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Neuroimaging in Pediatric Patients with Mild Traumatic Brain Injury: Relating the current 2018 CDC guideline and the potential of advanced neuroimaging modalities for research and clinical biomarker development

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Abstract

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CDC's 2018 Guideline for current practices in pediatric mild traumatic brain injury (mTBI; also referred to as concussion herein) systematically identified the best up-to-date practices based on current evidence and, specifically, identified recommended practices regarding CT, MRI, and skull radiograph imaging. In this commentary, we discuss types of neuroimaging not discussed in the guideline in terms of their safety for pediatric populations, their potential application, and the research investigating the future use of certain modalities to aid in the diagnosis and treatment of mTBI in children. The role of neuroimaging in pediatric mTBI cases should be considered for the potential contribution to children's neural and social development, in addition to the immediate clinical value (as in the case of acute structural findings).Selective use of specific neuroimaging modalities in research has already been shown to detect aspects of diffuse brain injury, disrupted cerebral blood flow, and correlate physiological factors with persistent symptoms, such as fatigue, cognitive decline, headache, and mood changes, following mTBI. However, these advanced neuroimaging modalities are currently limited to the research arena, and any future clinical application of advanced imaging modalities in pediatric mTBI will require robust evidence for each modality's ability to provide measurement of the subtle conditions of brain development, disease, damage, or degeneration while accounting for variables at both non-injury and time-post-injury epochs. Continued collaboration and communication between researchers and health care providers is essential to investigate, develop, and validate the potential of advanced imaging modalities in pediatric mTBI diagnostics and management.

INTRODUCTION

Understanding the human brain has intrigued medical researchers for centuries. However, not until the late 1900s were images of the human brain able to be generated noninvasively through the development of computed tomography (CT) scan technology.[1] Shortly after the introduction of CT scans, magnetic resonance imaging (MRI or MR scanning) technology became available.[1] Today, a wide variety of neuroimaging modalities are available to healthcare providers throughout the country to assist with evaluation of patients with a variety of health conditions, including traumatic brain injuries (TBI).

Caused by an external force or impact to the head or body,[2] a TBI can disrupt the life of the injured individual, as well as their family and loved ones. The Centers for Disease Control and Prevention (CDC) estimated that in 2014 there were nearly 2.9 million TBI-related emergency department visits, hospitalizations, and deaths occurred in the United States.[3] Of those injuries, approximately 800,000 involved children age 17 and under.[3] Most children with a TBI are treated and released from the ED and are typically classified by healthcare providers as having a mild TBI (mTBI) or concussion.[4,5] Symptoms of mTBI can wax and wane over the course of recovery.[6] However, the majority of patients will experience symptom resolution within one month after the injury.[7,8] Of concern, however, are the 11–30% of children with mTBI that experience persistent symptoms at 3 months post-injury.[7] Children are at increased risk for adverse outcomes from an mTBI compared to adults due in part to physiological factors related to ongoing brain development (e.g., brain water content, degree of myelination, blood volume, blood-brain barrier, cerebral metabolic rate of glucose, blood flow, number of synapses, and geometry and elasticity of the skull's sutures).[9–11] Thus, the complexities of the developing brain present a challenge for physiological testing

standards not only in healthy states, but in cases of brain injury. Over the last few decades, advanced neuroimaging techniques have helped researchers better understand the structural and functional changes in the brain that may occur following an mTBI.[12–15] Currently, CT is used to identify acute intervention needs, such as patients at risk for intracranial injury. While rates of neuroimaging for pediatric patients with mTBI vary significantly,[16] research suggests that approximately 35.3% of pediatric patients with mTBI undergo a head CT.[17,18] In its applied capacity, neuroimaging allows healthcare providers to more fully understand the extent of the injury and provide emergency intervention as needed. However, as the availability of neuroimaging, specifically CT scans, has increased in the healthcare setting, so have concerns about overuse, inconsistent use, and the potential risks (e.g., radiation) associated with using this technology for pediatric patients.[16–21]

As imaging technologies and research on neuroimaging continues to expand, healthcare providers will need to carefully consider whether an advanced imaging technique should remain limited to the research arena or can be translated to the clinic, balancing the benefits and potential risks of using imaging modalities while also ensuring the best care for their patients. To this end, the goal of this commentary is two-fold: 1) to provide a summary of the latest clinical recommendations on neuroimaging for pediatric patients with mTBI; and 2) to discuss select types of advanced neuroimaging technologies, their application within pediatric mTBI research populations, and the milestones required to bring these advanced imaging techniques to the clinic.

Clinical Recommendations on Neuroimaging for Pediatric Patients with mTBI

A more conservative approach to neuroimaging for clinical diagnosis and management of pediatric mTBI, as compared to adults, is often recommended.[22] However, prior to the publication of the CDC Pediatric mTBI Guideline in 2018,[23] no evidence-based guidelines on the diagnosis and management of pediatric patients with mTBI were available that were specific to the United States, relevant to both sport- and non-sport-related injuries, and applicable to younger as well as older age groups. In the area of diagnosis, CDC authors sought to answer a specific question regarding the usage of neuroimaging: “For children (18 years of age and younger) presenting to the emergency department (or other acute care setting) with mTBI, how often does routine head imaging identify important intracranial injury?”[24] Based on the confidence levels found across the thirty imaging-modality articles were ultimately included for quantitative synthesis from data extraction based on the inclusion criteria, the CDC mTBI guideline workgroup concluded that healthcare providers should not routinely image a pediatric patient with suspected mTBI for diagnostic purposes.[25] Similarly, based on the limited diagnostic and prognostic evidence, presumed low base-rates of positive findings, and high cost, neither routine nor advanced CT or MRI for diagnosis of mTBI and concussion are currently endorsed by the American Academy of Neurology[26] and the American Medical Society for Sports Medicine.[27] Instead of routine head imaging, the CDC guideline and other guidelines state that healthcare providers should use validated clinical decision rules to identify children at risk for intracranial injury and to determine if imaging is warranted.[23]

To this effect, several validated clinical decision rules are available to healthcare providers: the Pediatric Emergency Care Applied Research Network (PECARN)[17] rule; the Canadian Assessment of Tomography for Childhood Head Injury (CATCH) rule;[27] and the Children's Head Injury Algorithm for the Prediction of Important Clinical Events (CHALICE).[28] These decision rules evaluate a variety of clinical factors that when assessed together are predictive of more serious injury and should prompt head imaging.[29] These factors include: age < 2 years old; vomiting; loss of consciousness; severe mechanism of injury; severe or worsening headache; amnesia; non-frontal scalp hematoma; Glasgow Coma Score (GCS) < 15; and clinical suspicion for skull fracture. A multicenter validation study evaluating 20,137 children seen in an emergency department for head injury found that the PECARN, CATCH, and CHALICE decision rules accurately identified children with clinically significant head injuries.[29] Additional studies have also concluded that decision rules that combine the risk factors described above are more effective than CT scans alone in identifying children at low risk for intracranial injury.[17,27,30–32] When there is concern for *abusive* head trauma, imaging to determine the likelihood of abuse may be warranted to identify clinically insignificant but forensically important injuries.[33] The Pittsburg Infant Brain Injury Score (PIBIS) is such a clinical prediction rule being evaluated for its ability to aid physicians deciding which high risk cases should undergo head CT.[33]

Advanced Neuroimaging Modalities and their Potential Use in Pediatric mTBI Research and Management

Beyond the use of stereotypical imaging methodologies, the field of brain injury research has seen novel advanced imaging modalities, which may prove useful for pediatric mTBI. However, consideration as to their application, safety, and evidence-based usage must be fully discussed. One factor increasing interest in additional or supplemental diagnostic tools for pediatric mTBI is the lack of definitive indicators as to when children can safely return to sports and school. This may engender uncertainty among healthcare providers managing a pediatric patient with an mTBI. If allowed to return to sports too soon, a child is at increased risk for repeat injury, an exacerbation of current symptoms, and delayed recovery.[34–36] Conversely, children restricted from school and social activities for longer than is physiologically necessary can experience adverse health outcomes.[37] For children who experience a prolonged recovery (especially in those with a recovery time > 1 year), little high-quality research (e.g., randomized control trials) is available to guide return to activities.[38–39] Thus, interest is growing in quantifying the physiology of mTBI and identifying specific technologies that can support optimal outcomes and management strategies for healthcare providers caring for children with mTBI.[40]

The use of non-invasive imaging biomarkers to inform prognosis of patients with mTBI at the acute and chronic time points after injury is a focus of increasing research on mTBI. Neuroimaging has been proposed as a possible methodology to discover such markers for identifying brain changes related to pediatric mTBI that may be predictive of recovery time-course.[41] However, the development of imaging-related diagnostics is complex, especially in younger children, and currently no standardized biomarkers are available that healthcare providers can use to diagnose mTBI or predict recovery.[40–42] Current guidelines state that, while imaging biomarkers show promise for informing the pathophysiology of mTBI and

neurobiological recovery, they require further investigation and should not be used outside of the research setting.[23,26,43]

The development of biomarkers is particularly complex as the immediate and longitudinal effects of pediatric mTBI are superimposed on a rapidly changing brain. Neurodevelopmental trajectories vary as a function of age, sex, and developmental factors;[44] thus, findings relevant for one group of children may not directly translate to another despite outward similarities. Significantly, cortical thickness, subcortical volumes, and functional connectivity vary with age,[45] with significant differences in grey matter organization and cerebral blood flow.[46] Neurodevelopmental trajectory in pediatric populations adds an additional level of variability to biological assays relative to more homogeneous adult populations. This not only highlights the need for longitudinal designs and the collection of large normative data populations, but the need to factor in age and other factors. For example, some young children sometimes may be unable to follow instructions and remain stationary during image acquisition periods despite preparation, making quality images more difficult to obtain.[47] Nonetheless, many researchers are pursuing the discovery and development of non-invasive biomarkers of injury using imaging modalities, particularly to suit and accommodate the unique physiology and vulnerabilities of the developing brain.[48]

ADVANCED IMAGING MODALITIES

CT and MRI are not very sensitive to many pathological features of pediatric mTBI, including diffuse neural injuries, disruptions in cerebral blood flow, and mild edema.[49,50] Researchers and clinicians have been exploring the potential use of advanced imaging modalities, such as functional MRI and diffusion tensor imaging (DTI), to provide objective evidence of so-called “invisible wounds.”[40] The number of advanced neuroimaging modalities available for research and potential clinical use has both benefits and challenges.[42] Studies utilizing advanced neuroimaging continue to contribute to a better understanding of the neurological underpinnings of injury inflicted on the developing brain. In the future, imaging may allow for a multi-dimensional profiling of the complex and multifaceted physiological and pathological considerations associated with mTBI,[40,49] perhaps even eventually informing treatment.[50–52] Beyond standard structural imaging modalities (e.g., CT and MRI), advanced neuroimaging techniques differ in what kind of information they provide, such as alterations in brain microstructure and function (i.e., hemodynamics and metabolism), which are processes that have been posited to serve as potential biomarkers of pediatric mTBI. Given the complexities surrounding the study of advanced imaging modalities for pediatric mTBI for clinical practice, below we elaborate on several modalities not discussed in the CDC’s 2018 guideline: functional MRI (fMRI); DTI; single-photon emission computerized tomography (SPECT) and arterial spin labeling (ASL); and positron emission tomography (PET) and magnetic resonance spectroscopy imaging (MRSI).

Functional MRI

fMRI serves to indirectly measure neuronal activity through blood oxygen level dependent (BOLD) signal as a measure of brain function. This modality can be used not only to study how different regions of the brain are activated or deactivated in response to specific *tasks*

compared with a baseline, but also to study intrinsic or *resting-state* synchronous spontaneous brain activity.[53,54] It has been proposed that increased regional activation may reflect the recruitment of additional compensatory brain systems (e.g., those required to accomplish tasks in a compromised neural system) or may be due to injury-induced brain reorganization.[55] In comparison, decreased levels of activation may be related to several processes, such as impaired neural functioning or difficulty in allocating appropriate cognitive and attention-related resources to the task.[40,56] *Task-based* fMRI (i.e., where a subject is asked to perform a task while in the MRI scanner) has been applied in a range of publications to investigate both acute and chronic changes in brain activity in pediatric mTBI, and several groups have correlated deficits in neurovascular coupling with degree of persistent symptoms.[40] Increased activation in the cerebellum has been found to correlate with symptomatology during an inhibitory control component of a working memory task among pediatric mTBI patients evaluated around 1 month post-injury.[57] In a chronic population (+1 year post-injury), greater activation within working memory circuitry and expanded spatial extent of activation in mTBI patients compared to controls during a working memory task has also been shown.[58] To this effect, another study reported decreased activation in the dorsolateral prefrontal cortex, premotor, supplementary motor areas, and left superior parietal lobule during a verbal and non-verbal working memory task in children 9 to 90 days post-injury.[57] Additionally, decreases in activation were found in various areas (e.g., cerebellum, basal ganglia, and thalamus) during an auditory orienting task sub-acutely (<3 weeks post-injury).[59,60] Others have yet shown bidirectional functional changes, utilizing working memory and navigational tasks, finding increased and decreased activity levels in different areas—though during a wide range of time post-injury (0–3 and 3–6 months).[58,59] Interestingly, children with mTBI did not show significant deficits on traditional neuropsychological “paper and pencil tasks,” but showed greater impairment on symptom report measures and “real world” measures of executive functioning.[57,55] Thus, while variability in study design, post-injury time-points, and age groupings limit conclusions as to the standardized clinical applicability of task-based fMRI for pediatric mTBI, findings show positive support for the presence of detectable, symptom-correlated, and potentially diagnostic changes in brain function.

Resting-state fMRI also is based on the BOLD signal but, unlike task-based fMRI, it comparatively measures innate brain connectivity. Findings from resting-state fMRI studies in children with persistent symptoms after mTBI are not as ranged as those of task-based, but do suggest altered functional connectivity in the default mode, executive function, and ventral attention networks.[60] Furthermore, similar to task-based findings, alterations in brain dynamics and connectivity within functional networks have been posited to be related to neurocognitive dysfunction and posttraumatic symptoms.[61] Briefly, one preliminary report utilizing resting-state fMRI in adolescent athletes showed alterations within the default mode network, increased connectivity in the right frontal pole in the executive function network, and increased connectivity in the left frontal operculum cortex associated with the ventral attention network in the sub-acute phase of mTBI (~35 days post-injury).[63] A comprehensive study done by Iyer et al. recruited a large sample of children diagnosed with persistent symptoms after mTBI to study the relationship between resting functional brain connectivity, symptomology, and behavior.[64] They found that individual variations in

resting-state functional connectivity in the mTBI cohort were associated with various symptoms and behavior along a single negative to positive dimension (e.g., decreases in certain brain networks, problems with cognition, and emotion loaded negatively on the dimension, while high connectivity in other brain networks, poor sleep, and fatigue loaded positively). This data suggests the link between brain connectivity and persistent symptoms might provide a basis for improved prognosis and movement towards personalized therapeutic interventions. Nonetheless, 1) methodologically, supplementation of fMRI studies (such as blood flow and vascular reactivity variability) with may be beneficial given that the BOLD signal represents a multifaceted measure of NVC and additional indices may be necessary to accommodate for hemodynamics/perfusion[40] and 2) further studies are needed to assess dynamic connectivity, regional homogeneity, and global connectivity changes in pediatric mTBI.

DTI

DTI is a technique that measures diffusion of water molecules in order to explore the microarchitecture of the brain. DTI is a subset of diffusion-weighted imaging that is often used to map white matter (WM) tracts (tractography) in the brain.[65] WM analysis techniques have proven invaluable in noninvasively examining maturational changes during normal development, as well as in children with acquired injury.[65] Consequently, DTI in pediatric mTBI has been repeatedly examined for its applicability and biomarker potential in milder insults, especially as WM tracts are likely disturbed following brain injury.[50,66] Certain evidence even suggests that subtle abnormalities following brain trauma are better captured by observing WM metrics relative to conventional MRI sequences.[62,63] However, even recent data from studies investigating the modality in pediatric mTBI show puzzling discrepancies between studies and outcomes, particularly with regard to time post-injury.[66,68]

In the semi-acute time period post-injury, reports of increased fractional anisotropy (FA; a measure of diffusion restriction) have been observed in independent samples of pediatric mTBI patients.[69–70] A study of acute (within 96 hours post-injury) pediatric mTBI showed brain injury was associated with significantly higher levels of FA and axial diffusivity (AD; a measure of water diffusion along the principal axis of diffusion) in several WM regions including the middle temporal gyrus, superior temporal gyrus, anterior corona radiata, and superior longitudinal fasciculus.[71] The mTBI group also had significantly lower levels of mean diffusivity (MD; a measure of the total diffusion within a voxel) and/or radial diffusivity (RD; a measure of diffusion perpendicular to the principal axis) in a few WM regions including the middle frontal gyrus WM and anterior corona radiata. However, these diffusion alterations correlated poorly with acute symptom burden.[71] Some publications further completed post-acute (within 21 days post-injury) scans and/or correlated post-concussion symptoms, including one in which pediatric mTBI patients exhibited increased FA in the left temporal cortex and right thalamus relative to controls during the semi-acute injury phase, with the FA abnormalities associated with decreased performance on attentional measures.[70] Interestingly, in this study FA remained increased within the left temporal cortex, with a trend seen for the right thalamus at approximately 4 months post-injury despite cognitive assessments partially normalizing.[70] A study focusing on the

cingulum bundles and memory functioning in acute (~3 days post-injury) pediatric mTBI found FA of the left bundle was significantly correlated with 30-min delayed recall in injured group when given an episodic verbal learning and memory task.[72]

Interestingly, a number of DTI studies in chronic pediatric mTBI from the past decade reported decreased FA in the WM of chronic patients, mostly in the corpus callosum.[73] However, other groups have not found this to be the case, as some results indicate there were only group differences in two of the measures analyzed *post hoc,* MD and RD, with some limited results in AD.[73] And others showing increased whole brain FA and decreased MD within 2 months post-injury.[74] Recently, a study was conducted that utilized a prospective, longitudinal, and controlled cohort design to evaluate WM microstructure and persistent post-concussive symptoms in children following mTBI.[75] This study imaged subjects at one-month post-injury and 4–6 weeks later. They found FA of the left uncinate fasciculi was lower in symptomatic patients as compared to non-mTBI controls.[75] Regional FA and MD was associated with symptomology at both time points. However, no other significant differences were observed.[75] In contrast to this paper and prior data, a 2019 publication by Satchell et al. found no significant differences between age- and gender-matched symptomatic pediatric mTBI athletes with clinical controls at an average of 30 days post-injury.[66] Thus, despite trends in pediatric mTBI research, DTI has not been adequately shown to be a consistent, reliable measure for changes in pediatric mTBI, and therefore should not be used as a clinical diagnostic tool in individual patients. There is great interest in the potential source(s) of the variability in DTI findings before the methodology's applicability in pediatric mTBI biomarker development can be further assessed.[76,77]

SPECT and ASL

Two techniques for estimating brain hemodynamics in pediatric mTBI are SPECT, a nuclear medicine technique that requires the injection of a radio-nuclide trace, and ASL, a non-invasive way of estimating cerebral blood flow (CBF) using MRI. SPECT may not be as promising for a pediatric population, as it involves radiation. However, studies using SPECT have shown reduced CBF in children with concussion within 12 hours of the head injury.[78] In contrast, ASL does not rely on an external contrast agent to measure perfusion, which increases its utility in the clinical setting and pediatric populations.[79] In adult mTBI, alterations in CBF have been found, but the recovery progression does not appear to match what is observed in severe TBI.[80] Children with mTBI, however, exhibit cerebrovascular reactivity impairments similar to moderate or severe TBI, suggesting age-related CBF biomarkers may be discoverable for determining initial risk and during recovery.[80,81] Conducting pseudo-continuous ASL at 40 days post-injury, Barlow et al. demonstrated that cerebral perfusion was significantly higher in pediatric TBI patients with post-concussion symptoms than controls, and lower in the asymptomatic TBI patients.[79] They further postulated that children who were thought to have clinically "recovered" may still have ongoing decreases in cerebral perfusion and thus may not be fully "neurologically recovered."[81] In 2018, Stephens et al. sought to provide more consistency in the field and utilized ASL to study cerebrovascular physiology after sports-related concussion/mTBI with regard to symptomology.[79] The resulting data showed teenage athletes 2 weeks after concussion had significantly higher regional cerebral blood flow (rCBF) in the left insula

and left dorsal ACC; increases in the left dorsal ACC persisted at 6 weeks post-injury. In addition, perfusion in the left dorsal ACC was higher in athletes reporting physical symptoms 6 weeks post-injury compared with asymptomatic athletes.[79] Overall, these data seem to suggest pediatric mTBI symptomology is related to higher global CBF compared to controls, suggesting CBF perfusion may be a marker of physiological status after concussion. While there still exists variability in the literature in both brain hemodynamics study design and findings, which is compounded by variability in the current mTBI literature, the promise of longitudinal and age-matched studies alongside relating CBF indices to symptoms is a promising indicator of the potential use of brain hemodynamics as biomarkers for pediatric mTBI.

PET and MRSI

While both PET and MRSI have been used to assess metabolic changes following severe TBI in children, their ability to evaluate metabolic shifts that occur during the neurometabolic cascade of concussion does differ.[82,83] PET examines a wide variety of underlying neural pathophysiologies, such as changes in glucose metabolism or neurotransmitters, but necessitates exposure to radioactive tracers—rendering PET a less desirable modality for children and adolescents.[83,84] In contrast, MRSI measures brain metabolite concentrations reflective of components of the neurovascular unit, including neuronal and glial metabolism even across age groups, without such exposure.[85] However, pediatric MRSI studies are limited and have shown variable results. Maugans et al. 2012 performed combined neurocognitive and neuroimaging on pediatric mTBI patients <72 hours, 14 days, and 30 days+ post-injury.[86, 84] They found no longitudinal metabolic changes in thalamus, frontal grey or white matter, nucleus accumbens, or lactate in mTBI, and no differences compared to controls.[86] Another followed high-school football athletes longitudinally and found a significant metabolic change in the thalamus at both subacute (2 weeks post-injury) and chronic (~1 year post-injury) time points after injury, as well as differences in frontal WM metabolites at the chronic time point.[84,87] However, a following study using MRSI demonstrated metabolic changes in a mTBI group at 3 months post-injury, long after clinical scores had returned to normal and the athletes had been cleared to return to play.[88] More recently, one group has shown changes in specific frontal lobe metabolites (at ~30 days post-injury), as well as that mTBI patients lacked a correlation between frontal lobe metabolites and brain activation during a working memory fMRI task that was present in controls.[89] While intriguing, research to date highlights the need to control for temporal and case- specific variables (i.e. time since injury and number of injuries) in future research, as well as the need to fully highlight the potential of metabolic biomarkers for detection of mTBI and identification of the biological corelates of persistent symptoms.

SUMMARY AND CONCLUSIONS

Managing and ensuring optimal recovery for the millions of new cases of pediatric mTBI each year, in the absence of definitive indicators on readiness to return to activity, presents a challenge to healthcare providers. Importantly, the significance of pediatric mTBI for children both acutely (i.e. return to school and sports) and over time (i.e. developmentally) is

not yet fully understood.[34,40] Given the ability to quantitatively assess brain structure and function, advanced multimodal imaging may have potential for improving the diagnosis, prognosis, and targeted management and treatment of pediatric patients with mTBI. Thus, while they are currently not ready to be used for clinical diagnosis in individual patients, as evidence emerges, advanced multimodal imaging may be considered in future iterations of current pediatric mTBI guidelines.

Researchers are exploring the use of advance neuroimaging to identify objective and standardized neurobiological biomarkers, particularly with regard to the developing brain. However, as discussed here, there are a number of inconsistencies in the literature to date concerning physiological changes detected by certain imaging modalities in the pediatric brain after injury. While not comprehensive, the variability in the data discussed does appear to bring to light areas of the field of advanced imaging that currently limit conclusions as to these modalities being used in a clinical application. At its essence, the innate variability of the developing brain and the innate variability of pediatric mTBI makes development of imaging biomarkers a significant challenge. To address this challenge, we propose that researchers and clinicians collaborate to create a full ‘imaging map’ of age-related changes in the developing brain. This may serve as a keystone toward use of clinical imaging in the future. Such an endeavor would involve consistent application of longitudinal study design alongside matched controls, better definition of severity of the initiating TBI, increased study population size, among other considerations. These developments could be key to making advanced imaging a valuable source of information for the management of pediatric mTBI.

It is promising that groups are already seeking to fill these gaps with robust study design and novel application of imaging modalities. The Baby Connectome Project, one of the Lifespan Connectome Projects funded by the National Institutes of Health, is a large ongoing study aimed at characterizing brain and behavioral development from infancy across the first 5 years.[90] The ultimate goals are to chart emerging patterns of structural and functional connectivity during this period, map brain-behavior associations, and establish a foundation from which to further explore trajectories of health.[90] Methodologically, there is interest in determining how best to apply select imaging modalities. For example, a paper by Goodrich-Hunsaker et al. investigated which DTI techniques improved sensitivity at identifying group, developmental, and/or sex-related differences by comparing voxelwise methods (i.e., tract-based spatial statistics) to tractography methods (deterministic and probabilistic tractography).[76] While the results demonstrated consistency between a large number of tracts between the two methods, the authors found that the tractography methods provided improved sensitivity and better tract-specific results for identifying developmental and sex-related differences within the brain.[76] While the combination of imaging modalities is being further investigated for its utility, one study employed both MRSI and DTI in normal control subjects to establish a normative data set and evaluate maturational trends in pediatric patients. These results potentially provide age- and region-specific MR diffusion and spectroscopic metabolite normative ranges; additionally, these data also show brain maturation changes in a normal pediatric population and potentially provide the ability to be a comparative data set to an injured or diseased population.[91] In addition, emerging research demonstrates the value of using multimodal and multi-dimensional imaging methods to

improve the pathologic specificity of mTBI, and also highlights potential future directions that show the utility of multimodal imaging to improve diagnosis, predict clinical course, and assess the efficacy of existing and newly emerging pharmacologic and rehabilitative therapies of mTBI.[92,93] Information collected from neuroimaging will be crucial to understand the neural underpinning of heterogeneous symptoms after mTBI, develop new diagnostic and prognostic markers, and possibly implement targeted therapeutic interventions that are personalized to each patient's profile. Looking to the future, we may well be at the cusp of having biomarkers to assist with understanding the long-term impact of pediatric mTBI on academic and social functioning and the effect of age-at-injury on short-term and long-term clinical outcomes.

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Key Words/Abbreviations:

CDC	Centers for Disease Control and Prevention
mTBI	mild traumatic brain injury/concussion
CT	computed tomography
fMRI	functional MRI
DWI	diffusion-weighted imaging
DTI	diffusion tensor imaging
ASL	arterial spin labeling
SPECT	single-photon emission computerized tomography
PET	positron emission tomography
MRSI	magnetic resonance spectroscopy imaging

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