Applications of Resting State Functional MR Imaging to Traumatic Brain Injury

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KEYWORDS

• Resting state • BOLD • fMR imaging • TBI • Graph theory • Machine learning • Magnetoencephalography

KEY POINTS

- Resting state functional MR imaging (rs-fMR imaging) is typically not applicable to the individual in a clinical setting.
- Graph theory and machine learning methods are beginning to identify traumatic brain injury–specific features in rs-fMR imaging for group studies and starting to show promise as assistive tools for individual diagnoses.
- Resting state magnetoencephalography has a higher temporal resolution and may be able to supplement rs-fMR imaging findings.
- Moving rs-fMR imaging into the clinic should be approached with cautious optimism.

INTRODUCTION

A traumatic brain injury (TBI) can be caused by a bump, blow, or jolt to the head. TBIs can also be caused by penetrating, or open, head injuries. In the United States, approximately 1.7 million TBIs occur each year. More than 1.3 million result in an emergency department visit, 275,000 result in hospitalizations, and 52,000 result in deaths. On average, the most common cause of TBI is falls, and the rates are highest among very young children and adults older than the age of 75.[1] Most TBI cases are closed-head injuries, but some are open-head injuries, which occur when the skull is fractured or penetrated.

TBI encompasses a spectrum of brain abnormality with many variables affecting the type and severity of injury. Mechanism of injury plays a prominent role; however, the distribution of local forces sustained by the brain parenchyma during injury, and patient factors, including individual anatomic differences, age, gender, medications/substance use, and medical history, can also dramatically affect the severity of injury and subsequent patient outcome.[2–4] Multiple factors are used to classify the severity of the TBI. The most common include the Glasgow Coma Scale and the Abbreviated Injury Scale–Head.[5] The severity of the injury is often classified from mild to severe. The effects of mild TBI (mTBI) are often not visible on conventional imaging, whereas severe TBI can manifest as an obvious finding, such as an open-head injury or hematoma.

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Primary injuries occur from tissue damage during the time of impact from mechanical forces that produce tissue strains and stresses.[6,7] Head impact generates both contact and inertial forces and can result in extra-axial and/or intra-axial intracranial tissue damage. Some head injuries may be acutely life threatening and require emergent neurosurgical interventions, while other sequelae of traumatic head injury are more subtle with little or no evidence of tissue damage on conventional anatomic imaging and only result in evidence of dysfunction of functional connectivity using advanced techniques, including resting state functional MR imaging (rs-fMR imaging) or magnetoencephalography (MEG).

Extra-axial tissue damage commonly results in epidural hematoma, subdural hematoma, subarachnoid hemorrhage, and/or subdural hygroma. Associated secondary complications of extra-axial injury often requiring emergent intervention include cerebral herniation, edema, hydrocephalus, or ischemia. Focal primary TBIs of intra-axial tissue also occur with closed head trauma and result from both direct impact of the brain with the cranial vault and transmitted linear and rotational forces on the brain. The rigid cranial vault and skull base provide a non-deformable internal surface of contact with the relatively soft, deformable, and mobile brain. Secondary effects of intra-axial hemorrhage include hypoxic-ischemic damage, oxidative stress from reactive oxygen species, neuroexcitatory response, cerebral edema, neuronal cell death, blood-brain barrier permeability, and autonomic dysfunction.[8–11] Cortical/subcortical contusions may also be associated with subarachnoid hemorrhage as a result of extension of parenchymal hemorrhage beyond the pia.

Diffuse traumatic axonal injury (DAI) typically involves a wide distribution with regional involvement of white matter axons, which are vulnerable to shearing strains owing to their long, highly structured architecture. Using the word diffuse is somewhat of a misnomer because the pattern is more multifocal with affected areas interposed with non-affected areas. White matter axons are particularly vulnerable to rapid shearing strains. Classically, a histologic grading scheme of diffuse axonal injury based on region of involvement is often used to describe the severity of DAI. Grade 1 involves the cerebral hemispheres, corpus callosum, brainstem, or cerebellum; grade 2 involves the corpus callosum, whereas grade 3 involves the brainstem.[12] These sites, particularly cortical/subcortical white matter, splenium of the corpus callosum, and brainstem, are also the areas frequently demonstrating abnormalities on conventional neuroimaging studies. Primary axotomy at the time of impact is considered rare. Instead, it is thought that mechanical forces produce axonal deformation and cytoskeletal disruption, which results in accumulation of transported materials appearing as multiple axonal swellings, "axonal varicosities," or a single swelling referred to as "axonal bulb."[13] These findings correlate with axonal disconnection. Although contusional microhemorrhage, apoptosis, and necrotic cell death cascades likely occur with diffuse axonal injury, there has also been demonstration of neuronal plasmalemmal poration and disruption, leading to either necrosis or reactive change without cell death.[14,15] The progression from disruption in axonal transport leading to axonal disconnection, apoptosis, and Wallerian degeneration has been traditionally thought to occur over the acute and subacute period following trauma; however, axonal degeneration may occur for years following injury. For these reasons, DAI is considered a disease of disconnection, which has made it an ideal candidate for study of functional connectivity using tools such as rs-fMR imaging.

This review covers rs-MR imaging and resting state magnetoencephalography (rs-MEG) acquisition, processing, and findings. A specific focus is given to machine learning and graph theory given the multiple applications of these methods in the literature and the potential for automated detection and diagnoses in the future.

NORMAL ANATOMY AND IMAGING TECHNIQUE

Conventional noncontrast head computed tomography (CT) and MR sequences remain the standard of care in clinical neuroimaging in the setting of TBI. Noncontrast head CT is rapid, accessible, and safe for all patients, plus it is very sensitive for detection of hemorrhage and other potentially life-threatening sequela of closed head injuries. These features make CT an ideal tool in the acute/hyperacute setting and for serial follow-up imaging when there are changes in clinical status. In the acute or early subacute setting, conventional MR imaging is typically reserved for patients with clinical/neurologic symptoms that are discordant with CT findings or when the injury extent may be better assessed by MR imaging. A conventional brain MR imaging protocol typically includes T1-weighted spin-echo or 3-dimensional (3D) T1, T2-weighted fast-spin-echo, T2 fluid attenuated inversion recovery (FLAIR), and echo planar diffusion-weighted imaging. Susceptibility-sensitive sequences, including T2* gradient recalled echo or 3D susceptibility-

weighted imaging (SWI), which are sensitive to blood products and can reveal microhemorrhages associated with DAI, are frequently included in the routine posttrauma MR imaging protocols. Examples of mild and severe DAI are shown in **Figs. 1** and **2**, respectively. Additional advanced MR techniques include evaluation with diffusion tensor imaging, arterial spin labeling perfusion, dynamic susceptibility contrast perfusion, and MR spectroscopy, but are beyond the scope of this article. Typical imaging findings of TBI on CT or conventional MR sequences range from frank intracranial hemorrhages to petechial foci of hemorrhage, as are often seen in diffuse axonal injury. However, these techniques may appear normal and often are insensitive to sequela of mTBIs.

RESTING STATE FUNCTIONAL MR IMAGING PROTOCOLS

fMR imaging relies on coupling of cerebral blood flow with neuronal activity (hemodynamic response) and most commonly uses an MR imaging technique sensitive to changes in blood hemoglobin oxygenation (BOLD, blood oxygenation-level–dependent signal). As neuronal activity increases in an area of the brain, hemodynamic responses cause an overcompensation of blood flow to the region, resulting in increased signal from a local change in the deoxy:oxyhemoglobin ratio. BOLD-sensitive sequences rely on susceptibility differences in oxyhemoglobin and deoxyhemoglobin. Even in optimal situations, signal change from active and inactive areas is relatively small, and this technique suffers from low signal-to-noise ratio. Understanding the physical mechanism of fMR imaging acquisition is important to consider in patients with TBI because there are unique features of these patients that may affect analysis techniques and interpretation of fMR imaging results in these patients. Patients with TBI may have dysregulation in the coupling of hemodynamic response with neuronal activity, which may complicate whether abnormalities are due to actual decreased neuronal activity or alterations in hemodynamic response. Also, because fMR imaging relies on changes in susceptibility, intracranial blood products can cause artifacts that obscure true neuronal activation. fMR imaging can be acquired with a task (task-based fMR imaging), such as attending to a visual stimulus, or while the subject is at rest (rs-fMR imaging). rs-fMR imaging relies on low-frequency, spontaneous fluctuations in the BOLD signal that are present even in the absence of a stimulus or task.[16] No consensus exists on the optimal acquisition techniques for rs-fMR imaging. However, typically, acquisition entails an ultrafast single-shot, whole-head, gradient-echo echo planar imaging sequence with a TR ~2 to 3 seconds, over a period anywhere from 2 to 30 minutes.[17] Shorter acquisition times are less susceptible to patient motion, but fewer data points are available for analysis. Acquisition may occur with the patient's eyes open or closed.[18] Spatially discrete brain regions that exhibit strong interregional correlation, after excluding nonphysiologic sources of correlation, are assumed to be functionally connected. A suggested MR acquisition protocol for TBI patients is detailed in **Table 1** and should complement the existing clinical examination. A 3-T scanner would be preferred, and adjustments to the protocols optimized for particular scanners with techniques like parallel imaging can achieve data with better spatial or temporal resolution. Findings on fMR imaging in TBI patients reported in the literature are discussed later. Although this technique holds promise for further investigation in TBI patients,

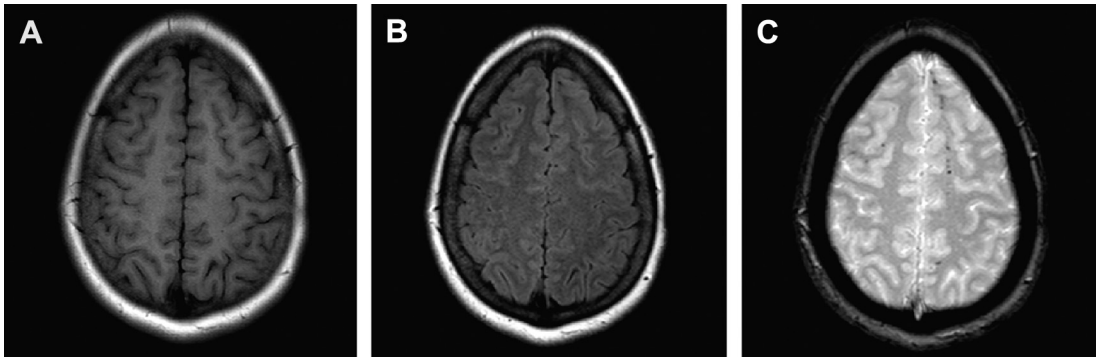

Fig. 1. Conventional MR findings of mild diffuse axonal injury. Axial T1 (*A*), axial T2 FLAIR (*B*), and axial SWI (*C*) demonstrate only petechial foci of susceptibility at the gray-white interfaces of bilateral frontal, and left parietal lobes. No other imaging findings are demonstrated on conventional sequences.

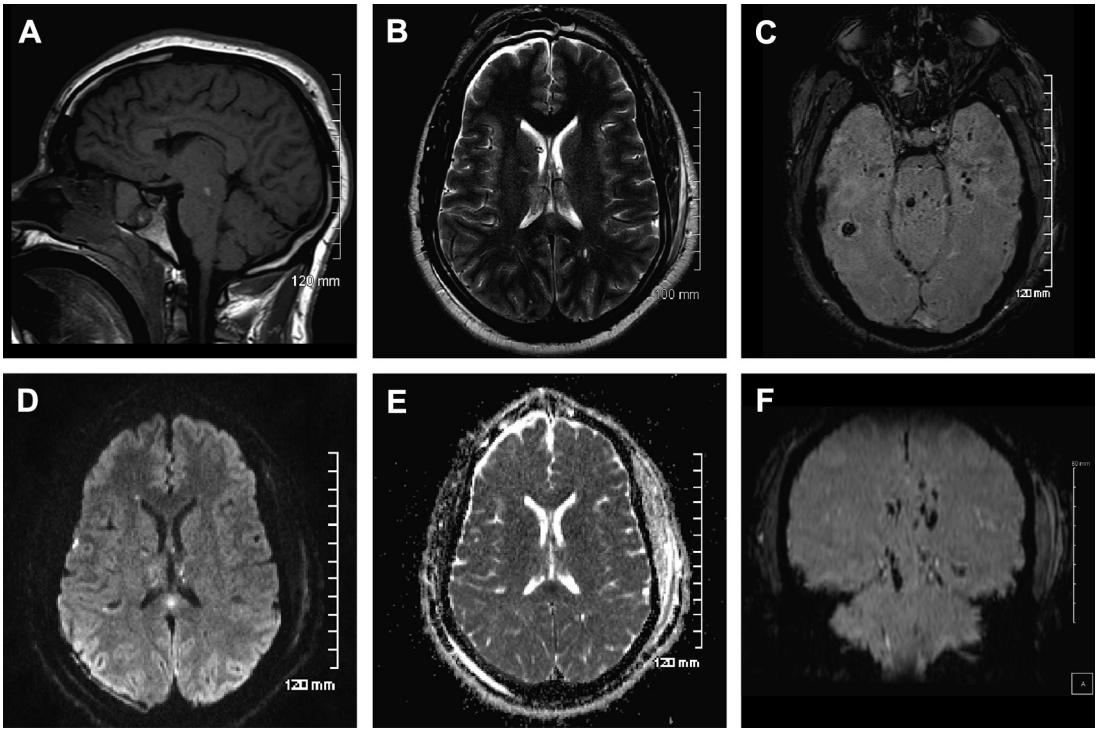

Fig. 2. Conventional MR findings of severe diffuse axonal injury. Sagittal T1 (*A*) demonstrates a petechial focus of T1 shortening compatible with subacute blood products in the midbrain. Axial T2 (*B*), axial diffusion-weighted images (*D*), and apparent diffusion coefficient map (*E*) demonstrate a focus of mild restricted diffusion in the splenium of the corpus callosum as well as foci of increased T2 signal in the periventricular white matter, right internal capsule, and right thalamus. Axial and coronal SWI (*C* and *F*) demonstrate numerous foci of susceptibility, consistent with foci of hemorrhage, in the brainstem, temporal lobes, periventricular white matter, and corpus callosum.

existing evidence is insufficient for routine clinical TBI diagnosis and/or prognostication at the individual patient level.[19] However, research is ongoing to determine the appropriate methods of application and interpretation in the clinical setting of TBI.

RESTING STATE FUNCTIONAL MR IMAGING FINDINGS

Subjects suffering from TBI tend to show impairment in high-level cognitive functions such as attention, memory, and executive function.[20,21]

Table 1
Suggested resting state functional MR imaging protocol for traumatic brain injury

Sequence	Sequence Parameters	Acquisition Parameters	Acquisition Time
Sagittal 3D T1 MPRAGE	TR 2500/TE 3	Isotropic, 1 × 1 × 1 mm	~5–8 min
Axial thin T2/FLAIR or sagittal 3D T2/FLAIR	TR 8000/TE 80	0.5 × 0.5 × 3 mm or isotropic 3D (1 × 1 × 1 mm)	~4–5 min
Axial 3D SWI	TR 30/TE 20	0.5 × 0.5 × 2 mm	~3–4 min
BOLD rs-fMRI, axial GE-EPI	TR = 2000–3000 ms, TE = 30–40 ms, α = 80°–90°	Near isotropic, 3 × 3 × 3 mm to 4 × 4 × 4 mm/matrix 64 × 64	~5–10 min
Diffusion tensor imaging, axial GE-EPI	TR = 4500/TE = 100, b = 0 and b = 1000 × 6–30 directions	1.5 × 1.5 × 3–5 mm/matrix 128 × 128	~10 min (with parallel imaging)

Because the integration of information across various regions of the brain is required for these high-level functions, researchers have often chosen to transform rs-fMR imaging data into a graph-based representation, also called a network representation. These graphs, or networks, consist of nodes connected by edges. The nodes can be brain regions, subnetworks, or individual voxels. Brain regions are determined by parcellating anatomic MR imaging and transferring these brain regions to the rs-fMR imaging through coregistration, whereas brain subnetworks are defined directly on the rs-fMR imaging data through a multivariate decomposition method, such as independent component analysis (ICA). For all of the parcellation schemes, the graph edges characterize a measure of connectivity between node pairs.

Graph Theoretic Measures

To make graphs amenable for quantitative analysis, graph theory is often used to convert the discrete graph into a set of descriptive numerical measures. Graph theoretic methods enable the study of functional integration through various metrics such as *small-worldness*, which measures the balance between network segregation and integration, and *network efficiency*, which is inversely proportional to the path length and thus strongest with the shortest path length. Functional segregation of the network can be studied through other metrics, such as the clustering coefficient, which quantifies how well connected the neighbors of a node are to one another. These network-based characterizations of the brain may provide insight into the dysfunction of interacting nodes in patients with TBI.[21] For example, it has recently been shown that network-based analyses offer the potential to understand subtle changes in cognitive function and the effects of rehabilitation.[22] It is important to bear in mind that these metrics provide sensitive but nonspecific markers of brain function.

Mounting Evidence for Connectivity Changes in Traumatic Brain Injury

In a graph analysis study by Pandit and colleagues,[23] TBI subjects exhibited a reduction in overall functional connectivity as evidenced by a reduction in the total number of connections present within the entire network. Longer average path lengths and reduced network efficiency in TBI patients particularly in a major network hub such as the posterior cingulate cortex were also found. However, the network segregation was not affected significantly. These findings suggest patients suffering from TBI may show a significant deviation from the healthy brain's small world network. Overall, the patterns of network dysfunction caused by TBI are complex, but some unifying principles are emerging, such as the abnormal interactions between the sensory network and the default mode network (DMN) after TBI. Highly connected hub regions, such as the precuneus, are particularly susceptible to alterations in functional connectivity following TBI.[21]

Recently, Murugesan and colleagues[24] have developed a machine learning approach that can automatically distinguish between youth (9–13 years) athletes who have experienced varying levels of head impact exposure in the course of a single season of play. The levels include no or minimal exposure for control athletes and low- and high-impact exposure for football players. The method achieves high labeling accuracy using just features from the intrinsic networks extracted from rs-fMR imaging. The major components of their approach are shown in **Fig. 3**.

Evidence for Hypoconnectivity in Traumatic Brain Injury

Multiple studies have shown evidence of hypoconnectivity following TBI using seed-based analysis. Xiong and colleagues[25] found decreased functional connectivity in the thalamus, caudate nucleus, and right hippocampus in mTBI patients. Johnson and colleagues[26] found the DMN to have a reduced number of connections and a reduction in the detectable connection strengths. A decreased number of connections and decreased strength of connections were found in the posterior cingulate and lateral parietal cortices, and an increased number of connections were found in the medial prefrontal cortex even in less severe subconcussive head impacts, a milder injury which typically exhibits no clinical symptoms. Rigon and colleagues[27] investigated the differences in interhemispheric functional connectivity of resting state networks between chronic mild to severe TBI patients and normal controls by selecting components such as the DMN, frontoparietal, executive, and sensory motor areas. Their results suggest decreased interhemispheric connectivity for externally oriented networks, such as the frontoparietal and executive networks, but increased interhemispheric connectivity for the DMN following TBI.

Other studies using ICA also demonstrate hypoconnectivity following TBI. Stevens and colleagues[28] used ICA to extract 12 distinct resting

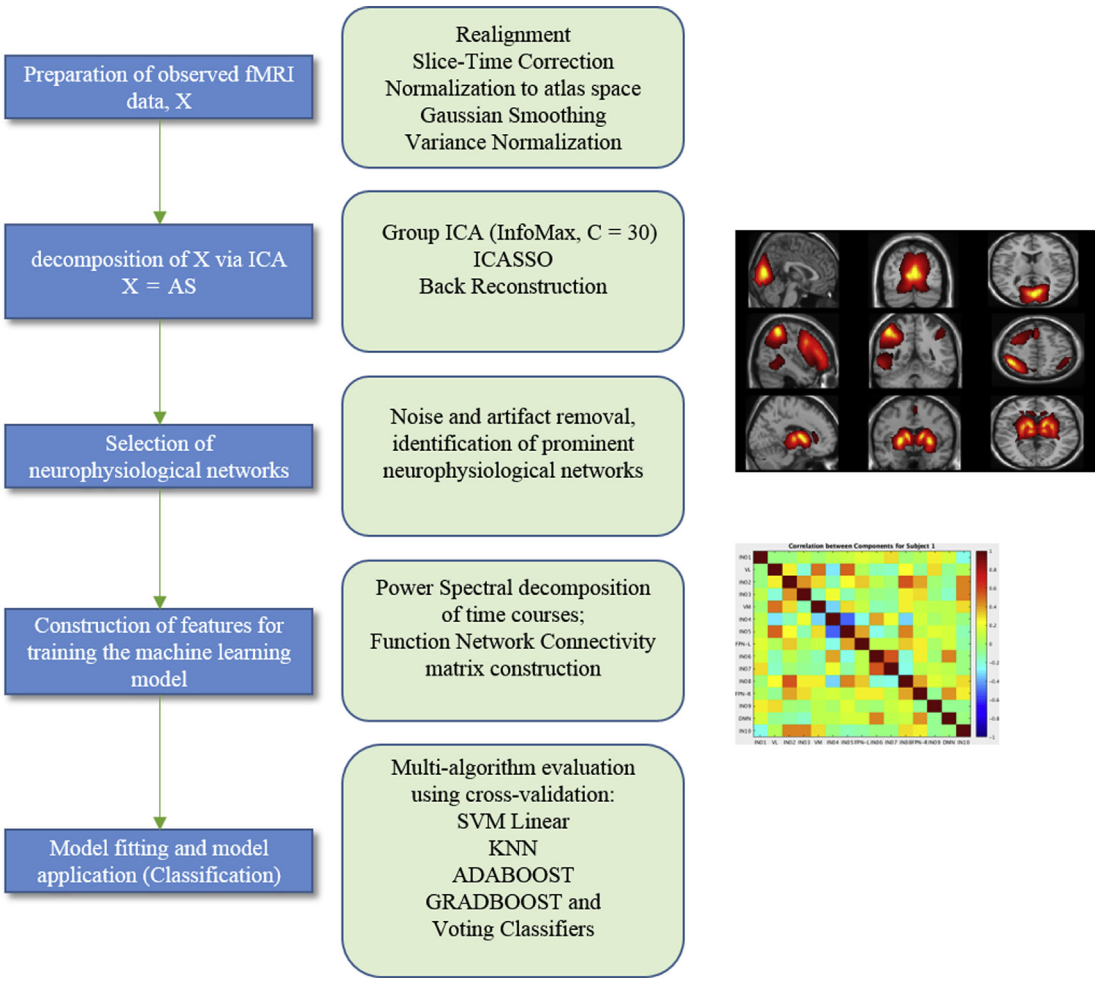

Fig. 3. Process flow for the training and application of a machine learning classifier that predicts head impact exposure using rs-fMR imaging. Left column highlights the main processing steps from preprocessing through classification. Right column provides details of each step presented by Murugesan and colleagues,[24] which automatically distinguishes athletes who, over the course of a single season of play, have experienced: no impact exposure, low-impact exposure, and high-impact exposure. ADABOOST, adaptive boosting; GRADBOOST, gradient boosting; ICASSO, software package for investigating ICA; KNN, k-nearest neighbors; SVM, support vector machine.

state networks from 30 mTBI patients and extended their study to all the extracted components. Diminished connectivity of the posterior cingulate cortex in the DMN was reported in mTBI. Iraji and colleagues[29] performed ICA analysis in 12 mTBI patients and reported reduced functional connectivity in the DMN and precuneus regions compared with controls. Palacios and colleagues[30] also used ICA on 75 mTBI patients, who also had CT within 2 to 3 hours of injury. The mTBI patients had significantly decreased connectivity in the frontal brain areas when conventional structural imaging (CT/MR) demonstrated evidence of TBI, and significantly decreased connectivity in the orbitofrontal network and the DMN when the conventional imaging was negative for evidence of TBI.

Evidence for Hyperconnectivity in Traumatic Brain Injury

There is also evidence for hyperconnectivity in TBI, and it is considered to be a common response to TBI. Shumskaya and colleagues[20] studied the relationship between functional connectivity patterns and cognitive abnormalities using resting state networks extracted from group ICA of 43 moderate/severe TBI patients and found that attention abnormalities in TBI were associated with increased connectivity in the sensorimotor networks. In addition, longitudinal studies have shown that despite decreasing functional connectivity during recovery, connectivity remained higher in moderate to severe TBI relative to healthy controls.[31,32] This work suggests that

hyperconnectivity in moderate and severe TBI patients may be present regardless of recovery phase (acute, subacute, or chronic phase) and does not represent a transient process as found in other mTBI studies. Thus, hyperconnectivity might become a useful prognostic tool to predict outcomes in moderate and severe TBI.[33] Differences in the results between studies may be attributed to differences in severity of TBI of the studied cohorts, region selection methods, time from injury, graph metrics used, the nature of connectivity studied, and extent of gray and white matter damage.

Automating Diagnosis with Machine Learning

Conventional neuroimaging techniques have limited ability to detect functional connectivity abnormalities, which underlie TBI-related neurocognitive deficits. Advanced neuroimaging, including rs-fMR imaging, can provide increased sensitivity to measure such deficits; however, these deficits can be subtle and diffuse and vary from patient to patient, which makes them hard to identify using standard statistical techniques. Therefore, it is important to develop tools that help automate clinical mTBI diagnostics using rs-fMR imaging. Promising machine learning methods have been developed for rs-fMR imaging interpretation that identify important diagnostic network features to predict mTBI severity, aim to automate mTBI diagnosis, and determine whether patients with TBI have similar functional network changes as patients with Alzheimer disease (AD).

Ravishankar and colleagues[34] used a machine learning framework to identify functional connectivity features associated with symptom severity in mTBI. In this study, 78 mTBI patients were imaged at 4 time points (3 days, 7 days, 21 days, and 3 months) after injury with 6-minute rs-fMR imaging. The investigators found that changes in the executive control and visual networks were most strongly associated with symptom scores. In particular, decreased connectivity between left executive control network and higher visual networks were found, which may correspond to some typical mTBI symptoms, including memory and visual deficits. This study suggests that rs-fMR imaging network features may be useful for predicting effects of mTBI and recovery trajectories.

Another machine learning approach developed by Iraji and colleagues[35] combines structural and functional network connectivity changes to predict whether a subject was a healthy control or an mTBI patient. In this study, 40 mTBI patients at the acute stage and 50 healthy controls were recruited. Sixty signatures were found that distinguish patients from controls with 100% specificity and 93.75% sensitivity. Specifically, the emotion network demonstrated decreased intranetwork connectivity, whereas perception networks demonstrated increased interactions among action-emotion and action-cognition regions.

Machine learning is also being used to characterize a putative association between TBI and AD. Previously, Van Den Heuvel and colleagues[36] suggested TBI may be a risk factor for developing AD. More recently, Vanderweyen and colleagues[37] hypothesized that there is a common network abnormality between the functional connectome of TBI and AD, and a machine learning-based model was developed to test this association. The model, when trained on AD and healthy control subjects, achieved 82% accuracy in distinguishing AD from healthy controls. Notably, the same classifier also achieves an accuracy of 80% distinguishing TBI from healthy controls without any retraining on TBI, indicating that there are common network abnormality aspects in the connectomes of AD and TBI. Moreover, these results suggest that existing large, longitudinal Alzheimer datasets may be able to jump start the machine learning process, perhaps obviating gathering as much longitudinal TBI imaging data in order to develop a diagnostic tool for TBI.

Longitudinal Recovery Monitoring and Outcome Prediction

Complementary to the development of machine learning-based methods has been the concurrent development of statistical methods that predict TBI outcomes from subacute and longitudinal rs-fMR imaging functional connectivity measures. These methods may be able to predict the future recovery profile and determine which patients will require the most aggressive cognitive therapy and careful monitoring and which patients may do well with simply palliative care.

In a study of the DMN using rs-fMR imaging by Zhu and colleagues,[38] there is evidence that longitudinal changes in functional and structural connectivity of the default-mode network (DMN) can serve as a potential biomarker to monitor sports-related concussion recovery. This study tracked 11 control subjects and the recovery of 8 concussed collegiate football players over the course of 30 days after injury. Resting state and diffusion MR imaging (DTI) were acquired from each subject within 24 hours, 7 days, and 30 days after concussion. In both cohorts, DTI-based structural connectivity

remained unchanged throughout the study; however, the cohorts differed significantly in the progression of overall DMN functional connectivity. Compared with the control group, the concussed group exhibited increased functional connectivity on day 1, significantly decreased functional connectivity on day 7, and partial recovery to that of the normal group by day 30. These results indicate rs-fMR imaging holds potential as a biomarker to monitor recovery in the concussed athlete.

Banks and colleagues[39] studied rs-fMR imaging differences between mTBI patients and healthy controls using a different set of functional connections, namely the functional connectivity of the thalamus with other regions and brain networks. This work examined longitudinal functional connectivity changes over a 4-month period in 13 mTBI subjects (mean age 39.3, 31% women) and 11 age- and gender-matched controls without mTBI (mean age 37.6, 36% women). Compared with controls, mTBI patients exhibited an increased functional connectivity between the thalamus and the DMN, whereas exhibiting a decreased functional connectivity between the thalamus and the dorsal attention network (DAN) and between thalamus and the frontoparietal control network. From 6 weeks to 4 months after injury, increased functional connectivity was identified between the thalamus and the DAN that was associated with decreased pain on the Brief Pain Inventory, and decreased postconcussive symptoms on the Rivermead Post-Concussion Symptoms Questionnaire. These findings suggest that thalamic connectivity may serve as a quantitative measure of recovery extent following mTBI.

MAGNETOENCEPHALOGRAPHY PROTOCOLS

MEG is a noninvasive form of brain imaging.[40] Clinically, MEG is used to identify seizure foci in patients with epilepsy.[41] Recent studies have shown MEG to be a useful tool in TBI research. One such study by Huang and colleagues[42] demonstrated changes in functional connectivity during rs-MEG in Veterans diagnosed with mTBI due to a blast. In this study, Veterans with blast-induced mTBI had increased functional connectivity in all frequency bands but the alpha band. Another study by Tarapore and colleagues[43] showed decreased functional connectivity in the alpha band in a group of civilian patients with mild, moderate, and severe TBI. A study by Alhourani and colleagues[44] found decreased local efficiency in different brain regions of patients with mTBI.

Acquisition

The high temporal resolution and wider dynamic range of MEG complements and extends standard rs-fMR imaging acquisition. Typical MEG scanners use between 250 and 300 sensors to measure the magnetic signals from the brain. These sensors are located within a dewar and do not come in direct contact with the subject's scalp. The acquisition is completely passive, and head position indicator coils are applied to track any head motion.[45] rs-MEG acquisition is similar to rs-fMR imaging from the subject's perspective. The subject is asked to keep their eyes open, closed, or look at a cross-hair displayed on a projector for 6 to 10 minutes. However, in MEG, the subject is often seated rather than in a supine position.

Reconstruction Techniques

The sources of these signals can be mapped from sensor space to source space (eg, brain space) using a variety of source localization algorithms. These algorithms are often simpler, yet more accurate, than those used in electroencephalography because the magnetic fields are relatively unaffected by the conductivity of the various tissues in and surrounding the brain, traveling seamlessly through the brain and skull. One source localization approach is beamforming, which builds a spatial filter and was originally developed for radar technology.[46] Beamforming methods used for MEG source reconstruction are often designated as source "scanning" methods because they search a grid for the best solution, usually by minimizing the noise in the output or source variance.[47] Compared with other methods, one benefit of the beamforming methods is that these methods do not limit the spatial solution to predetermined anatomic locations or regions of interest. Such data-driven solutions can minimize model bias for resting state analyses.

MAGNETOENCEPHALOGRAPHY FINDINGS

Frequency Domain

MEG data can also be analyzed in the frequency domain. The frequencies are primarily divided into functional categories, or spectral bands, of delta, theta, alpha, beta, and gamma. Changes in the magnitude and location of these frequencies during resting state scans may be informative of disease states. TBI literature often focuses on the delta band. Delta rhythms (0.5–4 Hz) are normally present during deep sleep but are also seen in pathologic states in adults. Pathologic delta waves originate in different locations depending on the disease. Predominantly, delta

waves arise in areas of the cortex overlying white matter lesions.[48] Research on these rhythms and their causes is still ongoing.

Of particular interest to TBI is work by Huang and colleagues[49] showing increased delta waves after TBI. This work describes an automated algorithm for delta wave quantification applied to 45 mTBI patients and 10 moderate TBI patients with rs-MEG. Abnormalities were detected in the delta waves of 87% of the mTBI patients and 100% of the moderate TBI patients. In addition, the number of cortical regions with abnormal delta waves correlated significantly with the post–concussive symptom scores.[49–52] Preliminary data from another study also showed coup contrecoup injury patterns.

Automating Diagnosis with Machine Learning

Manual analysis of the MEG data is typically used as a cursory inspection to ensure that the data have been collected properly, whereas quantitative statistical analyses and automated machine learning interpretations are important to bringing rs-MEG into routine clinical use. Recently, several machine learning methods have been developed for rs-MEG interpretation that help identify important diagnostic network features to automate mTBI diagnosis and help predict mTBI severity. An approach that can automate individual diagnosis would overcome subjectivity in concussion diagnosis commonly based on clinical judgment from self-reported measures and behavioral assessments.

Vakorin and colleagues[53] investigated the type of alterations that occur in resting state oscillatory network phase synchrony in adults with mTBI and whether machine learning can accurately detect mTBI in individual subjects. rs-MEG was recorded and structural MR imaging was acquired from 20 patients with mTBI and 21 age-, gender-, and handedness-matched healthy controls. mTBI was associated with reduced network connectivity in the delta and gamma frequency range (>30 Hz) and increased connectivity in the slower alpha band (8–12 Hz). The most discriminatory features were found in the alpha band (8–12 Hz). Classification confidence was found to be correlated with clinical symptom severity scores. Overall, the results demonstrate that combining MEG network connectivity and machine learning is a promising approach to diagnose mTBI and may also help estimate mTBI severity.

Antonakakis and colleagues[54] investigated the utility of a different set of features extracted from rs-MEG for discriminating mTBI from healthy controls. This study analyzed cross-frequency coupling from rs-MEG in 30 mTBI patients and 50 controls. A classification accuracy of greater than 90% was achieved in distinguishing mTBI patients from controls across many frequency band pairs. A maximum of 96% accuracy was achieved across the delta and low gamma bands, and this same coupling demonstrated 100% sensitivity and 93% specificity. Their findings showed that compared with mTBI patients, healthy controls formed a dense network of stronger local and global connections characteristic of higher functional integration. These results underscore the critical role development of machine learning tools for studying brain networks computed from rs-MEG serves and suggest that phase-to-amplitude coupling and tensorial representation of connectivity profiles may yield valuable biomarkers for the clinical diagnosis of mTBI.

PEARLS, PITFALLS, VARIANTS

There is significant heterogeneity in the current literature that may hinder direct translation to patient care. Imaging of patients with TBI faces many clinical challenges limiting its application. Timing of acquisition of rs-fMR imaging in patients with TBI, in relation to the patient's injury, provides several unique challenges.

First, it is difficult to image these patients in the hyperacute or acute setting because MR imaging is a relatively lengthy process that can preclude administration of critical resuscitative measures. Patients with TBI should only be sent to MR imaging if they are hemodynamically stable. Scanning patients under critical care who are intubated requires a team effort by technologists, nursing, respiratory therapists, and physicians to safely and effectively perform an MR imaging in the clinically critical patient. Frequently, a routine noncontrast head CT can be safely performed and will adequately answer the clinical question in the acute setting. Furthermore, when MR imaging is necessary, rs-fMR imaging acquisition is not typically included as part of an expedient brain MR imaging protocol, because it has not yet been proven clinically useful in these patients.

Second, in the acute setting, TBI patients have been demonstrated to have alterations in hemodynamic response that may confound rs-fMR imaging analysis and interpretation, if not properly accounted for in the analysis. Finally, hemorrhage and contusions may alter the BOLD signal or produce artifact that limits evaluation. Timing acquisition to minimize the effects of noninterest, while maximizing the effects of interest, is important; however, how to reliably establish this timing is yet to be defined because there is no clear consensus on the best time or times to perform rs-fMR imaging on TBI patients. Because the injury and subsequent healing process are dynamic, imaging only provides

a single snapshot in time of that process. Longitudinal studies with consistent imaging and analysis techniques need to be performed to understand the most useful time or times for performing rs-fMR imaging before it will be accepted as a useful biomarker for diagnosis and prognosis in TBI.

Translation of research to individual clinical patients poses many difficulties. Translation of postprocessing methods proposed in the literature may be difficult without the proper detailed documentation and computing resources. Application of group analyses to individual patients risks extrapolation from outside of the specific characteristics of the studied patient cohort and may lead to inaccurate interpretation of the results for an individual patient. Training machine learning methods to make individual diagnoses and prognoses is one step toward remedying this limitation. Given the complex biomechanics of closed head injuries and many additional variables involved in TBI, including patient characteristics, trauma mechanism, and post–trauma management, each individual injury is truly unique.

Pearls, Pitfalls, Variants

- Acquisition of rs-fMR imaging is difficult in the acute setting because of more pressing clinical needs.
- Hemorrhage and contusions may alter BOLD signal.
- Translation of research methods to individual clinical patients is difficult.
  - Postprocessing methods may not be reproducible.
  - Group analyses applied to an individual may be inaccurate.
    - Training machine learning methods may make individual diagnoses and prognoses possible.

DISCUSSION

Respecting the aforementioned limitations, rs-fMR imaging is a leading imaging candidate for translation to the clinic. Assignment of diagnosis and prognosis to patients carries serious ethical and medicolegal implications that must be considered; providing an inaccurate diagnosis or prognosis based on new techniques without adequate supportive evidence in the existing literature is unethical and may be negligent. In addition, because the topic of TBI has been recently in the news and social media, the interested public, including potential judges, jurors, and lawyers, may have preconceived ideas and biases. Furthermore, new and complex techniques, such as rs-fMR imaging, carry implicit risks of oversimplifying the pathophysiology, technique of acquisition, method of analysis, and interpretation for the lay public. In summary, care must be taken to ensure there is adequate evidence supporting the clinical utility of these techniques before incorporating them into routine clinical care.

In the future, the methods discussed in this review should be tested on large data sets to determine clinical relevance. Comorbidities such as depression and posttraumatic stress disorder should be included to determine their effects on the algorithms. In addition, the methods should be automated so that they can be easily reproducible in a clinical routine. One of the more promising avenues for rs-fMR imaging and rs-MEG may be the ability to predict recovery time and evaluate therapies. Both modalities allow us to study the healing process in a quantitative way that has not been available previously. In conclusion, there are many promising avenues for rs-fMR imaging and rs-MEG in TBI diagnosis and treatment. Moving these into the clinic should be approached with cautious optimism.

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