal cortex (dlPFC), and the right inferior temporal 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)	172	33, 11, −38
	R parahippocampal G.		
	R mid-brain	140	12, −25, 22
	R brainstem		
	R cerebellum		
	Right hippocampus		
cTBI > HC	R sup. temporal G.	87	48, −13, −22
	R Insula		
	R mid. temporal pole	54	27, 8, −42
	R parahippocampal G.		
Negative connectivity			
	Left hippocampus		
HC > cTBI	R angular G.	61	33, −58, 38
	R sup. parietal lobule		
	L inf. frontal G. (BA 9)	42	−54, 8, 38
	L mid. frontal G.		
	R inf. temporal G. (BA 37)	36	51, −61, −18
cTBI > HC	Corpus callosum	54	3, −22, 26
	Mid-line white matter	31	18, −40, 34
	Right hippocampus		
cTBI > HC	L cerebellum	63	−36, −46, −54

HC, healthy control; cTBI, chronic TBI; L, left; R, right; G, gyrus; sup, superior; mid, middle; inf, inferior; BA, Brodmann area; MNI, Montreal Neurological Institute.

Longitudinal investigation of seed-voxel connectivity

As individuals progressed from the subacute to chronic postinjury stages, a robust decrease in positive connectivity was observed from the PCC to frontal areas, notably involving regions covering the dorsal medial PFC (mPFC; Fig. 4A). Increased negative PCC connectivity during this same stage progression was found in a region encompassing the anterior insula and frontoparietal operculum and in the right supramarginal gyrus of the IPL (Fig. 4B; see Table 5).

From subacute- to chronic-stage TBI, positive connectivity increased from the right hippocampus to primarily parahippocampal and proximal subcortical regions (Fig. 5A; Table 6), whereas a loss of negative connectivity was observed most notably between the right hippocampus and clusters in the bilateral dlPFC (Fig. 5B; Table 6).

Functional connectivity and behavior

In the subacute stage of TBI, negative connectivity between the left hippocampus and a portion of the right dlPFC 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 dlPFC (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 predicting positive PCC connectivity with the left precuneus.

Discussion

The current findings reveal 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. Consistent with our predictions, the cross-sectional TBI group exhibited greater synchrony of the PCC with another principal DMN node, the vmPFC, compared to controls. Greater synchrony in TBI was also noted between the hippocampi and other medial temporal as well as subcortical and brainstem regions. There was also evidence of decreased antiphase synchrony between the left hippocampus and distributed task-related regions (e.g., dlPFC and posterior parietal cortex) in TBI. In contrast to our hypotheses, however, the TBI group exhibited increased antiphase synchrony between the PCC and posterior attentional network areas, compared to controls.

Using a subset of the cross-sectional TBI group, our longitudinal analysis revealed a remarkable dissociation between the connectivity profiles and trajectories of our seeds. Considered alongside cross-sectional analyses with controls, longitudinal TBI data

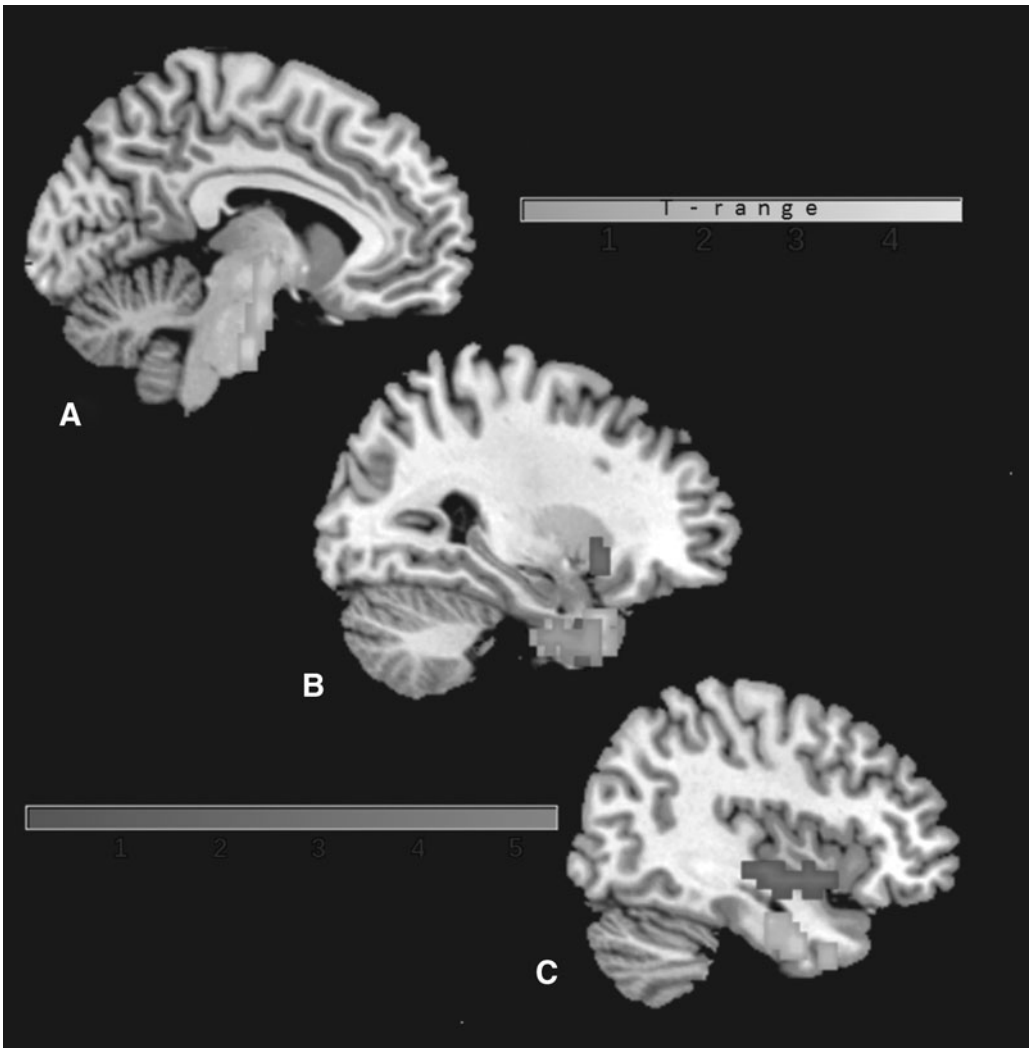

FIG. 3. Positive functional connectivity results for the hippocampal seeds in chronic TBI > healthy control contrasts, shown in sagittal slices. Images depict, in TBI, (**A**) increased connectivity of left hippocampus to brainstem; (B) overlap of significant clusters for each seed (right temporopolar regions); and (**C**) increased connectivity between left hippocampus and right temporal lobe, and between right hippocampus and right superior temporal gyrus and insular cortex. TBI, traumatic brain injury.

suggest that synchrony between the hippocampi and proximal temporal and subcortical areas might be an early consequence of trauma 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 the dlPFC, and these changes have implications for behavior in our sample. 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. Though consistent with the expected recovery trajectory, our 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 task-positive network (TPN) antiphase synchrony.

Incomplete resolution of posterior cingulate cortex connectivity patterns

Our observation of increased connectivity between the PCC and vmPFC in the cross-sectional TBI sample is likely a reflection of the PCC's central role in the DMN and its susceptibility to pathology.[6,8,20] These findings 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[15] and during the course of a task[14] in a mixed group of patients ranging from 3 months up to over 6 years after injury. It has been found that severe forms of TBI affect the integrity of the PCC as an influential receiver and director of neural information.[16] Thus, increased synchronization of PCC with the rest of the DMN may reflect a modulatory mechanism vis-à-vis disruption in distributed networks.[20] This is consistent with the view of hyperconnectivity as a generalized response to neural compromise, whether traumatic or insidious in nature.[101] In the current study, we extend the idea of such ''reactive'' hyperconnectivity 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.[13]

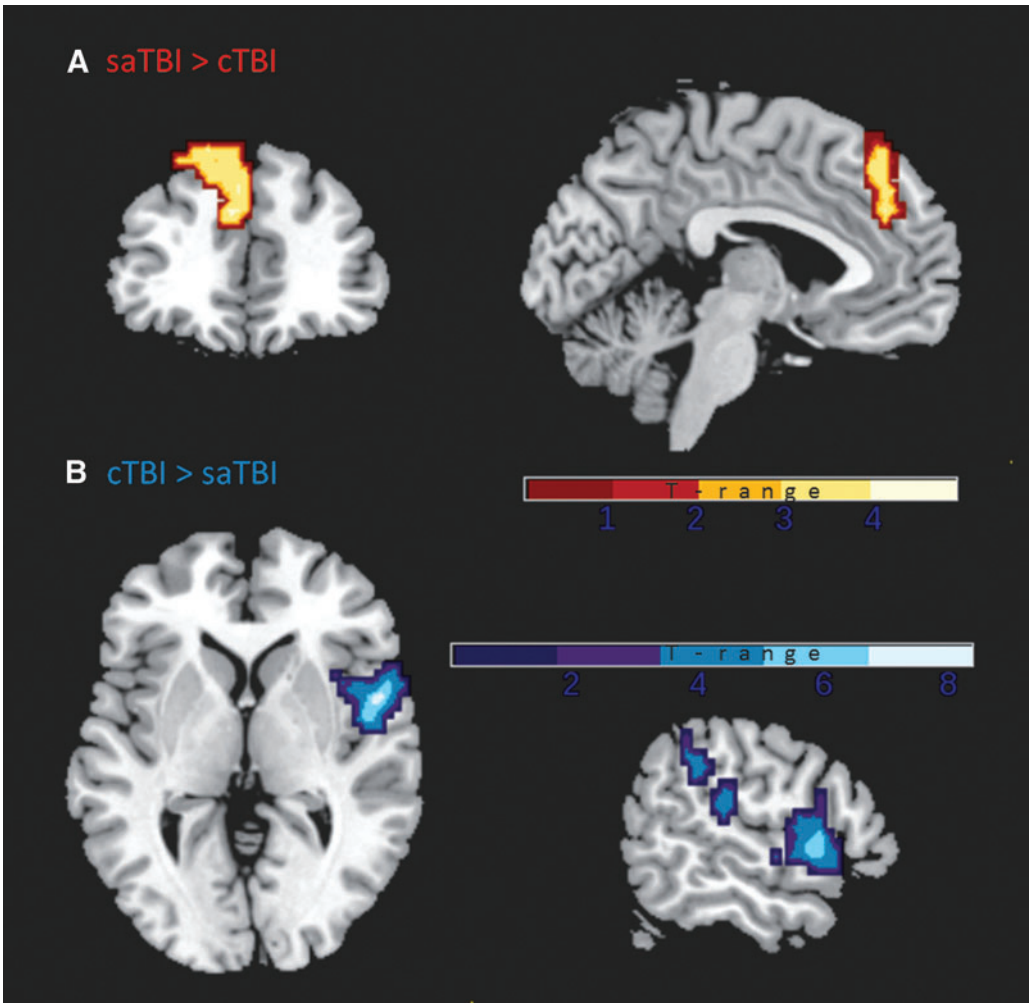

FIG. 4. Functional connectivity results for the posterior cingulate cortex seed in longitudinal analyses. (**A**) In subacute traumatic brain injury (saTBI) relative to chronic TBI (cTBI), there is increased positive connectivity between posterior cingulate cortex and dorsomedial prefrontal cortex. (**B**) In cTBI relative to saTBI, there is increased negative connectivity between posterior cingulate cortex and the frontoparietal operculum and inferior parietal lobule. Color image is available online at www.liebertpub.com/neu

The current findings in the PCC are contrasted with those from Arenivas and colleagues, 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.[61] However, in the absence of direct statistical testing, their approach makes it difficult to assess group differences in connectivity magnitude. Further, the increased connectivity within the DMN that we observed has been interpreted by some as a compensatory response to trauma.[14,15] For example, Sharp and colleagues found that faster performance on an attentional task was associated with greater within-DMN connectivity at rest.[15] These investigators also found that increased precuneus-DMN functional connectivity at the beginning of a task resulted in less-variable reaction times during the task, and concluded that this elevated functional connectivity supports performance.[14] In the current longitudinal study, we found a marginal effect only in the subacute group for PCC-precuneus connectivity predicting attentional ability. Therefore, our 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 that observed between the PCC and vmPFC in our comparison of chronic TBI and controls. Our results suggest that complementing increased PCC-DMN synchrony is a greater antiphase synchrony of the PCC with the right IPL and regions of other networks essential for goal-directed activity (e.g., frontal ''salience'' regions). In both cross-sectional and longitudinal analyses, the chronic TBI group emerged as exhibiting more-pronounced antiphase synchrony between the PCC and posterior regions of the TPN, involving especially the right supramarginal gyrus in the IPL. Chronic versus subacute stage individuals also demonstrated increased connectivity between the PCC and both the insula and frontoparietal operculum. The IPL is involved in a number of cognitive functions, including both episodic and working memory,[62] executive functioning,[63] and bottom-up attentional processes.[64–67] Similarly, the anterior insula and frontoparietal operculum have been

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

PCC, posterior cingulate cortex; saTBI, subacute traumatic brain injury; cTBI, chronic TBI; L, left; R, right; G, gyrus; sup, superior; med, medial; mid, middle; BA, Brodmann area; frontopar, frontoparietal; IPL, inferior parietal lobule; MNI, Montreal Neurological Institute.

implicated extensively in a network important for selecting salient stimuli and guiding behavior in coordination with multiple other brain systems,[68–70] and the structural integrity of this network has been found to be crucial for DMN functioning in severe TBI.[71] Given that concurrent modulations of the DMN and task-positive regions have been found to support task performance in healthy individuals,[72–75] an increase in antiphase synchrony during the clinical recovery period may signify a restoration of balanced network function necessary for efficient cognitive processing. 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 may be two parts of a larger effect involving the modulation and optimal balancing of distributed networks.

Development of hippocampal connectivity alterations

The results from our hippocampal analyses add to the characterization of DMN changes after injury, and are especially important given that hippocampal connectivity has not been well defined in the TBI literature. A previous study performed whole-brain connectivity analyses with bilateral hippocampi as seeds, but only

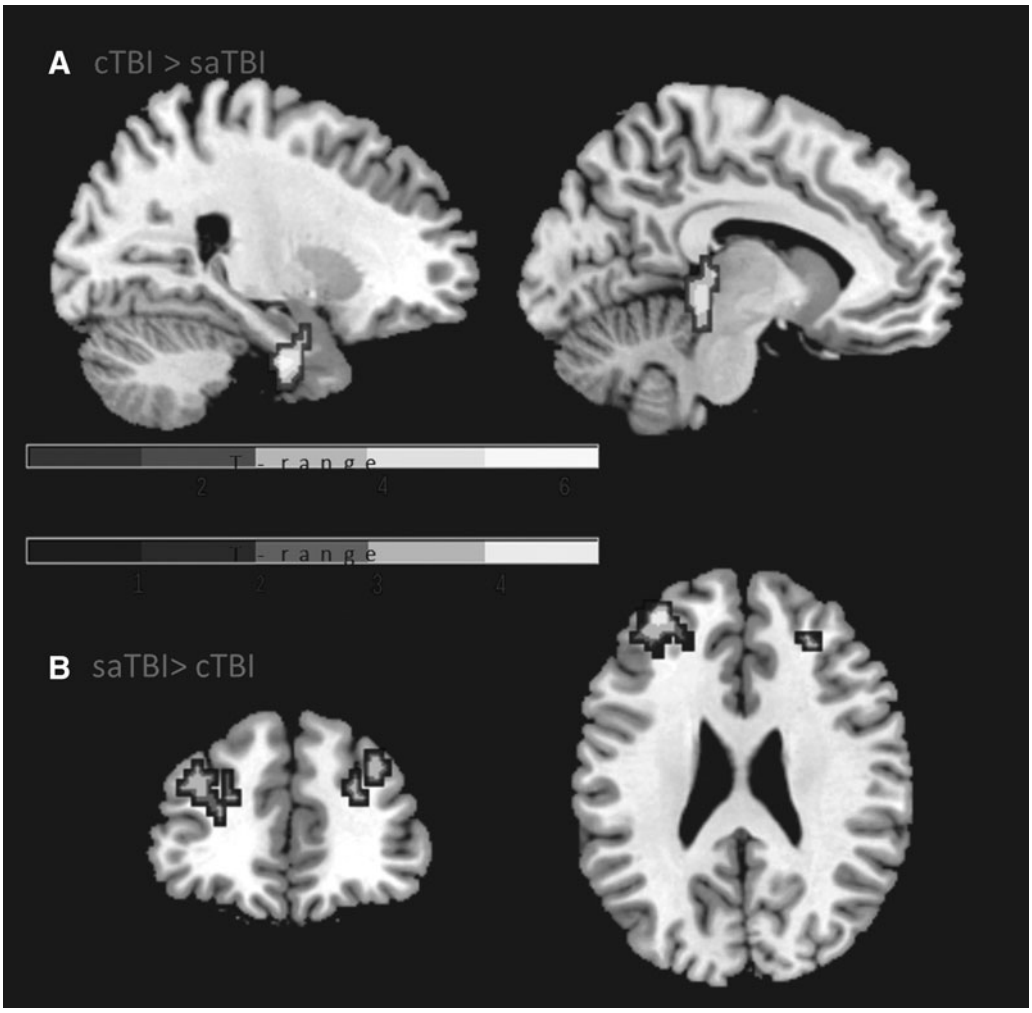

FIG. 5. Functional connectivity results for the right hippocampal seed in longitudinal analyses. (**A**) In chronic traumatic brain injury (cTBI) relative to subacute TBI (saTBI), there is increased positive connectivity between right hippocampus and proximal right temporal lobe and brainstem. (**B**) In saTBI relative to cTBI, there is increased negative connectivity between right hippocampus and bilateral superior and middle frontal gyri (dorsolateral prefrontal cortex).

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 mid-brain		
	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.		

saTBI, subacute traumatic brain injury; cTBI, chronic TBI; L, left; R, right; BA, Brodmann area; mid, middle; sup, superior; G, gyrus; MNI, Montreal Neurological Institute.

visually compared group-averaged maps of whole-brain connectivity, precluding inferences about group differences in connectivity magnitude.[76] In the current investigation, we used direct comparisons between groups to show 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 PFC, compared to controls. Further, longitudinal results indicate that both of these effects emerge relatively early after injury, with hypersynchrony progressing from a uni- to a bilateral phenomenon. These findings fit with previous literature documenting structural hippocampal anomalies[77,78] and episodic memory impairment[79–81] after brain trauma. Critically, our results show that the connectivity profiles of the hippocampi do not seem to ''recover'' with greater time postinjury. 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, studying the effects of sleep deprivation, Yoo and colleagues found that activation in unique regions of the frontal lobe predicting memory encoding in the experimental group was accompanied by nonspecific hippocampal-subcortical hypersynchronicity.[82] These findings bear notable resemblance to observations in our longitudinal TBI sample, where attentional performance at both time points was significantly and positively associated with antiphase synchrony between the left hippocampus and right dlPFC at the subacute stage. The same relationship did not hold at the chronic time point, and in our 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, our findings suggest that interplay between the hippocampi and frontal cortex may be essential for basic attentional abilities that are often impaired secondary to TBI, and that nonspecific hypersynchronous patterns may emerge in response to an attenuation of this relationship.

Potential markers of long-term outcome

Although there exists a relatively small literature in moderate-to-severe TBI with which to compare the current findings, our 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,[48,83–85] 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.[47] Hippocampal hypersynchrony with proximal regions and/or other regions of the DMN has been noted in risk groups for AD, including individuals positive for the apolipoprotein Eε4 allele[86–88] and mild cognitive impairment (MCI) patients[89,90] as well as individuals with early AD itself.[48] 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,[91] in MCI,[47,92,93] and in the very early stages of AD.[85,94,95]

The concordance between the current results and those in neurodegenerative disease orients us to the potential consequences of TBI-induced network changes on long-term neurological status. Whole-brain functional connectivity analyses, naïve of any seed definitions, have suggested that individuals advance toward a more ''healthy'' state in the months after injury,[13] corresponding to significant clinical recovery in the first year. However, the current findings do not fit readily into this narrative. Our study reveals that the courses of PCC and hippocampal connectivity patterns follow divergent trajectories, suggesting that, after TBI, there exists heterogeneity in both connectivity patterns and changes in these patterns within distributed networks.[96–99] Thus, our study underscores the importance for future work to investigate specifically compromised network nodes, which may provide a more nuanced view of connectivity changes after trauma and challenge the ''back to normal'' assumption.

Limitations and Conclusion

Our study was not without limitations. Although our sample size may be considered comparable to those in other studies of TBI, it remains modest, and findings need to be replicated to confirm our results and interpretations. Relatedly, brain injury by nature is extremely heterogeneous, and the effect of this heterogeneity in our sample is unknown. Third, whereas 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. We concede that though our study depicts important gross effects associated with two crucial nodes, it does not capture the inevitable complexity of changes induced by trauma. Finally, because we had limited behavioral data, 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, we demonstrated notable effects with our seeds in both cross-sectional and longitudinal analyses and were able to identify relationships between connectivity and cognition.

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. Further, we have noted several points of convergence between the current data and effects of age-related neurodegenerative disease. 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 thereby inform timely delivery of behavioral and pharmacological interventions.[100] Future research should proceed in the framework of TBI as a disorder that interacts with complex, dynamic neural systems throughout the lifespan, potentially creating further complications and thus necessitating long-term monitoring and rehabilitation efforts.

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No competing financial interests exist.

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