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Challenges and Opportunities for Neuroimaging in Young Patients with Traumatic Brain Injury: a Coordinated Effort towards Advancing Discovery from the ENIGMA Pediatric Moderate/Severe TBI Group

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Abstract

Traumatic brain injury (TBI) is a major cause of death and disability in children in both developed and developing nations. Children and adolescents suffer from TBI at a higher rate than the general population, and specific developmental issues require a unique context since findings from adult research do not necessarily directly translate to children. Findings in pediatric cohorts tend to lag behind those in adult samples. This may be due, in part, both to the smaller number of investigators engaged in research with this population and may also be related to changes in safety laws and clinical practice that have altered length of hospital stays, treatment, and access to this population. The ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) Pediatric Moderate-Severe TBI (msTBI) group aims to advance research in this area through global collaborative meta-analysis of neuroimaging data. In this paper, we discuss important challenges in pediatric TBI research and opportunities that we believe the ENIGMA Pediatric msTBI group can provide to address them. With the paucity of research studies examining neuroimaging biomarkers in pediatric patients with TBI and the challenges of recruiting large numbers of participants, collaborating to improve statistical power and to address technical challenges like lesions will significantly advance the field. We conclude with recommendations for future research in this field of study.

Introduction

Traumatic brain injury (TBI) is a significant, global public health issue that affects more than 3 million children worldwide annually [Dewan et al., 2016]. The annual economic burden of pediatric TBI in the United States alone may exceed $75 million [Brener et al., 2004]. TBI in children remains a particular concern given evidence for increased vulnerability to injury in the immature brain as well as unresolved questions related to injury that occurs within a dynamic developmental context. A growing body of literature has documented neural changes in pediatric patients with TBI, including widespread gray and white matter (GM and WM) loss and altered WM organization as long-term consequences of moderate/severe TBI (msTBI), along with alterations in brain function and connectivity [Dennis et al., 2018b; Keightley et al., 2014; Krogsrud et al., 2016] (see Figure 1). For an in-depth review of the current state of the field in neuroimaging of pediatric msTBI, see recent reviews [Dennis et al., 2018b; Rao et al., 2016; Roberts et al., 2016]. The corpus callosum appears to be particularly vulnerable to injury [Bigler et al., 2013; Dennis et al., 2015a; Ewing-Cobbs et al., 2012; Levin et al., 2000; Lindsey et al., 2019] since, during an injury, transverse forces may strain the *falx cerebri*, and stress the underlying corpus callosum [Hernandez et al., 2019]. The rapid synaptogenesis in childhood and myelination that continues throughout adolescence may increase the vulnerability of the brain when TBI occurs during development. Because msTBI can permanently alter normal developmental trajectories, understanding how early brain insult affects and interacts with brain development in the short- and long-term is essential for predicting outcome after TBI [Babikian and Asarnow, 2009; Dennis et al., 2014; Ewing-Cobbs et al., 2008]. While children and adults share some similarities that impact injury and recovery from msTBI, several important differences exist, and the literature regarding predictors of outcome after pediatric TBI is limited. Limited or insensitive measurement tools, misconception of the benefits of neuroplasticity in children, and the complex interplay of factors that can influence recovery in the developing brain contribute to this (for a review, see [Anderson et al., 2012]). As detailed in the introductory paper of this Special Issue [Wilde et al., 2019a], we have recently begun a collaborative effort to address some of the gaps in our knowledge of recovery after TBI via the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Brain Injury working group. Briefly, ENIGMA is a framework for global collaborative analysis of neuroimaging studies for which raw data sharing is not necessary, lowering the bar for participation [Thompson et al., 2019]. This manuscript is focused on pediatric msTBI, with the aims of briefly describing the limitations and challenges reflected in the current msTBI literature including heterogeneity in injury specifics, sample characteristics, and study parameters, and providing clinical and research recommendations for future studies. We will also describe how the ENIGMA Pediatric msTBI group is uniquely poised to address these issues.

The primary aims of the ENIGMA Pediatric msTBI group are:

1. Establish a collaborative network of researchers focused on TBI in pediatric patients, including those with an interest in neuroimaging, clinical, neuropsychological (cognitive, emotional, and behavioral) and other outcome, and fluid biomarker data

2. Leverage our combined existing and future datasets to determine factors associated with outcome, better understand the interaction between injury and development, and identify predictors of poor outcome that may suggest additional treatment windows or targets
3. Evaluate existing tools and develop and test new pipelines for processing neuroimaging data that include consideration of lesions, pediatric-based tissue changes and templates, and allow for longitudinal modeling of injury/recovery
4. Support the advancement of junior investigators and trainees through opportunities to lead and participate in analyses and to learn and develop new analysis techniques
5. Provide an opportunity for researchers planning new studies to discuss options for improving data comparability going forward, including sharing protocols and recommending measures and identifying collaborators with similar interests
6. Provide a forum for researchers to promote reproducibility across samples and techniques, discuss challenges and potential solutions, and debate unresolved scientific questions

Challenges and Opportunities

Numerous challenges exist for pediatric msTBI neuroimaging research that centralize on the complex relation between neuropathology and outcome, and involve the influence of demographic characteristics, interaction with developmental stage, heterogeneity of pathology, variability among methodological approaches, and moderating environmental factors in the post-injury phase. The dynamic nature of brain development requires large sample sizes to accurately model—and control for—multiple injury-related variables. The multifaceted quest for a better understanding of msTBI warrants a multimodal approach and datasets that enable construction of sophisticated models that account for the complexity of pediatric msTBI. The ENIGMA consortium provides a compelling opportunity to address these challenges by combining data across multiple cohorts using a meta-analytic approach and applying big data techniques such as machine learning to identify clinically meaningful patient subtypes. ENIGMA has created a set of validated MRI processing procedures that can be employed by collaborators and are freely available on the ENIGMA website. While including data with variations in protocol has some disadvantages, such an approach can lead to robust, generalizable effects [Dennis et al., 2018c]. Small sample sizes (mostly between 5-50 in TBI group, see tables in [Dennis et al., 2018b]), cross-sectional study designs, and basic image analyses of the published literature in msTBI have limited research to date. The ENIGMA approach is not well-suited to address some questions (e.g., responses to specific treatments) but many other questions regarding risk factors, relations to outcome and moderating factors that influence outcomes can benefit greatly from increased sample size. In the sections that follow, we describe individual differences between children and between injuries in response to TBI and potential mechanisms (suggested in smaller-scale studies with divergent findings) that could be addressed more definitively with harmonized data combined across cohorts.

Demographic variables - Age:

Brain injuries that occur during critical neurodevelopmental periods can alter regions undergoing accelerated neuronal maturation [Anderson et al., 2011; Anderson and Yeates, 2010], leading to cognitive, behavioral, emotional, and psychosocial dysfunction [Beauchamp and Anderson, 2010; Rosema et al., 2012]. Interpretation of structural and functional imaging data acquired from children after msTBI is informed by a developmental context that involves maturational changes in structure, function, and connectivity. Inter-individual variability in imaging findings, including sex differences (see section below), environmental effects, and genetic variation, also affect typical age-related trajectories. Brain plasticity—which is central to and beneficial in typical development—may be a source of vulnerability when it follows pediatric msTBI [Anderson et al., 2011; Ismail et al., 2017], as injury can derail predetermined developmental processes, deplete natural resources, and prevent typical recovery trajectories [Hebb, 1949; Pascual-Leone et al., 2005].

Increases in GM density follow a regionally-specific chronobiologic sequence characterized by early maturation of primary sensorimotor cortices and later development of higher order association cortex, including prefrontal and parietal cortical regions involved in executive function [Giedd et al., 1999; Gogtay et al., 2004] (Figure 2) as well as developmental changes in subcortical structures with connections to these regions. Due to the structure of the skull and mechanics of closed head injuries, the prefrontal cortex is particularly vulnerable to structural damage [Bigler, 2007]. Prefrontal GM volume peaks during adolescence and is followed by an apparent reduction due to continuing WM development [Gogtay et al., 2004; Natu et al., 2019]. Consequently, the loss of prefrontal GM volume after msTBI typically observed in adults is superimposed on age-related maturational changes in children and adolescents. Although WM volume typically increases with age through at least age 25 to 30 years [Schmithorst and Yuan, 2010], the trajectory may be affected by msTBI, depending on the severity of injury [Genc et al., 2017]. Reduced volumetric growth of the corpus callosum after msTBI in children is a prime example of how developmental context may modify the long-term effects of brain injury [Levin et al., 2000]. Training can lead to improvements in brain structure, however, demonstrating how experience can positively alter developmental trajectories [Keller and Just, 2009].

With functional neuroimaging, maturation affects the strength of connections in neural networks that underpin executive functions, including working memory, inhibition, and shifting response set [Bunge et al., 2002; Rubia et al., 2006]. The magnitude and regional specialization of task-related activation also depend on maturational status, evolving from a relatively diffuse pattern in young children to distributed activation of key regions (such as lateral prefrontal cortex and parietal cortex) in adolescents [Rubia et al., 2006]. Following msTBI in children, changes in the anatomic distribution of activation may reflect potentially altered brain development and reorganization of systems in brain tissue where maturation is underway, but likely incomplete. For example, the neuroanatomic distribution of activation during a social cognition task was altered in adolescents studied at least one year post-msTBI compared to healthy controls, with patients recruiting both areas associated and not typically associated with social cognition [Newsome et al., 2010]. Similar post-injury effects on the development of the default mode network (DMN) may affect resting fluctuations in

activation causing aberrant functional connectivity [Stephens et al., 2018]. Differentiating maturational changes from recovery processes and their interactions is difficult, and their synergies contribute to inter-individual variability in imaging data following msTBI.

The ENIGMA Pediatric msTBI group will investigate the complex impact of age at injury on neuroimaging measures and outcomes. While younger children have historically been considered to have greater plasticity, children who are older at the time of injury—with more mature brain structure, function, and connectivity—may have more neural and cognitive reserves to draw upon compared to those injured at a young age. Few studies have specifically examined the impact of age at injury, with conflicting results [Dennis et al., 2017c; Ewing-Cobbs et al., 2016]. Most studies have included patients between 8-18 years of age, a period of considerable brain change [Dennis and Thompson, 2013; Gogtay et al., 2004; Sowell et al., 2002] (Figure 2). A sensitive or critical growth period - or more likely, periods - of greater vulnerability for brain injury and more negative outcomes could exist. With the increased sample size of the ENIGMA Pediatric msTBI group, we will be able to examine the impact of age in several ways, both linear and non-linear relationships and discrete periods across development such as early childhood, late childhood (8-12 years) vs. early adolescence (12-15 years) [Zielinski et al., 2010].

Demographic variables - Sex:

Another open question is how dynamic neurobiological processes are influenced by sex, especially when studying a population that spans puberty. For an in-depth review of sex differences in pediatric TBI, see [Arambula et al., 2019]. Throughout development, many factors may be modified by sex, including biological, cognitive, socio-emotional, and psychological factors. Sex differences are a major topic across TBI neuroimaging and developmental neuroimaging in general [Etchell et al., 2018; Herting and Sowell, 2017; Ingalhalikar et al., 2014; Jahanshad and Thompson, 2017] and will be a central focus for the ENIGMA Pediatric msTBI group. Premorbid sex-related considerations include molecular differences in synapse protein expression, neurotransmitter sensitivity, recruitment of second-messenger cascades involved in sex-differentiation, synaptic density differences by brain region, and the role of sex and growth hormones (which may themselves be altered due to trauma to the hypothalamus and pituitary gland) [Arambula et al., 2019]. Also important are physical factors (e.g., neck strength and body mass), cognitive factors (e.g., intelligence, education, adaptive abilities), and socio-emotional factors (e.g., risk-taking behaviors, socioeconomic status, and psychiatric history) [Arambula et al., 2019].

Boys are approximately twice as likely to sustain a TBI than girls [Coronado et al., 2011] with the highest incidence in boys 0-4 years of age in the United States. Effects of sex on outcome are conflicting, with some evidence indicating longer recoveries and worse prognoses in females, while others show that females have reduced mortality and better cognitive function after injury [Arambula et al., 2019]. Research on sex-specific effects in msTBI is principally focused on animal models, adult patients, or retrospective observational cohort studies. Some studies of sex differences in TBI using animal models have shown significant differences, with greater survival rate in females acutely [Roof and Hall, 2000] and greater preservation of neuronal integrity weeks after injury [Semple et al., 2017], while

others have not reported differences [Russell et al., 2011]. These may suggest protective effects of hormones like estrogen and progesterone [Cutler et al., 2007; Djebaili et al., 2005; Roof and Hall, 2000]. Preclinical studies have also shown that progesterone may have a neuroprotective effect [Arambula et al., 2019], although large clinical trials have failed to demonstrate a benefit from administering progesterone to adults with msTBI [Goldstein et al., 2017; Wright et al., 2015]. The role of hormones in outcomes after pediatric TBI is unknown but the incidence of pituitary dysfunction after injury supports further investigation [Acerini and Tasker, 2007; Bondanelli et al., 2004; Rose and Auble, 2012]. Gonadal hormonal changes surrounding puberty remain understudied in relation to outcomes. Observational studies using hospital records are also conflicting, with some reporting greater injury severity in males while others report longer hospital stays for females [Morrison et al., 2004; Slewa-Younan et al., 2004]. In children, particularly, variability in age at puberty and the spectrum of gender must also be considered. Options are limited with legacy data, but when possible, we will examine the impact of pubertal status and encourage future data collection among our group to include more in-depth characterization of pubertal status and hormone measurements. In the ENIGMA Pediatric msTBI group, we will investigate sex as a potential moderating factor as well as whether potential sex differences vary across childhood and adolescence.

Pre-injury variables:

Another question that we intend to examine is how different comparison groups impact findings [Boedhoe et al., 2019]. Most of the published literature has included an uninjured, healthy control (HC) group (e.g., [Dennis et al., 2015b; Wilde et al., 2005]). However, HC groups do not always account for premorbid (psychiatric or neuropsychological) characteristics that may predispose children to injury (e.g., impulsivity or hyperactivity), post-injury effects of medication (e.g., analgesics), long-term medical care, time away from school, or psychological effects of exposure to trauma [Daviss et al., 2000; Delaney-Black et al., 2002; Hajek et al., 2010; Holbrook et al., 2005; Ponsford et al., 2012]. Thus, children with mild (uncomplicated) TBI, orthopedic injury (OI), or other extracranial traumatic injury have been used to account for these pre- and post-injury characteristics [Dennis et al., 2013; Wilde et al., 2019b; Wu et al., 2010; Yeates et al., 2013]. Despite similarities in premorbid characteristics and exposure to traumatic stress among patients with TBI and OI, using children with OI as a comparison group has several limitations. Premorbid social and behavioral difficulties may not be similar [Loder et al., 1995], and children with TBI may experience trauma differently from children with OI [Basson et al., 1991]. The literature provides an incomplete understanding of how functional outcomes are influenced by analgesic medications frequently prescribed for pain in patients with more severe extracranial injury [Borsook, 2012]. Less understood is the possibility of occult brain injury with OI, which could obscure differences between groups in outcome measures, including estimates of brain alterations and neuropsychological impairments. For example, brain structure of children with mild TBI and OI may differ from healthy children who are unexposed to traumatic injury [Wilde et al., 2019b]. While these recent findings support similarities between children with mild TBI and OI, we still lack a complete understanding of the underlying neurobiological mechanisms accounting for these similarities and work is greatly needed in this area. Even in the absence of an orthopedic or extracranial injury,

systemic trauma that is associated with a subsequent inflammatory response may alter blood brain barrier function and permeability, causing neuroinflammatory responses that might also result in structural and functional brain changes [McDonald et al., 2016; Nicholson et al., 2018; Sheeler, 2016; Yang et al., 2016]. With limited sample sizes, collecting both HC and OI controls has been beyond the capabilities of most studies to date. The ENIGMA Pediatric msTBI group will be able to examine this, comparing TBI to all control participants or just HC or OI.

Pre-injury psychiatric or developmental disorders are highly prevalent (30-50%) in children with msTBI and comorbidity is common [Brown et al., 1981; Max et al., 2012]. Pre-injury attention-deficit hyperactivity disorder (ADHD) is over-represented in populations with TBI, complicating research given that pre-injury symptoms of ADHD and post-injury sequelae present very similarly. Oppositional Defiant Disorder and anxiety disorders are also common before and after injury [Gerring et al., 1998]. Up to 60% of children sustaining an msTBI may develop novel psychiatric disorders [Brown et al., 1981; Max et al., 2012], which are heterogeneous and additional comorbidity is typical. These novel psychiatric disorders have demonstrable lesion correlates and show distinct neuropsychological profiles [Max et al., 2015] including when compared to developmental or pre-injury disorders [Ornstein et al., 2014]. Heterogeneity in novel psychiatric disorders combined with relatively small sample sizes complicate efforts to understand their neurobiological substrates. Until now, this problem has been dealt with by examining children with the novel psychiatric disorder of interest [Max et al., 2011]. Other studies examine symptom counts or behavioral checklist scores of selected behavioral or psychological traits such as oppositional defiant behavior, PTSD, or attention deficits [Max et al., 1998]. However, examining symptom load may have less clinical validity in the absence of diagnostic categories. As discussed in the introductory paper [Wilde et al., 2019a], working groups within ENIGMA are focused on these comorbid disorders, including ADHD [Boedhoe et al., 2019; Hoogman et al., 2019], anxiety [Groenewold et al., 2018], and PTSD [Dennis et al., 2019], facilitating well-powered cross-disorder analyses. We will work with these other ENIGMA groups to compare the neural signatures of psychiatric disorders after injury to those in the absence of injury to see whether they share common traits. We will also encourage groups collecting new data to include assessments of psychological and behavioral symptoms, such as the CBCL, K-SADS/KSADS-PL-DSM-5, and measures of quality of life, including those identified in the NINDS Common Data Elements for pediatric TBI.

Injury variables:

The mechanism of childhood injury is important to consider. During childhood, the primary mechanism of TBI varies considerably by age and can present in multiple ways, creating an important distinction between pediatric and adult TBI [Giza et al., 2007; Keenan and Bratton, 2006]. Falls, motor-vehicle accidents, and sports-related injuries are the primary cause of injury in children under age 18 [Coronado et al., 2015; Taylor et al., 2017]. Each of these injury types induces unique biomechanical forces to the brain [Bayly et al., 2012]. Additionally, very young children are more likely to sustain TBI as a result of intentional injury or abuse, and may therefore experience repeated and more severe forms of injury [Sills et al., 2005]. Variations in underlying injuries are closely related to the causal

mechanisms, though heterogeneous clinical presentations suggest that similar variability exists in the underlying pathological features of the damaged, developing brain. Inter-individual differences in body size can impact outcome, as well [Bigler et al., 2013; Rosenbaum and Lipton, 2012]. Relative to adults, children tend to be at greater risk of diffuse brain damage and chronic neurocognitive deficits resulting from injury, because brain tissue, skull, and head and neck musculature are not fully developed [Margulies and Thibault, 2000], rendering them more vulnerable, in general, to the biomechanical forces of injury [Bigler, 2007; Huisman, 2015].

Recovery following pediatric brain injury is highly dynamic, so it is important to assess children within a circumscribed window post-injury [King et al., 2019]. Within the first week of injury, primary injuries (e.g., bleeding and edema) can impact neuroimaging metrics. For example, bleeds can impact diffusion MRI metrics and complicate interpretation if the timing of the assessment varies between patients and/or across studies.

Anatomic lesions are characteristic of msTBI and may include focal or diffuse axonal injury as well as contusions. As a consequence of gliotic or encephalomalacic changes over time, these lesions can cause structural deformations in the brain that can complicate image registration, normalization, and quantification both in the acute and chronic stages of recovery (Figure 3). Attempts to model morphometric differences may not be robust in the presence of TBI, and some morphometric approaches lack validation in TBI [Goh et al., 2014; Kim et al., 2008]. Lesion variability and heterogeneity are hallmarks of TBI research [Bigler et al., 2013] so pooling datasets across centers may be necessary to provide sufficient power to perform subgroup analyses according to lesion characteristics. Furthermore, type of injury (axonal injury, focal lesions, and diffuse microlesions), severity (mild, moderate, severe), and secondary issues associated with systemic function including comorbid injuries or complications (especially those that affect pulmonary and cardiovascular function, see [Crawford et al., 2019] and post-traumatic seizure: [Bennett et al., 2017; Liesemer et al., 2011]) likely impact the relationship between lesion findings and functional outcomes. Single-site studies often lack the statistical power to consider multiple moderating factors, which could increase our understanding of the extent to which brain metrics are preserved or affected by the type and severity of injury. Importantly, advances in lesion-symptom mapping methods and the development of novel analysis pipelines are beginning to allow investigators to use volumetric measurements of lesion load to relate lesion topography to clinical and behavioral outcome measures in individuals with TBI.

Post-injury variables:

Questions regarding post-injury moderating factors (other than specific treatments) that influence outcomes can greatly benefit from the ENIGMA approach. For example, complex interrelationships exist between outcomes from pediatric TBI and family factors [Babikian et al., 2015] such as family functioning [Yeates et al., 2010], parent marital status [Raj et al., 2018], family stressors and resources [Yeates et al., 2004], and the family's response and adjustment to the injury [Wade et al., 2006]. While some of these factors may have been present prior to the injury, the injury itself could contribute additional stress (e.g., financial, emotional) that further affects the child's environment following the injury. While pre-injury

and injury variables may not be modifiable, some post-injury factors may be targeted to improve outcome. Additional environmental factors that could contribute to post-injury outcome include access to appropriate resources and academic support and access to rehabilitation [Semrud-Clikeman, 2010]. Our working group will examine whether measures of family functioning impact outcome and encourage more in-depth characterization of the post-injury environment in future studies.

Neuropsychological assessment:

Including age-appropriate neuropsychological assessment is imperative, but consistency in measurement can be a challenge to implement in developing populations as measures that are appropriate for older adolescents may not be suitable for younger children, both due to differences in the constructs as they are applied (or are applicable) over the age spectrum, but also in item content. In addition, although similar cognitive constructs can be measured, specific test batteries often differ. Additionally, practice effects in longitudinal assessments can undermine the validity of assessments and findings derived from repeated measures. In recognition of this problem, the National Institutes of Health (NIH) introduced a standardized means to collect normative data with a computer-based cognitive assessment battery (the NIH Cognitive Toolbox), which has been adapted for children 3-15 years of age [Bauer and Zelazo, 2013]. Cognitive development is inextricably linked to brain and physiological maturation. Therefore, pediatric TBI neuroimaging outcome studies must ensure use of repeatable, age-appropriate, and standardized neurocognitive measures to monitor whether significant delays and impairments have emerged with increasing time since injury [Li and Liu, 2013; Rabinowitz and Levin, 2014]. The full extent of functional deficits may not become apparent until years after the injury [Ryan et al., 2015]. As respective deficits become more protracted, the slower, atypical development can be exacerbated, increasing the functional gap in maturation in comparison to typically developing children [Anderson et al., 2005; Babikian and Asarnow, 2009; Wells et al., 2009]. Cultural and language differences must also be considered, as measures in which the normative sample is largely white and English-speaking may not generalize to other groups. The Common Cognitive Endpoints subgroup was recently formed within the ENIGMA Brain Injury group with the goal of testing and validating different strategies for combining data across disparate neuropsychological scales including traditional approaches (e.g., Z-scoring), item response theory, and machine learning approaches (e.g., random forest models). This is particularly critical and challenging for pediatrics as the emergence and saliency of different cognitive domains (in addition to the ability to measure them) may shift across childhood and adolescence. As discussed above, collaboration with ENIGMA groups focused on common comorbidities of TBI (i.e. ADHD) will be critical in teasing apart the myriad factors that can influence neurocognition.

Processing tools:

The vast majority of neuroimaging processing tools have been developed and tested on data from healthy adult participants. While these tools are likely appropriate for older adolescents, they may not perform adequately in younger children. Therefore, standard software tools such as FreeSurfer [Dale et al., 1999; Fischl et al., 1999] and FSL [Jenkinson et al., 2012; Smith et al., 2004] are not necessarily suitable without modification or

adaptation as these tools model the brains of children and adolescents using adult brain templates that are simply scaled to size. This may result in tissue segmentation and spatial normalization errors [Schoemaker et al., 2016]. Age-appropriate methods and templates can improve results for brain extraction, normalization, and segmentation [Alexander et al., 2017; Fonov et al., 2011; Lorenzen et al., 2006; Sanchez et al., 2012]. With very young children, specialized image acquisition may be necessary, as the contrast between gray and white matter is lower due to incomplete myelination.

Regulations:

In the US, general regulations for pediatric research require a balance between the necessity to protect the child from harm and the opportunity to participate in and benefit from research (US DHHS, 2018). Although ethical guidelines for pediatric research vary to some extent across countries, the core Belmont principles of respect for persons, beneficence, and justice remain universal [Department of Health, Education, and Welfare and National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 2014]. International collaborations offer many benefits [Hicks, 2015]; however, variation in international ethical policies across different socioeconomic, medical, and cultural contexts can pose additional challenges [Palk et al., 2019]. Parental consent is required for minors, but parents or legal guardians may not be immediately available in emergency situations; emergency waivers of consent may be considered with additional ethical considerations [Adelson, 2010]. In longitudinal and prospective cohort studies evaluating outcomes in pediatric TBI, re-consenting participants who have reached adulthood while the study is still in progress can prove challenging. Children who participate in acute msTBI studies may not remember doing so and may experience anxiety or confusion if they are re-contacted as adults [Resnik, 2009]. While non-accidental trauma (NAT) is not a focus of the ENIGMA Pediatric msTBI group, mandated reporting and medicolegal significance in cases of NAT is an additional challenge when working with patients under 18 years old. As ENIGMA is a globally-based effort, we intend to consider ways in which responsible data sharing can be expanded but operate within the policies and requirements of different countries.

Recommendations for Harmonized Data Collection and Analysis

In an attempt to facilitate data sharing and ensure greater consistency in data collection, the National Institute of Neurological Disease and Stroke (NINDS)/International Common Data Elements initiative detailed recommended elements (including variables, definitions, and case report forms) for pediatric studies, including demographic (sex, race/ethnicity, education/parental education, and socioeconomic status), clinical and injury variables, as well as recommended outcome measures in a host of outcome domains (cognitive, psychiatric, physical, family, and functional outcome), biomarkers, and neuroimaging. Canada has also recently published recommendations for common data elements (CDE) for studies in children with TBI, though these are focused on mild TBI. Additionally, recent recommendations have been published regarding common variables that can be collected from electronic health records to facilitate studies and clinical trials in pediatric TBI from the US National Institute of Child Health and Human Development Pediatric Trials Network. The following sections include recommendations from the ENIGMA Pediatric

msTBI group, incorporating CDEs mentioned above with additional input from researcher experience.

Non-imaging biomarkers:

Blood-based biomarkers collected at the time of recruitment or neuroimaging can provide complementary information in pediatric msTBI neuroimaging studies and may explain some of the interindividual variability in injury response. Very few genetic and biomarker studies have been conducted in pediatric msTBI due to the sample size required; the ENIGMA consortium provides the opportunity to coordinate collection methods and CDEs to enable multifactorial understanding of the injured pediatric brain. Recent work, for example, by the ENIGMA Epigenetics group, was able to detect two genome-wide significant loci where the level of methylation was associated with hippocampal volume [Jia et al., 2018], but imaging and epigenetic data from over 3,000 individuals were needed to perform a sufficiently powered study.

Products of different pathological processes initiated by brain injury and repair enter the circulation through the disrupted blood-brain barrier or the glymphatic system. Cell-specific macromolecules released following CNS injury include neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP), and myelin-basic protein (MBP) that are indicators of damage to neurons, astrocytes, and oligodendrocytes, respectively. Other neuronal markers can reflect damage to specific parts of the neuron (e.g., NF-L, tau). Inflammatory responses can be assessed by detection of cytokines such as Interleukin 6 (IL-6), and cell death by cytochrome c [Au and Clark, 2017]. Other emerging biomarkers such as novel protein biomarkers, miRNA, and metabolites [Banoei et al., 2018] may also provide information about these injury processes.

Blood collection procedures may be anxiety-inducing for both children and parents and may be best coordinated with clinical blood draws. Many biomarkers are elevated for a short period of time after injury; however, depending on the research question it may be appropriate to consider TBI biomarkers released by pathways active at later time points (subacute and chronic), including neurodegeneration markers such as total Tau protein, phosphorylated Tau, amyloid beta peptides, and inflammatory markers [Wang et al., 2018]. Consideration of the best complementary biomarker analysis for the research question is paramount as age-related restrictions on research blood volumes limits the number of exploratory tests that can be performed on any one sample.

Variability in the timing, collection method, biofluid type, and storage of biomarkers can make combining data from different studies difficult. When possible, blood collection should be coordinated with existing biobanks to ensure standardization of procedures and linking of data. A major consideration for pediatric TBI biomarkers is that most will have a variable pattern of release dependent on developmental stage (i.e., neonatal, toddler, school-age, or adolescent). For this reason, normal reference values need to be obtained from well-powered age-matched control samples [Shores and Everett, 2018].

Behavioral preparation for scanning:

Although children generally tolerate MRI scanning well, some children may experience anxiety, claustrophobia, fatigue, or restlessness which can lead to excessive motion and distraction from tasks. Preparation before scanning is essential, especially for the injured child [Bookheimer, 2000; Byars et al., 2002; Gaillard et al., 2001; Rivkin, 2000; Wilke et al., 2003]. We recommend a multi-step procedure to ensure the child's comfort in the scanner environment, ideally including the use of a mock scanner, exposure to MRI sounds through audio samples, description of study goals, incentives to encourage cooperation, breaks (if necessary) between series of sequences, and distractions to alleviate boredom or anxiety (e.g., watching a movie, when appropriate to the study protocol). Behavioral intervention methods can improve compliance and reduce attrition of pediatric participants [de Bie et al., 2010; Caeyenberghs et al., 2009; Gabrielsen et al., 2018] as well as reduce the need for sedation or general anesthesia [Edwards and Arthurs, 2011; Wilder et al., 2009]. Additionally, efforts are underway to optimize rapid and simultaneous multi-modal acquisition sequences.

MRS:

Magnetic resonance spectroscopy (MRS) is a non-invasive imaging technique that has been used to measure neural metabolites in pediatric TBI across all injury severities and at various time points post-injury. The most commonly reported metabolite change following pediatric TBI is reduced *N*-acetyl-aspartate (NAA), which is considered to reflect neuronal loss or dysfunction [Ashwal et al., 2000; Babikian et al., 2006; Babikian et al., 2010; Babikian et al., 2018; Dennis et al., 2018a; Holshouser et al., 2005; Holshouser et al., 2019; Hunter et al., 2005; Walz et al., 2008]. In general, MRS is highly sensitive to metabolic alterations following TBI, and these changes appear to correlate with cognitive and behavioral outcomes; however, the extent of metabolite change differs depending on injury severity, the region studied, the specific scan acquisition technique used, and time of assessment post-injury. The ENIGMA Brain Injury MRS subgroup has recently come together to define and encourage the use of standardized data acquisition and analysis protocols that can be used across all clinical MR platforms. For greater detail about the use of MRS in TBI we refer the reader to a companion paper in this special issue [Bartnik-Olson et al., 2019].

Diffusion MRI:

While ENIGMA dMRI protocols are relatively simple and appropriate for a range of acquisitions, for future data collection, we encourage the use of advanced dMRI acquisition and processing techniques to detect white matter alterations and inform what the biological underpinnings may be [Imms et al., 2019]. Specifically, future dMRI research should employ high angular resolution diffusion imaging (HARDI) with multiple diffusion weightings and an accelerated acquisition speed (e.g., multiband/compressive sensing) to minimize the impacts of motion. Acquisitions with phase encoding in opposite directions can provide additional correction for susceptibility-induced distortions beyond the current ENIGMA EPI correction steps. Moreover, researchers may benefit from employing robust estimation approaches for dMRI metrics (e.g., Slicewise OutLIer Detection (SOLID); [Sairanen et al., 2018]) and apply models that can resolve crossing fiber orientations (e.g.,

constrained spherical deconvolution, or the tensor distribution function model, [Nir et al., 2017; Zavaliangos-Petropulu et al., 2018]). Researchers should extract specific measures of white matter, such as fiber density and cross-section [Raffelt et al., 2017], to overcome the limitations of the commonly used DTI metric fractional anisotropy (FA). Deviations in FA have been widely demonstrated in patients with TBI as compared to control groups (for meta-analyses, see [Hunter et al., 2019; Wallace et al., 2018]). Increased WM pathology (observed as FA abnormalities) predicts greater behavioral deficits in TBI patients [Caeyenberghs et al., 2010; Caeyenberghs et al., 2011]. Yet, despite this large body of dMRI work in TBI patients, few attempts have been made to investigate these findings in more detail and pinpoint how FA is affected, or how it leads to or is associated with behavioral deficits. Tractography approaches that solely exploit orientational information (e.g., FA) are not able to capture the capacity of WM pathways to facilitate communication between brain areas. FA can be modulated by changes in myelination, axon density/diameter, inflammation, and the layout of the axons within the voxel [Jones et al., 2013]. When possible, researchers are encouraged to move beyond basic diffusion metrics averaged within regions of interest and instead use analytic techniques that calculate metrics specific to differently-oriented fiber bundles (fixel-based analysis framework [Raffelt et al., 2017]), though implementing these across sites will take further development. Finally, alternative myelin-sensitive sequences, such as quantitative magnetization transfer imaging and multi-component relaxometry (myelin water fraction mapping) [Dalamagkas et al., 2019; Lee et al., 2019; Tang et al., 2019] can complement the information obtained by dMRI acquisitions.

Task fMRI:

Task related blood oxygen-level-dependent (BOLD) fMRI is the most commonly used functional neuroimaging method in both adult and pediatric msTBI. With a few exceptions, [Khetani et al., 2019; Kramer et al., 2009], the frequent finding is that children and adolescents with msTBI demonstrate increased activation throughout the brain, often interpreted as compensatory recruitment patterns [Olsen et al., 2019; Turner et al., 2011]. The ENIGMA consortium is currently engaged in efforts to develop fMRI and rsfMRI processing and analytical protocols [Adhikari et al., 2018; Veer et al., 2019].

The BOLD signal is heavily influenced by task performance, effort, lesion characteristics (especially hemorrhagic lesions), changes in neurovascular coupling, and participant movement. Tasks should be designed to avoid floor and ceiling effects, and designs in which task load can be manipulated in a parametric fashion are especially powerful (e.g. working memory tasks; [Olsen et al., 2019]). Task performance should be matched or adjusted for when comparing task fMRI activations between groups [Price et al., 2006] to ensure that patients are similarly engaged in the task. This can be particularly challenging when studying children, as cognitive abilities vary substantially with age, in addition to injury effects. We recommend linking BOLD alterations to cognitive and clinical measures performed outside the scanner to determine functional and clinical relevance. Because of the heterogeneity of TBI pathology, task fMRI analyses may benefit from using a whole-brain approach when studying brain function. Accordingly, and especially when combining data across sites, a domain-general task that provides widespread activations is recommended (e.g. working memory or executive function)[Dennis et al., 2018b; Newsome et al., 2007;

Scheibel, 2017; Westfall et al., 2015]. One potential approach to combining data across different tasks and sites is to focus on modeling the BOLD signal based on common task-general dimensions, such as task load or difficulty. Core brain regions linked to working memory and cognitive control, such as the dorsolateral prefrontal cortex, medial frontal cortex, and the insula, consistently show increased BOLD activation as an effect of increased task demands, regardless of task type [Hillary et al., 2006; Olsen et al., 2013; Olsen et al., 2015; Power and Petersen, 2013]. Investigating how the BOLD signal in domain-general core brain regions responds to relative variations in task load, and how these responses are linked to external cognitive and clinical measures, may be a good approach to learning more about the functional consequences of msTBI.

Connectomics:

Given the widespread effects of TBI, especially in more severe injuries, typical approaches that treat brain regions as being independent of each other may not capture the full effects of the injury. A *graph theoretical* approach allows researchers to examine network topology based on a connectivity matrix for all region pairs, quantitatively characterizing both global and local network organization. Graph theoretic approaches using dMRI tractography (structural connectivity) have been examined in pediatric TBI populations [Caeyenberghs et al., 2012; Dennis et al., 2017a; Dennis et al., 2017b; Königs et al., 2017; Verhelst et al., 2018; Watson et al., 2019; Yuan et al., 2017]. While the network metrics differ across studies — likely due to methodological differences— widespread alterations in network topology are seen in TBI patients compared to orthopedic injury or healthy control subjects. In addition to simple group differences there are associations with injury severity and cognitive outcomes [Dennis et al., 2017a; Dennis et al., 2017b; Königs et al., 2017; Watson et al., 2019; Yuan et al., 2017]. These connectomic methods have the potential to elucidate diagnosis, prognosis, and ultimately therapeutic approaches to brain injury, based on conceptualizing the brain network itself as the substrate of pathology.

Several limitations hamper the meta-analysis of network topology across studies: brain region definition (e.g., different brain parcellations), edge weight definition (e.g., tractography streamline count vs. mean FA [Königs et al., 2017]), and network construction differences [Dell'Italia et al., 2018; Hallquist and Hillary, 2019]. Finally, no two injuries are identical, and some subjects may be "missing" brain regions that are present in others [Bigler et al., 2013]. Some of these problems can be mitigated by the ENIGMA approach: combining data from children with variable age at injury and injury location would facilitate modeling such effects on outcomes. Significant efforts are also being dedicated to specialized harmonization approaches for diffusion MRI, recognizing that protocols differ in their ability to detect neural pathways, depending on their spatial and angular resolution. Several harmonization methods are being tested in ENIGMA to mitigate this [Moyer et al., 2019; Nir et al., 2019; Zhu et al., 2019]. Furthermore, data from large-scale studies of typically-developing children and adolescents (e.g., Adolescent Brain Cognitive Development, Human Connectome Project in Development) allow for the creation of robust normative reference values, providing important context for alterations shown in TBI patients (see Supplementary Table 1).

GM metrics:

GM metrics - cortical thickness, gyrification, surface area, and signal intensity covariance - can also be harnessed to recover large-scale network-level topology using clinical MRI sequences [Bigler, 2016; Hasan et al., 2018; Hutchinson et al., 2018; Wilde et al., 2015]. All cortical thickness methods aim to quantify the distance between tissues along the cortical mantle. The ENIGMA cortical protocols (including critical quality control steps) rely on FreeSurfer to generate average measures of thickness and surface area averaged within regions of interest. Although the relationship between surface area, gyrification, and cortical thickness is mathematically straightforward, each process appears to be under distinct mechanisms of genetic control [Chen et al., 2015; Panizzon et al., 2009]. Intensity covariance approaches quantify interrelationships of signal density across all voxels of the brain, giving rise to conserved structural coherence maps that recapitulate functional brain networks, and have been shown to outperform other metrics including thickness in modeling age and sex effects in brain development [Gennatas et al., 2017; Zielinski et al., 2010].

Despite the well-characterized cellular, morphological, and gross anatomical changes that accompany TBI [Bigler, 2013; Sta Maria et al., 2019], there is a striking lack of research related to interregional correlations in brain structure metrics such as thickness, surface area, and gyrification, and such reports in pediatric TBI are exceedingly sparse. Use of these metrics to describe structural network-based changes post-injury represents an intriguing approach to characterizing distributed pathologic changes related to mechanism (blunt vs. shear), lesion location (cortical or subcortical area), lesion type (hemorrhage, contusion, microbleed), and lesion extent, and more clearly characterize the effect of network-based changes on outcomes after TBI.

Linking distributed patterns of injury after TBI will enable diagnostic approaches centered on brain networks as pathological substrates, and provide a path forward for both documenting dynamic changes after injury as well as devising therapeutic strategies to optimize recovery of impacted brain networks. Substantial hurdles remain, such as the impact of localized edema and blurring of the gray-white junction on cortical segmentation, the impact of acute blood or subsequent encephalomalacia on network-based structural techniques, and the characterization of gray-white tissue compartments in younger children with changing tissue contrast related to maturity. However, the ENIGMA framework is poised to undertake such a multifaceted effort. Large samples of heterogeneous patient populations are necessary to tease out common influences of network-level changes post-TBI, enabling new tools aimed at optimizing network recovery, and rescuing networks in decline.

Multimodal imaging:

As detailed above, there are a number of imaging sequences that can provide important information in assessing TBI-related alterations, but none can give a complete picture of disruption alone. To date, the vast majority of studies published have focused on a single modality, but future studies would benefit from simultaneous utilization and integration of the rich datasets which are often collected. For example, dMRI can reveal WM disruption, but has limited capacity to distinguish demyelination from inflammation. Combining dMRI

with MRS can provide additional evidence that WM disruption is due in part to neuronal loss [Dennis et al., 2018a]. DMRI combined with rsfMRI could provide a more complete picture of disruption and may reveal compensatory increases in functional connectivity related to disrupted structural connectivity. With large sample sizes and advancing big data techniques such as Symmetric Multivariate Linear Reduction (SyMILR), it will be possible to reduce high-dimensional multi-modal data to components that may reveal patterns that bridge modalities [Avants et al., 2014; Kandel et al., 2015].

Conclusions

Numerous hurdles exist in the field of pediatric msTBI, many of which pertain to heterogeneity in risk factors, injury variables, and ongoing patterns of development during childhood and adolescence, a period of dynamic maturation. With larger sample sizes and multi-site collaboration, ENIGMA Pediatric msTBI will address some of these issues, and big data approaches and machine learning should aid identification of patient subgroups. While a multi-cohort approach is not appropriate for all questions, it has the promise to address some critical questions in the field and to generate hypotheses for future studies. Researchers and clinicians interested in joining this effort are encouraged to contact the authors of this paper.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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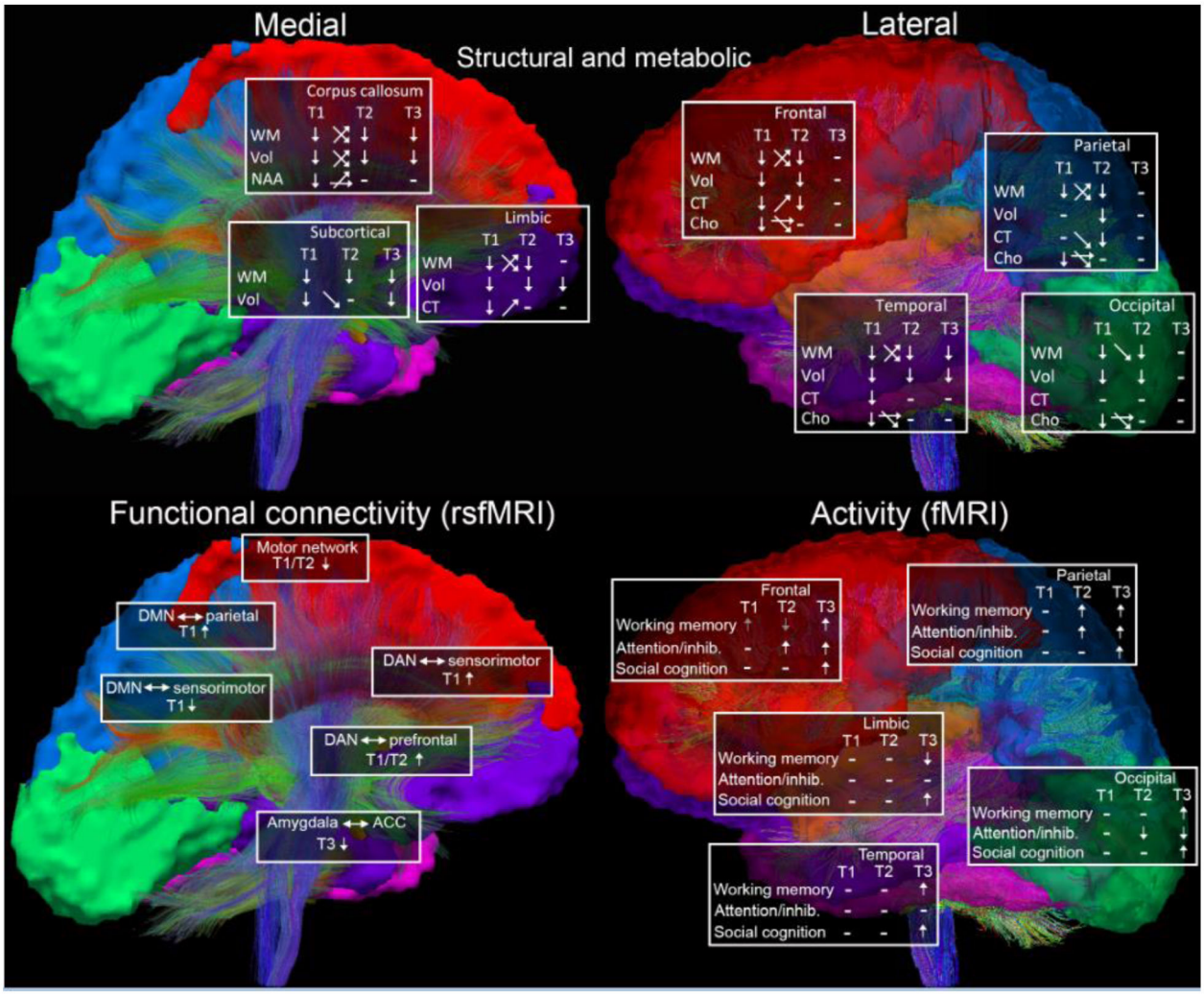

Figure 1.

Overview of reported neuroimaging differences in pediatric msTBI for structural, functional, and metabolic modalities (top panel, WM=white matter/DTI, Vol=volume, CT=cortical thickness, NAA=*N*-acetylaspartate, Cho=choline) and functional modalities (resting state fMRI left bottom, fMRI right bottom), divided by general brain region. T1=post-acute (2-6 months post-injury), T2=chronic (6 months-2 years post-injury), T3=long-term (>2 years post-injury). Arrows at timepoints indicate higher or lower relative to control group, arrows in between time points reflect changes in TBI group over time (increase, decrease, or no change). Mixed changes across the TBI group, or mixed results reported across studies, are reflected in crossed arrows. Dashes indicate no reported differences. For fMRI, gray arrows indicate that effects did not account for group differences in task performance. For rsfMRI, the seed is left of the arrow (alterations in the motor network were within network connections). DMN=default mode network, DAN=dorsal attention network, ACC=anterior cingulate cortex. Reported task-fMRI differences are divided by task - working memory, attention/inhibition, and social cognition. Adapted from [Dennis et al., 2018b].

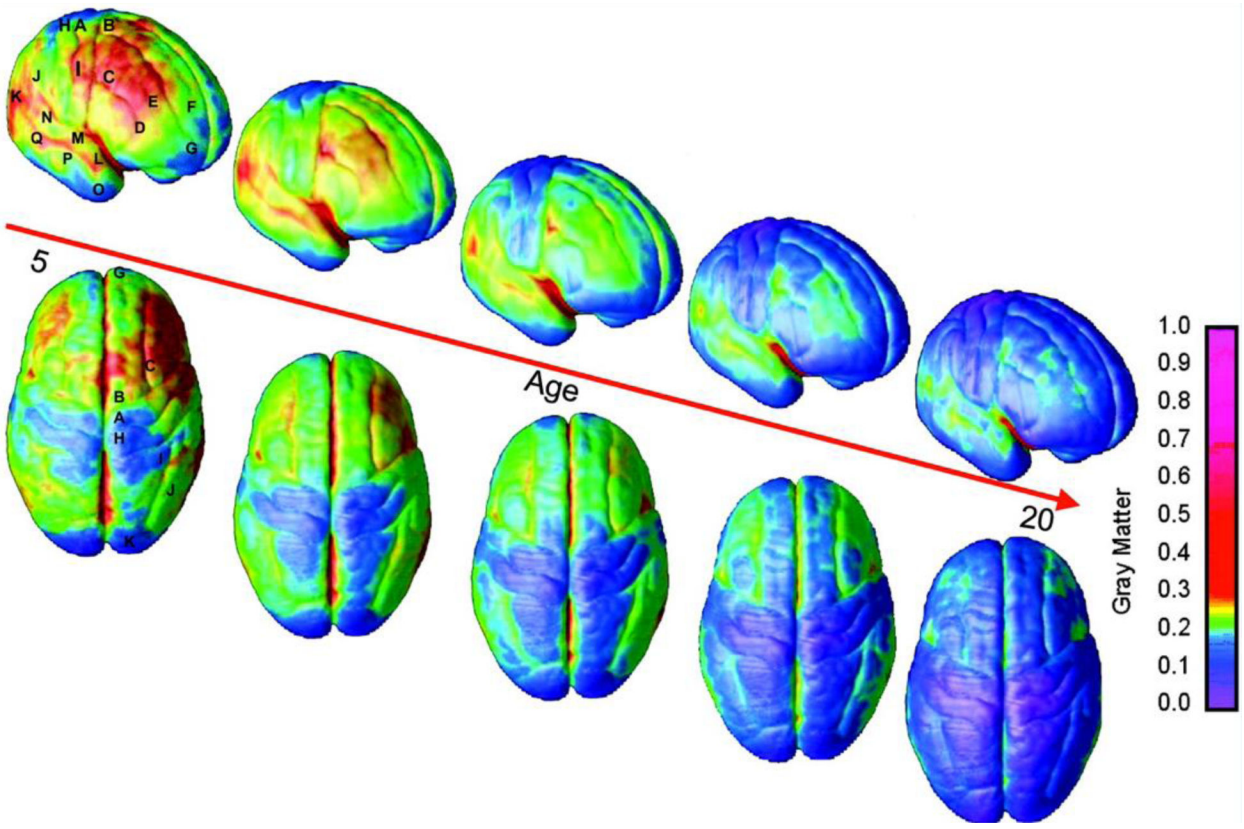

Figure 2.

Gray matter maturation between 5-20 years of age. Right lateral and top views of the dynamic sequence of GM maturation over the cortical surface. The sidebar shows a color representation in units of GM volume. A, precentral gyrus and primary motor cortex; B, superior frontal gyrus, posterior end near central sulcus; C, inferior frontal gyrus, posterior end; D, inferior frontal sulcus, anterior end in the ventrolateral prefrontal cortex; E, inferior frontal sulcus in the dorsolateral prefrontal cortex; F, anterior limit of superior frontal sulcus; G, frontal pole; H, primary sensory cortex in postcentral gyrus; I, supramarginal gyrus (area 40); J, angular gyrus (area 39); K, occipital pole; L–N, anterior, middle, and posterior portions of STG; O–Q, anterior, middle, and posterior points along the inferior temporal gyrus anterior end. Reprinted from [Gogtay et al., 2004].

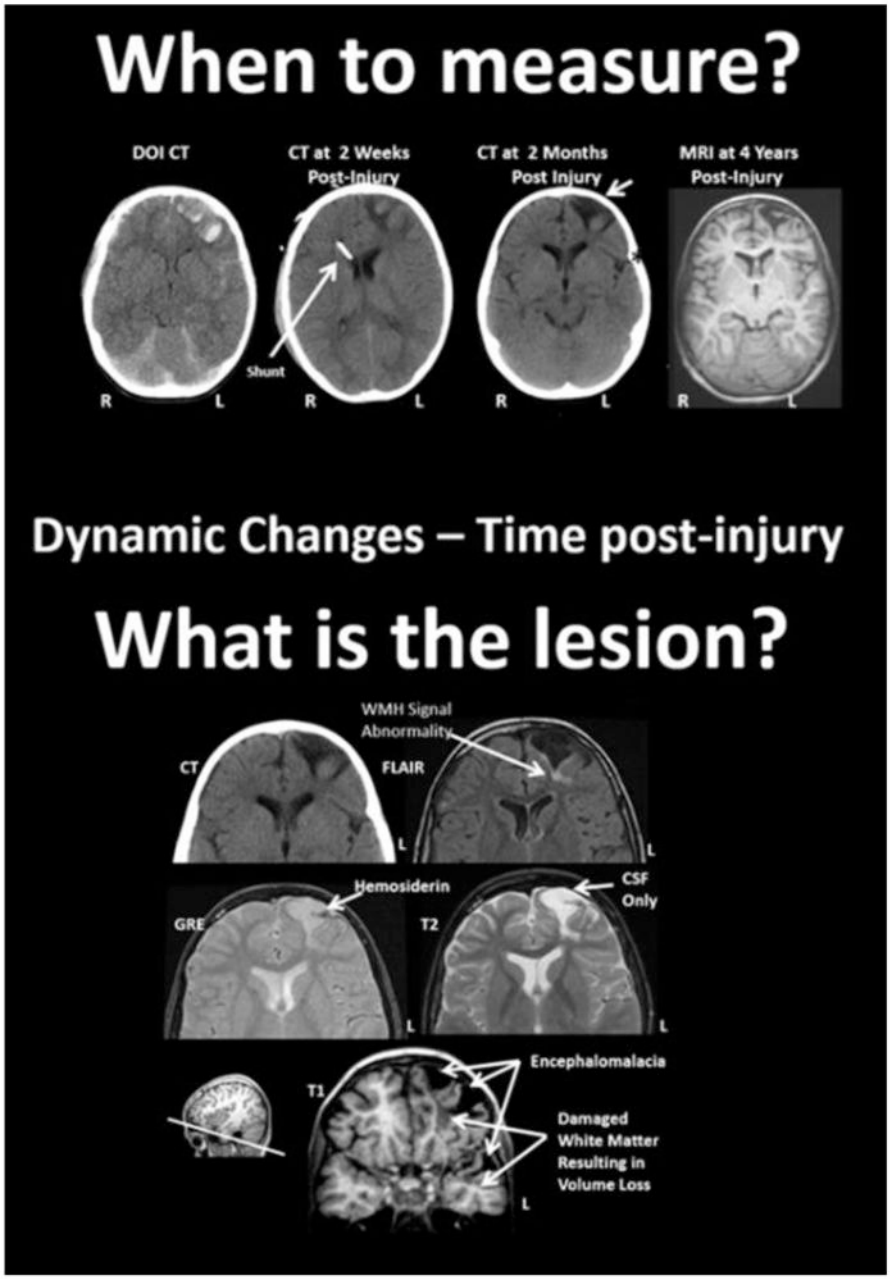

Figure 3.

Difficulties in assessing lesions - dynamic changes post-injury and multi-modal assessment. **Top**: Parenchymal changes over time from the DOI (day of injury) scan to 4 years post-injury. The DOI through the scan at 2 months are all from CT and the far right image is a T1-weighted MRI, at 4 years post-injury. The slice level of these images are all at the level of the anterior horn of the lateral ventricle. Note that where the most prominent acute hemorrhages and frontal contusions occur on the DOI scan that this also becomes the center-point for tissue dissolution (encephalomalacia) over time. Shortly after the DOI scan was obtained the child received an intraventricular shunt to aid in intracranial pressure reduction and monitoring. By 2 months post-injury the focal encephalomalacia is very prominent

(white arrow) and there is also prominence of the Sylvian fissure (black asterisk) along with ventricular enlargement, indicative of some generalized cerebral volume loss. R, right; L, left. **Bottom**: Different MRI sequences yield different facets of the brain injury and residual pathology. FLAIR, fluid attenuated inversion recovery; MRI sequence GRE, gradient recalled echo MRI sequence. Reprinted from [Bigler, 2016].