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Mapping the Connectome Following Traumatic Brain Injury

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Abstract There is a paucity of accurate and reliable biomarkers to detect traumatic brain injury, grade its severity, and model post-traumatic brain injury (TBI) recovery. This gap could be addressed via advances in brain mapping which define injury signatures and enable tracking of post-injury trajectories at the individual level. Mapping of molecular and anatomical changes and of modifications in functional activation supports the conceptual paradigm of TBI as a disorder of large-scale neural connectivity. Imaging approaches with particular relevance are magnetic resonance techniques (diffusion weighted imaging, diffusion tensor imaging, susceptibility weighted imaging, magnetic resonance spectroscopy, functional magnetic resonance imaging, and positron emission tomographic methods including molecular neuroimaging). Inferences from mapping represent unique endophenotypes which have the potential to transform classification and treatment of patients with TBI. Limitations of these methods, as well as future research directions, are highlighted.

Keywords Amyloid beta · Arterial spin labeling · Cognition · Coma · Diffusion tensor imaging · Diffusion-weighted imaging · Electroencephalography · Functional magnetic resonance imaging · Neurologic recovery · Magnetic resonance imaging · Magnetic resonance spectroscopy · Magnetoencephalography · Neural plasticity · Positron imaging tomography · Susceptibility-weighted imaging · Tau protein · Translocator protein · Traumatic axonal injury · Traumatic brain injury

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Introduction

Traumatic brain injury (TBI) is recognized as a major public health concern because it is a leading cause of death in children and young adults and a significant driver of long-term disability in survivors [1–3], with direct and indirect healthcare expenditures between $50 and 100 billion in the USA alone [3, 4]. Despite this tremendous burden, there is a lack of accurate and reliable biological markers to detect TBI, classify its severity, stratify patients for treatment, and predict outcome [5, 6].

In the acute clinical setting, TBI severity is classified on the basis of level of consciousness [7] and on structural abnormalities identified on cranial CT scan [8, 9]. While the clinical classification may be confounded by the presence of concomitant sedation or physiological and metabolic perturbations, structural imaging is less susceptible to this problem. However, cranial CT scan, the most widely used structural neuroimaging tool, lacks sensitivity for the detection of smaller,

microscopic lesions that constitute traumatic axonal injury (TAI), a pattern of multifocal white matter disruption seen in TBI of all severities (see below). TAI is a key determinant of clinical outcome following injury [10] and is identifiable with more sensitive magnetic resonance imaging techniques [11–16]. Lesions associated with TAI tend to be distributed in multiple sites across the central nervous system and evolve dynamically over time—disrupting systems responsible for integrated and temporally sustained cerebral function [17–19]. This disruption is more likely to affect domains of function which do not localize to a specific location site in the brain but are dependent on the connectivity and integrative capacity of distributed neural systems, e.g., conscious awareness, attention, memory, and planning—domains of cognition and behavior whose impairment are phenotypic hallmarks in patients with TBI [20–28]. This has led to the view that TBI is analogous to disorders of neural integration [18, 29], the corollary of which is that recovery of neurologic function following TBI will be closely linked with restoration or reconfiguration of integrative neural connectivity [30, 31•, 32].

In recent years, the detection and characterization of TBI have been transformed by the introduction of new MRI pulse sequences and enhanced sophistication in statistical and computational approaches to mapping of regional brain data [33]. The use of diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), and susceptibility-weighted imaging (SWI) has enlarged our understanding of TAI [14, 21, 25, 34–39]. Results obtained with MR spectroscopy reveal dynamic biochemical changes which track clinical severity and outcome following TBI [40–42]. Mapping of functional activation using positron emission tomography (PET), functional MRI (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) indicates changes in large-scale connectional architectures which may help differentiate cognitive phenotypes and classify outcome probabilities following TBI [30, 43–46, 47•]. Molecular probes used in conjunction with positron emission tomography reveal neurodegenerative and neuroinflammatory events associated with TBI in the acute or chronic setting [48–50]. Taken together, results from brain mapping are consistent with an emerging model of TBI "endophenotypes," clinically latent patterns which represent biological links between underlying molecular and cellular phenomena and externally observable clinical syndromes. Here, recent inferences from brain mapping in patients with TBI are selectively reviewed, together with current knowledge gaps and priorities in the scientific agenda.

Neurobiological Considerations

Three pathological processes are believed to contribute substantively to the disorder of systems observed in TBI: axonal injury, synaptic dysfunction, and modifications in glia (Table 1). TAI (also referred to as "diffuse axonal injury") is a unique pattern of multifocal neural damage induced by sudden shearing/stretching forces applied to projections lying within the white matter tracts of the central nervous system [51, 52•, 53–56]. TAI is linked to a sequence of events that may include cellular mechanotransduction, axoskeletal disruption, transport interruption, membrane failure, calcium entry, focal axonal swelling, mitochondrial dysfunction, lipid peroxidation, proteolysis, and, if the injury is severe or sustained enough, cell death [57–59]. Axonal damage is associated with increased inflammatory signaling mediated in part by activated microglial cells [60], and evidence of neuroinflammation may be detected years after the initial injury [48, 61, 62]. TAI is a common pathological substrate encountered in TBI of all severities. It is associated with many of the acute clinical manifestations of TBI including loss of consciousness, confusion, and impairments in cognition. Recent research suggests that TAI may be linked to neurodegenerative conditions whose clinical onset is observed years after exposure, such as Alzhemier's disease [63], non-Alzheimer's dementias [64], and chronic traumatic encephalopathy [19, 65••, 66].

The relationship between TBI and changes in synaptic structure and function is supported by an emerging body of literature [67]. In animal models of TBI, dendritic beading and fragmentation, decreased number of dendritic branches, and changes in dendritic spine density are observed in injured neurons and also in cells remote from, but monosynaptically connected to, sites of injury [68–70]. Experimental TBI is associated with downregulation in a number of key pre- and post-synaptic proteins including synaptotagmin, synaptophysin, synapsin, synaptojanin, post-synaptic density protein-93 and protein-95, and DISC1 [67, 71]. Finally, hippocampal long-term potentiation, a measure of synaptic efficiency and plasticity, is depressed acutely following experimental TBI [72–77]. However, this may be a time-dependent and/or location-specific effect, and increased synaptic efficacy and associated cortical hyperexcitability have been noted weeks after white focal matter transection [78], with implications for post-injury epileptogenesis and plasticity.

The central role of astrocytes and oligodendrocytes in central nervous system trauma is the object of intense investigation. Following injury, astrocytes may have both beneficial roles, such as restoration of neurotransmitter and ionic homeostasis in the extracellular milieu and modulation of inflammatory signaling, and deleterious effects, such as glial scar formation [79–81]. Impaired ability of astrocytes to exchange potassium across the cell membrane may contribute to acute neuronal or synaptic dysfunction [82]. There is also mounting evidence that TBI is associated with acute oligodendrocyte death, with consequent axonal demyelination, impaired action potential propagation, and spontaneous remyelination [83–85]—processes whose role in mediating chronic post-traumatic neurodegeneration is not well understood.

Table 1 Mechanisms of traumatic axonal injury

	Cellular substrate	Neuroimaging correlate or biomarker
Axonal injury	Cellular mechanotransduction Membrane failure Focal axonal swelling Mitochondrial dysfunction Lipid peroxidation Proteolysis Axoskeletal disruption Cell death	DWI—restricted diffusion DTI—decreased anisotropy MRS—decreased NAA fMRI, PET, ASL, EEG, MEG—changes in FC PET radioligands—binding of amyloid protein (PiB, florbetapir) and tau protein ([F-18]FDDNP)
Glial modifications	Astrocytes: glial scar formation Oligodendrocytes cell death: demyelination, remyelination, axonal regrowth Microglia	T2, FLAIR—hyperintense signal DTI—increased radial diffusivity MRS—increased Cho PET radioligands binding translocator protein-18 kDa (TSPO) fMRI—changes in FC?
Synaptic dysfunction	Changes in dendritic morphology Changes in pre- and post-synaptic proteins (synaptotagmin, synaptophysin, synapsin, synaptojanin, post-synaptic density protein-93 and protein-95, and DISC1) Changes in LTP	fMRI, ASL, EEG, MEG—changes in FC

DISC1 disrupted in schizophrenia 1 protein, *LTP* long-term potentiation, *DWI* diffusion-weighted imaging, *DTI* diffusion tensor imaging, *MRS* magnetic resonance spectroscopy, *NAA* N-acetyl-aspartate, *fMRI* functional magnetic resonance imaging, *PET* positron emission tomography, *ASL* arterial spin labeling, *EEG* electroencephalography, *MEG* magnetoencephalography, *FC* functional connectivity, *PiB* Pittsburgh Compound B, *FLAIR* fluid attenuated inversion recovery, *TSPO* translocator protein

Collectively, the post-injury cellular morphological and electrophysiological changes noted in axons, synapses, and glia represent a plausible biological framework to understand the alterations in anatomical and functional connectivity which have been identified with the help of brain mapping approaches [18].

Statistical Modeling

Meaningful advances in neuroimaging have been tightly coupled with the development of advanced novel analytical approaches. Early analysis of neuroimaging data was based on nonquantitative or semiquantitative examinations. Such methods were prone to bias since they overlook large areas of the brain, and they do not have standard application methods which challenge the reliability of the results. The establishment of standard image templates and advances in image registration and normalization have enabled innovative solutions for combining images across multiple subjects in one space for analysis [86]. Methods have evolved to quantitatively evaluate anatomical and functional differences in the whole brain across many subjects, generating large and rich datasets. New analytical tools have been developed to perform voxel-based analysis, such as voxel-based morphometry obtained with T1-weighted image sequences, or to generate tractographic representations of white matter using DTI data [87, 88].

The determination of neural connectivity, a measure of signal coherence or correlation across different regions of the brain, requires specific statistical modeling [86]. Three types of connectivity can be distinguished (Table 2): (1) structural connectivity which is based on the anatomical connections linking spatially discrete neural populations; (2) functional connectivity which describes the statistical covariance of time-dependent signals between neural populations; and (3) effective connectivity, which evaluates directionally specified cause-and-effect relationships between neural populations [89, 90]. The evaluation of connectivity in functional neuroimaging data is accomplished with either seed-based correlation or independent component analysis (ICA). In the seed-based approach, a region of interest is identified a priori on the basis of a model or hypothesis, and the correlation in signal time courses between the seed and other brain regions is computed [91]. Independent component analysis (ICA) is a model-free, data-driven technique which decomposes brain activation maps into discrete components each of which has its unique time course, then estimates covariance from predefined temporal windows [92].

Modeling and representation of brain connectivity data are increasingly reliant on graph theoretical methods. Nodes (vertices) are identified based on prior anatomical knowledge or brain atlases; then, internodal connections (edges) are mapped to produce a network graph [93, 94]. Different topological metrics may be used to describe the emergent graph. *Clustering coefficient* expresses the probability that two randomly selected nodes in a graph are connected to each other.

Table 2 Alterations in brain connectivity

	Definition	Data source	Analytical paradigms
Anatomical connectivity	Mono- or polysynaptic neuronal links	DTI	Fractional anisotropy, axial diffusivity, radial diffusivity, white matter tract volume
Functional connectivity	Statistical covariances between neuronal populations	PET, fMRI, ASL	Seed-based correlate Independent component analysis
		EEG	Coherence analysis
		MEG	Independent component analysis Distributed source models
Effective connectivity	Causal interactions between neuronal populations	EEG, ERP, MEG, fMRI, PET	Structural equation modeling Granger causality Dynamic causal modeling

DTI diffusion tensor imaging, *PET* positron emission tomography, *fMRI* functional magnetic resonance imaging, *ASL* arterial spin labeling, *EEG* electroencephalography, *MEG* magnetoencephalography

Path length is another measure that reflects integration of a network and is measured by any unique sequence of edges that connects two nodes with one another. Finally, *node degree*, defined as the number of edges which are connected to the node or the centrality of the latter, captures the importance of a given node in a network; the most highly connected nodes are referred to as "hubs" [89]. In the following sections, we will selectively review recent findings obtained when brain mapping approaches have been applied in patients with TBI.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is multiparametric allowing versatile image reconstructions including morphological images, susceptibility-weighted images, diffusion-weighted images, and metabolic and perfusion images [95]. Overall, MRI is more sensitive in detecting acute TBI compared to CT scan which is often normal on initial presentation [11–16]. Even commonly used MRI pulse sequences such as T1 and T2 may lack sensitivity for the detection of TAI [96]. Recent progress in MRI acquisition suggests it is possible to detect and characterize subtle structural and functional changes associated with TBI [97].

Gradient Recalled Echo and Susceptibility-Weighted Imaging

T2*-weighted gradient-recalled echo (GRE; also sometimes referred to as just T2*) and susceptibility-weighted imaging (SWI) are MRI pulse sequences that are highly sensitive to the paramagnetic susceptibility of iron found in hemosiderin, a breakdown product of hemoglobin which is deposited in the brain tissue following parenchymal bleeds [98–102]. GRE and SWI have greater sensitivity than CT and conventional MRI sequences (T1- and T2-weighted imaging) in detecting cerebral microbleeds in patients with hypertension, stroke, and small vessel disease [100]. Studies suggest that SWI is even more sensitive than GRE in the detection of microbleeds [101, 103]. MRI-identified microbleeds are used to support diagnosis, characterize disease burden, and predict clinical outcomes in patients with cerebral amyloid angiopathy (CAA) [104, 105]. A recent study—whose relevance to TBI is apparent in the subsequent discussion—combined results from SWI, PET identification of amyloid using Pittsburgh compound B, and DTI to evaluate network characteristics in patients with CAA and aged-matched controls [106]. In this study, graph analysis suggested that CAA patients had reduced global network efficiency which was linked to diminished cognitive and gait performance, effects which remained significant in multivariable analysis.

Recent work indicates that focal parenchymal microhemorrhages frequently co-locate with evidence of axonal damage and could represent a valuable biomarker in a subset of patients with TBI [38, 107–114]. The current model is that biomechanical forces responsible for TAI can induce extravasation of blood from multifocal damage to small vessels [109], leading to a pattern sometimes referred to as "diffuse vascular injury" [112] or "hemorrhagic DAI" [55]. On GRE or SWI, traumatic microhemorrhages appear as focal areas of reduced signal intensity caused by the paramagnetic effects of deoxyhemoblogin which may be undetectable using T2-weighted or FLAIR MRI sequences [115, 116]. The sensitivity of these techniques in detecting microbleeds associated with DAI increases with the strength of the magnetic field [117]. In addition, SWI is reported to have higher sensitivity in detecting traumatic microbleeds compared to $T2^*$-GRE [118]. The number and/or volume and distribution of SWI lesions have been found to correlate with clinical severity of TBI and with neurologic or cognitive outcome in both pediatric [38] and adult TBI populations [16, 108]. Some investigators have proposed traumatic microbleeds, when present, are unequivocal surrogate markers of TAI; building on this postulate and by training pattern classifiers via machine learning techniques, it

is possible to accurately classify patients with TAI even if they do not have microbleeds and, moreover, to better explain variances in post-injury long-term cognitive performance [113, 119••].

Diffusion-Weighted and Diffusion Tensor Imaging

Contrast signal in magnetic resonance diffusion-weighted imaging (DWI) is produced when water diffusion probabilities within tissue become less random—as, for example, when water is sequestered inside cells due to cytotoxic edema [120]. This pulse sequence has been extensively validated in the diagnosis of acute ischemic stroke [121, 122]. Diffusion tensor imaging (DTI) takes advantage of the anisotropic diffusion properties of water molecules in tissue to enable inferences regarding underlying white matter microstructure [123]; fiber tractography based on DTI provides a three-dimensional representation of white matter tracts in the central nervous system [124].

Studies conducted over the past two decades indicate that tissue diffusion characteristics are sensitive diagnostic and prognostic variables in patients with TBI. Water diffusion becomes restricted in acute TBI, presumably secondary to cytotoxic edema. The biological significance of post-TBI restricted tissue water diffusion has been supported by animal studies demonstrating histological changes which co-localize with areas of abnormal signal on DWI [125–127]. Areas of restricted diffusion detected with DWI represent a biomarker of nonhemorrhagic TAI that is more sensitive than CT or conventional T1 and T2 pulse sequences [14, 27, 34, 96, 110, 128–146]. Data suggest that DWI lesion number, volume, and location can increase the accuracy of outcome prediction in patients with TBI across the severity spectrum [34, 110, 128, 130, 131, 137, 146–148]. In an analysis of 77 patients with moderate–severe TBI, higher whole brain apparent diffusion coefficients were associated with discharge to home or rehabilitation [146]. In an earlier study involving 26 patients with TAI, the volume of lesions identified with DWI strongly correlated with modified Rankin scale at discharge [34]. Results from a larger cohort demonstrated a strong association between DWI lesions in the corpus callosum and the extended Glasgow outcome scale at 12 months [110].

In recent investigations, it has been shown that DTI is a sensitive method to detect and characterize tissue changes associated with TBI of all severities [149, 150]. In rodent models, changes in white matter anisotropy have been linked to histological evidence of TAI [36, 151–159]. In humans, DTI demonstrates a range of white matter alterations which are observed in mild, moderate, and severe TBI, and which may help classify post-injury functional and cognitive recovery phenotypes [14, 20, 21, 24, 25, 27, 35, 37, 42, 52•, 111, 119••, 160, 161, 162, 163, 164••, 165, 166, 167]. White matter tracts in which early post-traumatic DTI changes are most tightly linked to long-term outcome include the corpus callosum [20, 21, 37, 149, 160, 161, 166, 168, 169], internal capsule [37, 42, 170, 171], and brainstem [28, 37, 168, 172–174]. In a recent prospective multicenter study [37], 105 patients with severe TBI underwent brain MRI a mean of 21 days after injury, and DTI variables were evaluated in 20 predefined white matter regions based on the atlas established by Mori et al. [175]. Here [37], early discrimination between functional outcome categories was significantly improved with a prediction model that included DTI data, as compared to a model based exclusively on the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT) score [176].

Repeated DTI assessments during post-TBI recovery reveal dynamic changes in white matter, suggesting an active process whose biological underpinning might relate to different contributions of axonal damage, neuronal repair, demyelination, remyelination, and gliosis [21, 28, 177–180]. In one study, 30 patients with severe TBI were scanned with DTI 8 weeks post-injury and again at 12 months [21]. At follow-up DTI, fractional anisotropy had increased and reached normal or supranormal levels in the internal capsule and in centrum semiovale and the presence and magnitude of this increase was correlated with favorable functional outcome, while the presence of persistently low fractional anisotropy in the corpus callosum and cerebral peduncle was correlated with poor outcome [21]. In another study on moderate TBI patients evaluated 5–14 days after injury, fractional anisotropy was significantly reduced in the corpus callosum and/or internal capsule compared to controls and remained depressed 6 month later [177]. Newcombe et al. recently reported on 12 patients with moderate or severe TBI who underwent serial MRI in the acute phase and again 2–4 times during a follow-up period of up to 2.7 years after injury [178]. While there was considerable heterogeneity in individual time-courses, analysis suggested a dynamic process with time-dependent decreases in fractional anisotropy which were contingent on increases in axial and radial diffusivities and which were linked to performance on visual memory and learning tasks [178].

A growing body of research indicates that DTI might support predictions of cognitive recovery, or the outcome of neurorehabilitation, following TBI [20, 25, 27, 111, 119••, 166, 181–184], a detailed review of which is beyond the scope of this paper. A general finding is that pathological changes in regional white matter integrity are associated with impairments in a range of cognitive domains; however, the type, specificity, and magnitude of these associations are inconsistent across studies. In a very recent report, graph analysis was used to interpret DTI tractography data in 52 subjects who were scanned a mean of 37.56 months after moderate or severe TBI and compared to age-matched controls [119••]. Using machine learning techniques, the presence of TBI was predicted with 93.4 % accuracy, while information processing speed, associative memory, and executive function were

significantly associated with centrality measures in the cingulate cortex and caudate. In another recent study, Strangman et al. found that post-rehabilitation performance on tests of memory and learning were associated with reduced fractional anisotropy, respectively, in the parahippocampal white matter and anterior corpus callosum, left anterior internal capsule, and right anterior corona radiata [181]; however, fractional anisotropy predictions were no more accurate that pre-rehabilitation test scores.

Magnetic Resonance Spectroscopy and Magnetic Resonance Spectroscopic Imaging

Proton magnetic resonance spectroscopy (MRS) evaluates the signal of covalently bound protons to map regional concentrations of a range of chemical compounds. Commonly measured compounds include choline (Cho), creatinine/phosphocreatine (Cr), N-acetyl aspartate (NAA), lactate, and glutamate/glutamine (Glx) [185]. NAA is associated with neuronal and axonal integrity and decreased levels of NAA or NAA indexed to Cr (NAA/Cr) have been found after TBI in humans [40–42, 186–196]. Early reports indicated that brain NAA/Cr decreases acutely after TBI in the frontal lobe and that NAA/Cr correlated with injury severity (GCS) [188] and outcome (GOS) [40, 195]. Low NAA/Cr in the brainstem is strongly associated with unfavorable TBI outcome, often in tissue without discernible damage on conventional morphological MRI [186]. More recent work with serial MRS suggests that tissue NAA/Cr and NAA/Cho values decline rapidly then progressively recover over 1–4 weeks to near-normal levels in patients with favorable outcomes while levels remain lower in those with unfavorable outcome [41, 190, 196]. Linear discriminant analysis of combined MRS and DTI acquired 3–4 weeks after injury in patients with severe TBI suggested that these two approaches are complementary and when used in combination accurately discriminate between favorable and unfavorable 1-year functional outcomes [42]. Another study in mild TBI subjects which combined MRS with functional MRI suggested a positive correlation between NAA/Cr levels in the corpus callosum and interhemispheric functional connectivity [197]. Although results are promising, a number of questions remain regarding optimal methods for MRS data acquisition and analysis in patients with TBI [198, 199].

Functional Brain Mapping

Functional neuroimaging, the mapping of time-dependent signal changes to directly or indirectly track underlying neuronal activation, can be achieved with several modalities including positron emission tomography (PET), functional MRI (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG).

Positron Emission Tomography

PET methods identify the distribution of molecular probes labeled with a positron-emitting tracer or radionuclide [200]. Radionuclides best studied in the evaluation of TBI patients include ^{18}F Flourine-18-2-fluoro-deoxy-D-glucose (FDG) and ^{15}O-H2O which represent indirect markers of brain glucose and oxygen uptake. Both of these methods have been used to infer regional functional activation in the central nervous system because of the physiologic coupling between cellular energy metabolism and blood flow in normal situations [201]. Recently, it has been proposed that absolute indices of global and regional cerebral glucose metabolism could help differentiate unresponsive subjects with different levels of conscious processing [202–204]. In severe TBI patients evaluated less than 5 days after injury, comatose subjects had significantly reduced FDG-PET uptake in the thalamus, brainstem, and cerebellum when compared to noncomatose subjects [205]. Reduced glucose uptake has been observed in bilateral medial and basal frontal lobes, the cingulate gyrus, and the thalamus in severe TBI patients with chronic disorders of consciousness [202, 203, 206, 207]. Functional disconnection between brainstem arousal centers and the precuneus was described in a ^{15}O-H2O-PET study of patients who were in a persistent vegetative state. A remarkable case report combining DTI and FDG-PET documented recovery of verbal communication and motor function in a patient who remained unconscious for 19 years after severe TBI, a change which correlated with increased fractional anisotropy and glucose uptake in posteromedial parietal cortices that encompassed cuneus and precuneus [208].

In FDG-PET evaluations of patients in the subacute phase following severe TBI who did not have focal anatomical lesions on MRI, a correlation was established between reduced glucose uptake in the prefrontal cortex and the cingulate gyrus and impaired memory and executive function [209–211]. Investigation of memory task activation using ^{15}O-H2O-PET indicated that recovering moderate and severe TBI patients engage a frontal, anterior cingulate, and occipital network which is larger and less asymmetric than healthy controls, suggesting an impairment in cortical processing efficiency [212]. Resting FDG-PET studies in patients with mild TBI/concussion have yielded a range of findings [213–217]. No difference in resting FDG-PET uptake was noted on one comparison of patients with post-concussion symptoms and healthy controls [217]. Others have reported that concussion patients have reduced resting glucose metabolism in temporal and frontal regions [214, 215] or in cerebellum, vermis, pons, and medial temporal lobe [216]. An intriguing recent study completed in military mild TBI subjects during wakefulness and REM sleep identified a reduced metabolic rate of glucose in the amygdala, hippocampus, parahippocampal gyrus, thalamus, insula, uncus, culmen, visual association cortices, and midline medial frontal cortices [213].

Functional Magnetic Resonance Imaging

fMRI has emerged as the leading approach to map brain functional activation in humans. Correlative analysis conducted in TBI patients suggests a good match between regional activations obtained with PET and fMRI, although the spatial resolution is higher with fMRI [218]. The blood-oxygen-level-dependent (BOLD) fMRI signal correlates with neuronal activity as suggested by concurrent local field potential recordings in the visual cortex of nonhuman primates [219]. The value of fMRI has become increasingly apparent in the assessment of patients with disorders of consciousness, many of whom have had a TBI. These studies employ three distinct experimental paradigms [220]: (i) active fMRI studies which map BOLD signal changes associated with a specific motor or cognitive task; (ii) passive fMRI studies which map BOLD signal changes associated with an auditory, visual or sensory stimulus, and (iii) resting-state fMRI studies which map BOLD signal in the absence of any given task or stimulus. This literature has been reviewed elsewhere [220–222]. Here, we selectively review some of the recent fMRI studies.

Convergent lines of research indicate that spontaneous brain activity is organized topographically in dissociable large-scale functional networks which have quantifiable intrinsic and extrinsic connectivities (Table 2) [29, 223–226]. The resting-state paradigm has particular relevance in brain-injured patients in whom task responsiveness may not be reliably present. Resting-state fMRI activity associated with loss and recovery of consciousness following severe TBI has been characterized in several recent studies [43, 45, 47•, 163, 164••, 184, 227, 228, 229, 230, 231, 232, 233, 234•].

A significant number of studies have centered on activity or connectivity within the structures of the default mode network (DMN), a neuronal system which includes nodes in the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices [223, 235, 236]. Deactivation of the DMN is associated with engagement in goal-oriented activity [235], and changes in DMN activity or coherence have been identified in a range of neurological and psychiatric disorders. A recent coordinate-based meta-analysis of resting functional neuroimaging data (PET and fMRI) found that patients with disorders of consciousness have consistent reductions in activity within cortical structures associated with the DMN [43]. Resting functional connectivity of nodes within the DMN is significantly decreased in TBI patients across the severity spectrum [47•, 184, 229, 232, 233, 234•, 237–240], a pattern which has been linked to DTI evidence of white matter damage within the DMN [163]. Disruption of selected edges within the DMN may have particular significance in predicting emergence from coma: thus, in a cohort of patients who underwent fMRI within the first week after injury, connectivity strength between the posterior cingulate cortex (PCC) and medial prefrontal cortex was significantly greater in patients who recovered consciousness when compared to those who did not [233].

Recently, other non-DMN networks have been explored to describe neural changes following brain injury and to enhance the accuracy of phenotype and outcome classification. Deficiencies in task-induced deactivation of the DMN, or loss of the anticorrelation normally observed between the DMN and other networks, have been reported in patients with impaired consciousness [241–243], post-TBI cognitive impairment [164••, 239, 244, 245], and post-concussion syndrome [246]. In 133 brain-injured subjects who underwent fMRI 3–10 months after injury, functional connectivity within the salience network (in particular between the ACC and left anterior insula) accurately differentiated between vegetative state and minimally conscious state patients, while DMN connectivity (especially between PCC and left lateral parietal cortex) was linked to emergence from the vegetative state [234]. Using machine learning techniques, another group found that intrinsic network functional connectivity strength discriminated between vegetative state and minimally conscious state patients with an accuracy of >80 % in several large-scale networks (frontoparietal, salience, auditory, sensorimotor, and visual networks), with auditory network intrinsic connectivity providing the best discrimination, in particular, edges of the auditory network that connect auditory and visual cortical centers [47•].

In addition to investigating loss and return of consciousness in brain-injured patients, fMRI can map cognitive states and trajectories following TBI [227]. A graph analysis of resting fMRI data demonstrated that recovering TBI patients have longer average path lengths and reduced network efficiency most prominently affecting the posterior cingulate cortex hub [45]. While reduced network or edge functional connectivity is widely reported in many studies of TBI and could represent a valuable biomarker of TAI, selective increases in within-network fronto-parietal connectivity measures have been reported in patients in the chronic stage of post-TBI recovery and could represent compensatory mechanisms [163, 184, 230, 247•, 248, 249]. Task-fMRI studies conducted in TBI patients have indicated wider recruitment of cortical resources suggesting a loss processing efficiency in patients recovering from TBI [250–253]. Impaired working memory in chronic TBI patients has been correlated with decreased activation of frontal sites which are nodes in well-characterized memory networks [254]. Tracking of memory task-induced superior frontal activation in patients with TAI revealed a progressive normalization over time that correlated with improved task performance [255].

Arterial Spin Labeling

Arterial Spin Labeling (ASL) is an MRI acquisition sequence which allows a direct measure of regional cerebral blood flow

[256, 257] and can serve as a marker of functional activation albeit with temporal and spatial characteristics that are distinct from BOLD [258, 259]. In ASL, arterial blood is labeled magnetically and serves as an endogenous tracer, which allows the noninvasive quantification of regional brain tissue perfusion. In the chronic phase following moderate to severe TBI, resting ASL demonstrates reductions in the cerebral blood flow with more prominent regional hypoperfusion in the posterior cingulate cortices, the thalami, and multiple locations in the frontal cortices correlating with structural changes on DTI [260, 261]. During sustained attention and working memory tasks, chronic phase TBI patients had paradoxical increased activation of superior occipital cortices and the left superior temporal cortex whereas these areas were deactivated in healthy controls [262]. ASL has recently been used to evaluate patients with mild TBI [263, 264]. A longitudinal evaluation of concussed collegiate football players who underwent ASL 1 day, 1 week, and 1 month after injury found a reduction in right insular and superior temporal sulcus perfusion acutely that normalized at 1 month, although dorsal insular perfusion remained lower in subjects with persisting post-concussion symptoms [264].

The relationship between ASL measures of cerebral blood flow and BOLD functional connectivity was recently evaluated in healthy controls both in the resting state and during a working memory task [265]. Findings suggest that nodes with high resting or task-evoked BOLD functional connectivity (i.e., hubs) are also regions with comparatively elevated perfusion, a correlation which was most prominent in the DMN and executive control network [265]. ASL time courses may be may be used to evaluate large-scale functional activation and connectivity patterns with significant homologies to those obtained with BOLD [266–269]. The relevance of ASL connectivity analysis in patients with or recovering from TBI is currently unknown.

Electroencephalography

Electroencephalography (EEG) expresses, in the frequency domain, the composite electrical signal generated by dendritic synapses in the superficial layers of the cerebral cortex. When compared to fMRI, EEG has higher temporal resolution but lower spatial resolution; however, the pragmatic possibilities of EEG which can be deployed at the bedside in hospitalized or critically ill patients are of considerable interest. Quantitative EEG employs computational approaches to analyze amplitude, frequency, power, phase, and coherence, either independently or in different combinations. The analysis of EEG coherence or connectivity represents a unique opportunity to evaluate the impact of TBI on functional integration. Although early work in patients with severe TBI suggested an association between EEG coherence and MRI markers of neural integrity [270], a relation was not found between interhemispheric EEG coherence and post-injury outcome [271]. Subsequent quantitative EEG studies provide evidence of a loss of functional connectivity in patients with TBI [272–280]. Spatially distributed neuronal synchronization in the gamma frequency—which has been associated with perceptual awareness [281]—is impaired in patients with severe TBI [274]. In mild TBI patients studied with a high-density EEG array, interhemispheric and intrahemispheric (fronto-parietal, fronto-temporal, and temporo-parietal) coherence was comparable to healthy controls in the resting condition but significantly decreased during a working memory task [272]. Graph theoretical analysis applied to high-density EEG data acquired in the resting state of mild TBI subjects indicates that while global network efficiency is unchanged, the connectivity of dorsolateral prefrontal cortex and inferior frontal gyrus was increased, supporting the hypothesis that TBI results in a reorganization of network topology that may represent injury-associated or post-injury compensatory processes [280]. Similarly, in subjects with mild TBI following blast exposure, reduced EEG phase synchrony (indicating diminished interhemispheric connectivity) was noted in the frontal region, a finding which was associated with DTI evidence of damage to frontal white matter tracts [279]. Application of ICA and graph theory to EEG data from mild TBI patients suggests a significant decrease in the long-distance connectivity associated with a loss of small-world network topology [273].

Magnetoencephalography

Magnetoencephalography (MEG) records magnetic fields produced by neuronal electrical activity. Magnetic course imaging (MSI) combines MEG and MRI to map functional activation in the brain. MEG and MSI may be particularly valuable in the evaluation of patients with mild TBI and post-concussion syndromes [282]. Among 84 patients with mild TBI, MEG identified focal abnormalities in prefontal, posterior parietal, inferior temporal, hippocampus, and cerebellum [283]. MEG recordings made during cognitive flexibility tasks demonstrated disorganized and inefficient cortical activation of executive networks in mild TBI patients when compared to healthy volunteers [284]. In a direct head-to-head comparison, MEG was found to be significantly more sensitive to focal abnormalities in patients with post-concussion syndrome than structural MRI or EEG [285], single-photon emission tomography [286], or even DTI [287]. Resting-state MEG recordings in the alpha band in TBI patients compared to healthy controls indicate reduced functional connectivity [288] or, analogously, reduced Lempel–Ziv complexity [289], changes which suggest underlying distributed network damage. MEG-identified deficiencies in functional connectivity were recently described in multiple frequency bands (delta, theta, and alpha) and linked to post-TBI symptoms of inattention, anxiety, and depression [290].

Data acquired with MEG may also represent sensitive biomarkers of post-injury adaptation and plasticity. In a remarkable longitudinal evaluation of patients recovering from moderate to severe TBI who were studied before and after rehabilitation, resting-state MEG data revealed a loss of local and long-distance slow-frequency (delta and theta bands) connectivity and an increase in higher-frequency (alpha and beta) connectivity, changes which correlated with improved performance on neuropsychological testing [30]; moreover, network topologies in the post-rehabilitation patients more closely matched those observed in healthy controls than topologies seen in the pre-rehabilitation state [30]. Graph analysis applied to the same dataset showed that topological parameters following TBI are differentially affected in the delta band and decreased in the alpha band and that, following rehabilitation, these parameters evolve towards those of the control group [291]. These results support the hypothesis of a balance or trade-off between neural synchrony in slow and fast spectral bands as a fundamental mechanism driving post-injury recovery [291].

Molecular Neuroimaging

Recent work conducted with PET radioligands in vivo has generated invaluable insights on molecular mechanisms which may drive axonal injury and disrupt brain connectivity in TBI, including the deposition of amyloid protein, tau protein, and the detection of cerebral inflammatory activity [48–50, 292–301].

There is extensive evidence of an association between brain amyloid pathology and TBI [19, 296, 302–305]. Imaging of amyloid protein using carbon 11-labeled Pittsburgh Compound B ([11C]PiB) in a heterogeneous sample of 15 patients who were assessed 1 day to 1 year after TBI demonstrated cortical and striatal amyloid deposition which was not detected in healthy controls, findings which were corroborated in the postmortem brains of subjects who died after TBI [50]. Among patients with mild cognitive impairment, PiB-defined amyloid deposition is significantly higher in subjects with a history of TBI than those without, a difference which was not observed in cognitively normal individuals [306].

The role of tau protein as a molecular determinant of TAI and in post-TBI neurodegenerative disorders has been illustrated in a number of recent reports [19, 52•, 65••, 66, 307, 308]. [F-18]FDDNP, a selective tau protein radioligand, has been used to evaluate retired American football players who had a documented history of TBI and presented with cognitive or psychiatric manifestations [49, 309]. Tau protein deposition was prominent in several subcortical structures including midbrain, basal ganglia, thalamus, amygdala, frontal, parietal, posterior cingulate, medial and lateral temporal—a distribution which closely matches postmortem neuropathological analyses in subjects who died of chronic traumatic encephalopathy, a neurodegenerative syndrome linked to TBI exposure [49, 66, 309].

Innate and adaptive immunologic responses occur both acutely and in the chronic setting after TBI and may represent targets for therapeutic modulation [310–315]. Two studies using selective PET markers of activated microglia documented persisting inflammation in the brain months to years after TBI [48, 62], corroborating neuropathological findings in deceased patients with a history of TBI [316]. Labeling of activated microglia was increased in several brain regions of retired American football players with a history of TBI, findings which appeared to correlate with performance on tests of learning of memory [297].

Conclusions and Future Directions

Recent work in brain mapping supports the paradigm of a "human connectome": a multi-level representation of the neural matrix which constitutes the central nervous system [317]. The connectome model appears particularly valuable in the detection, diagnosis, classification, and recovery prediction in patients with TBI, which is a distributed, multifocal brain disorder. The connectome approach also suggests potentially transformative therapeutic possibilities such as the modulation of brain network activity to restore appropriate functional connectivity following TBI. Achieving these goals will require a comprehensive, organized approach to characterize and classify TBI and post-TBI recovery in cellular and molecular terms and to build models that link biological events to endophenotypes (including imaging) and clinical phenotypes. In the realm of functional neuroimaging, we need to understand how neural–hemodynamic coupling, which constitutes the basis of fMRI inference, might be confounded in the acute and chronic phases of TBI. The effects on the fMRI (or EEG) signal of prior neurological disease and cognitive impairment, concurrent physiologic variation, and sedative medication need to be identified and separated to reliably map neural activity. Registration methods should account for deformation associated with brain injury such as cerebral edema and mass effect in the acute phase and atrophy and hydrocephalus in the chronic phase. To enhance TBI data sharing, collaboration, and multisite investigation, standardized approaches will be needed for neuroimage acquisition, quality control, storage, analysis, and interpretation. Collectively, it is hoped that these advances will advance the goal of alleviating the burden associated with TBI.

Compliance with Ethical Standards

Conflict of Interest Yousef Hannawi and Robert D. Stevens declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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