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The long-term outcomes of sport-related concussion in pediatric populations

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ABSTRACT

Although the field of concussion research is rapidly growing, the majority of research has focused on injured adults, with children being an often-neglected population. Traumatic brain injury is a leading cause of death and disability in children, with over 1.5 million cases being treated in North America annually. Approximately 75% of these injuries are classified as a concussion. Further, children are disproportionately affected by sports-related injuries, with 65% of all pediatric concussions occurring during sport and recreation. Therefore, understanding the outcomes of pediatric sportrelated concussion is of great importance, particularly given the vulnerability of the developing brain. The purpose of this review is to provide an up-to-date understanding of the outcomes of pediatric sport-related concussion from a data-driven perspective, focusing heavily on experimental studies.

1. Introduction

Sport-related concussion (SRC) is a form of mild traumatic brain injury which occurs during sport and recreation. Recent epidemiological investigations indicate that SRCs are increasing, with 569.4/100,000 injuries occurring in 2006 and 807.9/100,000 injuries occurring in 2012 (Cancelliere et al., 2017). Furthermore, 3.4 million cases were treated in US emergency departments between 2001 and 2012 (Coronado et al., 2015). However, many SRCs are not evaluated in emergency departments (i.e., primary care, sport medicine clinics, etc.), and some SRCs are never evaluated by medical doctors, particularly in settings when athletic trainers are charged with referral decisions (Corrigan et al., 2017). As such, it is believed that the incidence of these injuries is greatly underestimated by traditional epidemiological evaluations, with a true incidence of 4 million annually in the US (Langlois et al., 2006), and lifetime incidence of up to 20% (Corrigan et al., 2017).

Given this incidence, SRC represents a significant public health concern. Furthermore, recent high-profile cases of post-concussion syndrome (PCS) and chronic traumatic encephalopathy (CTE) have caused researchers and clinicians to rethink SRC as a transient injury. Accordingly, increased efforts are being dedicated to understanding the long-term outcomes of SRC in laboratory and clinical settings. Despite these efforts, most resources have been dedicated towards collegiate and professional athletes, with SRC in developing populations receiving less attention.

Approximately 70% of all injuries occur in persons between the ages of 0 and 19 years (Coronado et al., 2015). Until recently, pediatric SRC was trivialized as inconsequential, as clinicians and researchers claimed that these injuries were offset by physiological and adaptive factors with little to no long-term repercussions for brain and behavioral health (Carroll et al., 2004; Babikian and Asarnow, 2009). This view was bolstered by findings from large-scale clinical studies and reviews which observed only a small portion of children exhibiting persistent clinical symptoms or neuropsychological deficits (Asarnow et al., 1995; Yeates and Taylor, 2005; Babikian and Asarnow, 2009; Babikian et al., 2011). However, it is increasingly clear that traditional clinical assessments are insufficient for detecting and delineating the subtle and heterogeneous pathologies associated with SRC, and studies utilizing experimental measures of brain and behavioral functioning (EEG, MRI, oculography, etc.) indicate that pediatric SRC can in fact lead to significant alterations which persist beyond the "clinical recovery" period (Baillargeon et al., 2012; Maugans et al., 2012; Albaugh et al., 2015; Urban et al., 2015; Wang et al., 2015; Anzalone et al., 2017; Kraus et al., 2016; Master et al., 2016; Moore et al., 2016).

Thus, like the adult literature, there is a divergence between findings from clinical practices and experimental research. Although this divergence may seem perplexing, few clinicians examine injury pathophysiology or the relation between pathophysiology and functional outcomes (McCrea et al., 2017; Kamins et al., 2017). Additionally, most clinicians evaluating SRC rely on commercialized batteries such as the SCAT and IMPACT test. Although these tests are better than basic

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symptom reports, research demonstrates they lack the reliability and sensitivity to detect concussion-related deficits beyond the acute phase of injury (Resch et al., 2013; Bruce et al., 2014; McCrory et al., 2017). As such, our current understanding of the long-term outcomes of pediatric SRC is provisional.

Accordingly, the purpose of this review is to provide an up-to-date understanding of the long-term outcomes of pediatric SRC from a data-driven perspective. To do so, we will give special attention to studies utilizing experimental measures of brain and behavioral health, as they are neglected in clinical reviews. We will also include clinical studies that go beyond minimal sports-medicine assessments (SCAT, or IMPACT) to evaluate outcomes in a more comprehensive manner. First, we will address the neuroanatomical and neurophysiological consequences of pediatric SRC, followed by the long-term neurocognitive outcomes. We will then address the long-term sensory, motor, and mental health outcomes, followed by the impact of concussion on scholastic performance. Finally, we will discuss the predictors/moderators of outcomes and recovery, as well as limitations and future directions for research.

2. Neuroimaging & long-term pediatric SRC outcomes

Despite the traditionally benign prognosis of pediatric SRC, evidence from studies employing objective neurophysiological measures indicate that these injuries reliably lead to alterations in brain structure, function, and connectivity, which can persist beyond the acute phase of injury. Changes in electrophysiology, hemodynamic response, network connectivity, and glucose metabolism are protracted relative to clinical metrics of functioning (Catroppa et al., 2016; Kamins et al., 2017; McCrea et al., 2017). Utilization of these measures is essential to gaining a more comprehensive and accurate understanding of the long-term outcomes of SRC. The purpose of this section is to provide a comprehensive understanding of the neuro-structural and neuro-functional consequences following sport-related concussion in children, and how the changes may relate to alterations in symptoms and functional domains.

2.1. Neuro-structure

Although the neuro-structural sequelae of SRC is typically below the threshold for clinical imaging modalities (e.g., computed tomography), the advancement of experimental imaging protocols reveals a much finer understanding of SRC on neural macro- and micro-structure. For example, Urban et al. (2016) observed that young asymptomatic athletes (age 10–14) with a history of concussion exhibited significant reductions in cortical thickness within regions of the prefrontal cortex, anterior-cingulate cortex, and parietal lobes when compared to uninjured controls. These differences in cortical thickness were associated with deficits during both single- and dual-task memory paradigms. In another study examining adolescents and young adults (age 14 to 23 years; mean age 17.8 years), Albaugh et al. (2015) observed that in the post-acute phase of injury, symptom scores were inversely associated with cortical thickness in frontal, parietal, and temporal brain regions. Further, an age x cortical thickness interaction was observed, suggesting that younger athletes have greater reductions in cortical thickness which correspond to greater symptoms. In contrast to these findings, a recent large-scale cross-sectional study, which examined 238 children and adolescents (8–18 years of age) at 6 months post-injury, failed to observe any consistent morphological differences between children with SRC/mTBI and orthopedic controls (Bigler et al., 2018). Thus, it remains unclear whether a SRC can lead to developmental alterations in cortical grey matter.

In addition to brain morphology, other imaging studies examined white matter integrity following pediatric SRC. Utilizing a diffusion tensor imaging technique, Virji-Babul et al. (2013) found that adolescent athletes (age 14–17 years) who were six months from their last concussion exhibited a significant increase in whole-brain fractional anisotropy (FA), which is a measure of microstructural integrity—myelination, fiber density, etc. (Feldman et al., 2010). Adolescents with a history of concussion also exhibited a significant decrease in mean diffusivity (MD), which is an inverse measure of membrane density (Alexander et al., 2011). In contrast, a longitudinal evaluation of children revealed that although children showed acute alterations in white matter integrity (as indexed by FA), by six months their values returned to a normal range relative to controls (Van Beek et al., 2015a, 2015b). Given these apparent inconsistencies, additional research is needed to delineate the influence of SRC on white-matter integrity during development.

2.2. Neuro-metabolism

Recently, researchers have examined neuro-chemical changes as a diagnostic and prognostic biomarker of SRC. In adults, MR spectroscopy investigations commonly reveal increases in molecules such as glutamate (Glu; Gasparovic et al., 2009), choline (Cho; Yeo et al., 2006), creatine (Cre; Vagnozzi et al., 2013) and decreases in *N*-acetyl aspartate (NAA; Vagnozzi et al., 2013). These molecules play an important function in brain metabolism, and variations in the expression of these neuro-metabolites following SRC correlate with neuropsychological (Babikian et al., 2006) and experimental task performance (Yeo et al., 2006). More recently, studies using positron emission tomography (PET) have confirmed significant variations in brain metabolism in children following concussive injury, with an initial increase in glucose uptake, followed by a significant decrease indicative of a hypo-metabolic state (Halstead and Walter, 2010). Although these findings are indicative of functional deficits, the correlation between this observation and clinical outcomes is poorly understood. Furthermore, few studies have examined these neuro-metabolic alterations in children with SRC, and metabolic ratios change with development (McCrea et al., 2017). As such, it is currently unknown how SRC affects neuro-metabolic balance in developing populations.

3. Functional connectivity

One of the most frequently reported consequences of SRC is disturbed neuronal activation (Ellemberg et al., 2009; Slobounov et al., 2011; McCrea et al., 2017). Recent studies in youth athletes point towards concussion leading to altered functional connectivity during both rest (default mode network, DMN) and task performance (task-related networks, TRN). For example, Abbas et al. (2015) observed significant changes in functional connectivity within the DMN across a season of American high school football in both those incurring a concussion and those incurring repetitive sub-concussive blows. Further, in the only study to evaluate functional connectivity during task performance, Urban et al. (2015) observed that pediatric patients (age 12–18 years) with persistent post-concussion symptoms exhibit asynchronous brain activity in the motor cortices during a finger tapping task. Thus, it appears that SRC and sub-concussive blows persistently influence the communication of resting-state and active-state neuronal networks in youth athletes.

4. Cerebral blood flow

A growing body of evidence reveals altered blood flow during rest and task-related activity in children. For example, Len et al. (2011) found that the cerebrovascular systems of young concussed athletes (age 16–22 years) were slower to recover following conditions of hypo- and hyper-ventilation when compared to healthy controls. Although the authors observed participants only in the subacute period of recovery (> 6 weeks), the results indicate impaired cerebrovascular reactivity as a pathophysiological mechanism of pediatric SRC. Other studies demonstrate chronic alterations in cerebrovascular function. For example,