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Advanced Biomarkers of Pediatric Mild Traumatic Brain Injury: Progress and Perils

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Abstract

There is growing public concern about neurodegenerative changes (e.g., Chronic Traumatic Encephalopathy) that *may* occur chronically following clinically apparent and clinically silent (i.e., subconcussive blows) pediatric mild traumatic brain injury (pmTBI). However, there are currently no biomarkers that clinicians can use to objectively diagnose patients or predict those who may struggle to recover. Non-invasive neuroimaging, electrophysiological and neuromodulation biomarkers have promise for providing evidence of the so-called "invisible wounds" of pmTBI. Our systematic review, however, belies that notion, identifying a relative paucity of high-quality, clinically impactful, diagnostic or prognostic biomarker studies in the sub-

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acute injury phase (36 studies on unique samples in 28 years), with the majority focusing on adolescent pmTBI. Ultimately, well-powered longitudinal studies with appropriate control groups, as well as standardized and clearly-defined inclusion criteria (time post-injury, injury severity and past history) are needed to truly understand the complex pathophysiology that is hypothesized (i.e., still needs to be determined) to exist during the acute and sub-acute stages of pmTBI and may underlie post-concussive symptoms.

Keywords

concussion; mild traumatic brain injury; pediatric; neuroimaging; electrophysiology; neuromodulation

Introduction

Clinicians face multiple challenges when treating the 750,000 new cases of pediatric mild traumatic brain injury (pmTBI) that occur each year (Zemek et al., 2016a). Specifically, the etiology (e.g., diffuse brain injury vs. disrupted cerebral blood flow [CBF] vs. psychological factors) of post-concussive symptoms (PCS), the long-term impact of pmTBI on academic and social functioning, and the effect of age-at-injury on short-term and long-term clinical outcomes are largely unknown (Dennis et al., 2013; Taylor et al., 2010; Yeates et al., 2012). Animal and emerging human literature demonstrate both white (WM) and gray (GM) matter pathologies following injury, with each pathology exhibiting unique time-courses for recovery (Barkhoudarian et al., 2016; Mayer et al., 2011; Meier et al., 2015; Mondello et al., 2011). Computed tomography (CT) scans used for assessment of macroscopic intracranial hemorrhage are not sensitive to the most *probable* pathological features of pmTBI, including diffuse neural injuries, CBF disruptions and edema (Keightley et al., 2014b). Further, neither routine nor advanced magnetic resonance imaging (MRI) are currently endorsed by either the American Academy of Neurology (Giza et al., 2013) or the American Medical Society for Sports Medicine (Harmon et al., 2013) for m BI, primarily because of limited diagnostic/prognostic evidence, presumed low base-rates of positive findings, and high cost. In contrast, The Head Injury Institute of the American College of Radiology does recommend MRI in the context of persistent symptomatology following mTBI or in the presence of new or worsening symptoms (Wintermark et al., 2015).

Thus, no clear, objective neurobiological biomarkers exist upon which physicians can predict recovery from pmTBI despite the unique vulnerabilities of the developing brain. As a result, clinicians do not know when it is truly safe for children of different ages to return to play/learn. This potentially places children at risk for a second, temporally proximate injury resulting in increased symptoms, pathology and delayed recovery (Broglio et al., 2007; Gilbert and Johnson, 2011; Prins et al., 2010; Van Kampen et al., 2006). Conversely, the lack of objective markers may also result in unnecessary restriction of children from social, cognitive and physical activities for longer than is physiologically necessary. These issues have recently risen to the forefront, with growing concerns regarding the possible neurodegenerative sequelae (such as Chronic Traumatic Encephalopathy, CTE) of both

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clinically apparent and clinically silent injuries (i.e., subconcussive blows), and the increasingly recognized need to quantify the physiology of concussion (Mayer et al., 2017).

This systematic review addresses this gap by providing a critical review of the pmTBI biomarker (i.e., imaging, electrophysiology and neuromodulation) literature to date, as well as by discussing the major obstacles for performing research in this challenging population. In contrast to the adult literature, existing pmTBI biomarker reviews have predominantly focused on sport-related concussion (SRC; Chamard and Lichtenstein, 2018; Guenette et al., 2018) or chronic injury effects in mixed severity groups (Ashwal et al., 2014; Keightley et al., 2014b). The current review includes pmTBI from all injury mechanisms, and specifically focuses on biomarkers obtained during the acute and sub-acute injury phases. Importantly, we also include studies that assessed non-routine biomarkers as part of clinical care in the hospital setting.

General Background

The terms “concussion” and “mTBI” have either been used synonymously or to describe distinct diagnostic entities based on differing injury severity (mTBI > concussion); however, to date, no formal clinical criteria have been proffered to support the latter clinical distinction (Mayer et al., 2017). Thus, for the purpose of the current paper, these terms are used interchangeably. pmTBI represents a large public health concern due to the sheer volume of new cases (approximately 750,000) that occur each year (Zemek et al., 2016b). Importantly, the rates of reported high school concussions increased 4.2-fold between the mid-1990s and the mid-2000s, with similar increases in those seeking care in the emergency room (ER; Lincoln et al., 2011). Recent studies suggest that this may only be the tip of the iceberg, with pmTBI patients often seeking care with their primary care providers for concussion rather than in the ER setting (Arbogast et al., 2016). The highest incidence rates for all TBI severities occur in the first four years of life, with a secondary spike occurring between the ages of 15 and 19 years of age (Faul et al., 2010), suggesting that concussion is a particularly pertinent problem for children and adolescents. The increased incidence in adolescence is primarily driven by participation in organized sports and engagement in other risk-taking behaviors, including the initiation of driving.

It has been established that pmTBI patients experience cognitive, neurosensory and emotional symptoms during the acute to sub-acute injury phase (Master et al., 2016; Mayer et al., 2018; Yeates et al., 2009), with a recent ER-based study indicating that up to 30% of pmTBI patients remain symptomatic at 4 weeks post-injury (Zemek et al., 2016a). According to the International ollaboration on Mild Traumatic Brain Injury Prognosis, literature on long-term outcomes is sparse, with few well-designed prospective studies (Hung et al., 2014; Keightley et al., 2014b). Of particular concern are reports of increased incidences of neuropsychiatric conditions, serious academic delays, and decreases in overall quality of life following pmTBI (Bijur et al., 1990; McKinlay et al., 2009). In one large prospective study, pmTBI patients exhibited increased somatic and cognitive symptoms relative to orthopedic injury (OI) controls for up to 12 months post-injury (Yeates et al., 2012). Deficits in attention, memory, and processing speed are also commonly observed in

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the sub-acute phase of pmTBI (Babikian et al., 2011; Catroppa et al., 2007), with long-term executive dysfunction also being reported 12 months post-injury (Sesma et al., 2008).

The Role of Neurodevelopment

Childhood trauma is unique in that both the immediate and longitudinal effects of injury are superimposed on a rapidly changing brain. Neurodevelopmental trajectory varies as a function of age and biological sex (Gogtay et al., 2004; Lebel et al., 2008), suggesting that findings relevant for one group of children (e.g., male adolescents, the typical sample in most pmTBI studies) may not directly translate to other developmental phases or biologic sex. In general, females develop faster than males both in terms of behavior and cognition, a trend that is accelerated by differential entry points into puberty (Gogtay et al., 2004; Lebel et al., 2008). Classic theories espoused by Piaget and Erikson (reviewed in Berk, 2014; Berk and Meyers, 2016) separate childhood into distinct developmental stages including infancy/very young childhood (≤ 5 y.o., spanning multiple developmental stages), middle childhood (6 or 7 to 11 or 12 y.o.; single stage) and adolescence (≥ 12 y.o.; single stage), with each stage primarily distinguished based on emotional and cognitive capabilities. The National Institutes of Health defines four separate periods of growth and development corresponding to infancy (0–3 y.o.), preschool (3–6 y.o.), middle childhood (6–12 y.o.) and adolescence (12–18 y.o.).

However, other literature suggests more distinct neurodevelopmental stages occurring within middle childhood. For example, a single factor is derived across tests of executive functioning in 6–7 y.o., whereas children aged 8–13 tend to demonstrate the 3-factor structure commonly observed in adult models (Lehto et al., 2003). Similarly, Anderson (2002) outlined a steep development trajectory between the ages of 7 and 9 years for cognitions frequently impaired in brain injury (e.g., cognitive flexibility, goal setting, and information processing), with full maturation by 12 years. For the purposes of the current review, we divide childhood into the following 6 developmental stages: infancy (0–3 y.o.), preschool (3–6 y.o.), early childhood (6–8 y.o.), middle childhood (9–12 y.o.) and adolescence (13–19 y.o.).

Accounting for the variance associated with neurodevelopment and biological sex is especially relevant for imaging studies (see Guenette et al., 2018 for review). Sensorimotor development is typically complete by ages 6–7 years, but the development of association areas involved in top-down control/executive functioning occurs later (Casey et al., 2005). Neurodevelopmental trajectories differ markedly between middle childhood and adolescence, with linear and quadratic effects reported in WM volumes (Lenroot et al., 2007). Although WM tracts are developed by age 11 or 12 years, fractional anisotropy (FA) increases in association and projection fibers through age 20 years (Lebel et al., 2008), driven primarily by changes in axial diffusivity (Qiu et al., 2008; Snook et al., 2005).

Cortical thickness, subcortical volumes and functional connectivity (fcMRI) also vary with age (Lenroot et al., 2007; Paus, 2007; Power et al., 2012), with significant differences in GM organization (Khundrakpam et al., 2013) and cerebral blood flow (CBF; Satterthwaite et al., 2014a) arising between middle childhood and adolescence. Finally, research suggests

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reductions in the amplitude of delta and theta band oscillations, more prominent alpha and beta band oscillations, and increased short distance beta band coherence during adolescence (Thatcher et al., 2008; Uhlhaas and Singer, 2011). Developmental trajectories also differ between sexes, with a notable divergence at the onset of puberty (females=10–14 y.o.; males=12–16 y.o.) in subcortical brain development (Goddings et al., 2014; Satterthwaite et al., 2014b), cortical GM (Mutlu et al., 2013), WM (Giedd et al., 2012) and fcMRI (Satterthwaite et al., 2015). Testosterone levels further predict differential effects in males (Herve et al., 2009). Thus, large samples, relatively homogenous age groups, and appropriate control groups are necessary to overcome individual variability when trying to disambiguate pmTBI from typical brain development, especially when one considers that developmental trajectories may be fundamentally affected by injury.

It has been suggested that younger pmTBI patients are less likely to accurately self-report symptoms and may underestimate the risks involved in continued sports participation, frequently resulting in the under-diagnosis of pmTBI and premature decisions about return to physical activity (Broglio et al., 2007; Gilbert and Johnson, 2011; Van Kampen et al., 2006). Additional distinctions between adult versus childhood injuries include mechanisms of injury (fall/sports-related concussion versus motor vehicle crash), tissue mechanics (skull thickness, water content and ongoing myelination), musculoskeletal development (head to body weight ratio, decreased neck strength), incidence of cerebral edema, incidence of auto-dysregulation, and immaturity of excitatory neurotransmitter systems (Giza et al., 2007; Kochanek, 2006). Finally, both animal (Bayly et al., 2006; Huh et al., 2008) and human (Hessen et al., 2007) studies have shown that the developing brain is more susceptible to mild diffuse brain injury, providing a potential neuroimaging biomarker for the field to investigate moving forward.

Age also interacts with recovery in animal models as a result of differences in plasticity (early vulnerability vs. early plasticity) or due to critical periods (Kolb et al., 2011; Kolb and Teskey, 2012). However, empirical evidence on the influence of age-at-injury on pmTBI outcomes in the human literature is currently mixed as a result of heterogeneous sampling strategies that frequently conflate injury severity (i.e., mild through severe TBI) and overlapping neurodevelopmental periods (Ewing-Cobbs et al., 2016; Ryan et al., 2015a; Ryan et al., 2015b). There is some evidence that injury during middle childhood represents a critical period for developing cognitive deficits later in life (Alosco et al., 2017; Anderson et al., 2009; Crowe et al., 2012; Ryan et al., 2015a). Other studies examining age-at-injury effects on brain microstructure report different trajectories of brain damage and recovery in adolescents versus middle childhood (Ewing-Cobbs et al., 2016; Ryan et al., 2015a; Ryan et al., 2015b). For example, mixed-severity TBI patients injured during middle childhood exhibited more WM microstructure damage, yet showed the greatest recovery over time, suggestive of plasticity (Ewing-Cobbs et al., 2016). In contrast, initial changes in WM microstructure post-injury were smaller for adolescent patients relative to controls yet persisted over time (Ewing-Cobbs et al., 2016). These findings have been interpreted to suggest that middle childhood TBI is associated with continued neurodevelopment whereas this process is slowed in adolescents, leading to more detrimental outcomes.

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Rationale and Additional Issues for Biomarker Research in pmTBI

There has recently been a proliferation of interest in developing non-invasive biomarkers of injury using advanced imaging (Eierud et al., 2014), electrophysiology (Haneef et al., 2013; Huang et al., 2009) and biofluids (Mondello et al., 2011; Yuh et al., 2013) to provide objective evidence of so-called “invisible wounds”. For any biomarker to be clinically useful in diagnosis, prognosis and treatment, it must be 1) sensitive and specific, 2) provide biologically meaningful information about underlying mechanisms of injury, and 3) provide information/evidence about the course of recovery or non-recovery. As reviewed in the sections below, far fewer biomarker studies exist in children, especially in younger age ranges. The following sections review the most pertinent issues to consider when conducting imaging, electrophysiological and neuromodulation biomarker studies following pmTBI.

Potentially the biggest concern for conducting imaging and electrophysiological studies in pediatric cohorts is the increased risk of head motion (Power et al., 2012; Wehner et al., 2008). Head motion degrades quality on basic MRI structural scans, increasing the challenge of quantifying different lesions for radiological common data elements. The impact of head motion on more advanced imaging is even more deleterious, altering fundamental properties in functional connectivity (i.e., altering short versus long distance connectivity relationships) and diffusion (scalar values) metrics (Ling et al., 2012; Power et al., 2012), and further decreasing already low signal- or contrast-to-noise ratios. Head motion also affects both electro- (EEG) and magnetoencephalography (MEG) estimates in children by “smearing” sources, confounding localization and affecting evoked waveforms (Wehner et al., 2008). Critically, cranial (e.g., scalp lacerations) or musculoskeletal pain associated with trauma also increases the likelihood of excess head motion in pmTBI patients, even relative to their own uninjured state. Total acquisition time is therefore an important factor for younger patients. Recent advances such as simultaneous multi-slice technology has increased clinical feasibility of obtaining more advanced imaging data in children, as well as increased quality, due to reduced motion.

Second, work in both adults (Kamins et al., 2017; Mayer et al., 2011) and children (Mayer et al., 2012) suggests that physiological recovery may lag behind resolution of behavioral and cognitive symptoms, further emphasizing the need for objective biomarkers of injury. Multiple imaging modalities are also necessary for capturing the complex and multifaceted pathologies associated with mTBI in human (Bigler and Maxwell, 2012) and animal studies (Barkhoudarian et al., 2016). Similarly, animal models indicate a dynamic and temporally complex pattern in terms of how individual biomarkers are affected by injury which varies over the course of minutes to days to weeks (Barkhoudarian et al., 2016). Thus, the field of pmTBI must recognize that “recovery” does not represent a unitary concept as currently posited in the majority of research studies and clinical practice, but is likely multidimensional and fluid. Finally, known variability in the type, location, and time-course of various pathologies should influence analytic considerations in biomarker-based research. For example, assuming that each individual injury (e.g., head rotation in a motor vehicle crash, an intentional blow to the left temple, or a fall with occipital strike) results in a homogeneous pattern of “lesions” within the brain is undoubtedly flawed (Mayer et al., 2015b).

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The preceding section detailed a complex neurodevelopmental trajectory that, even in normal/uninjured children, adds additional levels of variability for biological assays relative to “more” homogenous adult populations, implicitly highlighting the need for longitudinal designs. Another critical consideration is the choice of appropriate control groups. The utilization of OI patients has been posited to be a superior strategy to control for non-specific symptoms (pain, increased fatigue, disruptions to normal routine, etc.) that may differentiate pmTBI patients from typically developing children. However, research with large adult cohorts has indicated no clear advantage for utilization of OI in terms of injury factors, PCS, psychosocial outcomes or confounding variables (Mathias et al., 2013). Moreover, the impact of non-specific symptomatology is likely greater on functional biomarkers (i.e., studies of active cognition or emotion) relative to structural studies (e.g., diffusion or spectroscopy), suggesting that the optimal control group may also depend on the biomarker being examined. Finally, most samples of SRC have utilized either contact or non-contact athletes to control for other confounding effects such as the effect of cardiovascular fitness on autonomic regulation.

There are also growing concerns that concussions, and potentially even participation in collision sports, may detrimentally affect brain functioning over both short- and long-term periods of time (Gardner and Yaffe, 2015; McKee et al., 2016; Montenigro et al., 2016). Several studies have implicated both “diagnosable” mTBI (i.e., an injury that meets existing diagnostic criteria), as well as exposure to repeated, sub-clinical blows (also known as sub-concussive or non-concussive injury), as contributing to neurobehavioral sequelae and the potential development of neuropathology (Gardner and Yaffe, 2015; McKee et al., 2016; Montenigro et al., 2016; Nordstrom et al., 2014; Smith et al., 2013; Stein et al., 2015; Stewart et al., 2017). A history of previous concussion not only increases the risk of future concussions, but also increases pre-injury symptoms and long-term cognitive and psychiatric dysregulation in athletes (Harmon et al., 2013) and ER samples (Dams-O’Connor et al., 2013).

Pertinent to the current systematic review, recent studies have demonstrated progressive WM changes as a function of participation in a single season of contact sports (Bazarian et al., 2014; Koerte et al., 2012; McAllister et al., 2014) and heading the ball in soccer players (Lipton et al., 2013). Other studies have correlated microstructural changes with independent measures of head impact (Bazarian et al., 2014; Davenport et al., 2014). Exposure history has been variably estimated by examining dose, frequency and duration of concussive, as well as sub-concussive, brain trauma (Erlanger, 2015; Manley et al., 2017). The quantification of sub-concussive blows remains a controversial topic, and currently there are no diagnostic criteria available (Mayer et al., 2017). However, there is a considerable amount of ongoing biomarker work in this area with several recently published reviews (Bailes et al., 2013; Manley et al., 2017; Tarnutzer et al., 2017). Although the majority of sub-concussive studies focus on more chronic effects, there is the potential for overlap of participants in terms of single acute injury (Talavage et al., 2014). Therefore, although sub-concussive terms were included as part of the overall search strategy, studies predominantly focused on the long-term effects of exposure/subconcussive blows were excluded from the current review.

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Criteria for Literature Review

The systematic literature search was developed in consultation with an expert medical librarian (E.S.) and was conducted in Ovid/Medline, Scopus, Cochrane Library, and Web of Science databases. The MeSH terms are shown in Appendix, and the review was registered in the international prospective register of systematic reviews (PROSPERO). A sensitive filter developed by the Cochrane Child Health Field for identifying pediatric studies was used to maximize the number of reviewed articles (Boluyt et al., 2008). Articles were included if they met the following criteria: (1) peer-reviewed original research articles (i.e., no case studies or reviews) published or e-published in English between January 1990 and December 31 2017; (2) focused on patients with TBI; (3) included participants only ≤ 19 years of age; (4) pertinent to only pmTBI or concussion; and (5) included at least one advanced biomarker assessment on average within 4 months after injury. Studies with heterogeneous injury severities (i.e., mild to severe traumatic brain injury), mixed age ranges (i.e., adolescents through early adults) or those solely focused on intentional trauma were excluded. The four-month cut-off was chosen based on 1) current clinical conceptualizations of prolonged post-concussive syndrome (Quinn et al., 2017) and 2) to minimize the likelihood of obtaining a biased sample for studies that enrolled patients at later post-injury times.

A graphical representation of the entire review process is provided in Figure 1. The search results across the multiple databases were first collated (N= 2480 articles) and checked for duplicates (N= 1025 articles). The title and abstract of all articles (N= 1455 articles) were next reviewed by two coauthors (either A.M., M.K., E.S., or T.M.) in an independent and blinded fashion using the Rayyan platform (Ouzzani etal., 2016) as the first step for determining eligibility. Disagreements between the reviewers were reconciled by consensus. The review process was then repeated for all screened articles that appeared to meet eligibility criteria (N= 311 articles) by two independent reviewers (either A.M., M.K., or T.M.), using the full text to make more granular decisions regarding inclusion. The selected articles were then reviewed to determine whether the study primarily focused on the effects of sub-concussive blows (22 articles, subsequently excluded), or included the assessment of acute to subacute pmTBI within the specified 4 month window (N= 56 articles). Exclusion criteria for the remaining articles are detailed in Figure 1, whereas Figure 2 depicts the frequency of all 56 articles as a function of year. Data extraction focused on diagnostic inclusion criteria, cohort type, sample size, sample age and primary biomarkers utilized in the study. Cohorts were classified based on predominant sample type, point-of-care and presence absence of lesions, recognizing that these categories are not mutually exclusive (e.g., ER samples typically include SRC and motor vehicle crashes).

Finally, to avoid erroneous inflation for quantitative meta-statistics, we determined which studies utilized either completely unique (N= 26 articles) or overlapping samples (N= 30 articles). Overlap was determined based on comparison of previous publications from the same group or through direct contact with the corresponding author. All articles presented in the review were verified in this fashion. In the case of multiple published studies with overlapping samples, the single study having a longitudinal design or with the highest pmTBI sample size was considered to be the “primary” article. Quantification for meta-

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statistics was therefore based on 26 unique and 10 primary articles. The extracted information from articles meeting all inclusion criteria is presented in Table 1. All studies were evaluated according to the Newcastle-Ottawa Quality Assessment Scale to determine bias (Wells et al., 2016) as well as Strength of Recommendation Taxonomy (SORT) criteria for determining levels of evidence (Ebell et al., 2004).

Literature Review Results

Structural MRI (43 Studies)

Standard clinical neuroimaging methods (e.g., computed tomography scans; T_{1-} and T_{2-} weighted images) represent a long-standing biomarker that has been used for diagnostic and prognostic purposes and to denote the presence of lesions in pmTBI (i.e., complicated pmTBI). These first generation scans are typically negative for the majority (75–90%) of concussed patients (Hughes et al., 2004; Iverson, 2006), a finding that initially helped propagate the view that mTBI does not lead to frank neuronal pathology. Second generation MRI sequences, such as fluid-attenuated inversion recovery (FLAIR) and gradient recalled echo (T_2*)/susceptibility weighted imaging (SWI), were developed in mid-1990s and early 2000s, and demonstrated increased sensitivity for detecting lesions across a wide-spectrum of neurologically injured patients (Bigler and Maxwell, 2012; Gardner and Yaffe, 2015; Haacke et al., 2009; McKee et al., 2016; Mittal et al., 2009; Montenigro et al., 2016; Yuh et al., 2013). T2* and SWI are particularly sensitive to the by-products of hemorrhage (e.g., deoxyhemoglobin and hemosiderin) that have been observed both in-vivo and at autopsy following mTBI (Bigler and Maxwell, 2012; Huang et al., 2015). Structural MRIs can be rated according to radiological common data elements (Broglio et al., 2018; Haacke et al., 2010) or can be quantified to measure changes in cortical thickness or volume occurring either as a function of disease progression (i.e., atrophy; Beauchamp et al., 2011) or through typical neurodevelopment (Giedd et al., 1999).

Although structural MRI is rarely prescribed following pmTBI as part of clinical care, several studies (typically retrospective in nature) have evaluated its utility across various clinical settings. Importantly, the types of imaging sequences utilized (e.g., T_1 vs. FLAIR) are rarely reported in these studies, and are thus subsequently assigned the generic label of “MRI” in Table 1. One study (Chern et al., 2014) reported that surveillance imaging (including structural MRI) performed as part of clinical care was not associated with additional operative procedures. Morgan and colleagues (Morgan et al., 2015) observed that structural MRI in pmTBI with chronic PCS (>2 weeks post injury) resulted in little additional diagnostic yield (1 new finding on 19 MRIs) and therefore was not cost-effective. Another study (Rose et al., 2017) reported that CT scans were acquired sooner on average than structural MRI following SRC, and that ordering either scan was associated with the presence of prolonged symptoms. Patients were more likely to receive an MRI if they had a prior concussion, were still participating in the activity that caused the concussion or had cephalic or emotional symptoms on the day they visited the clinic (Rose et al., 2017). Bonow and colleagues (Bonow et al., 2017) reported that only 2 out of 427 SRC patients (0.5%) who received a structural MRI (T_1-weighted, T_2-weighted, FLAIR, SWI, diffusion weighted imaging) as part of clinical care (total sample of 3338 CT-negative patients)

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exhibited findings potentially related to trauma (petechial microhemorrhage). Finally, a retrospective survey (Wendling-Keim et al., 2017) reported that ambulatory pmTBI patients were less likely to seek follow-up care after discharge and were less likely to have positive imaging findings (including but not limited to MRI and sonography) relative to a hospitalized sample.

Structural MRI is most frequently used qualitatively to denote the presence (i.e., complex pmTBI) or absence of lesions. In the first study of this nature, Yeates and colleagues (Yeates et al., 1999) observed trauma-related lesions on structural scans (T_1-weighted,T_2-weighted, PD, T_2*-weighted) for 1/23 pmTBI patients in an ER-based sample. A series of articles by a multisite consortium (Fay et al., 2010; Maillard-Wermelinger et al., 2009; Taylor et al., 2010; Taylor et al., 2015; Yeates et al., 2009) reported that 32/182 pmTBI exhibited intracranial abnormalities on MRI, and that these abnormalities were associated with loss of consciousness, increased PCS, impaired cognitive performance and worse outcomes in younger children. The multisite team also reported that pmTBI patients were slower to return to preinjury levels than OI controls, and exhibited 4 different longitudinal trajectories in terms of PCS recovery. nother multisite study focused on the development of new psychiatric disorders in ER patients (Max et al., 2013a; Max et al., 2013b; Max et al., 2015) reported lesions in 38/73 (52%) of pmTBI patients (T1–weighted and FLAIR). Several pre-injury factors and the presence of frontal WM lesions were associated with the development of novel psychiatric disorders in 17/54 participants at the 6 month and 2 year follow-up periods.

Evidence of trauma-related pathologies have been observed in some research studies that used *multiple* structural MRI sequences (T_1-weighted, T_2-weighted, FLAIR and T_2*-weighted: Wilde et al., 2008), but not all multi-sequence studies demonstrate this finding (T1-weighted, T2-weighted and SWI: Babcock et al., 2015; T1-weighted and SWI: Maugans et al., 2012; Mayer et al., 2012; Yuan et al., 2015). Independent studies by several groups using only a T_1-weighted scan (Friedman et al., 2017; Keightley et al., 2014a; Wu et al., 2017) did not observe any lesions in pmTBI patients, which is not surprising given the known high negative rate previously reported in the literature with first generation sequences. Finally, several of the research studies reviewed herein did not specify whether MRI structural scans were read by a radiologist or whether the presence or absence of lesions was determined based on the results from CT or MRI scans.

Lastly, several studies have quantified changes in volume or cortical thickness using structural MRI. In the first quantitative study (T_1-weighted, T_2-weighted, PD, T_2*-weighted), Yeates and colleagues (Yeates et al., 1999) observed no differences in GM or CSF volume at 3 months post-injury in an ER-based cohort of pmTBI patients relative to sibling controls. However, WM volumes significantly varied between pmTBI with increased PCS (smaller volume) relative to patients with lower PCS (larger volume). The New Mexico group (Mayer et al., 2015b) next reported decreased cortical thickness in an overlapping pmTBI cohort at 4 months post-injury based on a quantitative analyses performed with Freesurfer. In contrast, no volumetric differences on quantified MRI structural data were noted by another group between SRC and OI/typically developing control groups over a three month period (Wu et al., 2017).

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In summary, evidence from both routine-care and research-based studies suggest that the incidence of lesions on structural MRI scans is relatively low following pmTBI. However, the presence of lesions is more likely to be detected on certain sequences (SWI, T2*-weighted, FLAIR > T_1-weighted and T_2-weighted) and in certain pmTBI samples (ER > concussed athletes recruited from field). Importantly, even though the presence of positive findings is relatively rare, current evidence suggests that MRI-identified lesions may be associated with increased adverse events in the long- (e.g., increased PCS, new psychiatric diseases) rather than short-term (e.g., new surgical intervention or required hospitalizations).

Diffusion MRI (19 Studies)

Accumulating evidence from both animal (Budde et al., 2011; Mac Donald et al., 2007; Spain et al., 2010) and human (Dodd et al., 2014; Shenton et al., 2012) studies suggests that subtle abnormalities following trauma are better captured by diffusion magnetic resonance imaging (dMRI) relative to the conventional MRI sequences reviewed in the preceding section. It is now well established that the rate (CSF > GM > WM) and anisotropy (WM > GM > CSF) of diffusion differs in tissue types as a function of microstructural properties (Basser and Jones, 2002). Non-Gaussian diffusion is restricted or hindered (i.e., membranes and organelles), with at least two differential rates (i.e., intraaxonal ≈ 0.07 μm^2/ms and extraaxonal ≈ 0.85 μm^2/ms) based on compartment type (Fieremans et al., 2011; Maier et al., 2004; Mulkern et al., 2000). While any trauma-related change to parenchymal microstructure will alter the rate of diffusion, the most frequently cited pathologies include structural damage (e.g., changes in axonal membranes or myelin), alterations in the net concentration of intraaxonal and extraaxonal water (cytotoxic or vasogenic edema) and inflammatory processes (Bazarian et al., 2007; Mayer et al., 2010; Wilde et al., 2008). Although animal studies (Budde et al., 2011; Zhuo et al., 2012) indicate that diffusion sequences are capable of capturing microstructural changes (reactive gliosis) in GM, certain dMRI scalars (i.e., FA) approach the noise floor in GM and thus may be less reliable (Holleran et al., 2017).

In the first of a series of dMRI articles on pmTBI, the Baylor group (Chu et al., 2010; Wilde et al., 2008; Wu et al., 2010; Yallampalli et al., 2013) reported increased FA/reduced mean diffusivity (MD) in the corpus callosum, fornix and cingulum in the sub-acute stage of pmTBI patients recruited from the ER. dMRI scalars were also associated with severity of PCS and deficits in word recall. The New Mexico group conducted the first prospective dMRI study in pmTBI, reporting increased FA in conjunction with reduced radial diffusivity across several WM tracts (Mayer et al., 2012) as well as within deep and cortical GM (Mayer et al., 2015b) in an ER-based cohort. These abnormal diffusion metrics remained elevated at 4 months post-injury in a subset of patients and were able to classify pmTBI from HC with 90% accuracy.

The British Columbia group (Borich et al., 2013; Virji-Babul et al., 2013) next reported increased FA and decreased MD in anterior WM/motor tracts (ROI and voxel-wise analyses) in a cohort of SRC relative to uninjured contact athletes. These diffusion abnormalities were associated with worse performance on neurocognitive testing. In a series of articles on 20 pmTBI patients, a group from Belgium (van Beek et al., 2015b; van Beek et al., 2015c)

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observed increased FA in conjunction with mathematical task difficulties in the sub-acute phase relative to HC (van Beek et al., 2015b), findings which largely resolved in the early chronic phase (van Beek et al., 2015c). In contrast, pmTBI patients continued to demonstrate both working memory deficits and developmental abnormalities within the corpus callosum across the 6–8 month follow-up period.

The Cincinnati group (Babcock et al., 2015; Yuan et al., 2015) reported that pmTBI patients assessed within 96 hours of injury exhibited several abnormalities in graph theory metrics (i.e., higher small-worldness, higher normalized clustering coefficients, higher normalized characteristic path length, higher modularity and lower global efficiency), increased FA and reduced MD in diffusion data relative to OI controls, with PCS associated with nodal degree in the superior and middle frontal gyrus. PCS was also associated with decreased radial diffusivity observed in the corpus callosum and medial frontal gyrus. Yuan and colleagues (Yuan et al., 2017) reported that pmTBI with prolonged PCS exhibited a number of abnormal graph metrics (e.g., higher small-worldness, higher normalized clustering coefficient, and lower global efficiency) relative to controls. Following either aerobic or stretching regimens, there was a significant increase in global efficiency and a decrease in normalized characteristic path length in the aerobic training group (Yuan et al., 2017).

Manning (Manning et al., 2017) observed significant group differences across several WM tracts across various diffusion metrics in a cohort of SRC and uninjured athlete controls prospectively studied up to 3 months following injury. Wu and colleagues (Wu et al., 2017) reported that FA and apparent diffusion coefficient (ADC) did not significantly differ between SRC and OI/typically developing control groups in any ROI at 96-hours post injury. At 3 months post-injury, FA was significantly reduced and ADC elevated for SRC relative to healthy controls across several different WM tracts. In a series of within-group analyses, Wu further demonstrated that FA was decreased over visits only for SRC, whereas ADC increased over visits in SRC and decreased in OI.

In contrast to these positive findings, there have also been reports of null findings in the literature. Goodrich-Hunsaker and colleagues (Goodrich-Hunsaker et al., 2018) observed no differences in diffusion metrics between pmTBI and OI across multiple automated methods (TBSS, AFQ, TRACULA). Maugans and colleagues (Maugans et al., 2012) reported no significant differences across several dMRI metrics in a sample of SRC. Similarly, Friedman and colleagues (Friedman et al., 2017) did not observe any differences between SRC and a matched cohort on various diffusion metrics (FA and MD).

In summary, in contrast to widespread opinion (Hulkower et al., 2013), the majority of studies reporting abnormalities have observed increased, rather than decreased, FA during sub-acute pmTBI (Dodd et al., 2014). To date, all diffusion studies in pmTBI have utilized a single b-value and linear modelling (i.e., diffusion tensor imaging). The use of multiple b-values and more advanced modeling to potentially understand such findings as compartmental water fractions (Fieremans et al., 2011; Zhang et al., 2012) is of particular interest for future studies given reports of increased edema in children relative to adults for more severe forms of trauma (Adelson and Kochanek, 1998).

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Metabolic Imaging (3 Studies)

Positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) have been used to assess metabolic changes following severe TBI in children (Ashwal et al., 2014; Munson et al., 2006). PET assays a wide variety of underlying pathophysiology (e.g., glucose metabolism, tracers for different neurotransmitters) and has reasonable spatial resolution (Munson et al., 2006). However, exposure to radioactive tracers (radiopharmaceuticals) renders PET a less desirable modality for children and adolescents. In contrast, MRS measures the concentration of various metabolites in the brain, with each metabolite potentially sensitive to different pathophysiology. For example, N-acetylaspartate is a marker for neuronal loss/dysfunction, choline for demyelination or cell membrane synthesis/repair and glutamate/glutamine for excitotoxicity. MRS studies have typically reported decreased N-acetylaspartate, increased choline and glutamate/glutamine, and the existence of lactate and lipids after more severe forms of pediatric TBI (Ashwal et al., 2004; Ashwal et al., 2014).

To date, no studies have used PET imaging in pmTBI. In the first MRS study, Maugans (Maugans et al., 2012) did not observe any group differences (SRC vs. controls) or longitudinal changes (acutely and approximately 2 months post-injury) in concentrations of N-acetylaspartate or N-acetylaspartate/creatine ratio across several ROI. In another multimodal study which also employed dMRI and functional connectivity (fcMRI), Manning (Manning et al., 2017) demonstrated that choline was significantly reduced in a SRC group at 3 months relative to uninjured athlete controls. In the most recent study to date, Friedman and colleagues (Friedman et al., 2017) reported an increased frontal lobe gamma-aminobutyric acid/creatine ratio in SRC patients relative to OI in conjunction with null findings for other metabolites (N-acetylaspartate and glutamate). Moreover, a positive correlation existed between gamma-aminobutyric acid/creatine levels and evoked blood oxygen level dependent (BOLD) data during a working memory task in the frontal cortex for OI, a finding which was absent in SRC.

Static Measures of Hemodynamics (8 Studies)

Similar to axonal pathology measured with dMRI, the structural integrity of the microvasculature is also directly affected by trauma. educed CBF is purportedly the longest lasting sign of injury in animal models (Giza and Hovda, 2014). Animal models indicate a sub-acute reduction in capillary number and diameter both at the injury site and distally (Park et al., 2009), with other research suggesting a similar reduction in cerebral vascular reactivity (CVR; Metting et al., 2009). More severe forms of TBI have been shown to directly affect CBF transit time, as well as cerebral perfusion (Soustiel and Sviri, 2007). Clinical researchers have examined TBI-related changes in CBF through the use of single photon emission computed tomography (SPECT), arterial spin labeling (ASL) and ultrasonography. During ASL, the spin magnetization history of arterial blood water is inverted through the application of a radiofrequency pulse (i.e., a “tagged” proton), which is then contrasted with “untagged” protons to quantify CBF (Alsop et al., 2015). In contrast, CVR is typically either measured directly through carbon dioxide gas challenges (Lu et al., 2014) or via more endogenous techniques such as the breath-hold, both of which are based on BOLD contrast.

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In the first study to examine CBF deficits following pmTBI, Agrawal and colleagues (Agrawal et al., 2005) reported that 14/30 pmTBI patients exhibited hypoperfusion in the medial temporal lobe when scanned within 72 hours of injury using SPECT imaging. These perfusion deficits persisted for 3 months in 13/14 patients, and no additional children developed perfusion deficits between acute and follow-up visits. Twelve of the 14 patients with perfusion deficits exhibited prolonged PCS at 3 months relative to 2/16 patients without perfusion deficits (Agrawal et al., 2005). Maugans and colleagues (Maugans et al., 2012) reported decreased CBF in SRC relative to uninjured controls, with perfusion deficits persisting through the final study visit (approximately 2 months post-injury). However, the CBF abnormalities were not associated with scores on neurocognitive testing. Auerbach (Auerbach et al., 2015) assessed CBF pulsatility using a novel cranial accelerometry approach. They reported higher harmonics of cardiac-induced pulsations of the skull following concussion, which was 77% sensitive and 87% specific at a diagnostic level. The time course of CBF abnormalities began hours to days after concussion and appeared to outlast the duration of clinical symptomatology.

In an ER cohort with overlapping patients (see Neuromodulation section), the Calgary group reported higher global CBF in symptomatic pmTBI and lower global CBF in asymptomatic pmTBI relative to HC (Barlow et al., 2017). Povzun (Povzun et al., 2017) found a 7.2% incidence of structural intracranial changes in an ER-based sample, and clinical ultrasonography was both sensitive (90%) and specific (97%) for identifying these intracranial changes. Finally, Stephens and colleagues (Stephens et al., 2018) used ASL to assess relative CBF in SRC at 2 weeks and 6 weeks post-injury compared to uninjured control athletes (scanned only once). Results indicated increased CBF in the left insula and dorsal anterior cingulate cortex of SRC patients at 2 weeks post-injury, which remained elevated in the left dorsal anteriorcingulate cortex at 6 weeks post-injury. CBF was also increased in SRC patients with higher physical symptoms relative to those with a lower symptom burden.

In summary, within this limited body of research there is yet little consensus, with increased CBF, decreased CBF and varying levels of CBF that depend upon PCS reported across only a small number of pmTBI studies to date. There have been no published studies on CVR in this cohort.

Functional MRI (fMRI)/Near Infrared (NIR; 12 Studies)

Neurovascular coupling is frequently disrupted following trauma (Jang et al., 2017) as part of a complex process that can directly involve neurons, astrocytes, the vasculature or any combination of the above. Following excitatory neurotransmission, excess glutamate must be rapidly removed from the synaptic cleft by astrocytes and converted to glutamine (Attwell et al., 2010; Logothetis, 2008). Oxidative metabolism and CBF become decoupled as a result of vasodilation, ultimately culminating in an excess of oxygenated blood and an associated decrease in the ratio of deoxyhemoglobin relative to oxyhemoglobin. Differences in the magnetic or refractive properties of these two forms of hemoglobin form the primary physical basis of fMRI or NIR signals, respectively. Thus, these techniques measure disruptions in neurovascular coupling after TBI, but are unable to distinguish whether the

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underlying cause is neuronal or hemodynamic in nature (Mayer et al., 2015a). Importantly, in contrast to previously discussed imaging modalities, both techniques also provide the opportunity to examine the brain “in action” during challenging tasks, when patients frequently complain of increased symptom burden.

In the first fMRI study to examine the impact of pmTBI on neurovascular coupling, Krivitzky and colleagues reported no differences in brain activation between pmTBI patients (ER-based sample) and HC on a working memory task. However, behavioral deficits and hyperactivation in the posterior cerebellum were observed during an inhibitory control task for pmTBI patients, with imaging findings in the cerebellum negatively correlating with PCS (Krivitzky et al., 2011). The New Mexico group (Yang et al., 2012) similarly reported inhibitory deficits during an auditory spatial orienting task as well as hypoactivation within deep GM structures (primarily cingulate gyrus, thalamus and cerebellum) in ER patients during the sub-acute injury phase (see dMRI and quantitative structural imaging findings presented in Mayer et al., 2012; Mayer et al., 2015b). In the first prospective study, Hammeke and colleagues (Hammeke et al., 2013) compared activity during a Sternberg working memory task at approximately 13 hours and 7 weeks post-injury in a SRC sample relative to uninjured contact athlete controls. SRC patients demonstrated worse task performance and hypoactivation in a right lateralized network consisting of prefrontal, parietal and occipital regions. Conversely, activation was greater for SRC relative to controls in these same regions at 13 weeks post-injury with no differences in task performance.

The Montreal group reported hypoactivation (HC > pmTBI) within several frontal and parietal regions during a working memory task in a sample of concussion clinic patients, with dorsolateral prefrontal cortex activity positively associated with task performance (Keightley et al., 2014a). In an overlapping sample, Saluja and colleagues (Saluja et al., 2015) observed both hyper- and hypoactivation across a variety of regions in patients during a navigational memory task, some of which correlated with PCS. Finally, Ho and colleagues (Ho et al., 2017) observed that engaging in inhibitory control processes resulted in fewer areas of brain activity in comparison to simple, automated tasks in adolescent pmTBI patients within a week of injury (no control group studied). Sub-group analyses indicated that patients with elevated levels of depressive symptoms engaged more frontal lobe regions during the task than did patients with typical depressive symptomatology.

BOLD contrast can also be used to indirectly measure intrinsic neural activity that occurs synchronously over spatially distributed networks, which accounts for approximately 60–80% of the brain’s overall metabolic load (Raichle and Mintun, 2006). Critical for pediatric studies, these resting state fcMRI studies also reduce several confounds (inability to perform complex tasks, lack of effort, differences in behavioral performance, effects of pain, effects of fatigue, etc.) that influence evoked BOLD signals (Mayer et al., 2015a). For similar reasons, fcMRI also permits the comparison of results across the entire (e.g., mildest injury to minimally conscious patients) TBI spectrum (Sharp et al., 2014), and can be used to assay the neuronal integrity of multiple sensory, motor and cognitive networks in a relatively short period of time (Mayer et al., 2015c; Smith et al., 2009) without the complicated equipment necessary for evoked fMRI studies.

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The first fcMRI study in pmTBI was performed by Borich and colleagues (Borich et al., 2015) using a similar SRC cohort as previously described (Borich et al., 2013; Virji-Babul et al., 2013). The authors reported both increased and decreased fcMRI within the default-mode, executive, right frontal pole and left frontal operculum networks using independent component analyses. Newsome and colleagues (Newsome et al., 2016) found that asymptomatic pmTBI patients recruited from a concussion clinic demonstrated increased connectivity relative to OI between the posterior cingulate cortex and the ventral lateral prefrontal cortex, as well as between the right lateral parietal cortex and lateral temporal cortex. These findings were not associated with differences in verbal learning and memory at 30 days post injury.

Using a cohort of SRC patients and uninjured athlete controls, Manning and colleagues (Manning et al., 2017) reported that pmTBI had significant increases in resting state connectivity at 3 months post-injury within visual and cerebellar resting state networks (see DTI and MRS findings in same cohort). Dona and colleagues (Dona et al., 2017) calculated fractal dimension as a measure of complexity in rsfMRI data, reporting that it was reduced throughout GM in pmTBI patients relative to HC. Somewhat paradoxically, higher fractal dimension (i.e., greater time series complexity) in GM was positively associated with post-concussive symptoms. However, the results from this study should be interpreted with caution, as the authors utilized a subject-specific analyses method (i.e., uncorrected z-score transformations) that is known to be associated with bias in imaging data (Dodd et al., 2018; Mayer et al., 2014). In contrast to these positive findings, Friedman (Friedman et al., 2017) did not observe any fcMRI differences in a cohort of SRC that also involved several other imaging modalities.

In summary, the majority of evoked BOLD studies report hypoactivation following a variety of attention, inhibition or working memory tasks, with deficits in neurovascular coupling correlating with the degree of PCS. clear pattern of fcMRI deficits has not been observed in this population. To date, no studies have examined alternative connectivity metrics in pmTBI including dynamic connectivity, regional homogeneity or global connectivity. To our knowledge, there was only a single study that utilized NIR technology at the time of this systematic review, with no studies examining the functional NIR signal in the acute or sub-acute phases of pmTBI. Specifically, Semenova and colleagues (Semenova et al., 2016) examined the effectiveness of a NIR scanner for detecting intracranial hematomas relative to CT scans following pmTBI in an ER-based cohort. Results from the two modalities coincided in 39 cases, with both identifying intracranial hematomas in eight patients. NIR resulted in additional false-positives in three patients.

Electroencephalography (EEG) and Magnetoencephalography (MEG; 7 Studies)

EEG was the first clinical neurodiagnostic assessment to reveal compromised brain function following TBI (Glaser and Sjaardema, 1940; Jasper et al., 1940), and has continued to be a useful clinical tool for such routine procedures as the evaluation of post-traumatic epilepsy (for a reveiw see Arciniegas, 2011). Unlike the multiple signal sources that underlie fMRI and NIR, EEG and MEG directly measure neural electrical currents at millisecond-level temporal resolutions during both rest and cognitively active states (Jackson and Bolger,

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2014; Lewine and Orrison, 1995). Using these techniques, investigators are able to quantify the dynamics/coherence of neuronal function, measuring the amplitude of event-related potentials/fields, or the absolute or relative amplitude/power within different frequency bands, localized to either an electrode/channel or brain area (magnetic source imaging; co-registration with structural MRI). Slow wave abnormalities in delta and theta bands and changes in long-range connectivity are thought to be generated by injured neuronal tissue in adult mTBI (Dunkley et al., 2015; Huang et al., 2009) and coherence/disconnectivity between cortical regions have been reported across the TBI spectrum (Amyot et al., 2015; Dunkley et al., 2015).

The first published EEG study on pmTBI (Korinthenberg et al., 2004) reported that 64/98 patients (ER based cohort) exhibited abnormal findings within 24 hours of injury, and that acute EEG abnormalities correlated with somatic PCS. Although 23 patients remained symptomatic at 4–6 weeks post-injury, EEG was qualitatively deemed to be normal in 73 cases. Moreover, there was no correlation between PCS on the second visit and either the acute or follow-up EEG. Oster and colleagues (Oster et al., 2010) observed that EEG ordered within 48 hours of admission as part of clinical care (N=118) was normal for the majority of pmTBI in an ER-based setting. Of the 11 children (9.3%) with pathologic EEG, none of them exhibited abnormal imaging (CT or MRI), and the presence of abnormal EEG was not associated with either persistent symptoms or adverse clinical outcomes.

In a cross-sectional study utilizing resting-state EEG, the British Columbia group (Balkan et al., 2015; Virji-Babul et al., 2014) reported increased beta, reduced theta, and reduced delta power across several frontal sources for SRC patients relative to uninjured control athletes, as well as abnormal connectivity metrics. In a study with overlapping samples, the Belgium group (van Beek et al., 2015a) utilized EEG to demonstrate that pmTBI patients exhibited lower amplitude in a late positivity component (posited to reflect attentional failure) during cognitive tasks, but were similar across more basic early sensory components. Finally, Broglio and colleagues (Broglio et al., 2016) prospectively (symptomatic, self-report asymptomatic, return to play, and one-month post asymptomatic) examined an SRC sample and matched uninjured athlete controls for changes in Brain Network Activation, an EEG measure of interconnectedness, during auditory oddball and go/no go tasks. Although several significant differences were observed on clinical measures, EEG findings were unable to differentiate SRC and control groups. In another study with the same EEG metric, Broglio (Broglio et al., 2017) reported that *both* SRC and control group's data changed in a similar fashion across pre- and post-injury visits. Moreover, EEG interconnectedness failed to improve diagnostics beyond traditional clinical measures. The authors therefore concluded that EEG metrics of interconnectedness did not have any clinical utility for pmTBI (Broglio et al., 2017).

To our knowledge, MEG studies have not been performed in this population.

Neuromodulation (1 Study)

Unlike previously reviewed biomarkers which only measure brain functioning, transcranial magnetic stimulation (TMS) has the potential to both measure and alter neuronal activity. TMS is based on the principle of electromagnetic induction, delivering a magnetic pulse to a

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targeted brain region (e.g., primary motor cortex) leading to induction of secondary ionic current that produces neuronal depolarization (Kobayashi and Pascual-Leone, 2003). Depending on the types of pulses delivered, TMS can assess cortical excitation (e.g., motor threshold, central motor conduction time) or inhibition (e.g., cortical silent period, intracortical inhibition) mediated by a variety of underlying receptors (Lefebvre et al., 2015; Major et al., 2015). Both excitation and inhibition can be altered following the initial TBI as well as the secondary neurometabolic/chemical cascade (Barkhoudarian et al., 2016). Studies reviewing TMS findings after mTBI in adults most often report changes in intracortical inhibition (Lefebvre et al., 2015; Major et al., 2015), with additional findings of increased stimulation threshold and reduced conduction time.

TMS has only recently been used to examine cortical excitation and inhibition following pmTBI. Seeger and colleagues (Seeger et al., 2017) examined multiple TMS parameters at approximately 1 month post-injury in symptomatic pmTBI, asymptomatic pmTBI and HC. Results indicated that the TMS procedures were safe and well-tolerated. Although the cortical silent period was similar across groups (primary analyses), significant differences were observed between HC and symptomatic pmTBI patients for long-interval intracortical inhibition, suggestive of inhibitory deficits.

Meta-Statistics Summary

The meta-statistics for the 36 articles (26 unique + 10 primary) are presented in Figures 3–7. Our review suggests that a total of 1987 pmTBI patients were assessed with biomarkers during the acute and sub-acute injury phase either as part of clinical care (16.7%) or during research protocols (83.3%) over the past 28 years. To place this number in context, it represents approximately 0.26% of the 750,000 new cases of pmTBI that occur *each* year alone (Zemek et al., 2016a) and 0.009% of the cases that have occurred over the 28 year period spanning the review. The majority of the study designs (Figure 3A) were either cross-sectional (36.1%) or prospective cohort (44.4%) in nature, with case series (13.9%) and retrospective cohort (5.6%) studies typically conducted on convenience samples derived from clinical care. Among all of the studies, 33.3% used mixed samples consisting of patients with and without evidence of lesions, whereas 38.9% did not specify lesion status. The majority of studies were derived from ER (38.9%) and concussion clinic (27.8%) cohorts (Figure 3B). Somewhat surprisingly, a substantial portion of studies used mixed samples or did not explicitly state how their samples were derived (19.4%). Similarly, 61.1% of studies did not specifically identify which formal diagnostic criteria (e.g., ACRM, AAN, Berlin) were used for establishing patient inclusion into the study (Figure 3C). The problem of multiple diagnostic criteria from different organizations is potentially the largest barrier facing the field of mTBI (Mayer et al., 2017), and appears to be compounded by the myriad of different criteria applied in each individual study.

Due to the preponderance of cross-sectional and convenience samples, the SORT level of evidence was deemed to be relatively weak (i.e., score of 3) in the majority (72.5%) of studies. The evidence of bias (Newcastle Ottawa Scale) across studies was more variably distributed (see Table 1), with increased risk for bias associated with studies that were conducted during clinical care. Not surprisingly, biological sex was disproportionally

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represented by males (60.6% of pmTBI patients), a rate that is similar to the overall incidence rate reported in the literature (Meehan, III and Mannix, 2010). However, more studies are clearly required to identify any potentially moderating effects of biological sex on injury. Large gaps in the literature also exist for younger patients, with the majority of pmTBI studies focused on late childhood through adolescence (Figure 4). Among ER studies, 38.5% used typically developing youth as a control sample whereas 15.4% utilized OI. Studies on SRC more typically used uninjured athletes (57.1%), rather than typically developing youth (7.1%), as controls. Figure 5 demonstrates that the majority of studies were conducted in the first days to week post-injury, with others studies looking at a larger range of days post-injury falling across the entire acute to sub-acute phase. Importantly, as evidenced by the preponderance of off-diagonal elements in Figure 6, the majority of studies did not use similarly powered control groups, a critical factor for understanding the impact of injury on neurodevelopment.

Assessment with standard structural scans (variable use of T_1, T_2, T_2*, FLAIR, PD and SWI sequences) represents the most common biomarker utilized following pmTBI (Figure 7), several of which were conducted as part of clinical care. dMRI studies represent the most commonly used advanced imaging modality (33.9% of total 56 studies), potentially a result of the field's focus on WM injury in both pre-clinical and clinical injury models (Bigler and Maxwell, 2012). Unlike these structural biomarkers, fMRI, EEG, MEG and functional NIR offer great promise for directly correlating the neurobehavioral sequelae (e.g., poor attention) of acute/sub-acute pmTBI with perturbed physiology (Mayer et al., 2015a; McDonald et al., 2012). fMRI (7 evoked and 5 fcMRI studies) is relatively unique in the ability to probe both superficial cortical and deep gray matter structures at similar signal-to-noise ratios, which represents a powerful advantage since both modeling and animal studies suggest that shear stresses are more likely to accumulate in these regions (Zhang et al., 2004).

However, the BOLD signal (fMRI/NIR) is temporally sluggish and represents a complex measure of neurovascular coupling. Thus, separate indices of CBF and CVR are necessary to disambiguate hemodynamic/perfusion (i.e., vascular injury) from true neuronal abnormalities following injury. To date, 8 studies have examined CBF in pmTBI with mixed results, and no studies have examined CVR in sub-acute pmTBI or employed multiple hemodynamic measures in the same cohort of patients. In contrast to hemodynamic measures, EEG and MEG offer exquisite temporal resolution and the ability to directly measure neuronal dysfunction related to trauma. Although EEG has been deployed in both clinical care and experimental research settings, MEG has been underutilized in the study of pmTBI. Similarly, neuromodulation (e.g., TMS) offers the unique confluence of diagnosis, prognosis, and treatment, but has only been used in 1 sub-acute pmTBI study. Ultimately, studies that combine information across various neuroimaging modalities are necessary to capture the multi-faceted pathology that characterizes mTBI in animal models (Barkhoudarian et al., 2016).

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Conclusions

In summary, results from current and previous (Hung et al., 2014; Keightley et al., 2014b) systematic reviews identify relatively few diagnostic or prognostic biomarker studies in pmTBI to date. Importantly, only 1/36 pmTBI studies (see Yeates et al., 2009 and associated studies) received a SORT score of 1, indicating the lack of high quality, clinically impactful research in the field. Results from structural MRI studies highlight the potential importance of point-of-care and cohort-type for advanced biomarkers, with several ER samples (e.g., 52% in Max et al., 2015; 17.6% in Yeates et al., 2009) reporting much higher incidence rates of positive MRI findings relative to athlete only samples (e.g., 0.5% in Bonow et al., 2017). Although there is a general paucity of research for most biomarkers outside of structural and dMRI, specifically identified gaps in the literature include studies in MEG, functional NIR, PET, CVR and neuromodulation across any pediatric age group. Reports of increased FA during the sub-acute stage of pmTBI represents the only relatively consistent finding observed across multiple dMRI studies in pmTBI (Dodd et al., 2014). There are almost no published biomarker studies for infancy (0–3 y.o.) and preschool-aged children (3–6 y.o.), with relatively few studies in middle childhood (6–12 y.o.) as well.

The results of this review reinforce the assertion that there is considerable “heterogeneity” and “chaos” inherently associated with mTBI research (Rosenbaum and Lipton, 2012). However, several simple steps such as 1) specifying and using formal diagnostic criteria for patient inclusion, 2) specifying the point-of-care from which the patient sample was derived, and 3) reducing known sources of bias (e.g., no or limited control groups, convenience sampling, disproportionate numbers of older children/males) would greatly advance the field. Ultimately, well-powered longitudinal studies with appropriate control groups, as well as standardized and clearly-defined inclusion criteria (time post-injury, injury severity and past history) are needed to truly understand the complex pathophysiology which *may* (i.e., still needs to be determined by biomarkers) exist following pmTBI. Well-designed studies represent an essential first step towards both distinguishing typical from atypical recovery and for determining when it is safe to return children to typical activities.

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Appendix A:

List of search terms used. Pediatric and Brain Injury Search Terms were used for all searches.

Pediatric Search Terms:

exp Infant/ or Infant*.mp. or infancy.mp. or Newborn*.mp. or Baby*.mp. or Babies.mp. or Neonat*.mp. or Preterm*.mp. or Prematur*.mp. or Postmatur*.mp. or exp Child/ or Child*.mp. or Schoolchild*.mp. or School age*.mp. or Preschool*.mp. or Kid.mp. or kids.mp. or Toddler*.mp. or exp Adolescent/ or Adoles*.mp. or Teen*.mp. or Boy*.mp. or

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Girl*.mp. or exp Minors/ or Minors*.mp. or exp Puberty/ or Pubert*.mp. or Pubescen*.mp. or Prepubescen*.mp. or exp Pediatrics/ or Paediatric*.mp. or Paediatric*.mp. or Peadiatric*.mp. or exp Schools/ or Nursery school*.mp. or Kindergar*.mp. or Primary school*.mp. or Secondary school*.mp. or Elementary school*.mp. or High school*.mp. or Highschool*.mp.

Brain Injury Search Terms:

Exp Brain Concussion/ or mild traumatic brain injury.mp. or mtbi.mp or concuss*.mp. or sub-concuss*.mp. or subconcuss*.mp.

Advanced Imaging Search Terms:

exp Magnetic Resonance Imaging/ or mri.mp. or fluid-attenuated inversion recovery.mp. or FLAIR.mp. or magnetization transfer.mp. or susceptibility weighted imaging.mp. or swi.mp. or cortical thick*.mp. or exp atrophy/ or atroph*.mp. or morphometr*.mp. or volumetr*.mp. or dmri.mp. or exp Diffusion Tensor Imaging/ or Diffusion Tractography.mp. or dti.mp. or diffusion tensor imaging.mp. or exp Magnetic Resonance Spectroscopy/ or Magnetic Resonance Spectroscopy.mp. or Spectroscop*.mp. or Magnetic Resonance.mp. or fmri.mp. or Functional Magnetic Resonance Imaging.mp. or exp hemodynamics/ or hemodynamic*.mp. or connectivit*.mp. or resting state*.mp. or functional near infrared spectroscopy.mp. or fnirs.mp. or exp optical imaging/ or fluorescence Imaging.mp. or autofluorescence Imaging.mp. or exp Electroencephalography/ or eeg.mp. or Electroencephalogra*.mp. or exp magnetoencephalography/ or magnetoencephalo*.mp. or exp Transcranial Magnetic Stimulation/ or Transcranial Magnetic Stimulation*.mp. or TMS.mp. or exp Ultrasonography, Doppler, Transcranial/ or (transcranial and (doppler or sonograph*)).mp. or neurosonolog*.mp. or exp perfusion imaging/ or perfusion*.mp. or cerebrovascular reactivit*.mp. or vascular reactivit*.mp. or CVR.mp. or exp Cerebrovascular Circulation/ or cerebral circulation*.mp. or cerebral blood flow*.mp. or Cerebrovascular circulation*.mp. or CBF.mp. or arterial spin labeling.mp. or asl.mp. or tcd.mp. or tomograph*.mp. or Positron-Emission.mp. or PET.mp. or exp Tomography, Emission-Computed/ or SPECT.mp. or Single Photon Emission.mp. or proton*.mp.

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Highlights

- Only 1987 pmTBI have been examined over 28 years, or 0.26% of the *annual pmTBI burden*
- Only one of the reviewed studies meets criteria for high level of scientific evidence
- Very few of the reviewed studies included infants, early or middle childhood
- Incidence of structural MRI findings depends on sampling strategy and point-of-care

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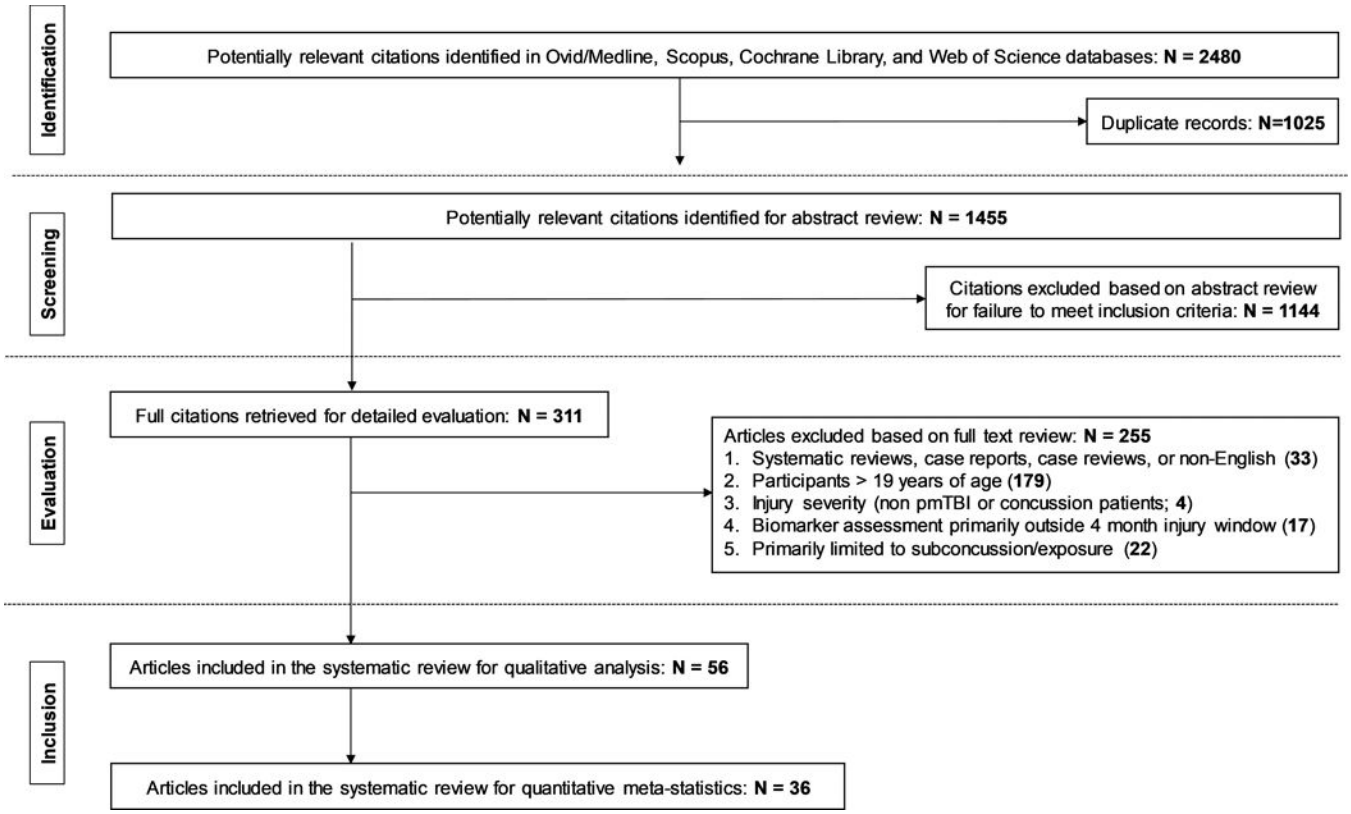

Figure 1: Review Process.

Figure 1 presents the PRISMA flow diagram detailing the identification, screening, evaluation, and inclusion and exclusion of articles at each stage of the current systematic review.

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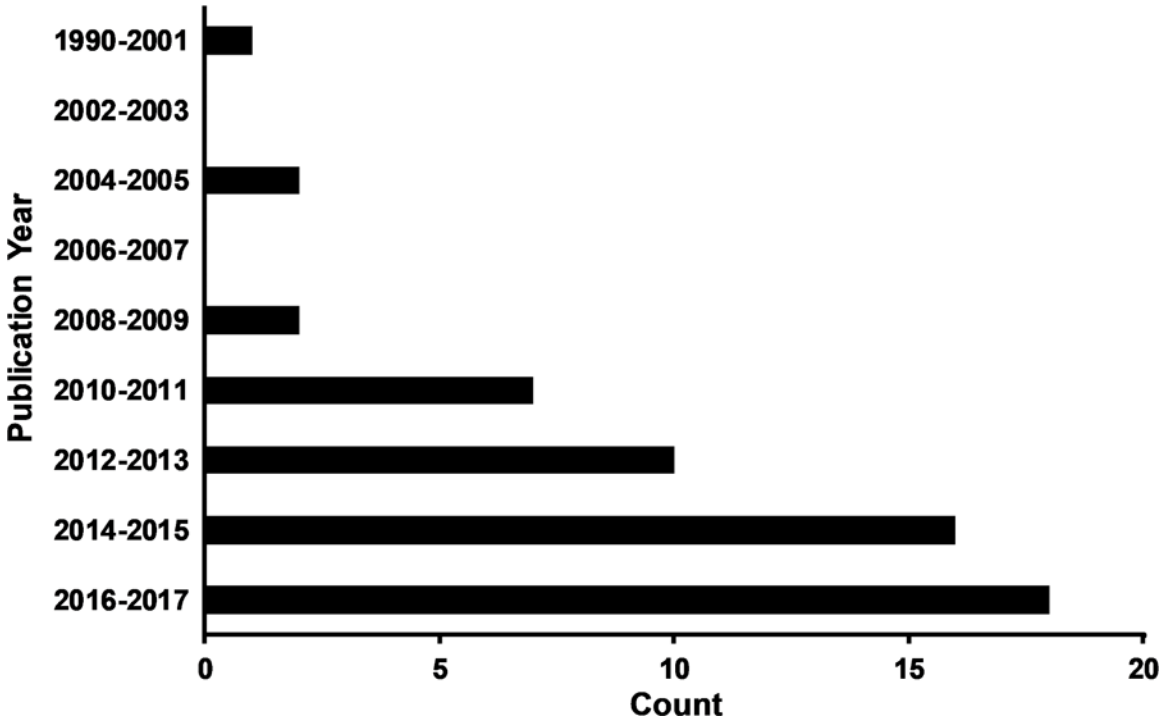

Figure 2: Number of Articles per Year.

Figure 2 presents the total number of peer-reviewed biomarker studies (N=56) that were published on acute to semi-acute pediatric mild traumatic brain injury during the period under review (1990–2017). With the exception of the first bin (1990–2001), years are grouped into 2 year intervals.

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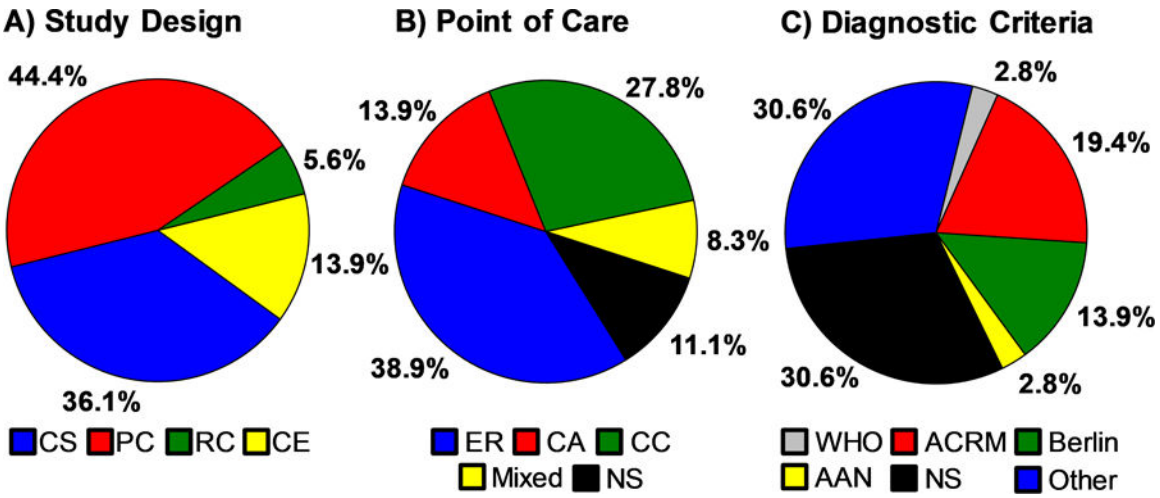

Figure 3: Pie Charts of Primary Study Parameters.

Panel A displays the percent age of the studies that utilized each study design (CS cross-sectional; PC = prospective cohort; RC = retrospective cohort; CE = case series). Panel B indicates the source for patient recruitment/point-of-care(ER=Emergency Room; CA = community athletes with concussion; CC = concussion clinic; Mixed = multiple recruitment sources; NS = Not Specified). Note that R, CC and Mixed samples likely contain athletes with concussions as well. Finally, Panel C presents the different diagnostic criteria (WHO = World Health Organization; ACRM = American ongress of Rehabilitation Medicine; Berlin = Berlin Consensus Statement; AAN = American Academy of Neurology; Other = criteria defined but not matching a formal system; NS = Not Specified) used in these same studies. The denominator for percentages is represented by unique plus primary studies (N=36).

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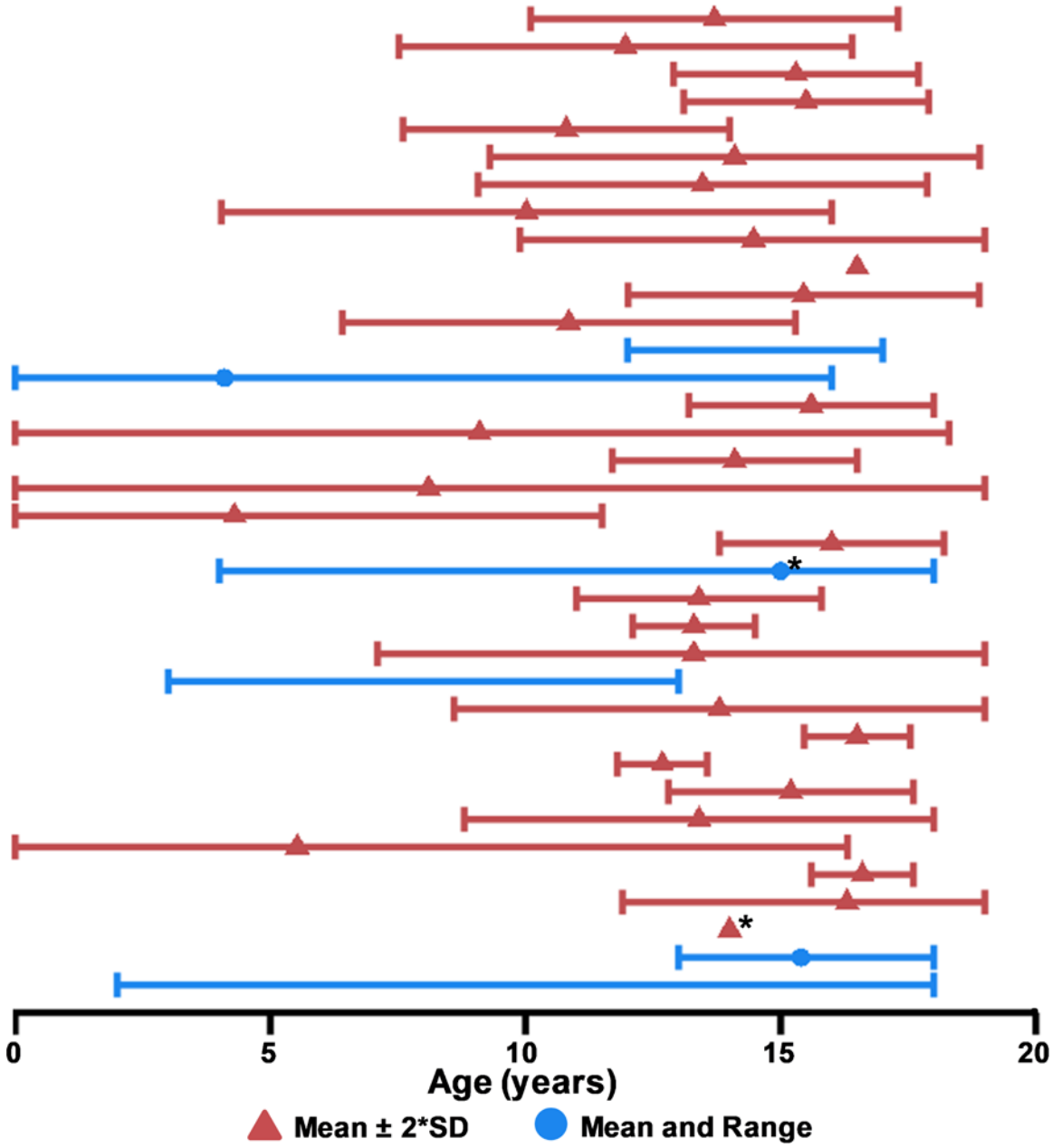

Figure 4: Patient Age Across Studies.

The mean age (triangle) and either two times the standard deviation (SD; red) or age range (minimum to maximum; blue) of included patients with pediatric mild traumatic brain injury (pmTBI) are presented in Figure 4. Asterisks (*) denote studies reporting the median rather than mean as a measure of central tendency. Studies which did not report an explicit age statistic are not graphed, and those that did not list SD or range are depicted by a single point. All SDs were artificially capped at 0 and 19 for data display purposes as studies exceeding these bounds were not considered for review. Only data from unique or primary studies (N=36) are presented in Figure 4.

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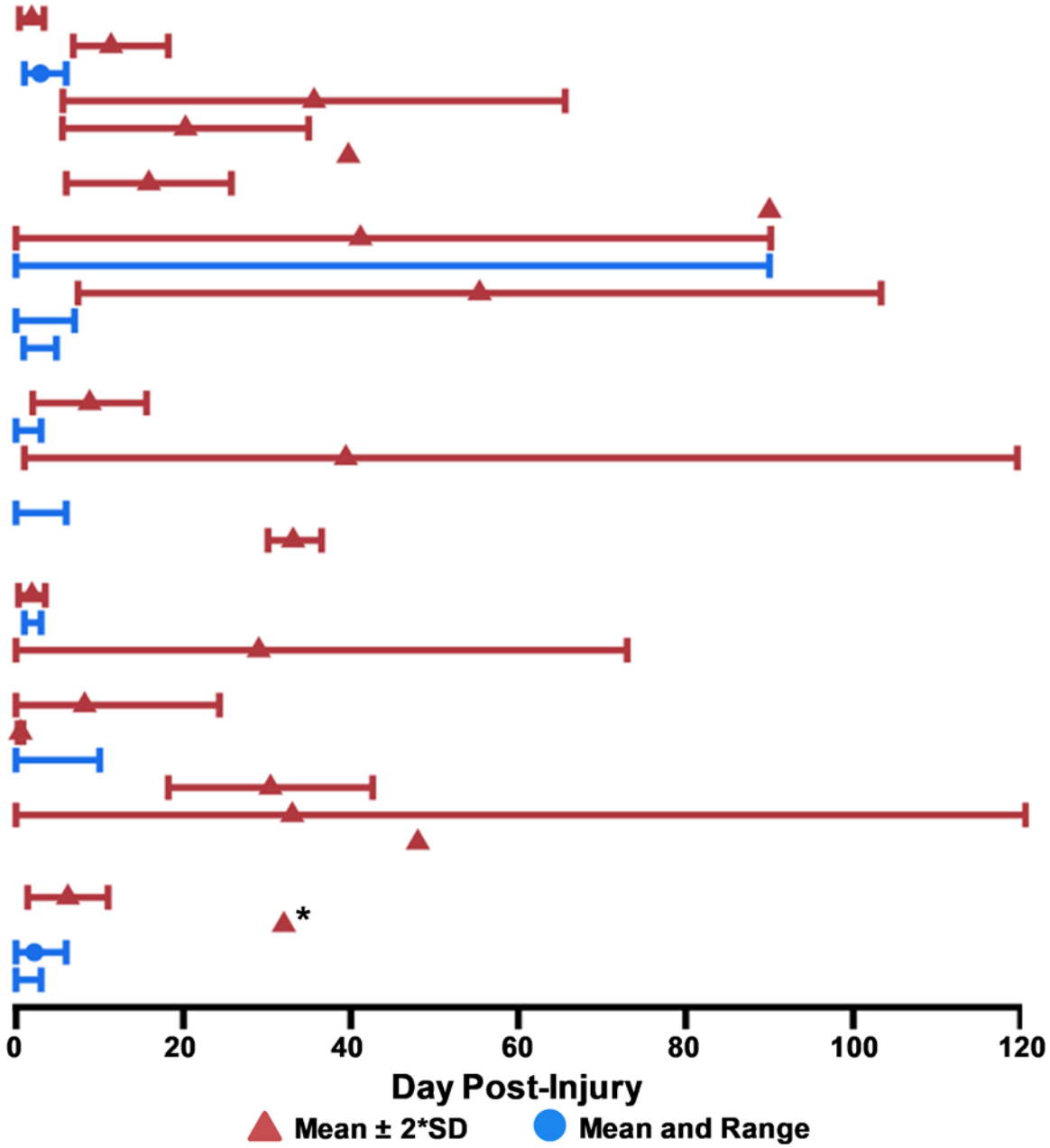

Figure 5: Day Post-Injury at First Biomarker Assessment.

The mean day post-injury (triangle) and either two times the standard deviation (SD; red) or day post-injury range (minimum to maximum; blue) of patients with pediatric mild traumatic brain injury (pmTBI) is presented in Figure 5. Asterisks (*) denote studies reporting only a median rather than mean as a measure of central tendency. Studies that did not report explicit day post-injury statistics are not graphed, and those that did not list SD or range are depicted by a single point. All SDs were artificially capped at 0 and 120 days for data display purposes. Only data from unique or primary studies (N=36) are presented in Figure 5.

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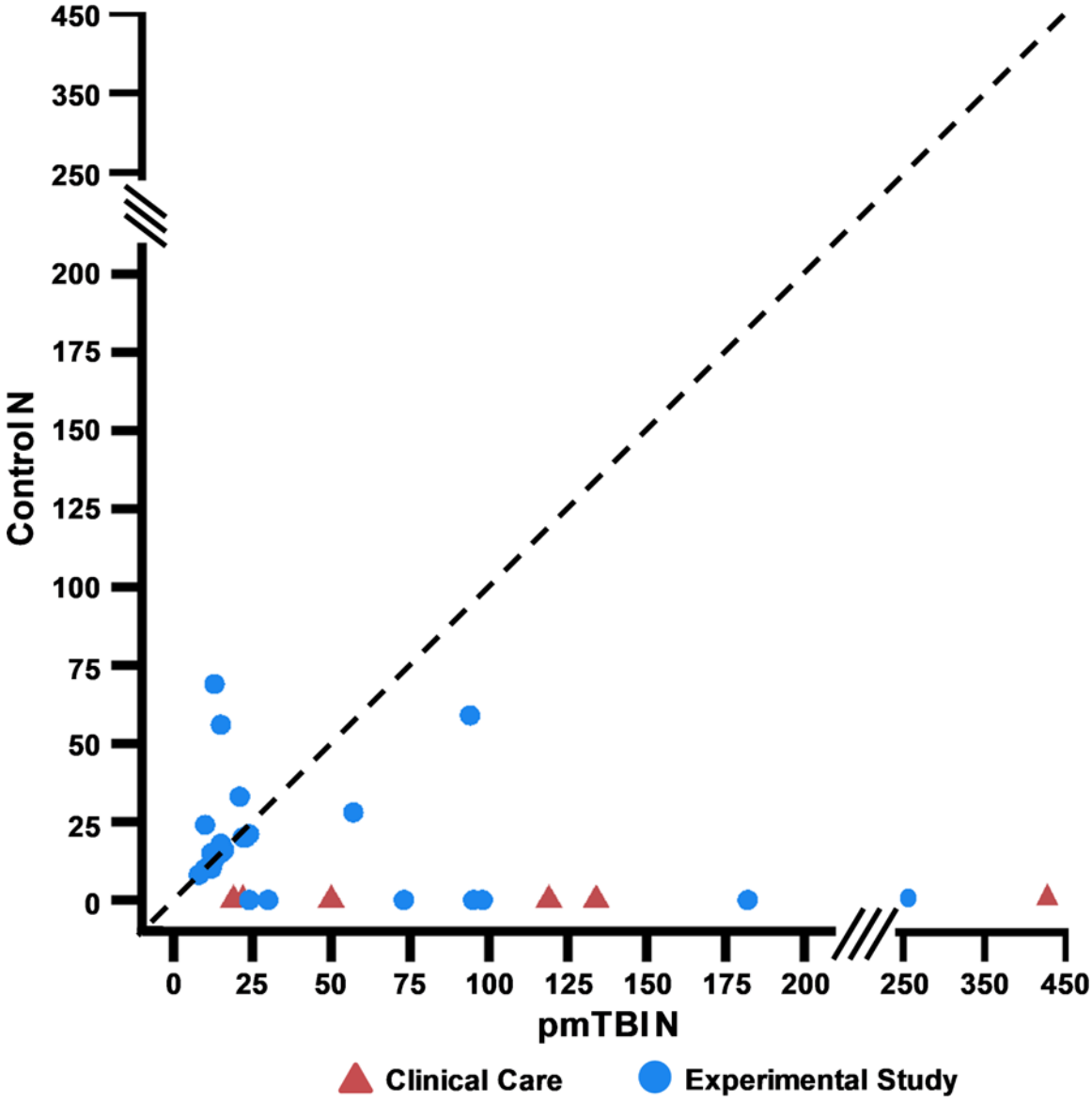

Figure 6: Sample Sizes.

Figure 6 plots the number (N) of patients with pediatric mild traumatic brain injury (pmTBI; X-axis) relative to the number of controls (Y-axis) utilized in the unique and primary studies (N=36). Only the number of participants who were characterized with biomarker data are plotted for studies that obtained clinical data on larger cohorts. To represent the data with higher fidelity, the X and Y axes are both split (see solid slanted lines) between N=0–200 (interval=25) and N=250–450 (interval=100) range. Red triangles indicate that the study was conducted as part of clinical care whereas blue circles indicate that the study design was experimental in nature. The dashed line represents an ideal study design in which equal numbers of pmTBI and controls are included. The majority of studies exhibit a rightward deviation from the dashed line, which was much more pronounced for clinical care studies and suggests increased risk of bias.

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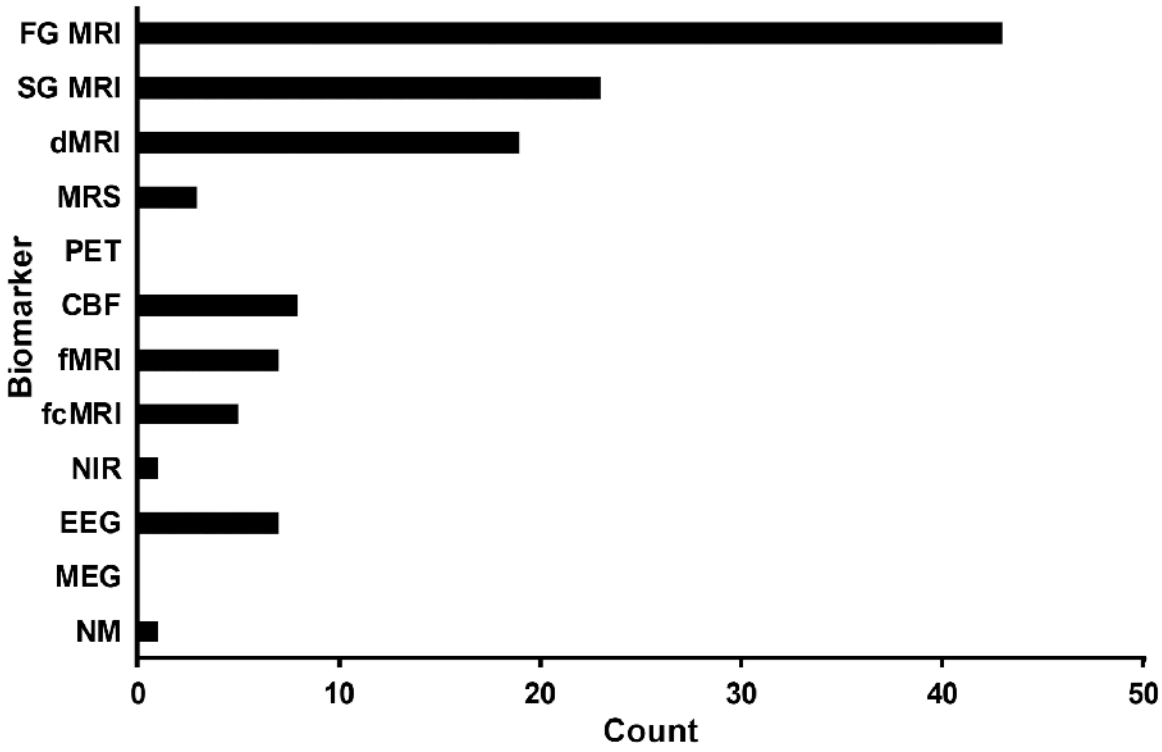

Figure 7: Utilization of Individual Biomarkers.

Figure 7 depicts the number of studies that utilized biomarkers as part of clinical care or through experimental research. Biomarkers were stratified into first generation (FG) MRI structural sequences (T-weighted,-weighted,proton density), second generation (SG) MRI structural sequences (fluid attention inversion recovery, susceptibility weighted imaging, 2*-weighted/gradient-recalled echo), diffusion MRI (dMRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), hemodynamics (CBF; arterial spin labeling, single photon emission computerized tomography, sonography, and cranial accelerometry), task-based functional MRI (fMRI), functional connectivity MRI (fcMRI), near infrared (NIR), electroencephalography (EEG), magnetoencephalography (MEG), and neuromodulation (NM). The utilization of each modality was summed within and across all 56 articles. Therefore, the total sum is greater than the total number of articles (e.g., an article that utilized fMRI, MRS and dMRI was assigned a value of 1 for each biomarker category).

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Table 1:

Summary of reviewed biomarker literature during acute and sub-acute stages of pmTBI.

				pmTBI Characteristics				HC Characteristics			
Author & Year (Related publications)	**Biomarkers**	**Design (Referral/ Lesion)**	**Dx Criteria**	**N (% BM)**	**Age**	**1st Visit**	**Additional Visits**	**Type (% BM)**	**Age**	**SORT**	**NOS**
Yeates 1999	$T_1/T_2/T_2^*$/PD	PC (ER/$^{\pm}$)	Other	26 (92%)	10.85$^{\pm}$2.22 (8-15)	(0-7)	~3 months	8 HC (0%)	12.38$^{\pm}$2.13 (8-15)	3	6.5
Yeates 2009 (Maillard-Wermelinger 2009; Fay 2010; Taylor 2010/2015; Yeates 2012)	T_1/T_2/PD/T_2^*/ FLAIR/DWI	PC (ER/$^{\pm}$)	Other	186 (97.8%)	11.96$^{\pm}$2.22 (8-15)	11.35$^{\pm}$3.42 (≤21)	~1 month*; ~3 months*; ~1 year*	99 OI (0%)	11.76$^{\pm}$2.23 (8-15)	1	6.5
Chern 2014	MRI	RC (ER/±)	NS	937 (2.35%)	5.53$^{\pm}$5.39 (0-19.5)	(Acute)*	48			3	3
Max 2015 (Max 2013a/b)	T_1/FLAIR	CE (ER/$^{\pm}$)	Other	87 (84%)	10.02$^{\pm}$2.99 (5-14)	(1-14)*	~3 months; (6-12 months)*; ~24 months*			2	3
Morgan 2015	MRI	CE (CC/$^{\pm}$)	Other	52 (37%)	15 (4-18)	(>14)				2	3
Bonow 2017	T_1/T_2/FLAIR/ SWI/DWI	CE (CC/$^{\pm}$)	Berlin	3338 (12.8%)	14	32: [21-45]				3	3
Rose 2017	MRI	CE (CC/$^{\pm}$)	Berlin	1953 (6.86%)	14.1$^{\pm}$2.1 (10-19)	39.4$^{\pm}$40.1 (1-201)				3	3
Wendling-Keim 2017	MRI/ Sonography	RC (ER/$^{\pm}$)	Other	267 (18.72 %)	4.1 (0-16)	(Acute)	(3-8 months)*			3	3
Wu 2010 (Wilde 2008; Chu 2010; Yallampalli 2013)	dMRI/$T_1/T_2/T_2^*$	CS (ER/$^{\pm}$)	Other	12 (100%)	15.3$^{\pm}$1.2 (14-17)	2.92 (1-6)		11 HC (100%)	15.8$^{\pm}$1.8 (14-19)	3	9
Mayer 2012 (Mayer 2015b; Yang 2012)	dMRI/T_1/ SWI/T_2	PC (ER/-)	ACRM	15 (100%)	13.47$^{\pm}$2.2 (10-17)	15.87$^{\pm}$4.93 (7-21)	127.82$^{\pm}$14.60 (3-5 months)	15 HC (100%)	13.4$^{\pm}$1.84 (11-17)	3	8
Virji-Babul 2013 (Borich 2013/2015)	dMRI/T_1	CS (CA/NS)	NS	12 (100%)	15.5$^{\pm}$1.2 (14-17)	35.6$^{\pm}$15.0 (17-61)		10 UCA (100%)	15.7$^{\pm}$0.9 (14-17)	3	6.5

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				pmTBI Characteristics				HC Characteristics			
Author & Year (Related publications)	**Biomarkers**	**Design (Referral/ Lesion)**	**Dx Criteria**	**N (% BM)**	**Age**	**1st Visit**	**Additional Visits**	**Type (% BM)**	**Age**	**SORT**	**NOS**
Van Beek 2015c (Van Beek 2015a/b)	dMRI	PC (ER/NS)	ACRM	20 (80%)	10.8±1.6 (7.0-13.1)	12.85±7.52 (2-26) *	20.25±7.35 (6-30); 201.23±21.55 (170-248)	20 HC (80%)	10.9±1.5 (7.6-12.8)	2	6.5
Yuan 2015 (Babcock 2015)	dMRI/T_1/T_2/SWI	CS (ER/-)	ACRM	23 (100%)	13.7±1.8 (11.0-16.7)	1.89±0.73 (≤4)		20 OI (100%)	13.2±1.4 (11.1-16.6)	3	8
Wu 2017	dMRI/T_1	PC (ER/-)	ACRM	10 (100%)	(12-17)	(0.92-4.83)	(84-143)	12 HC/ 12 OI (100%)	(12-18)	2	8.5
Yuan 2017	dMRI/T_1	PC (Mixed/-)	ACRM	22 (100%)	15.45±1.72	55.37±23.98 (4-16 weeks)	(9-13 weeks later)	20 HC (100%)	16.28±1.38	2	8.5
Goodrich-Hunsaker 2017	dMRI/T_1	CS (NS/NS)	NS	94 (100%)	12.68±0.45 (8-17)	(0-10)		59 OI (100%)	12.46±0.50	3	4
Friedman 2017	MRS/T_1/SWI/ dMRI/fMRI/fcMRI	CS (CC/-)	Berlin	11 (91%)	15.2±1.2	12±8 (2-28) *	30.4±6.1 (23-44)	11 OI (91%)	15.26±1.2	3	8.5
Agrawal 2005	SPECT	PC (ER/-)	ACRM	14 (100%)	(2-18)	(0-3)	~3 months	16 Other (100%)	(2-18)	2	7.5
Maugans 2012	ASL/dMRI/MRS/ SWI/T_1	PC (Mixed/-)	Berlin	12 (100%)	13.4±1.2 (11-15)	1.9±0.8 (0.7-2.9)	14; 54.9±8.7 (41-70)	12 HC (100%)	13.4±1.2 (11-15)	2	7.5
Auerbach 2015	Cranial accelerometry	PC (CA/NS)	NS	13 (100%)	15.4 (13-18)	(Pre-season)	2.2 (0-6); (Post-season)	69 UCA (100%)	15.2 (13-17)	3	7
Barlow 2017≠ (see Seeger 2017)	ASL/T_1									3	8
Povzun 2017	Sonography	PC (ER/±)	Other	256 (100%)	8.10±5.56 (0-18)	(Acute)	(Acute to sub-acute)			3	3
Stephens 2017	ASL/T_1	PC (CC/NS)	Other	15 (80%)	15.6±1.2 (13-17)	8.8±3.4	43.2±12.5	15 NCA (100%)	15.2±1.7 (13-17)	2	9

				pmTBI Characteristics				HC Characteristics			
Author & Year (Related publications)	**Biomarkers**	**Design (Referral/ Lesion)**	**Dx Criteria**	**N (% BM)**	**Age**	**1st Visit**	**Additional Visits**	**Type (% BM)**	**Age**	**SORT**	**NOS**
Krivitzky 2011	fMRI/MRI	CS (CC/-)	Other	13 (100%)	13.3±3.1	29±22 (8-82)		13 HC (100%)	12.2±3.5	3	9
Yang 2012≠ (see Mayer 2012)	fMRI/T_1/SWI/T_2									3	8
Hammeke 2013	fMRI/T_1	PC (CA/NS)	AAN	12 (100%)	16.5±0.52	0.54±0.15 (0.5-2)	49±6.8 (35-63)	12 UCA (100%)	16.5±0.52	3	7.5
Keightley 2014a (Saluja 2015)	fMRI/T_1	CS (CC/-)	WHO	15 (100%)	14.47±2.29 (10-17)	41.13±24.50 (9-90)		15 HC (100%)	14±2.3 (10-17)	3	8.5
Ho 2017	fMRI/T_1	CS (Mixed/NS)	NS	30 (100%)	13.8±2.6 (10-17)	5.9±8.0*	8.2±8.1			3	3
Borich 2015≠ (see Virji-Babul 2013)	fcMRI/T_1									3	7
Newsome 2016	fcMRI/T_1	CS (CC/NS)	Berlin	13 (100%)	16.0±1.1 (13-19)	33.1±1.7 (<37)		13 OI (100%)	16.4±1.3 (13-19)	3	7
Dona 2017	fcMRI/T_1	CS (NS/NS)	NS	15 (100%)	13.4±2.3	33.0±43.8		56 HC (100%)	13.7±7.8	3	1
Manning 2017	fcMRI/dMRI/ MRS/T_1/T_2/FLAIR	PC (CC/NS)	NS	17 (88%)	13.3±0.6 (11-14)	(1-3)	~3 months	26 UCA (69%)	13.0±1.0	3	5
Semenova 2016	NIR	CS (ER/±)	NS	95 (100%)	9.1±4.6 (0.58-17)	(0-3)				3	3
Korinthenberg 2004	EEG	PC (NS/±)	Other	100 (98%)	(3-13)	(Acute)	(4-6 weeks)			2	5
Oster 2010	EEG/MRI/ Sonography	CE (NS/-)	ACRM	150 (79%)	4.3±3.6 (0-16)	(0-6)				3	3.5
Balkan 2015 (Virji-Babul 2014)	EEG	CS (CA/NS)	NS	21 (100%)	16.5	(<3 months)		33 UCA (100%)	16.0±0.9	3	2
Van Beek 2015a≠ (see Van Beek 2015c)	EEG									3	8

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				pmTBI Characteristics				HC Characteristics			
Author & Year (Related publications)	**Biomarkers**	**Design (Referral/ Lesion)**	**Dx Criteria**	**N (% BM)**	**Age**	**1st Visit**	**Additional Visits**	**Type (% BM)**	**Age**	**SORT**	**NOS**
Broglio 2016	EEG	PC (CC/NS)	NS	24 (100%)	16.3±2.2	6.2±2.4	26.2±43.8; 49.2±60.9; 79.5±60.1	21 UCA (100%)	17.1±2.9	2	8.5
Broglio 2017	EEG	PC (CA/NS)	NS	8 (100%)	16.6±0.5	(Pre-season)	(0-3); (Asymptomatic); (Post-season);	8 UCA (100%)	16.6±0.5	3	7.5
Seeger 2017 (Barlow 2017)	TMS	CS (ER/NS)	Other	62 (92%)	14.1±2.4 (8-18)	39.7		28 HC (100%)	14.31±3.14 (8-18)	3	8

Notes: Research groups who published multiple articles in the same modality but with overlapping samples are noted in parenthesis next to the primary article. In addition, ǂ indicates a research group who published a separate article on a distinct biomarker but utilized a shared sample of patients as the primary article. Summary statistics are only presented for primary articles to avoid inflation of meta-statistics. Age and post-injury visit are given as mean ± standard deviation (SD) or by median: [interquartile range] depending on the reported measure of central tendency. single point value denotes that the authors only reported the mean or median. Ranges of age and post-injury assessment time are also included in parenthesis when reported. Years and days are the default units for age and assessment time, respectively. An * denotes that biomarkers were not collected at that assessment visit.

Abbreviations: Biomarkers: ASL = arterial spin labeling, EEG = electroencephalography, dMRI = diffusion magnetic resonance imaging, DWI = diffusion weighted imaging, fcMRI = functional connectivity magnetic resonance imaging, FLAIR = fluid attenuated inversion recovery, fMRI = functional magnetic resonance imaging, MRI = unspecified structural magnetic resonance imaging sequence, MRS = magnetic resonance spectroscopy, NIR = near infrared, PD = proton density, SPECT = single-photon emission computed tomography, SWI = susceptibility weighted imaging, TMS = transcranial magnetic stimulation. Study design: CE = case series, CS = cross-sectional, PC = prospective cohort, RC = retrospective cohort. Referral source: CA = concussed community athlete, CC = concussion clinic, ER = emergency room, Mixed = heterogeneous source, NS = not specified. Lesion status: - = patients with negative imaging findings only, ± = patients with both positive and negative imaging findings. Diagnostic (Dx) criteria: AAN = American Academy of Neurology, ACRM = American Congress of Rehabilitation Medicine, Berlin = Berlin Consensus Statement, WHO = World Health Organization, Other = criteria defined but not matching a formal system. N = sample size. % BM = percentage of sample for which biomarker data were collected. Control type: HC = typically developing healthy control, NCA = non-contact athlete, OI = orthopedically injured control, UCA = uninjured contact athlete. NOS = Newcastle-Ottawa Quality Assessment Scale (average score from two raters). SORT = Strength of Recommendation Taxonomy.