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Review article

Factors affecting increased risk for substance use disorders following traumatic brain injury: What we can learn from animal models

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ABSTRACT

Recent studies have helped identify multiple factors affecting increased risk for substance use disorders (SUDs) following traumatic brain injury (TBI). These factors include age at the time of injury, repetitive injury and TBI severity, neurocircuits, neurotransmitter systems, neuroinflammation, and sex differences. This review will address each of these factors by discussing 1) the clinical and preclinical data identifying patient populations at greatest risk for SUDs post-TBI, 2) TBI-related neuropathology in discrete brain regions heavily implicated in SUDs, and 3) the effects of TBI on molecular mechanisms that may drive substance abuse behavior, like dopaminergic and glutamatergic transmission or neuroimmune signaling in mesolimbic regions of the brain. Although these studies have laid the groundwork for identifying factors that affect risk of SUDs post-TBI, additional studies are required. Notably, preclinical models have been shown to recapitulate many of the behavioral, cellular, and neurochemical features of SUDs and TBI. Therefore, these models are well suited for answering important questions that remain in future investigations.

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1. Introduction

Traumatic brain injury (TBI) is a prominent public health concern affecting millions of Americans and their families each year. These injuries may produce lifelong deficits in physical, cognitive, social, emotional, and behavioral function (Centers for Disease Control and Prevention, 2015). In fact, current estimates suggest that as many as 5.3 million people living in the United States may

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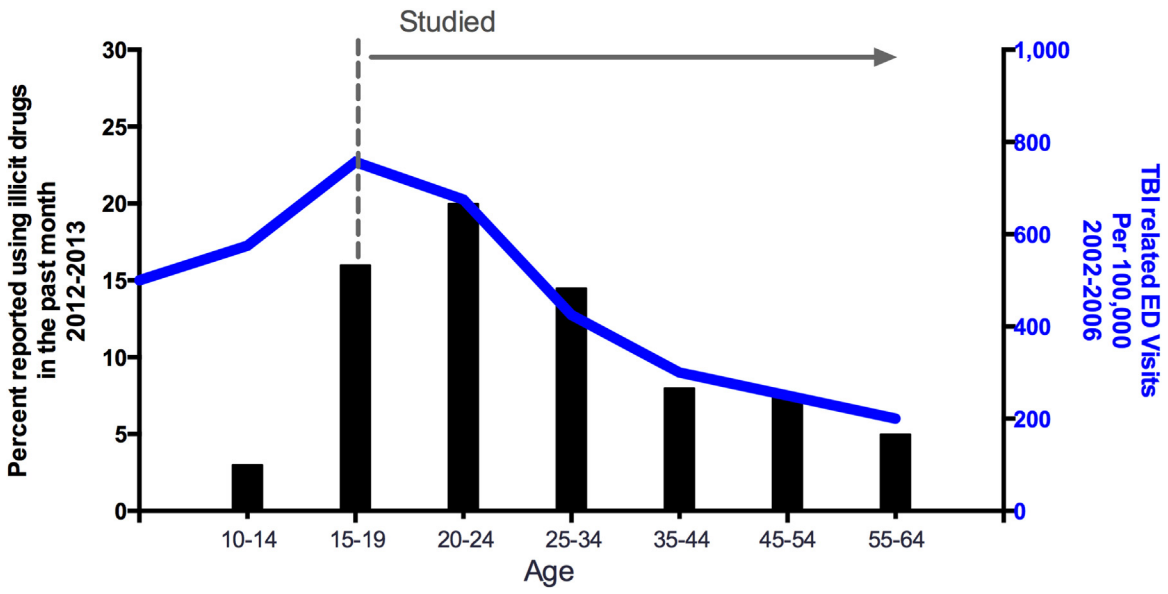

Fig. 1. Observing the distribution of illicit drug use and TBI-related emergency department (ED) visits by age identifies understudied populations in reports that evaluate the effect of TBI on SUDs.
The majority of reports evaluating TBI as a risk factor for substance abuse fail to account for the incidence of early-life TBI (dashed line and arrow identify the age groups commonly included in published reports). Furthermore, these studies do not account for the initial peak in the incidence of TBI (TBI-related ED visits per 100,000, 2002–2006; gray line, right-hand y-axis), and instead have drawn conclusions based on a downward trend in drug use that exists among the general population (percent of U.S. population using illicit drugs in the past month, 2012–2013; black bars, left-hand y-axis). Therefore, future studies that account for the incidence of early-life TBI and monitor the rise in drug and alcohol use rather than its decline may help to more accurately assess the risk of SUDs post-TBI (Faul et al., 2010; Administration S.A.M.H.S., 2014).

struggle with a TBI-related disability (Centers for Disease Control and Prevention, 2015). Notably, this figure is likely an underestimate, as some disorders that are highly prevalent among TBI patients, like substance use disorders (SUDs), are typically considered to be pre-existing conditions rather than a consequence of TBI (Rogers and Read, 2007). However, dedicated research in the field of head trauma rehabilitation and the emergence of the first preclinical studies to investigate the effects of experimental TBI on drug abuse behavior have led to the identification of multiple factors affecting risk of SUDs post-TBI.

Results of the 2014 National Survey on Drug Use and Health show that approximately 21.5 million Americans are currently diagnosed with SUDs (Center for Behavioral Health Statistics and Quality, 2015). Importantly, these disorders are the most common psychiatric diagnoses among TBI patients prior to injury, and the third most common psychiatric diagnoses post-TBI (Whelan-Goodinson et al., 2009). Alcohol is the most common drug abused by individuals with a history of TBI. In fact, estimates indicate that 37–66% of TBI patients struggle with alcohol use disorders, while 10–44% of TBI patients abuse illicit drugs (Parry-Jones et al., 2006). Notably, within illicit drug use, studies have shown that TBI patients are most likely to abuse cannabis, cocaine, methamphetamine, and prescription medications, including opioids, stimulants, benzodiazepines, antidepressants, and antipsychotics (Ilie et al., 2015a; Farinde, 2014). Furthermore, additional studies have shown that daily cigarette use is significantly elevated in TBI patients when compared to age-matched controls, suggesting that brain injuries may also affect nicotine-dependence (Ilie et al., 2015a,b).

In addition, many reports find that patients with co-morbid TBI and SUD have poorer long-term outcomes (Parry-Jones et al., 2006; Corrigan, 1995). These patients experience higher mortality rates, show deficits in physical and neurological recovery, display greater brain atrophy and diminished white matter integrity, are more likely to behave aggressively, show signs of impulsivity and reduced executive function, and have higher arrest rates (Parry-Jones et al., 2006; West, 2011; Fazel et al., 2014; Olson-Madden et al., 2012; Unsworth and Mathias, 2016). Furthermore, these patients have poorer neuropsychological outcomes, higher rates of psychiatric disease, increased risk of attempted suicide/suicidal ideation, and greater likelihood of sustaining additional TBIs (West, 2011; Corrigan, 1995; Olson-Madden et al., 2012). Despite these findings, research in the field has met much adversity due to two commonly held beliefs: 1) that data generated to assess the risk of SUD post-TBI are very difficult to interpret because of shared risk factors in co-morbid TBI and SUD patients, and 2) that TBI is more often a consequence of substance abuse rather than a cause of SUDs (Rogers and Read, 2007; Miller et al., 2013). However, by refining clinical studies and utilizing animal models to assess the risk of SUDs post-TBI, biomedical researchers have identified novel factors rarely accounted for in previous studies.

This review will address each of the following factors affecting increased risk for SUDs following TBI: age at the time of injury, repetitive injury and TBI severity, neurocircuits, neurotransmitter systems, neuroinflammation, and sex differences. First, the recent clinical and preclinical studies that have helped identify patient populations at greatest risk for SUDs post-TBI will be discussed. Next, a review of TBI-related neuropathology occurring in the neurocircuits, neurotransmitter systems, and neuroimmune signals that are heavily implicated in substance abuse behavior will be presented. Finally, gaps in knowledge and critical next steps will be discussed to better understand the causal relationship that exists between TBI and SUDs. Notably, employing the use of preclinical models will be essential to expediting this process as *in vivo* microdialysis, electrophysiology, and drug self-administration assays are well suited to answer questions that remain illusive in the link between SUDs and TBI.

2. Age at the time of injury

Most studies assessing the risk of SUDs post-TBI have monitored the incidence of SUDs in adult TBI patients (typically patients age 18+). These studies have produced two key findings: 1) that SUD rates decline following adult TBI and 2) that very few SUDs are newly diagnosed in adult TBI patients (Whelan-Goodinson