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Neuroimaging of the Injured Pediatric Brain: Methods and New Lessons

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Abstract

Traumatic brain injury (TBI) is a significant public health problem in the United States, especially for children and adolescents. Current epidemiological data estimate over 600,000 patients younger than 20 years are treated for TBI in emergency rooms annually. While many patients experience a full recovery, for others there can be long-lasting cognitive, neurological, psychological, and behavioral disruptions. TBI in youth can disrupt ongoing brain development and create added family stress during a formative period. The neuroimaging methods used to assess brain injury improve each year, providing researchers a more detailed characterization of the injury and recovery process. In this review, we cover current imaging methods used to quantify brain disruption post-injury, including structural magnetic resonance imaging (MRI), diffusion MRI, functional MRI, resting state fMRI, and magnetic resonance spectroscopy (MRS), with brief coverage of other methods, including electroencephalography (EEG), single-photon emission computed tomography (SPECT), and positron emission tomography (PET). We include studies focusing on pediatric moderate-severe TBI from 2 months post-injury and beyond. While the

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morbidity of pediatric TBI is considerable, continuing advances in imaging methods have the potential to identify new treatment targets that can lead to significant improvements in outcome.

Keywords

pediatric; traumatic brain injury; multimodal; longitudinal; brain imaging; DTI; MRI; MRS; cognitive; fMRI

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children, who have higher rates of TBI than adults (Langlois and others 2006). Patients younger than 20 years account for nearly 40% of emergency room visits for TBI, but they only make up roughly a quarter of the U.S. population (Langlois and others 2006; Thurman 2016). Among children and adolescents, primary causes of moderate/severe TBI are motor vehicles accidents (either as a passenger or pedestrian), falls, and being struck by an object or person (unintentionally). Recent advances in neuroimaging have given researchers an unprecedented level of detail about the injured brain, and with the increasing pace of improvements to imaging protocols and analytical tools, the future of imaging in TBI is exciting. There are far fewer studies examining pediatric TBI than adult TBI. This is surprising given that injury to an immature brain can potentially be even more devastating in the long term than injury to a mature brain. Factors central to outcome differ between children and adults (Giza and others 2007). In this article, we review findings using structural, functional, and metabolic/neurochemical imaging, along with neurophysiological assessments in pediatric moderate-severe TBI (msTBI) and cognitive disruptions that may result from these neural disturbances post-acutely. We focus on the post-acute phase and beyond, as imaging during the dynamic acute phase can be complicated by acute issues such as edema and hemorrhages.

Immediately post-injury, neuronal cell membranes are compromised, and rotational forces stretch and shear axons. This leads to a flux of ions and neurotransmitters, placing stress on the injured cells to restore balance, depleting energy resources in the process. The axonal stretching that occurs similarly affects ion balance and action potential propagation, disrupting the integrity of the axon structurally and functionally (Barkhoudarian and others 2011). This diffuse axonal injury (DAI), also called traumatic axonal injury (TAI), is more common in severe injuries, and is associated with a poorer outcome (Paterakis and others 2000). TAI cannot be definitively diagnosed in vivo and traditional computed tomography (CT) imaging does not detect TAI. Diffusion magnetic resonance imaging (dMRI), however, can detect TAI. There is no one imaging modality that is sensitive to the wide variety of neuropathology caused by TBI; different imaging modalities are sensitive to different aspects of brain structure or function. For a review of imaging modalities in adult TBI, see Saatman and others (2008). As multiple modalities are necessary for a full picture of neuropathology in TBI, and because pediatric TBI is distinct from adult TBI, we believed a review covering multiple structural, functional, and metabolic modalities relating to pediatric TBI would be useful.

In this article, we review imaging modalities commonly used to study pediatric moderate/severe TBI (msTBI). These include structural magnetic resonance imaging (sMRI), diffusion MRI (dMRI), functional MRI (fMRI), resting state fMRI (rsfMRI), magnetic resonance spectroscopy (MRS), and a few examples with single-photon emission computed tomography (SPECT) and positron emission tomography (PET), along with electroencephalography (EEG) as another tool commonly used to assess brain function. Given the risk of exposure to radiation and cost of tracers in SPECT and PET, there are very few pediatric studies using these approaches. We are not including ASL (arterial spin labeling) as there are not enough studies of ASL in pediatric msTBI to discuss. There have been previous reviews that partially overlap with ours, but considering the accelerated pace of advanced imaging in pediatric TBI, we believe a comprehensive review of these methods to be timely (Ashwal and others 2014; Hulkower and others 2013; Munson and others 2006). We cover some studies that also include mild TBI, but none that exclusively cover mild TBI. For further review of imaging in mild TBI, see Shenton and others (2012) and Koerte and others (2016). We will not review studies of adult patients, but there are several recent reviews that do, some focusing specifically on dMRI, mild TBI, or TBI in military service members (Hayes and others 2016; Hulkower and others 2013; Shenton and others 2012; Wilde and others 2015). For a recent comprehensive review about the global burden of TBI and recommendations for tackling this issue, see Maas and others (2017). Intentional TBI has a different epidemiology and pathobiology from unintentional TBI and so is not included here. We focus on studies that cover the post-acute period and beyond, as the acute period post-injury is very dynamic, often yielding conflicting results between studies. We divide this post-injury period into three groups: 2 to 6 months is the post-acute time period, 6 months to 2 years is the chronic time period, and beyond 2 years is the long-term period. Most studies reviewed here cover the first two post-injury periods, but we include long-term follow-ups when available.

Each section of the review focuses on a specific modality and begins with a brief background. For additional background on structural and functional connectivity methods, see the recent review by Hayes and others (2016). We then cover the results of the studies using that modality, with special attention to longitudinal studies that describe the course of brain changes following TBI. Finally, where applicable, we will review any cognitive correlates of brain imaging results. This article also briefly summarizes long-term outcomes in neurocognitive, behavioral, and functional outcomes.

Structural Imaging

Structural Magnetic Resonance Imaging—Structural magnetic resonance imaging (sMRI) creates an image of the brain through the variation in water concentration in different tissues. As gray matter (GM), white matter (W), and corticospinal fluid (CSF) all have different water concentrations, they relax back to equilibrium during a scan at different rates, giving different image intensities. In T1-weighted imaging, WM is brightest because the fatty myelin relaxes fastest. With high-resolution maps, researchers can measure regional brain volume. The simplest approach is the region of interest (ROI) approach, where the structure or region of interest is segmented manually or automatically and compared in size across groups. As with other ROI approaches, the downside to this is requiring a priori

hypotheses and good quality segmentation. One whole-brain approach is voxel-based morphometry (VBM), in which each participant's anatomical image is aligned to a template image. The image intensity corresponds to tissue concentration, and regional differences in brain volume can be assessed (Ashburner and Friston 2000). This does not require a prior hypothesis, but it does require good quality segmentation of the GM-WM boundary. A newer whole-brain approach is tensor-based morphometry (TBM), which uses deformation fields to indicate expansion or atrophy relative to a template. Unlike VBM, TBM does not require prior segmentation and assesses differences from the deformation fields rather than intensities (Kim and others 2008; Thompson and others 2000). Related to regional brain volume is cortical thickness, in which the thickness of the GM is assessed across the cortex. Cortical thinning can indicate disruption, but in a pediatric study must be interpreted in the developmental context. Most areas of the cortex thin over the course of development (Gogtay and others 2004). To map the thickness across the cortex, tissue is segmented into GM, WM, and CSF. The inner and outer boundaries of the GM mask indicate the thickness of the cortex, often measured at thousands of vertices across the brain or averaged within a given ROI.

The most consistent finding across cross-sectional studies, regardless of time since injury,¹ is smaller corpus callosum (CC) volume post-injury, which is more pronounced in severe injuries (Levin and others 2000; Wu and others 2010). Further evidence of this callosal atrophy is often shown in ventricular expansion (Dennis and others 2016b; Tasker and others 2005; Wilde and others 2005). CSF expansion coincides with volume loss in subcortical and limbic structures, including the thalamus (Dennis and others 2016b; Fearing and others 2008) and globus pallidus (Wilde and others 2007), which could underlie motor deficits. The limbic system is central to emotion, motivation, and memory processing, and includes the hippocampus, amygdala, hypothalamus, cingulate/cingulum, fornix, uncinate, and orbitofrontal cortex. The anterior and posterior cingulate cortex (ACC and PCC) are thinner post-TBI post-acutely (McCauley and others 2010; Wilde and others 2012b), but the ACC may begin to recover in the chronic phase (Wilde and others 2012b). The hippocampus and amygdala, however, are still significantly smaller years post-injury (Tasker and others 2005; Wilde and others 2007). Post-acutely, the parahippocampal gyrus is smaller both in volume and thickness (Dennis and others 2016b; McCauley and others 2010). The orbitofrontal cortex (Berryhill and others 1995; Tasker and others 2005; Wilde and others 2012b), which is highly connected to limbic structures, and fusiform gyrus (Dennis and others 2016b; McCauley and others 2010; Wilde and others 2012b), which supports visual (including facial) recognition, are smaller and thinner in TBI patients at multiple time-points post-injury, as are the prefrontal cortex and temporal cortex (Berryhill and others 1995; Dennis and others 2016b; McCauley and others 2010; Wilde and others 2005; Wilde and others 2012b). Last, the parietal cortex also shows smaller regional volumes and cortical thinning, but this does not appear until the chronic phase (Dennis and others 2016b; Wilde and others 2012b). Ryan and colleagues found widespread areas of lower volume in a large group of pediatric TBI patients, which they grouped by functional network, including the default mode network (DMN), executive control network (ECN), salience network (SN), which are

¹This review covers only the post-acute, chronic, and long-term time-points, at least 2 months post-injury.

described in more detail in the rsfMRI section. These deficits were related to performance on a series of theory of mind tasks (Ryan and others 2017).

The deficits in the CC continue longitudinally (Dennis and others 2017a; Levin and others 2000; Wu and others 2010). Some patients show hypothalamic atrophy, while in healthy children the hypothalamus increases in volume (Dennis and others 2017a), which may underlie neuroendocrine dysfunction after injury (Acerini and Tasker 2007; Bondanelli and others 2004; Rose and Auble 2012). Cortical thinning continues in the parietal cortex, while parts of the prefrontal cortex appear to show recovery (Wilde and others 2012b). Longitudinal differences in cortical thickness can be seen in Figure 1, reprinted from Wilde and others (2012b).

Cognitive correlates of these changes in volume and thickness provide a clear link between disrupted structure and disrupted function. Working memory performance is associated with brainstem and midbrain volume (Fearing and others 2008). Poor prospective memory, central to daily tasks like planning ahead, is associated with cortical thinning in the cingulate, prefrontal cortex, temporal cortex, and parahippocampal gyrus (McCauley and others 2010). Emotional control and behavior regulation, commonly disrupted post-TBI, are correlated with cortical thickness in the medial frontal lobe and ACC (Wilde and others 2012b). Finally, Dennis and others (2016b) examined a composite cognitive performance score, including processing speed, working memory, verbal learning, and cognitive flexibility (Moran and others 2016). Poor performance in TBI patients was associated with ventricular expansion along with diffuse areas of volume loss (Dennis and others 2016b). Studies of sMRI included in this review can be seen in Table 1.

Diffusion Magnetic Resonance Imaging—Diffusion magnetic resonance image (dMRI) captures the motion of water molecules in the brain. In well-myelinated tracts, diffusion is primarily along axons (Basser and others 1994). After injury, the diffusion signal can become more isotropic (equal in all directions) as the myelin is less intact. However, normal developmental changes in myelination may also affect dMRI, so longitudinal controls are crucial. The most commonly reported measure from dMRI is fractional anisotropy (FA), the degree to which water is confined to the primary direction (along tract), with high FA indicating good WM organization. Mean diffusivity (MD, also called apparent diffusion coefficient) is the average of the eigenvalues (magnitudes) along all three eigenvectors (directions of diffusion), with high MD generally indicating poor WM organization. Radial diffusivity (RD) is the magnitude of diffusion along two non-primary eigenvectors, and AD is the magnitude of diffusion along the primary eigenvector.

The simplest approach in dMRI is to average these WM measures within an ROI. The advantage of this approach is that it can smooth out noisy data, might be less affected by focal lesions than more high-level methods, and yields summaries that are easy to synthesize across cohorts in multisite data. The disadvantage of this approach is that it requires a priori hypotheses, requires segmentation of the ROI (either manually or automatically, both of which can be problematic in TBI), and is harder to tie to disrupted cognitive functions than more advanced tract-based approaches. Another common method for processing dMRI data is tract-based spatial statistics (TBSS) (Smith and others 2006). In TBSS, the voxel-wise

WM organization information is interpolated for each subject to a common skeleton of central WM. TBSS has a smaller search space than whole-brain voxel-wise analyses, but it does not require the a priori hypotheses and segmentation of ROI methods. In tractography, WM tracts are reconstructed using the dMRI information. Until recently, a major downside of tractography was difficulty in running group-level analyses on tract-wise data, as tract coordinates and fiber reconstruction varies across individuals. But several tools have emerged to facilitate group-level tract-wise analyses (Jin and others 2014; O'Donnell and Westin 2007; Yeatman and others 2012). Last, graph theory is a framework from mathematics with many applications, including brain connectomics. Along with whole-brain tractography, the brain structural scan is partitioned into a number of brain regions (there are many atlases of varying resolutions and definitions for this purpose). One can then construct a matrix of the number of fibers interconnecting these brain regions. With graph theory we can examine an expansive set of network parameters such as efficiency, clustering, and modality (Rubinov and Sporns 2010). As graph theory can be applied to all graphs, it can also be applied to functional connectivity, as will be discussed below.

Coincident with smaller CC volume post-injury, studies also show lower WM organization in the TBI group in the CC (Caeyenberghs and others 2010; Dennis and others 2015b; Ewing-Cobbs and others 2008; Levin and others 2008; Oni and others 2010; Wilde and others 2006; Yuan and others 2007). Disrupted callosal organization can have broad consequences, ranging from difficulty with bimanual coordination (Caeyenberghs and others 2011; Hilleary and others 2009; Marion 2007) to poorer neuropsychological performance (Ewing-Cobbs and others 2008). Motor structures, including the internal capsule, corticospinal tract, and posterior thalamic radiation, also show poorer WM organization (Caeyenberghs and others 2009; Caeyenberghs and others 2010; Dennis and others 2015b; Levin and others 2008; Yuan and others 2007). These disruptions can lead to difficulties in balance and motor coordination that are common post-injury (Caeyenberghs and others 2009; Walker and Pickett 2007). The superior longitudinal fasciculus (SLF), a large tract involved in many sensory, motor, and cognitive tasks (Urger and others 2015) also has poorer WM organization (Dennis and others 2015b; Ewing-Cobbs and others 2016; Johnson and others 2015; Yuan and others 2007). Similar disruptions are found in the inferior fronto-occipital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF) (Dennis and others 2015b; Ewing-Cobbs and others 2016; Johnson and others 2015), which are critical for integrating sensory information as well as language functions (Ashtari 2012; Sarubbo and others 2013). The cingulum and uncinate fasciculus, components of the limbic system (central to emotional regulation), are also disrupted after TBI (Dennis and others 2015b; Dennis and others 2017b; Ewing-Cobbs and others 2016; Johnson and others 2011; McCauley and others 2011; Wilde and others 2010). Some longitudinal studies have found FA differences to be more prominent in the post-acute phase, while MD and RD differences become more significant in the chronic phase (Dennis and others 2015b; Wilde and others 2012a), which suggests an evolving pathology that affects myelin and neuronal organization. Changes in axonal pathology is supported by experimental TBI models with imaging-pathology correlates seen acutely, sub-acutely, and chronically in rats (Mac Donald and others 2007). Using graph theory, researchers have found higher path length, higher small-worldness, and lower efficiency in TBI patients, indicating that tract disruption disrupts

information flow in the brain's structural network (Caeyenberghs and others 2012; Yuan and others 2017). Path length and efficiency are measures of network integration, where path length is the average distance between regions across the network (not physical distance but rather the number of jumps across nodes) and efficiency is effectively the inverse. Small-worldness represents a balance between network integration and segregation, so that increases in the small-world coefficient could be caused by increases in clustering and/or decreases in path length.

Longitudinal studies of pediatric msTBI are few, but they tell an interesting story that is still evolving. Wu and others (2010) focused on the CC, finding poorer WM organization in TBI at both 3 and 18 months post-injury, with small increases in WM organization longitudinally. Examining the same sample with TBSS, Wilde and colleagues found poorer WM organization across the central WM, which showed a mixture of increases and decreases in organization longitudinally in the TBI group (Wilde and others 2012a). Ewing-Cobbs and others (2016) also found mixed results, with younger patients showing signs of recovery while adolescent patients did not. Dennis and others (2017) found separate subgroups in the TBI patient group, one showing WM recovery longitudinally, the other showing degeneration. One group had significantly slower interhemispheric transfer time (IHTT) as measured by visual event-related potentials (ERP). These subgroups did not differ in demographic or clinical variables but show different patterns of WM changes longitudinally (Dennis and others 2015a; Dennis and others 2016a). Results from this article are shown in Figure 2. The heterogeneity of TBI is especially noticeable in these longitudinal studies and highlights the need to examine variability within the patient group.

Processing speed is associated with WM organization in the CC, especially the splenium, in both the post-acute and chronic time-points (Ewing-Cobbs and others 2008; Wilde and others 2006; Wu and others 2010), as well as the overlying cingulum (Adamson and others 2013; Wilde and others 2010). Similarly, working memory performance post-injury is correlated with WM organization in the CC and cingulum tracts (Ewing-Cobbs and others 2008; Wilde and others 2010). Johnson and others (2011) found that disruption to the uncinate predicted disrupted executive function later on. The WM organization of the splenium and cingulum also support reading comprehension (Ewing-Cobbs and others 2008; Johnson and others 2015). The WM organization of the frontal cortex is associated with executive function and emotional control (Wozniak and others 2007). Finally, disruption of association tracts (ILF and IFOF), and the ventral striatum is associated with poor performance on a Stroop-like inhibition task (Dennis and others 2015b; Faber and others 2016). Studies using dMRI included in this review can be seen in Table 1.

Functional Imaging

Task-Based Functional Magnetic Resonance Imaging—Functional MRI (fMRI) relies on the blood oxygen level-dependent (BOLD) signal, which measures the ratio of oxygenated and deoxygenated blood. Increases in brain activity are associated with increases in the blood oxygenation level as energy is needed (Ogawa and others 1990). For task fMRI, there are three basic designs. A block design is marked by alternating blocks of task and rest, with the independent variable kept constant during a block. Block designs are simple to

implement and have strong detection power but may not be well suited for some tasks and are less sensitive to the true shape of the hemodynamic response. In event-related designs, stimuli are presented in a randomized order and the interval between stimuli can vary. Event-related designs are better at estimating the shape of the hemodynamic response, but they have less power than block designs. Finally, mixed design is a combination of block and event-related, where stimulus presentation is confined to discrete blocks, but within a given block there can be multiple types of events (Huettel and others 2009).

The majority of task-based fMRI studies in pediatric patients have used working memory tasks. Longitudinally, Cazalis and others (2011) found that in the post-acute phase patients recruited the ACC for difficult tasks, but by the chronic phase ACC activity had decreased and sensorimotor cortex (SMC) activity increased. Tlustos and others (2015) found hypoactivation in the ACC in the long-term phase, during an inhibition task (see Fig. 3). Newsome and others (2007) found that frontal cortex hypo- or hyperactivation differentiated TBI patients on working memory performance. In the long-term phase, studies show more activation in TBI patients in the medial frontal, parietal, occipital, temporal, and fusiform cortices and less activation in lateral frontal and inferior frontal cortices, as well as the hippocampus, parahippocampal gyrus, and insula (Kramer and others 2009; Newsome and others 2008; Wilde and others 2011). Karunanayaka and others (2007) examined language performance in the long-term phase, finding less activation in TBI patients in the temporal and angular gyri, and more activation in frontal and parietal areas. Greater activation in frontal and parietal regions in TBI patients is also seen during inhibition (Tlustos and others 2011) and attention tasks, along with decreased activation of the cerebellum and occipital lobe (Kramer and others 2008; Strazzer and others 2015). Studies using fMRI included in this review can be seen in Table 2.

Resting State Functional Magnetic Resonance Imaging—RsfMRI examines the functional relationships between brain regions—how they fluctuate in activity together in absence of a task. Correlated fluctuations in the BOLD signal at rest in healthy individuals were found, with left and right motor cortex fluctuating in synchrony (Biswal and others 1995). Multiple consistent intrinsic connectivity networks (ICNs) have been found across studies, including the default mode network (DMN, also called the task negative network), executive control network, dorsal attention network, and the salience network (Fox and others 2005). There are two main methods for extracting these networks. The seed-based approach involves selecting a seed region and extracting its time course, then searching for brain regions with correlated or anti-correlated activity. The advantages of the seed-based approach are that it extracts networks in a relatively homogeneous manner across subjects, but the disadvantage is that it constrains the data with a model. Independent components analysis (ICA) is model free and decomposes the data into numerous components. The disadvantages are that some methods require input to constrain the number of components to extract, and coherent components can be broken if too many components are specified. Finally, graph theory can also be applied to rsfMRI. As explained above, graph theory describes the brain as nodes (regions) and edges (connections or functional relationships) and can measure local and global characteristics of network topology such efficiency, identify hub nodes, and so on. With graph theory, ICN are not the target, but rather the

whole network of functional relationships can be examined for global and local changes. Functional connectivity can also be assessed during a task, the processing methods are similar, but this approach can reveal disruption in networks needed to support particular functions.

In adults with TBI, there are significant differences in several ICNs and in graph theoretical measures of functional connectivity (Gratton and others 2012; Nakamura and others 2009; Pandit and others 2013). There have been far fewer studies in children. Using a seed-based approach, Newsome and others (2013) examined a small group of pediatric patients 2 to 3 years post-injury and found decreased connectivity between structures involved in emotional regulation (see Fig. 4) (Newsome and others 2013). Risen and others (2015) also used a seed-based approach and found less connectivity between the DMN and the sensorimotor cortex and greater connectivity between the dorsal attention network (DAN) and the sensorimotor cortex, which they suggest might reflect increased attention necessary to complete motor activities. Stephens and others (2017b) found significantly lower connectivity within motor regions during response inhibition tasks. Furthermore, this was correlated with performance of the task. They also found aberrant positive connectivity between the DMN and a cluster in the parietal cortex, which was also correlated with task performance (Stephens and others 2017a). Clustering the brain into modules informed by structural and functional similarity information, Diez and others (2017) found increased connectivity between prefrontal regions and a subcortical network and the DAN, which was correlated with postural control. While ICA and graph theory have been used to examine TBI in adult patients, and patients with mild TBI (Pandit and others 2013; Stevens and others 2012), to our knowledge there are no studies of pediatric msTBI applying these methods to functional connectivity analyses. Studies using rsfMRI included in this review can be seen in Table 2.

Metabolic/Chemical Imaging

Magnetic Resonance Spectroscopy—The neurometabolic cascade (including physiologic, ionic, and metabolic changes) initiated by moderate/severe TBI can cause secondary damage following initial structural changes. Magnetic resonance spectroscopy (MRS) provides non-invasive quantitative measurement of neurometabolites that compliment measures of brain structure. One of the most studied metabolites in neurological disorders, including TBI, is *N*-acetylaspartate (NAA) because it can be noninvasively measured with MRS. NAA is a robust marker of both neuronal and axonal integrity (Croall and others 2015), plays an important role in oligodendrocytes and myelin production that can be involved in repair of white matter (McKenna and others 2015; Nordengen and others 2015), and is a marker of mitochondrial dysfunction (McKenna and others 2015). Reductions or alternations in NAA may reflect ongoing mitochondrial dysfunction, loss of viable neurons, or disruption in myelination (McKenna and others 2015). MRS studies in TBI have also focused on Choline-containing compounds (Cho), which are precursors and catabolites of the phospholipids that form cell/organelle membranes and myelin membranes, though the MRS-derived Cho signal is more likely to measure free Cho, glycerophosphorylcholine and phosphorylcholine. Whereas decreased Cho can reflect cell loss, increased Cho can signify membrane turnover, cellular proliferation, and/or gliosis

(Croall and others 2015; McKenna and others 2015). Other metabolites that produce quantifiable MRS signals include creatine (Cre), which can also be an indicator of cellular function and dysfunction (Ashwal and others 2000; Ashwal and others 2006b; Hoon and Melhem 2000), glutamate/glutamine (Glx), which are excitatory amino acids released following brain injury and involved in neuronal death, lactate (Lac), which accumulates as a result of anaerobic glycolysis and may be a response to the release of glutamate, and myoinositol (mI), which is an organic osmolyte in astrocytes and increases after glial proliferation (Ashwal and others 2006a).

The majority of MRS studies are completed in the acute post-injury phase, which we have included here if they also included longitudinal cognitive follow-up. Using single voxel or single slice MRS methods in acute pediatric mTBI, studies have found reductions in NAA and elevations in Cho, which correlate with later adverse neurologic and neuropsychological outcomes (Ashwal and others 2000; Babikian and others 2006; Brenner and others 2003; Holshouser and others 1997; Holshouser and others 2005). Figure 5 shows group differences in metabolite ratios. Similar neurometabolic alterations have been reported at longer post-injury times (Yeo and others 2006), with correlations observed with neuropsychological and behavioral functioning (Babikian and others 2010; Parry and others 2004; Walz and others 2008). Studies also show the presence of lactate post-injury, which was found to be an even stronger predictor of poor outcome than NAA and Cho (Brenner and others 2003), as well as elevated myoinositol (mI) (Ashwal and others 2004).

Few longitudinal studies have been conducted, but Yeo and others (2006) found evidence of recovery over a 2- to 5-month interval, with NAA/Cre ratios increasing and Cho/Cre ratios decreasing. Advances in imaging technology have recently made whole-brain 3D-MRSI acquisition possible. Post-acutely, children with moderate/severe TBI had elevated Cho in all four brain lobes and the CC and lower in NAA CC compared with controls. Subgroups of TBI patients showed variable patterns chronically, however. Patients with slow IHTT (as described above in the dMRI section) had lower lobar Cho chronically than those with normal IHTT; the slow IHTT group showed low NAA chronically as well, while the normal IHTT group showed significantly higher levels of CC NAA relative to controls. These contrasting patterns from MRS in two patient subgroups may represent differential pathobiology resulting in diverging outcomes (Babikian and others 2018, unpublished data). Deficits in NAA appear to coincide with deficits in dMRI measures, suggesting decreased neuronal and myelin integrity post-injury (Dennis and others 2016a). Studies using MRS included in this review can be seen in Table 3.

Other Methods

Single-Photon Emission Computed Tomography—Single-photon emission computed tomography (SPECT) uses gamma rays that provide 2-/3-dimensional images by injection of gamma-emitting radioisotopes into the patient. Tracers are taken up by brain tissue, proportional to cerebral blood flow, which reflects regional metabolism (Hunter and others 2012). One study using SPECT to evaluate children with severe TBI 3 years post-injury detected areas of increased perfusion compared to normally developing controls (Chiu Wong and others 2006). This study can be seen in Table 3.

Positron Emission Tomography—Positron emission tomography (PET) uses radiopharmaceutical tracers. In brain injury research, the most common tracer is ^{18}F -labeled fluorodeoxyglucose (FDG) (Amyot and others 2015) as it is an analog of glucose and, therefore, sensitive to metabolic activity related to regional glucose uptake. A few studies have used PET imaging to study TBI in adults (Amyot and others 2015; Hattori and others 2003; Kato and others 2007), but given the risk/benefit ratio of exposure to radioactive substances and the high cost associated with radiopharmaceuticals, such studies are rare in children. A study using ^{18}F FDG PET conducted within 12 weeks post-injury found reduced glucose metabolism was correlated with poorer long-term outcomes (Worley and others 1995). This study can be seen in Table 3.

Electroencephalography—Electroencephalography (EEG) quantifies brain electrical activity by using scalp electrodes. While not an imaging method, it is a common modality to assess brain function after injury (Hunter and others 2012; Nadlonek and others 2015; O'Neill and others 2015). For a review of acute EEG in the PICU, see Gallentine (2013). There are three broad applications of EEG in TBI: spontaneous brain electrical activity (Brenner and others 2003; Mouthon and others 2017; Nenadovic and others 2008; Tomkins and others 2011), evoked potentials (Ellis and others 2016), and long-term potentiation (Dixon and Kline 2009). Event-related potentials (ERPs) refer to electrical activity elicited by exposure to an “event” or stimulus. The ERP to these events reflect cognitive processing. Protocols using high-frequency, repetitive presentation of visual or auditory stimuli provide a naturalistic method for inducing non-invasive long-term-potentiation, or the repetitive strengthening of synapses based on a pattern of responding. Long-term-potentiation paradigms have promise as a method for assessing the integrity of synaptic processes involved in memory consolidation. Studies using EEG can be seen in Table 3.

Neuropsychology

A recent meta-analysis of neurocognitive outcomes following pediatric TBI generally indicated a dose-response to injury (Babikian and Asarnow 2009). Although the moderate and severe injury groups both showed impaired cognitive function initially, the moderately injured patients showed continuing recovery 2 years post-injury. While more severely injured patients showed some recovery, their rate of cognitive development was much slower than in children with mild and moderate injuries. There typically is a global impairment of cognitive function in children with moderate/severe injuries with wide variation among patients in the specific cognitive skills that are most impaired. Early injury (<5 years) results in greater problems in intellectual skills (Anderson and others 2009b; Anderson and others 2011; Ewing-Cobbs and others 2006), though when middle and later childhood were examined separately, one study suggested middle childhood (age 7–9 years) as a period of greatest vulnerability (Crowe and others 2012).

With regard to attention, skills emerging at the time of injury are most vulnerable and may not develop normally long term (Catroppa and others 2011; Catroppa and others 2007). Attention is particularly important as the foundation for other higher order skills, including academic functions. Most children experiencing memory issues improve over time, although with severe injuries there may be ongoing issues years post-injury (Anderson and Catroppa

2007). With executive functions, there is a dose-response to injury and younger children appear more vulnerable, especially if the skills are still developing (Ewing-Cobbs and others 2004; Levin and Hanten 2005). Language comprehension and reading is relatively spared (Babikian and others 2010; Ewing-Cobbs and Barnes 2002) and aphasia are rare, but higher order language skills are compromised, including inferences and pragmatic language, which result in social problems. Grade failures and repetition of a grade are common, and special education services are often needed (Durber and others 2017; Ewing-Cobbs and others 2006). In academics, arithmetic (vs. reading) is more likely to be affected, with younger children more impacted (Ayr and others 2005; Catroppa and others 2009). Young adults with a history of TBI are less likely to finish high school (3 times) or university (2.3 times), and 1.7 times more likely to be unemployed or in an unskilled career compared to national census data, especially when compounded with a disadvantaged background (Anderson and others 2009a). Adaptive functioning has a dose-response to injury (Di Battista and others 2012) and is mediated in part by problems with fluid reasoning and processing speed (Treble-Barna and others 2017). Behavioral and emotional functioning are often affected, with irritability, moodiness, social disinhibition, aggression, poor self-control, and problems with the law relatively common, but may not emerge initially (Yeates and others 2007). In severe injuries, novel psychiatric diagnoses are three times more common than in the general population (Max and others 2000), with internalizing symptoms common in younger ages and externalizing in older (Bloom and others 2001). Neuropsychological studies included in this review can be seen in Table 4.

Discussion

We provide a comprehensive review of neuroimaging findings in pediatric msTBI in the post-acute phase and beyond (2 months +). We have covered structural (MRI, dMRI), functional (fMRI, rsfMRI), and metabolic/chemical imaging (MRS), with brief coverage of PET, SPECT, and EEG. We have also included a review of a sample of neurocognitive studies across domains. A summary of changes in brain structure and metabolism in TBI patients can be seen in Figure 6, with changes in brain volume, cortical thickness, white matter organization, and metabolic markers (NAA, Cho). Only MRS studies that completed imaging in a well-defined time period outside of the acute phase are included in this figure. Functional results are not shown as the locations of differences adds little without the context of the functional task completed. The figure shows broad disruption in the post-acute phase, both across the brain and across modalities. By the chronic time-point, some of these disruptions have resolved, but others have worsened. There is wide variation in the course of changes in brain structure and function over time following moderate/severe TBI (recovery vs. ongoing degeneration), in some cases based on age, in others based on subgroups as described above. There does not appear to be a particular brain region that is specifically disrupted, but this may be due to the resolution (there could be variation within a lobe or tract) and that some studies limit their analysis to particular regions and thus only report those difference. Figure 6 also highlights the need for long-term follow-up, and more longitudinal studies.

Normal brain development in children can interact with injury and recovery processes. Structurally, myelination is continuing, and connections are pruned as networks are fine-

tuned. Studies of autism suggest that failure to prune unnecessary connections can lead to network inefficiency (Tang and others 2014). Functionally, there is a long list of cognitive processes emerging and developing through adolescence that can be disrupted by injury. While the neural plasticity of childhood can mean enhanced responses to enriched environments, it can also mean that immature structures and processes are more likely to be derailed (Giza and Prins 2006). Plasticity is not unique to childhood, but it is far more extensive than in adulthood. During childhood there is still some flexibility in how the brain is organized, with more possibilities for compensatory pathways and networks to emerge. But these studies have also shown that the heterogeneity we expect among TBI patients can be even greater during development. Although the younger brain is considered to be more plastic and therefore better able to reorganize after focal injuries, more diffuse injuries in the younger brain, in general, can have far more negative consequences compared to mature brains, since disruptions, even if transient, to networks early on disrupt the normal trajectory of connections that support subsequent functional areas. We expect that certain brain systems and functions are more vulnerable to disruption than others, depending on when during development they become mature. Larger studies are needed though, to truly answer how disruption post-injury depends on age. The unique vulnerabilities of childhood and adolescence means that we cannot translate all results from adults to children; we need to examine this period specifically to understand how to improve outcome.

There have been considerable advances recently in imaging acquisition and processing methods, giving us a clearer picture of injury and recovery processes than possible before. However, there is still a lot unknown about these processes and factors that influence them. Translating advanced neuroimaging results to clinical recommendations is a goal on the horizon, but will require larger, more diverse samples, more longitudinal imaging studies, comprehensive characterization of cognitive and psychological functioning post-injury, and multimodal datasets including non-imaging data like genetics, electrophysiology, and blood markers. Integration of multimodal imaging is key as different sequences can provide complementary information about the underlying pathobiology. The role of inflammation, for example, has been receiving increasing attention across numerous neurological and psychiatric disorders in recent years, but we do not understand the time course of the inflammatory response after TBI in children and at what point it becomes maladaptive, exacerbating injury. Given the wide range of disruptions and heterogeneity across TBI patients, multi-modal information is critical for understanding recovery or ongoing degeneration. With advances in brain imaging in the future, and better multimodal integration, we will be able to more accurately identify signs of disruption, and more fully understand the molecular pathways and brain networks that both contribute to those disruptions and are responsible for recovery or creating compensatory systems. MsTBI can lead to lifelong problems in all patients, but this is especially an issue in children and adolescents, as it can arrest development of key brain structures and functions. The morbidity of pediatric msTBI is high, but that also means that there is considerable room for improvement and prognoses are not always based on linear or static variables. Advances in the neuroscience of characterizing variations in pathophysiology will help inform the development of targeted, timely interventions. Interrupting degenerative responses to TBI during development could reduce disability in the decades post-injury. The articles reviewed

here show widespread deficits post-injury across domains, but they also show signs of recovery so we are optimistic that research in the coming years will lead to advances in treatment and improved outcomes.

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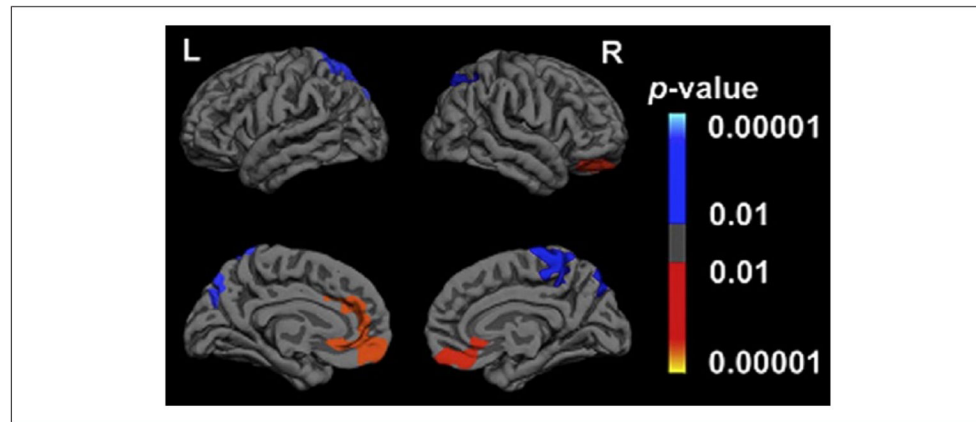


Figure 1.

Between-group longitudinal changes in cortical thickness. Blue regions indicate relative cortical thinning, and red-orange regions indicate relative cortical increase in the traumatic brain injury (TBI) group over the 3- to 18-month post-injury time interval. Reprinted with permission from Wilde and others (2012b).

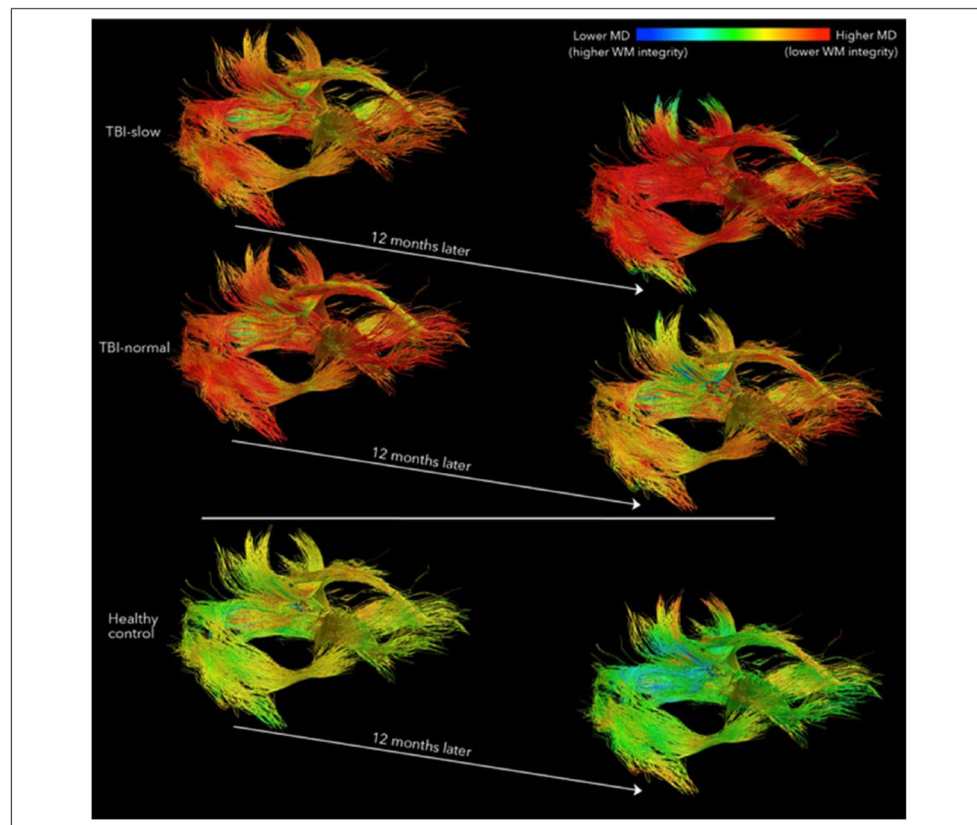


Figure 2.

Longitudinal changes in along-tract mean diffusivity in TBI-slow-IHTT, TBI-normal-IHTT, and healthy controls. The group-averaged maps are shown for both time points, across TBI-slow-IHTT (N = 11), TBI-normal-IHTT (N = 10), and healthy controls (N = 20). Approximately 12 months passed between the beginning and ending time point. As indicated in the legend, blue areas have the lowest mean diffusivity (MD) and therefore highest WM organization, while red areas have the highest MD. The healthy controls show minimal decreases in MD. The TBI-slow-IHTT group shows widespread increases in MD. The TBI-normal-IHTT group shows a mixture. TBI = traumatic brain injury; IHTT = interhemispheric transfer time; WM = white matter. Reprinted with permission from Dennis and others (2017).

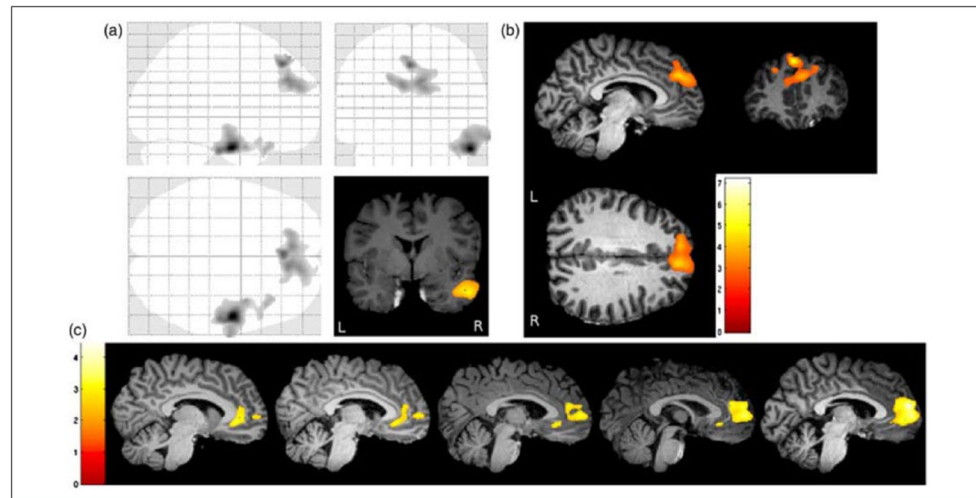


Figure 3.

Significant differences between groups in resting state functional magnetic resonance imaging (rsfMRI). Relative to the typically developing (TD) group, the traumatic brain injury (TBI) group demonstrated lower functional connectivity between the rostral anterior cingulate cortex (rACC) seed and temporal pole (a) and dorsal medial prefrontal cortex (MPFC) (b), and between the right amygdala seed and rostral and ventral MPFC (c). Activation is overlaid onto an individual subject's brain transformed into Talairach space. Left side of brain is on left side of the figure. Reprinted with permission from Newsome and others (2013).

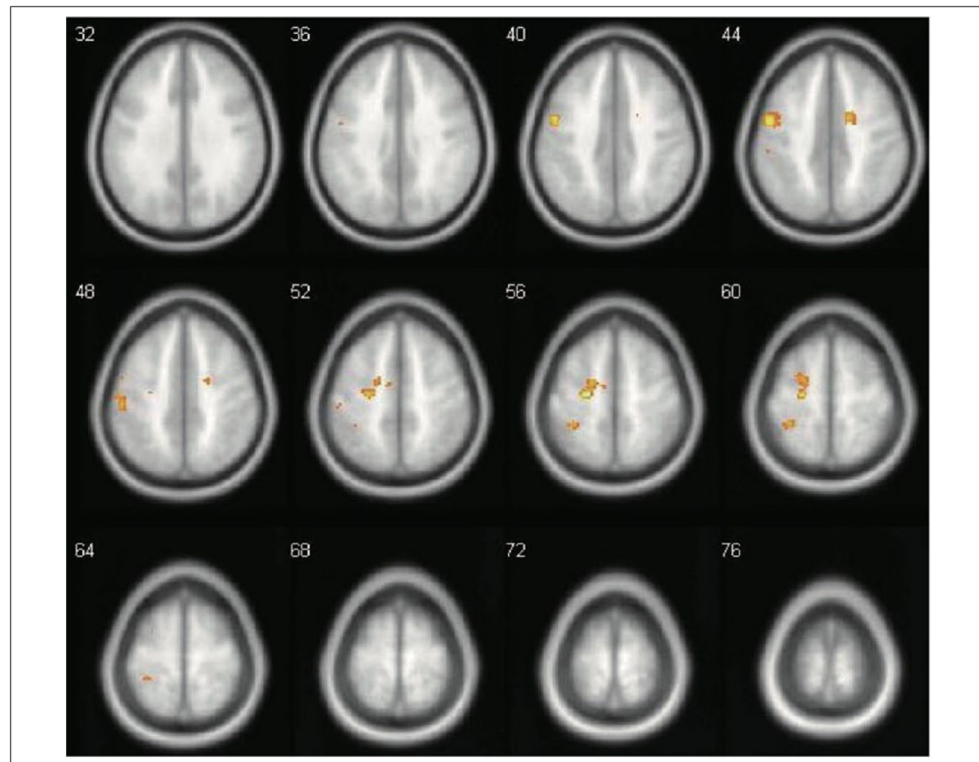


Figure 4.

Between-group comparison (typically developing [TD] > traumatic brain injury [TBI]) of inhibition-related activation. Positive activation regions are where TD controls demonstrated greater activation than TBI (TD > TBI). Images are from $z = +32$ to $z = +76$, with the following parameters: p -threshold = 0.001 uncorrected, cluster size threshold = 50.

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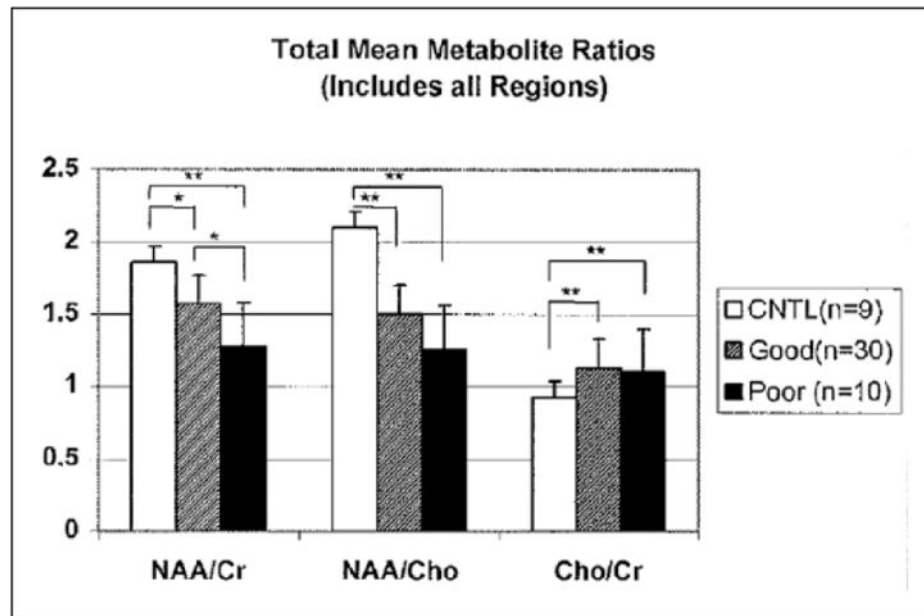


Figure 5.

Total mean metabolite ratios plotted by neurologic outcomes or control (CNTL). Ratios were calculated from all voxels including those containing hemorrhagic and nonhemorrhagic diffuse axonal injury (DAI) lesions for patients with traumatic brain injury (TBI). Asterisk indicates $P=0.01$; double asterisk, $P=0.000$. Reprinted with permission from Holshouser and others (2005).

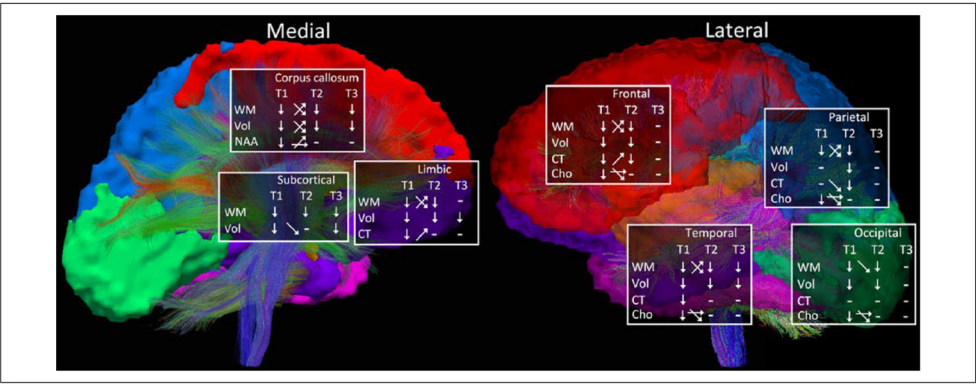


Figure 6. Summary of group differences in structural and metabolic data. Results from structural MRI, diffusion MRI, and magnetic resonance spectroscopy (MRS) are summarized in this figure. WM = white matter organization; vol = volume; CT = cortical thickness; NAA = *N*-acetylaspartate; Cho = choline. Results are summarized by brain lobe. T1 = post-acute (2–6 months post-injury), T2 = chronic (6 months to 2 years post-injury), T3 = long term (>2 years post-injury). Downward arrows indicate areas/measures that were lower in traumatic brain injury (TBI) versus typically developing (TD). Angled arrows indicate differences in longitudinal changes between time-points—upward angled arrows indicate greater increases in TBI versus TD over time, downward angled arrows indicate greater decreases in TBI versus TD over time, straight arrows indicate no change. Dash (–) indicates no significant result to report. Mixed changes are reported for some areas, indicating that either studies are conflicting, or that subgroups within the TBI group show opposite effects.

Table 1Summary of Structural Studies Included.^a

Article	N	Age Range (Years)	Long/CSx	TSI	Method	Dataset
sMRI						
Levin and others (2000)	53 TBI	7–17	Long	3 and 36 months post-injury	ROI	a
Wu and others (2010)	23 TBI/25 OI	7–17	Long	3 months and 18 months post-injury	ROI	a
Wilde and others (2012b)	20 TBI/21 OI	7–17	Long	3 months and 18 months post-injury	Cortical thickness	a
Dennis and others (2017)	21 TBI/20 HC	8–18	Long	2–5 months and 13–19 months post-injury	TBM	b
Berryhill and others (1995)	28 TBI	7–17	CSx	At least 3 months post-injury	ROI	a
Verger and others (2001)	19 TBI/19 HC	3–15	CSx	Years post-injury	ROI	Indiv
Tasker and others (2005)	33 TBI	2–16	CSx	Years post-injury	VBM	Indiv
Wilde and others (2005)	16 TBI/16 HC	8–17	CSx	1–10 years post-injury	ROI	c
Wilde and others (2007)	16 TBI/16 HC	8–17	CSx	1–10 years post-injury	ROI	c
Fearing and others (2008)	16 TBI/16 HC	8–17	CSx	Years post-injury	ROI	c
McCauley and others (2010)	40 TBI/41 HC	7–17	CSx	3 months post-injury	Cortical thickness	a
Dennis and others (2016)	36 TBI/35 HC	8–18	CSx	2–5 months and 13–19 months post-injury	TBM	b
Ryan and others (2017)	103 TBI/34 HC	Not given	CSx	2 years post-injury	ROI	Indiv
dMRI						
Wu and others (2010)	23 TBI/25 OI	7–17	Long	3 months and 18 months post-injury	ROI	a
Wilde and others (2012b)	20 TBI/21 OI	7–17	Long	3 months and 18 months post-injury	TBSS	a
Ewing-Cobbs and others (2016)	16 TBI/18 OI	6–15	Long	3 months and 24 months post-injury	TBSS	d
Dennis and others (2017)	21 TBI/20 HC	8–18	Long	2–5 months and 13–19 months post-injury	Tractography	b
Yuan and others (2017)	17 TBI/11 HC	9–19	Long	>12 months post-injury, then 3 months later	Graph theory	Indiv
Wilde and others (2006)	16 TBI 16 HC	8–17	CSx	1–10 years post-injury	ROI	c
Wozniak and others (2007)	14 TBI/14 HC	10–18	CSx	6–12 months post-injury	ROI	Indiv
Yuan and others (2007)	9 TBI/12 OI	6–9	CSx	>12 months post-injury	ROI	e
Ewing-Cobbs and others (2008)	41 TBI/31 HC	0–15	CSx	3 months - years post-injury	ROI	d
Levin and others (2008)	32 TBI/36 OI	7–17	CSx	3 months post-injury	Tractography	a
Caeyenberghs and others (2009)	12 TBI/14 HC	8–20	CSx	9 months to years post-injury	Tractography	f
Caeyenberghs and others (2010)	17 TBI/14 HC	8–20	CSx	9 months to years post-injury	Tractography	f
Oni and others (2010)	46 TBI/47 OI	8–16	CSx	3 months post-injury	Tractography	a

Article	N	Age Range (Years)	Long/CSx	TSI	Method	Dataset
Wilde and others (2010)	46 TBI/43 OI	7–17	CSx	2–7 years post-injury	ROI	a
Johnson and others (2011)	15 TBI/15 OI	6–15	CSx	Scan at 3 months, BRIEF at 1 year	TBSS	d
McCauley and others (2011)	40 TBI/37 OI	7–16	CSx	3 months	Tractography	a
Caeyenberghs and others (2012)	12 TBI/17 HC	8–20	CSx	6 months to years post-injury	Graph theory	f
Dennis and others (2015)	28 TBI/28 HC	8–18	CSx	2–5 months and 13–19 months post-injury	Tractography	b
Johnson and others (2015)	29 TBI/27 OI	6–16	CSx	Scan at 3 months, cognitive function at 1 year	TBSS	d
Faber and others (2016)	21 TBI/18 HC	10–17	CSx	5–15 years post-injury	ROI	Indiv

^aWe list the number of participants (TBI = traumatic brain injury, OI = orthopedic injury, HC = healthy control), age range of participants, whether the study used a cross-sectional (CSx) or longitudinal design, the post-injury time-points assessed (TSI = time since injury), the method used (ROI = region of interest, TBM = tensor-based morphometry, VBM = voxel-based morphometry, TBSS = tract-based spatial statistics), and whether the dataset included overlapped with others reviewed in this article (indiv = individual study). Articles from which we included figures are highlighted.

Table 2**Summary of Functional Studies Included.^a**

Article	N	Age Range (Years)	Long/CSx	TSI	Method	Dataset
Task functional MRI						
Cazalis and others (2011)	11 TBI/12 HC	8–18	Long	2–5 months and 13–19 months post-injury	Working memory	b
Newsome and others (2008)	8 TBI/8 HC	7–17	CSx	2 months to 4 years post-injury	Working memory	a
Karunanayaka and others (2007)	8 TBI/9 OI	6–9	CSx	At least 12 months post-injury	Language	e
Kramer and others (2008)	5 TBI/8 OI	3–7	CSx	Years post-injury	Attention	e
Newsome and others (2008)	8 TBI/8 OI	7–17	CSx	1–2 years post-injury	Working memory	a
Kramer and others (2009)	7 TBI/13 HC	3–7	CSx	At least 12 months post-injury	Working memory	e
Wilde and others (2011)	6 TBI/11 OI	7–17	CSx	1.4–2.1 years post-injury	Working memory	a
Thustos and others (2011)	11 TBI/10 HC	12–16	CSx	Years post-injury	Stroop	g
Straazler and others (2015)	20 TBI/7 HC	7–18	CSx	2 weeks to 7 years post-injury	Attention	Indiv
Thustos and others (2015)	11 TBI/14 HC	12–16	CSx	At least 12 months post-injury	Inhibition	g
Resting state functional MRI						
Newsome and others (2013)	9 TBI/9 HC	7–17	CSx	2–3 years post-injury	Seed-based	a
Risen and others (2015)	14 TBI/14 HC	11–17	CSx	2 months post-injury	Seed-based	h
Diez and others (2017)	14 TBI/27 HC	8–19	CSx	4 months to 11 years post-injury	Whole-brain	Indiv
Stephens and others (2017b)	17 TBI/14 HC	12–18	CSx	1–5 years post-injury	Seed-based	h
Stephens and others (2017a)	11 TBI/11 HC	10–17	CSx	1 year post-injury	Seed-based	h

^aWe list the number of participants (TBI = traumatic brain injury, OI = orthopedic injury, HC = healthy control), age range of participants, whether the study used a cross-sectional (CSx) or longitudinal design, the post-injury time-points assessed (TSI = time since injury), the method used, and whether the dataset included overlapped with others reviewed in this article (indiv = individual study). Articles from which we included figures are highlighted.

Table 3

Summary of Metabolic/Chemical and Electroencephalography Studies Included.^a

Article	N	Age Range (Years)	Long/CSx	TSI	Method	Dataset
Magnetic resonance spectroscopy						
Yeo and others (2006)	36 TBI/14 HC	6–18	Long	1–6 weeks, and 5, 13, or 24 weeks post-injury	MV single slice	Indiv
Babikian and others (2018, unpublished data)		8–18	Long	2–5 months and 13–19 months post-injury	Whole-brain	b
Holshouser and others (1997)	82 TBI/24 HC	0–15	CSx	Scan at 2–42 days	SV: occipital	j
Ashwal and others (2000)	53 TBI	0–15	CSx	Scan at 1–2 weeks, outcome 6–12 months	SV: occipital	j
Brenner and others (2003)	22 TBI	0–14	CSx	Scan at 3–5 days, outcome 1–7 years	SV: occipital	i
Ashwal and others (2004)	38 TBI/10 HC	1–17	CSx	Scan at 1–2 weeks, outcome 6–12 months	SV: occipital and parietal	k
Parry and others (2004)	15 TBI/15 HC	10–16	CSx	4 months to 12 years	SV: frontal	Indiv
Holshouser and others (2005)	40 TBI/9 HC	1–17	CSx	Scan at 1–2 weeks, outcome 6–12 months	MV single slice	k
Babikian and others (2006)	20 TBI	1–17	CSx	Scan at 1–2 weeks, outcome 2 years	SV: several	k
Walz and others (2008)	10 TBI/10HC	3–6	CSx	12 months post-injury	SV: frontal	e
Babikian and others (2010)	15 TBI/10 HC	8–18	CSx	3–8 months and 13–18 months post-injury	Whole-brain	b
Single-photon emission computed tomography						
Chiu Wong and others (2006)	8 TBI/8 HC	8–12	CSx	3 years post-injury		Indiv
Positron emission tomography						
Worley and others (1995)	22 TBI	0.5–19	CSx	Scan at 2 weeks–21 months, outcome at 2–47 months post-injury		Indiv
Electroencephalography						
Brenner and others (2003)	22 TBI	0–14	CSx	EEG at 3–5 days, outcome 1–7 years	Spontaneous	i
Neenadovic and others (2008)	17 TBI/10 HC	Not given	CSx	EEG at 1–5 days and 2–10 days, outcome 12 months	Spontaneous	Indiv
Ellis and others (2016)	44 TBI/39 HC	8–18	CSx	3–5 months post-injury	Evoked potential	b
Mouthon and others (2017)	22 TBI/52 HC	4–16	CSx	3 weeks – 15 months	Spontaneous	Indiv

^aWe list the number of participants (TBI = traumatic brain injury, OI = orthopedic injury, HC = healthy control), age range of participants, whether the study used a cross-sectional (CSx) or longitudinal design, the post-injury time-points assessed (TSI = time since injury), the method used (SV = single voxel, MV = multiple voxel), and whether the dataset included overlapped with others reviewed in this article (indiv = individual study). Articles from which we included figures are highlighted.

Table 4Summary of Neuropsychological Studies Included.^a

Article	N	Age Range (Years)	Long/CSx	TSI	Domain	Dataset
Neuropsychological studies						
Max and others (2000)	94 TBI	5–14	Long	2 weeks and 3, 12, and 24 months post-injury	Psychiatric disorders	Indiv
Ewing-Cobbs and others (2006)	23 TBI/21 HC	0.5–6	Long	2, 12, 24 months, and 3+ years post-injury	Intelligence and academic	l
Anderson and others (2009b)	54 TBI/16 HC	2–7	Long	<3, 12, 30 months, and 5 years	Intelligence	m
Caroppha and others (2009)	84 TBI	3–12	Long	<3, 12, 24 months, and 7 years	Academic	m
Caroppha and others (2011)	40 TBI/19 HC	1–7	Long	>3 months and 10 years	Attention	m
Durber and others (2017)	54 TBI/70 OI	3–7	Long	>3 months and 7 years post-injury	Academic	n
Treble-Bama and others (2017)	58 TBI/72 OI	3–7	Long	>3 months and 7 years post-injury	Multiple	n
Bloom and others (2001)	46 TBI	6–15	CSx	>12 months post-injury	Psychiatric disorders	Indiv
Ewing-Cobbs and others (2004)	44 TBI/39 HC	0.5–6	CSx	1 month – >12 months	Executive function	l
Ayr and others (2005)	27 TBI/26 OI	8–15	CSx	>12 months post-injury	Arithmetic	Indiv
Anderson and Caroppha (2007)	53 TBI/17 HC	6–14	CSx	5 years post-injury	Memory	m
Caroppha and others (2007)	54 TBI/16 HC	7–12	CSx	5 years post-injury	Attention	m
Crowe and others (2012)	181 TBI	0–13	CSx	24–45 months post-injury	Intelligence	Indiv

^aWe list the number of participants (TBI = traumatic brain injury, OI = orthopedic injury, HC = healthy control), age range of participants, whether the study used a cross-sectional (CSx) or longitudinal design, the post-injury time-points assessed (TSI = time since injury), the domain assessed, and whether the dataset included overlapped with others reviewed in this article (indiv = individual study).