The Current State of Functional MR Imaging for Trauma Prognostication

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KEYWORDS

- Functional MRI • Traumatic brain injury • Post-traumatic stress disorder • Coma
- Post-concussive syndrome

KEY POINTS

- Network activity changes from baseline are greatest in the first few weeks following a head injury and reflect an attempt the brain makes to compensate for the sentinel injury and the ensuing metabolic shift associated with healing
- The degree of alteration of brain activation or network connectivity change over time correlates with the severity of postconcussive symptoms and time to normalization and may be used for prognostication or treatment planning
- Heterogeneity in study design and limitations in sample sizes contribute to an imperfect representation of healing brain networks; however, rapid progress in accumulating data inspires optimism for a future of brain diagnostic, prognostic, and therapeutic capabilities

INTRODUCTION

Traumatic brain injury (TBI) has the largest influence on morbidity and mortality in trauma patients.[1] Mild-to-moderate concussive injuries affect more than 69 million people worldwide annually, and traumatic coma occurs in approximately 1 million people worldwide each year.[2] Mild-to-moderate TBI is the most common cause of neurologic injury among athletes and military personnel.[3] In total, the US health care expenses related to these traumatic deficits are estimated at $17 billion annually.[4] The health care costs of these injuries relate to cognitive impairment in the acute post-concussive state, which typically lasts up to 10 days after the injury and less commonly may continue for weeks to months as post-concussive syndrome (PCS).[5] Common concussion symptoms include headache, nausea, visual disturbance, imbalance, distractibility, delay in verbal expression/bradyphrenia, memory disturbance/fogginess, sleep disturbance, and emotional lability.[6] Health care providers often advocate avoiding continued exposure to reinjury in the days to weeks following the initial insult, as patients that experience second impacts may go on to worse morbidity and mortality.[6] Primary injury to the brain is the result of direct impact and is followed by an inflammatory response with neurotransmitter release and vascular dysfunction.[7] Animal models demonstrate that neuronal energy metabolism disruption from aerobic to anaerobic partially triggered by overrelease of glutamate drives clinical symptoms in the days to weeks following the insult and may persist for up to 4 weeks post-injury (Fig. 1).[7] Hemodynamic and metabolic network activity shifts are of interest to investigators that use functional data and imaging to better understand the brain in its post-traumatic state.[1] These observations improve the understanding of brain network activity that conventional imaging lacks.

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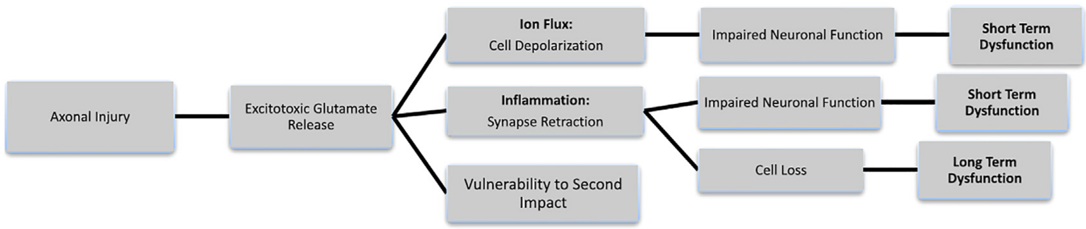

Fig. 1. Neurometabolic basis of traumatic brain injury.[8] (*Adapted from* Giza C, Greco T, Prins ML. Concussion: pathophysiology and clinical translation. Handb Clin Neurol. 2018;158:51-61.)

Limitations of Structural Imaging

Structural imaging modalities, such as computed tomography (CT) scans as well as MR imaging, are helpful in diagnosis and to some extent acute prognostication.[9] CT's sensitivity for detecting fractures and hemorrhages may provide large-scale structural information characteristic of moderate to severe TBI.[10] For parenchymal shear injuries that may be associated with microhemorrhage or tract swelling, 20% are recognized by CT and 80% by MR imaging.[11] A milder variety of partial shear injuries can be difficult to detect without significant hemorrhage or swelling but may longitudinally manifest through volume loss.[2] In addition, structural imaging techniques only characterize parenchymal abnormalities rather than provide a physiologic assessment of network activity that may better predict ongoing physical, cognitive, or emotional disability.[10] Therefore, functional imaging techniques have been beneficial in recognizing neural network disruption.[8] Furthermore, physiologic data could then be helpful in prognostication and evaluation of the effects of future therapies on brain networks. As a result, investigators are evaluating functional networks through electroencephalography (EEG), magnetic encephalography (MEG), and functional MRI (fMRI) to increase the sensitivity in recognizing injuries to brain networks that can influence clinical outcomes.[12] This review expands on the utility of fMRI to evaluate network activity, as well as patterns of injury and their clinical prognostic data.

BACKGROUND OF FUNCTIONAL MR IMAGING

Characterization and understanding of brain network activity have advanced tremendously as a result of Dr Bharat Biswal's recognition that low-frequency blood-oxygen-level-dependent (BOLD) signal fluctuations can be detected using sequential echo-planar MR imaging in 1995.[13] His team's research noticed focal BOLD signal intensity decrease corresponding to local increases in blood flow that increased the concentration of diamagnetic oxyhemoglobin compared with the baseline oxygen tension that is relatively paramagnetic.[14] Through BOLD imaging, the neurovascular coupling of network activity with increased local blood flow helps investigators demonstrate the energy demands necessary to sustain network function as well as piece together network components and characteristics.[13]

A typical hemodynamic response after neuronal activity that can accomplish neurovascular coupling involves a change in vascular tone within 500 ms and a peak in cerebrovascular dilatation approximately 3 to 5 s following the onset of activity.[15] These functions become more complex with increased duration and/or sequential activity where peak and plateau patterns may occur, and the hemodynamic response functions rely on local and remote vascular architecture, as well as potential pathomechanisms of cerebrovascular uncoupling.[16] As a result, the technique used in fMRI sequences captures images every 250 ms to observe these shifts related to neuronal activation.[17]

Certain design factors help organize network behavior around a relative state of rest (resting-state or rs-fMRI) or through periods of instructed activity such that investigators can observe network activity through segmental blocks, continuous event-related triggering, and continuous rapid event-related and mixed recording of data.[17] These iterations of study design uncover specific characteristics, such as similar frequencies in discrete brain regions at the same time, which suggests functional connectivity that over time may be seen as dynamic connectivity, or in a specific sequence of regional activation such as with effective connectivity of the brain's networks in their varied states of rest and activation.[18] Using different analysis methods, investigators can observe functionally connected brain regions, such as individual sensorimotor (or somatomotor), executive control, three visual, two lateral frontoparietal, auditory, and temporoparietal networks (Fig. 2, Table 1).[20]

Through appropriate design, studies can focus on differences between varied cognitive states

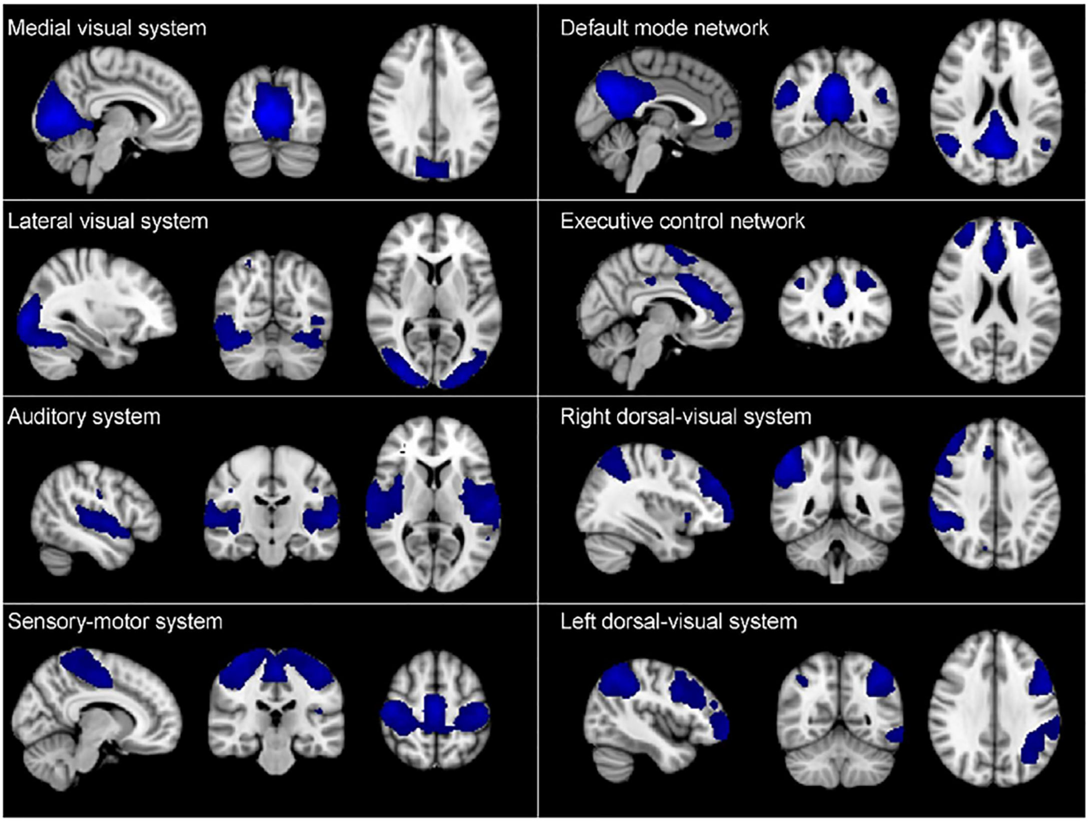

Fig. 2. Blue regions demonstrate selected spatially distinct areas of the brain that demonstrate synchronous BOLD fluctuations at rest (resting state functional networks). Original Figure previously published by Adriaanse and colleagues[19] in PLOS ONE. (*From* Adriaanse SM, Binnewijzend MA, Ossenkoppele R, et al. Widespread disruption of functional brain organization in early-onset Alzheimer's disease. PLoS One. 2014;9(7):e102995. Published 2014 Jul 31.)

(ie, subtraction), variations in similar cognitive processes (ie, factorial), variance in intensity of cognitive state (ie, parametric), and/or coexistence of variant cognitive processes (ie, conjunctional).[21] Interestingly, when investigators analyze network activity after subjects are instructed to perform tasks, task-specific networks are recruited and resting-state networks that integrate emotional and sensory information demonstrate suppression.[18] These observations not only teach us about adaptive prioritization of network activity but help reinforce the reactive and recompose cycles that underlie the brain's processing, and exemplify disordered resting-state or task-related network activity.[18]

In patients where task-based design is not a limitation, network activity comparison is best observed after periods of intention, recorded as blocks, events, or mixed-block events recording the subject performing tasks for an interval separated by a period of rest.[22] Because task-based fMRI (tb-fMRI) requires appropriate auditory processing, language fluency, comprehension, alertness, and ability to carry out instructions, resting-state examinations may be more suitable for people with language barriers, those who have the inability to perceive or process instructions, those with difficulty with maintaining attention to instructions, those with mental illness, those in a vegetative state, or those with the physical inability to accomplish tasks, among other reasons.[23] The block design also enables a variety of pre-processing methods to correct for potential section-dependent time shifts, intensity differences, head motion, and/or cardiac/respiratory noise.[24] Whole-brain regression models may average time course or seed regions of interest to areas of activity in other regions by establishing boundary thresholds.[25] Identifying components of networks provides further component analyses that can help decompose data into variables to find patterns of activity for network identification.[26] Transformations and clustering algorithms can plot and organize data into hierarchical, K-means, c-means, and graph-based displays to evaluate, compare, and demonstrate features of dependence of networks within or between individuals.[26] As a

Table 1
Common resting state network functions and involved regions of the brain

Network	Regions of Connectivity	Function
Default Mode Network (DMN)	• Ventromedial prefrontal cortex • Inferior parietal lobe • Posterior cingulate cortex • Precuneus	Self-referential/mind-wandering aspects of cognition
Central Executive Network	• Dorsolateral prefrontal cortex • Bilateral inferior, middle, and superior frontal cortices • Inferior parietal lobule • Anterior cingulate cortex (ACC)/supplementary motor area (SMA) • Bilateral insular cortices	High-level cognitive/executive function
Salience Network	• Dorsal anterior cingulate cortex • Anterior insula (fronto-insular) connections to subcortical and limbic structures	Attention to biological stimuli
Auditory Network	• Primary and secondary auditory cortices, including Heschl's gyrus • Bilateral superior temporal gyri • Posterior insular cortex	Audition (tone/pitch distinction), music, speech
Sensorimotor Network	• Supplementary motor area/ midcingulate cortex • Bilateral primary motor cortex • Bilateral middle frontal gyri	Motor tasks

result, scrutiny in methods of data acquisition and processing is of utmost importance as each method is associated with data transformation or has assumptions applied to the data that alter our analysis of network activity.[27]

FINDINGS IN FUNCTIONAL MR IMAGING

Tb-fMRI has been helpful in diagnosing, characterizing, and predicting the severity of deficits in specific functions such as learning/memory, motor, and cognition in trauma patients. Rs-fMRI is often easier to perform than tb-fMRI in trauma patients with alterations in mental status or children and provides information on changes in the network connectivity of the brain. fMRI has been used to assess the chronologic changes in brain function in trauma and has a potential for prognostication of recovery. We searched PubMed for all the studies using fMRI techniques in trauma patients (a total of 1253 articles) and found 504 articles relevant to rs-fMRI and tb-fMRI in the setting of trauma. Here, we have summarized the studies with a longitudinal design (at least two fMRI studies in different time standpoints) in **Table 2** (rs-fMRI) and **Table 3** (tb-fMRI). These studies have variations in results that can be attributed to factors including age, individual variability, gender, the severity of the trauma, and more importantly study design (timing of scans, scan parameters, and analysis techniques). However, some general trends have been identified.

Default Mode Network: Some investigators have found increased connectivity and cerebral blood flow during the first 3 to 5 days after injury within portions of the default mode network, such as the hippocampus, which later may show reduced connectivity.[60] Patients with chronic PCS over multiple stages of recovery have demonstrated an overall imbalance in the ratio of cerebral blood flow between the default mode network and the task-positive networks suggesting that alterations in perfusion may underlie and predict chronic morbidity.[33] A traumatically decreased synchronization of neurons often requires an overall increased need for global connectivity to maintain signals as well as an increased metabolic need with increased cerebral blood flow and without this increase in blood flow prolonged impairment may occur.[32,34]

As a result, decreased fractional amplitude of low-frequency fluctuations within the motor, default-mode, and visual networks measured less than 10 days after injury with resting-state fMRI were

Table 2
Summary of longitudinal resting-state functional MR imaging studies in trauma patients

Study's First Author and Year	Participants	Timing of Scan	Findings
Harnett et al,[28] 2021	109 mTBI patients average age 35.31 y	∼2 wk and 3 mo	• Left dorsolateral prefrontal cortex to arousal network connectivity at 2 wk post-trauma was negatively related to 3-mo PTSD symptoms and depression. • Right inferior temporal gyrus to DMN connectivity was positively related to 3-mo PTSD symptoms and depression. • Following trauma exposure, acutely assessed variability in RSN connectivity was associated with PTSD symptom severity approximately two and a half months later. • Decreased top-down cortico-limbic regulation and increased network-mediated fear generalization might contribute to dysfunction in the aftermath of trauma.
Manning et al,[29] 2017	31 concussed Hockey players aged 11 to 14 y	24 to 72 h (n = 17) and 3 mo (n = 14)	• Increased connectivity at 3 mo in sensorimotor, cerebellar, and DMN compared with 24 to 72 h • The adolescent brain may be more vulnerable to brain dysfunction and elongated periods of recovery after an acceleration-related injury.
Chong et al,[30] 2019	15 patients aged 16 to 55 with mTBI	1 and 5 mo	• At 1 mo post-concussion, patients had significantly weaker homotopic functional connectivity in several pain-processing regions which showed significant recovery at 5 mo. Better symptom recovery is associated with better functional somatosensory improvement.
Moreira da Silva et al,[31] 2020	23 mild-to-moderate TBI, median age of 36	6 d, 12 mo	• Sixteen brain network metrics were found to be discriminative of different post-injury phases. Eleven of those explain 90% of the variability observed in cognitive recovery following TBI.

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Table 2
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Study's First Author and Year	Participants	Timing of Scan	Findings
			• Brain network metrics that had a high contribution to the explained variance were found in the frontal and temporal cortex, as well as the anterior cingulate cortex. This suggests that network reorganization may be related to the recovery of impaired cognitive function in the first year after a TBI.
Meier et al,[32] 2017	43 collegiate athletes concussion	1 d, 1 wk, 1 mo	• Regional homogeneity (ReHo) in sensorimotor, visual, and temporal cortices increased over time post-concussion and was greatest at 1-month post-injury. • ReHo in the frontal cortex decreased over time following concussion, with the greatest decrease evident at 1-month post-concussion. • Results are suggestive of delayed onset of local connectivity changes with no change in global connectivity following concussion
Sours et al,[33] 2015	28 patients, 28 controls average age 39 mTBI	11 d, 1 mo, ∼6 mo	• Chronic mTBI patients with normalized cognitive performance, demonstrate increased resting-state connectivity (rs-FC) between the DMN and regions associated with the salience network and task-positive networks, as well as reduced strength of rs-FC within the DMN at the acute stage of injury. • Patients with chronic PCS reveal an imbalance in the ratio of cerebral blood flow between the DMN nodes and task-positive nodes across multiple stages of recovery. • Altered network perfusion with the associated changes in connectivity may be a possible predictor of which mTBI patients will develop chronic PCS.

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Table 2
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Study's First Author and Year	Participants	Timing of Scan	Findings
Churchill et al,[34] 2020	228 university athletes, 61 concussion, 167 control average age 20	Acute (1 to 7 d), subacute (8 to 14 d), clearance to return to sport (RTS), 1 mo post-RTS and 1 y post-RTS	• BOLD scale-free signal (c1) was lowest at the acute injury, became significantly increased at RTS, and returned near control levels by 1-y post-RTS. • Clinical measures of acute symptom severity and time to RTP were related to longitudinal changes in c(1). Athletes with both greater symptoms and prolonged recovery had elevated c(1) values at RTS, while athletes with greater symptoms but rapid recovery had reduced c(1) at the acute injury.
Churchill et al,[35] 2021	167 university athletes age 20 monitored for 5 y	Baseline, concussed in the same season, (*n* = 17), concussed in later seasons (*n* = 15)	• Prior to the injury, concussed in the same season athletes had significantly elevated total symptom severity scores and elevated salience-DMN network rs-FC. • Salience-DMN network connectivity are associated with short-term but not long-term concussion risk.
Madhavan et al,[36] 2019	91 mTBI 15 to 51 y	<3 d, 5 to 10 d, 15 to 30 d and, 83 to 103 d	• Decreased fractional amplitude of low-frequency fluctuations (fALFF) was observed in specific functional networks for patients with higher symptom severity scores and fALFF returned to higher values when the patient recovered. • Functional connectivity immediately after injury was capable of predicting symptom severity at a later time. • Connectivity between motor, default-mode, and visual predicted 3-mo clinical outcome.
Dall'Acqua et al,[37] 2017	49 mTBI and 49 healthy controls mean age 35	5 d and 1 y	• Early phase: functional hypoconnectivity in default mode network. • One year: partial normalization which correlated with improvements in working memory, divided attention, and verbal recall.

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Table 2
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Study's First Author and Year	Participants	Timing of Scan	Findings
Abbas et al,[38] 2015	10 male high school football athletes	Baseline, two in-season within 48 h of the game (2 months), six post-season	• In-season DMN connections were reduced in the first month and increased in the second month. • Post-Season connections were significantly reduced at all sessions except the December measurements.
Sours et al,[39] 2015	32 mTBI patients (15 with PCS	10 d, 6 mo	• Decreased strength of DMN connectivity within 0.125 to 0.250 Hz frequency range in patients with PCS compared with patients without the syndrome during both the acute and chronic phases.
Stephens et al,[40] 2018	17 children (10 to 17 y), mild–moderate TBI	2 mo, 12 mo	• Decreased anti-correlated functional connectivity between DMN and right Brodmann Area 40. • Worse performance on response inhibition tasks linked to more anomalous less anti-correlated connectivity between DMN and right Brodmann Area 40.
Johnson et al,[41] 2014	24 current collegiate rugby players	Baseline, 24 h after play	• DMN: increased connectivity from the left supramarginal gyrus to the bilateral orbitofrontal cortex and decreased connectivity from the retrosplenial cortex and dorsal posterior cingulate cortex. • Decreased functional connectivity after subconcussive head trauma in those with a history of trauma, while increased connectivity in those with no history.
Zhu et al,[42] 2015	8 concussed football athletes and 11 controls	within 24 h, 7 $\pm$ 1 d, and 30 $\pm$ 1 d after concussion	• Increased DMN functional connectivity on Day 1, a significant drop on Day 7, and partial recovery on Day 30
Kuceyeski et al,[43] 2019	26 mTBI (29.4 $\pm$ 8.0 y)	1 mo, 6-mo	• Increased functional connectome integration was related to better cognition recovery
Roy et al,[44] 2017	14 patients with moderate and severe TBI age 18 to 36	3, 6, and 12 mo following injury	• Increased network strength early after injury, but by 1-year post injury, hyperconnectivity was more circumscribed to frontal DMN and temporal-parietal attentional control regions.

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Table 2
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Study's First Author and Year	Participants	Timing of Scan	Findings
Threlkeld et al,[45] 2018	17 acute severe TBI ICU patients, 16 healthy control	Acute imaging in all, 8 returned in 6 mo	• Acute: Those who remained in coma showed no DMN inter-network correlations. Those who recovered from coma to a minimally conscious or confusional state illustrated partially preserved DMN correlations. • Patients who recovered beyond the confusional state by 6 mo showed normal DMN correlations and anticorrelations similar to healthy subjects. • Recovery of consciousness after acute severe TBI is associated with partial preservation of DMN correlations in the ICU, followed by long-term normalization of DMN correlations and anticorrelations.
Hillary et al,[46] 2014	21 moderate and severe TBI and 15 controls	3 and 6 mo	• Hyperconnectivity during the first year disproportionately represented in the brain's core subnetworks.
vanderHorn et al,[47] 2017	30 mTBI patients and 20 control	1 mo and 3 mo post-injury	• Increased functional connectivity between the anterior and posterior components of the DMN at 1 mo post-injury was associated with a larger number of complaints at 3 mo post-injury.
Nakamura et al,[48] 2009	6 patients with severe TBI	3 mo and 6 mo	• Decreased strength of network connectivity from 3 mo to 6 mo post-injury.

associated with increased symptom severity and were useful in predicting 3 weeks to 3 months symptom severity.[36] Functional hypo-connectivity among regions involving the default mode network and hyper-connectivity in regions including cingulate cortex during the early phase of mTBI correlated well with early symptom severity.[37] However, 2-week post-injury connectivity of the left dorsolateral prefrontal cortex and the arousal network (amygdala, hippocampus, mammillary bodies, midbrain, and pons) was negatively associated with 3-month PTSD, in contrast to the connectivity of the right inferior temporal gyrus and default mode network which was positively correlated with 3-month PTSD and depression symptoms.[28]

Task Positive Networks: Interestingly, regional hyperactivation of task-positive networks, such as regions involved in working memory tasks, have been associated with persistent cognitive symptoms lasting beyond 1 week after injury.[53] In a group of adolescents with moderate to severe TBI exposed to varying difficulty working memory loads, lower response accuracy and longer reaction times were associated with elevated activity in the anterior cingulate gyrus and decreased activity in the left sensorimotor region that was relatively normalized on retesting 12 months later.[49] Even among patients with no reported deficit significantly higher activity within the parietal cortex, right dorsolateral prefrontal cortex, and right hippocampus

Table 3
Summary of longitudinal task-based functional MR imaging studies in trauma patients

Study's First Author and Year	Participants	Timing of Scans	Paradigm	Findings
Cazalis et al,[49] 2011	Adolescents (13 to 18 y of age) with moderate to severe TBI	Acute and 12 mo	Spatial working memory task	• Over 12 mo, patients' behavioral performance improved, suggesting cognitive recovery and patients recruited less of the anterior cingulate gyrus and more of the left sensorimotor cortex with increasing task difficulty.
Sanchez-Carrion et al,[50] 2008	12 patients with severe TBI, 10 control	Twice at a 6-mo interval	Working memory	• Low activation of the right superior frontal gyrus in the TBI group, with near resolution at 6 mo.
Chen et al,[51] 2012	20 mTBI and 18 healthy controls	Within 1 mo after injury and 6 wk later	Working memory	• Impaired increase in activation in working memory circuitry under both moderate and high working memory load conditions which improved at 6 mo. Able to detect abnormality in mTBI patient with normal neurobehavioral test.
Dettwiller et al,[52] 2014	15 athletes (mean age 20) 7 with concussion	3 d, 2 wk, and 2 mo post-injury after a concussion	Verbal/spatial working memory task	• Increased activation in bilateral dorsolateral prefrontal cortex in all time points and in inferior parietal lobe in 3 d and 2 weeks in the concussed group while normal standard working task.
Wylie et al,[53] 2015	27 Adult mTBI, 19 control	< 72 h, 1-wk	Working memory	• Increase in activation of posterior cingulate in mTBI subjects compared with controls which were greater in those without cognitive recovery.
Lovell et al,[54] 2007	28 concussed, 13 controls between (age 13 to 24)	Within 1 wk, after clinical recovery	Working memory	• Twice longer recovery time in athletes with a higher degree of activation of middle and inferior frontal cortex.

Hsu et al,[55] 2015	30 mTBI (15 M, 15 F), 30 control	Within 1 mo, 6 wk after the first study	Working memory	• Hyperactivation in male and hypoactivation in female patients initially which improved in male patients but persisted in female patients.
Coffey et al,[56] 2021	8 patients severe TBI	Acute, 6 mo	Speech	• Re-emergence of language-processing cortex activity by 6 mo in those with recovered language function.
Kim et al,[57] 2009	17 TBI, 15 control	Acute, repeat in 10 after cognitive rehabilitation	Visuospatial attention task	• Cognitive training in TBI patients improved performance of attention tasks and networks by increased activation of the anterior cingulate and precuneus.
Wu et al,[58] 2020	20 TB mild to severe	Acute and in 5 wk	Attention and working memory	• Increased activity patterns over time in the right dorsolateral prefrontal cortex and right insula. Decreased activity patterns in the left posterior cingulate cortex (PCC), bilateral precuneus, right inferior occipital gyrus, and right temporo-occipital junction.
Chen et al,[59] 2015	13 younger (mean 26 y), 13 older (mean 57 y) mTBI	1 mo, 6 wk later	Working memory	• Younger patients: initial hyperactivation in the right precuneus and right inferior parietal gyrus; Older patients: hypoactivation in the right precuneus and right inferior frontal gyrus. • Increased activation associated with increased postconcussion symptoms. • Partial recovery of activation pattern and decreased postconcussion symptoms in younger patients but not in older patients.

were demonstrated after visual and spatial memory tasks suggesting a reduced ability to recruit additional neuronal network power that may be indicative of early reorganization.[30,38] As a result, increased functional connectivity or reduced relative regional homogeneity in the right frontoparietal network were linked to elevated awareness of external stimuli and associated with increased cognitive fatigue even if it normalized 6 months later as working memory improved.[32,50]

These findings suggest that a temporal window of a few weeks to months is available for the brain to reorganize its connectivity by increasing the overall numbers of connections that have different frequency characteristics to account for the decreased strength of previously few but strong functional connections.[31] Despite this, some regions such as the hippocampus have a greater difficulty reorganizing and demonstrate reduced hippocampal volume and corresponding regional neural activity similar to that of patients of older age.[61] An individual's baseline introspective strength and adeptness at task performance may define how susceptible one is to dysfunction and the potential emotional sequelae of injury.[62] As a result, excess reactivity of threat-detection and fear-response regions of the brain after injury or exposure to psychological trauma, such as the amygdala, insula, and dorsal anterior cingulate cortex, as well as low-reward reactivity in affect-evaluation regions, such as the nucleus accumbens, amygdala, and orbitofrontal cortex, have been associated with higher stress vulnerability and elevated likelihood for chronic depression and post-traumatic stress disorders.[63]

Most tb-fMRI studies have assessed the working memory and to lesser extent attention and speech activation in the acute to the chronic setting (see **Table 2**). There is a general trend of cortical hyperactivation in the acute setting that improves over time. TBI patients have increased activation of the posterior cingulate gyrus[49,53] dorsolateral prefrontal cortex,[52] and inferior parietal lobe[59] with memory tasks, which improves over time. Interestingly, even in patients with mTBI and normal neurocognitive testing, there may be abnormal activation of task-related networks.[51] The degree of hyperactivation is a negative prognostic factor for normalization and the length of time needed for the recovery of cognitive abilities[53,54] and is associated with worse postconcussive symptoms.[59]

SUMMARY AND FUTURE DIRECTIONS

Multiple studies have demonstrated that in the first few weeks following an injury, the brain makes its greatest shift in network activity that likely reflects a microstructural reorganization in an attempt to compensate for damaged connections. Longitudinal fMRI studies demonstrate a correlation between the degree of hyperactivation and network shifts in connectivity and post-concussive symptoms that may be helpful for predicting time to recovery, such as determining the timing to return to sport. In the future, genetic and injury-related fMRI clinical markers might stratify an individual's risk of ensuing morbidity that may guide neurochemical or ion channel-modulating therapeutic options or potential stem cell therapies. Current heterogeneity between study designs as well as limitations in sample sizes contributes to an imperfect representation of the healing brain networks. By normalizing fMRI as a regular evaluation for extended follow-up on trauma patients as well as refining inclusion criteria to decrease heterogeneity in the investigation of TBI, investigators could achieve an unprecedented advancement of neural health and science that may extend beyond the setting of trauma.

CLINICS CARE POINTS

- In the first few weeks following an injury, the brain makes its greatest shift in network activity that likely reflects a microstructural reorganization in an attempt to compensate for damaged connections.
- Some brain regions are less versatile than others.
- Longitudinal fMRI studies demonstrate a correlation between the degree of hyperactivation and network shifts in connectivity and post-concussive symptoms that may be helpful for predicting time to recovery, such as determining the timing to return to sport.
- Current heterogeneity between study designs as well as limitations in sample sizes contributes to an imperfect representation of the healing brain networks.

DISCLOSURE

None of the authors have any commercial or financial conflict of interest related to this article.

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