HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2023 March 01.

Published in final edited form as:

Biol Psychiatry. 2022 March 01; 91(5): 421–437. doi:10.1016/j.biopsych.2021.07.013.

Does Traumatic Brain Injury Cause Risky Substance Use or Substance Use Disorder?

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Abstract

There is a high co-occurrence of risky substance use among adults with traumatic brain injury (TBI), although it is unknown if the neurologic sequelae of TBI can promote this behavior. We propose that to conclude that TBI can cause risky substance use, it must be determined that TBI precedes risky substance use, that confounders with the potential to increase the likelihood of both TBI and risky substance use must be ruled out, and that there must be a plausible mechanism of action. In this review, we address these factors by providing an overview of key clinical and preclinical studies and list plausible mechanisms by which TBI could increase risky substance use. Human and animal studies have identified an association between TBI and risky substance use, although the strength of this association varies. Factors that may limit detection of this relationship include differential variability due to substance, sex, age of injury, and confounders that may influence the likelihood of both TBI and risky substance use. We propose possible mechanisms by which TBI could increase substance use that include damage-associated neuroplasticity, chronic changes in neuroimmune signaling, and TBI-associated alterations in brain networks.

Given the high co-occurrence of risky substance use and/or substance use disorders (SUDs) among adults with traumatic brain injury (TBI) (1–3), investigators have asked whether TBI causes SUD and/or SUD causes TBI. Several reviews have concluded that at-risk substance use is more likely to cause TBI than TBI is to cause SUD (4–6), while others have concluded that there is insufficient evidence to make definitive conclusions about the directionality of causal influences (1,2). There is little doubt that engaging in risky substance use can cause TBI. Intoxication, whether by alcohol, cannabis, or other drugs, increases the likelihood of injury, which can include a TBI (7). At least 2 studies have found that among those treated for an injury in an emergency department, the greater the alcohol intoxication, the more likely the injury included a TBI (8,9).

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The authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2021.07.013.

The more nuanced question is whether TBI causes risky substance use. Some authors have cited the tendency for TBI cohorts to reduce use immediately after injury, especially if the injury is associated with use (10–12), as evidence that TBI does not cause risky substance use. However, several studies have shown that most people who used alcohol before TBI eventually return to pre-injury patterns of use unless a medical condition precludes use (11–13). The logic of this argument is further undermined by what Corrigan *et al.* have called the chicken or the egg problem (14). The difficulty in examining a causal relationship between TBI and SUD is highly affected by the injury used to anchor the question. Previous investigators who concluded that SUD causes TBI but TBI does not cause SUD anchored their analyses in studies that used samples of patients in adult trauma or acute rehabilitation units. A large percentage of participants in these samples had histories of at-risk substance use or a diagnosable SUD that preceded their injury. However, these studies did not determine whether the TBI that led to their inclusion in the cohort was their first TBI, which ignores whether one or more TBIs earlier in life may have influenced their development of risky use behaviors. Several studies support the conclusion that childhood TBI could lead to the development of adolescent or adult at-risk substance use (15–19); thus, the conclusion that causality is only in the direction of substance use causing TBI appears flawed.

In this review, we will explore this more nuanced direction of causality—can TBI cause the development of at-risk substance use and/or SUD? To allow a focused consideration of this question, we will not address whether a TBI can make preexisting substance use worse. To confidently conclude that TBI is the cause for the development of at-risk substance use and/or SUD would require establishment of several relationships among these conditions. First, most obviously, the TBI would need to precede the development of the problematic substance use. Second, the relationship between TBI and problematic substance use could not be due to a confounder that precedes both and causes each. Confounders that have been hypothesized include childhood exposures (e.g., parental attributes, parenting, adverse childhood experiences, socioeconomic status, community risk factors) and a behavioral phenotype for risk taking (e.g., a personality trait that could lead to both TBI and problematic substance use). Finally, and perhaps most challenging, to establish causality, there would need to be a mechanism of action that provides a plausible explanation for how TBI could do so. In the following sections, we will explore first human, then preclinical evidence for the conditions required to conclude causality (summarized in Tables 1 and 2, respectively). Evidence from these two sources of findings is uneven, and surprisingly, despite the greater control afforded via preclinical studies, unequivocal evidence to inform this question is not easily derived.

HUMAN STUDIES CONTRIBUTING TO CAUSALITY

Human studies that allow scrutiny of a causal relationship between TBI and problematic substance use have been limited to examining the temporal onset and presence of confounders. These studies have used three methods: 1) eliciting lifetime exposure in TBI cohorts; 2) population surveys examining the association of the two conditions; and 3) birth cohorts examining both onset and association. TBI cohorts in which lifetime exposure was studied have included the TBI model systems (20), Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) (21), and Army Study to Assess Risk

and Resilience in Servicemembers (STARRS) 22). Lifetime TBI identification has been done with standardized methods of self-report, and substance use is typically self-reported past-month behavior. Population surveys have used a variety of methods for detecting both TBI and substance use, with the former varying from single-item elicitation [i.e., New Haven, Connecticut (23); Southeast Australia (24); Ontario, Canada (25,26)] to protocols based on standardized methods of retrospective self-report [i.e., Colorado (27), Ohio (28,29), North Carolina (30)]. Only a small number of birth cohort studies have allowed examination of the onset and development of TBI and at-risk substance use, including those conducted in Christchurch, New Zealand (25); Northern Finland (31–33); and Avon, United Kingdom (34). TBI identification is typically based on medical records; substance use has been both medically documented or self-reported recent behavior. Each of these methodologies has strengths and weaknesses for examining the temporal onset and presence of confounders, as shown in Box S1.

Temporal Onset

Several studies support a relationship between childhood TBI and later adolescent or adult at-risk substance use (20–22). Studies in TBI cohorts that capture lifetime history of TBI have found that earlier life injuries are more common among those with alcohol use problems, although temporal ordering is not possible. Studies in 2 U.S. states did not find that children injured earlier in life (before age 15 and before age 18 years) than persons injured after those ages were not more likely to engage in risky alcohol use as adults (28,30). In contrast, Corrigan *et al.* found that adults who had experienced a mild TBI with loss of consciousness before age 20 were more likely to engage in binge drinking than those who had a first mild TBI with loss of consciousness at an older age (29). This risk was largely due to a first TBI being incurred both at 10 to 14 and 15 to 19 years. These two groups were equally likely to engage in adult binge drinking. Indeed, had either 15 or 18 years been used as the cut point for age at first TBI, as was done in the two other state population studies, the difference would not have been significant. While any adolescent onset of TBI seems to increase the likelihood of problem alcohol use in adulthood, unfortunately, it is not definitive that TBI preceded the problematic use.

The Christchurch birth cohort study found that children hospitalized with a mild TBI before the age of 6 were more likely to develop alcohol problems in adolescence than children with no TBI or those with a mild TBI that did not require hospitalization (35). The birth cohort study in Avon found that TBIs occurring before age 17 were associated with problem alcohol consumption at age 17 (34). The Northern Finland birth cohort study did not find a difference in heavy drinking for those with or without childhood TBI; however, those children who incurred a TBI before age 12 initiated heavy drinking 6 years earlier than those with a first TBI at 12 to 15 years old (33). Note that the Christchurch results would appear to un-equivocally support that TBI preceded problematic substance use, but the Avon cohort is more ambiguous due to the possibility that alcohol consumption could begin in early adolescence.

Potential Confounders

Studies using the Northern Finland birth cohort reported multiple risk factors associated with incurring a TBI, including that if parents misused alcohol, there was a twofold greater chance of childhood TBI (31), and that a first TBI after age 12 that occurred while drinking alcohol resulted in a fourfold greater risk of repeat TBI by age 34 (32). Findings noted above for the Christchurch and Avon birth cohort studies were significant after controlling for multiple demographic, parental, and developmental characteristics (34,35). The Avon birth cohort studies also compared those with a TBI to an orthopedic injury control group intended to represent a behavioral phenotype for risk taking. While the association with problem alcohol use was significantly higher in the orthopedic injury group than the uninjured comparison group, the TBI group was still significantly greater than the orthopedic control group. Their findings were specific to alcohol because the TBI and orthopedic injury groups did not differ significantly in their likelihood of smoking either cannabis or nicotine.

These few studies may lend support for the effect of TBI not being due to influences such as parental attributes, parenting, or socioeconomic status. Influences from adverse childhood experiences or community characteristics have not been explored. The single study that investigated a risk-taking behavioral phenotype still found an additional effect of TBI on drinking at age 17 (34). This finding is perhaps strengthened by risk taking having equivalent risk for the likelihood of cannabis and tobacco use. Still, it is a single study.

In summary, from human studies, a significant association is frequently found between TBI and at-risk substance use and/or SUD. These studies have been largely limited to alcohol. The strength of association observed may be small, thus contributing to variation in findings. The ability to detect the relationship may be masked by variations in manifestation of the influence of TBI, for instance, age at injury or context of the injury (e.g., whether it occurs during a period of stress). The utility of the human literature for establishing a causal relationship between TBI and risky substance use is specifically limited by uncertainty about temporal onset during adolescence. Without specificity about the age at injury and the age at initiation and/or risky use of substances, temporality will be difficult to ascertain. Finally, the study of confounders is limited by the ability to operationalize constructs such as adverse childhood experiences or behavioral phenotypes in population-based cohorts. However, studies that have controlled for characteristics of parents, parenting, and the home environment seem to consistently suggest that these factors are unlikely sources of confound.

PRECLINICAL STUDIES CONTRIBUTING TO CAUSALITY

Temporal Onset

An advantage of preclinical research is that temporal ordering of TBI and exposure to drugs of abuse is controlled. To date, most preclinical research has focused on modeling the question of whether TBI can increase risky drug use (see Box S2 for commonly used models of drug reward/reinforcement; see Table 2 for a summary of experimental findings).

Early studies on the effects of TBI on subsequent drug use focused on alcohol. In mice, experimental TBI led to reduced alcohol intake within the first 2 weeks following injury (36,37). In rats, blast TBI resulted in similar alcohol intake during a 7-week course of two-bottle choice but divergent responses on a final 1-hour session (38). Similar results were found in mice after repeated blast TBI: the proportion of daily alcohol consumed in the first 2 hours was higher in injured mice (39). Weil and colleagues demonstrated that adolescent mice had elevated alcohol drinking 1 week after TBI (40). A subsequent study found that females but not males had higher alcohol consumption and conditioned place preference (CPP) (41).

Adolescent, but not adult, TBI resulted in elevated cocaine CPP in male mice (42–44), but female mice showed differential effects based on estrus status. Mice in met- or diestrus at the time of injury had significantly elevated cocaine CPP, while those in proestrus or estrus had no change (45). Moderate to severe frontal TBI increased cocaine self-administration (46), while mild TBI found no difference in self-administration, extinction, or cue- or cocaine-primed induced reinstatement (47). Repeated blast resulted in similar levels of oxycodone self-administration, but subsequent drug seeking was elevated in the injured group (48). Thus, there are several examples of increased susceptibility for substance use in rodent models, but outcomes differ based on factors such as injury mechanism and severity, age at the time of injury, the drug studied, and time after injury.

Potential Confounders

Although preclinical studies can be designed to reduce the impact of confounding variables, these may not always be considered. Unknown individual differences that are present prior to experiment onset could independently contribute to both TBI recovery and addiction-related outcomes. Many studies use outbred rats [e.g., (46,48)] or mice [e.g., (40)], and this genetic variability may explain individual differences in drug reward/reinforcement following TBI (38,46). Similarly, individual differences in traits such as impulsivity exist in experimental animals and, similar to humans, can explain differences in addiction-related behaviors (49–51). Consideration of these differences and testing models of human confounders [e.g., models of early-life adversity (52,53)] will be important to better understand human variability in the relationship between TBI and risky substance use.

Plausible Mechanisms of Action

TBI induces myriad neurochemical changes, the nature of which is affected by factors including injury mechanism and severity, genetics, age, and sex. This section will focus on biological effects of TBI that are linked with neuroplasticity and describe plausible mechanisms by which these effects could increase addiction liability (summarized in Table 3). The reader is referred to (54–57) for more comprehensive reviews on the neurochemical sequelae of TBI. For simplicity, we will discuss these mechanisms in 2 broad timeframes: acute (within the first few days of injury) and chronic (after the first few days). The acute stage will be discussed in terms of the initial effects of injury that can set the stage for enduring neuroplasticity relevant to addiction liability, and the chronic stage will present evidence that persistent sequelae could influence physiological responses to drugs of abuse and addiction liability.

Acute Effects: Damage-Associated Molecular Pattern Mediated Increases in Ca^{2+}-Permeable AMPA Receptors.—Primary mechanisms of TBI involve impact-associated forces, which stretch tissue and shear axons (54). At impact, mechanical deformation and/or mechanoporation leads to ion flux that ultimately leads to profound membrane depolarization of neurons (54,58,59). This depolarization promotes neuronal excitotoxicity and necrosis, which releases damage-associated molecular patterns (DAMPs) (59–61). DAMPs promote activation of astrocytes and microglia (collectively referred to as gliosis), resulting in release of cytokines and chemokines (54,61). DAMP-associated TLR4 (toll-like receptor 4) signaling triggers robust synaptic plasticity, increasing synaptic levels of Ca^{2+}-permeable AMPA receptors (CP-AMPARs) and increasing Ca^{2+} conductance through NMDA receptors (62). Both experimental TBI and injury to cultured neurons were found to elevate synaptic CP-AMPARs (63,64). In rodents, drugs of abuse also increase synaptic CP-AMPARs in areas of the brain involved in drug seeking, including the ventral tegmental area (VTA), nucleus accumbens, and prefrontal cortex (PFC), and these effects often persist for weeks or months (65,66). Elevated CP-AMPAR expression is observed in the VTA after exposure to morphine, cocaine, ethanol, and cannabis (65). CP-AMPARs are also increased in the nucleus accumbens after cocaine withdrawal, and reversal of this phenomenon is sufficient to reduce drug seeking (67,68). Thus, the DAMP→TLR4→CP-AMPAR cascade is one plausible mechanism by which TBI could promote subsequent substance use.

Acute Effects: Cytokine Regulation of Neuronal Transmission.—Glial and peripheral cytokines can influence synaptic plasticity and have been linked to addiction liability. Interleukin 1β (IL-1β) modulates neuronal ion flux via several mechanisms (69,70), and chronic IL-6 downregulates metabotropic glutamate 2/3 receptors (mGluR2/3) (71). Reduction of mGluR2/3 function in mesocorticolimbic brain regions is also observed following exposure to nicotine, cocaine, or alcohol, and treatment with mGluR2/3 agonists or positive modulators reduces the reinforcing effects and seeking of drugs (72–76). Tumor necrosis factor α strongly increases the balance of excitatory/inhibitory transmission by increasing cell surface CP-AMPARs and internalizing $GABA_A$ (gamma-aminobutyric acid A) receptors (77). Although cytokine responses occur acutely following injury, there is extensive evidence for prolonged elevations in excitatory neurotransmission following immune challenge, including susceptibility to seizures (78–80). Persistent increases in neuronal excitability and seizure susceptibility are also common following TBI (81,82). Thus, IL-6–associated reduction of mGluR2/3 and tumor necrosis factor α–associated elevation of CP-AMPARs are plausible mechanisms by which TBI-associated cytokine signaling could promote subsequent substance use.

Chronic Effects.—Postmortem and neuroimaging studies demonstrate gliosis that persists months or years after injury (55,57), and elevated levels of IL-1β, major histocompatibility complex class II, and IL-6 have been reported several months after experimental TBI (55,57). Drug use has been linked to chronic gliosis. Alcohol (83), cocaine (84,85), methamphetamine (86), and opioids (87,88) engage innate immune signaling, and alcohol and methamphetamine can also induce gliosis via other mechanisms, such as the generation of reactive oxygen species (89,90). Methamphetamine users had elevated binding of the

microglial activation marker (R)-[^{11}C]-PK11195, which was inversely proportional to abstinence duration (91). Similarly, upregulation of immune-related genes is a consistent finding in postmortem tissue from chronic alcohol users (92), and gliosis is prominent in animal studies of alcohol and opioid self-administration (92–94).

Chronic Effects: Microglial Priming—Implications for Drug Exposure, Craving, and Relapse.—TBI can lead to microglial priming, where the cells are hyperresponsive to subsequent immune challenge, even at distal time points (95–97). It is plausible that TBI-associated priming could also affect immune responses to drugs of abuse. Morphine and other opioids prolong recovery from nerve injury (98,99), and this has been proposed to be due to injury-induced priming of spinal microglia (100). Neuroimmune activation has previously been proposed to create the biology of addiction (101). In the context of TBI, injury-associated priming may contribute to addiction liability by altering biological responses to substances and triggers of drug craving: re-exposure to the drug, stress, and drug-associated cues (102–105).

Prenatal immune activation increased drug-primed reinstatement to methamphetamine seeking and CPP for amphetamine (106,107), and adult immune activation increased alcohol drinking (108,109). These data suggest that immune activation primed the response to these substances of abuse in a manner consistent with greater risk of risky substance use. In a model of comorbid TBI and cocaine use, cocaine intake was positively correlated with neuroinflammatory markers in the frontal cortex (46). Drug exposure itself can also prime neuroimmune responses. A history of cocaine primes the cocaine-induced increase in IL-1β, nuclear factor-κB, and CD11b messenger RNA in the VTA, and blockade of IL-1 receptors in the VTA suppresses cocaine-primed reinstatement of drug seeking (110). Similarly, rats exposed to morphine in adolescence had an exaggerated immune response to morphine-elevated morphine CPP in adulthood (111). The glial modulator ibudilast given during adolescent morphine exposure blocked the later increase in morphine CPP, suggesting that gliosis is a critical mediator of the effect (111). Supporting the notion that a TBI-primed response to drug can influence subsequent drug seeking, the steroidal anti-inflammatory drug dexamethasone reduced the TBI-associated elevation in cocaine CPP without affecting CPP in noninjured animals (43). Similarly, the glial modulator minocycline reduced TBI-associated increase in voluntary alcohol consumption but had no effect in uninjured animals (40). Complementing these studies that demonstrate the necessity of neuroimmune signaling for drug seeking, intra-VTA injection of the TLR4 agonist lipopolysaccharide was found to be sufficient to reinstate cocaine seeking (110).

Stress is the most-reported trigger of drug craving for several drugs of abuse (112). Stress triggers a neuroimmune response and has been proposed to act as a potential trigger for microglial priming (113,114). In mice, early-life stress increased central immune responses to cocaine (115), suggesting that stress-associated microglial priming is relevant to the immunologic response to drugs of abuse. Preclinical studies support the notion that stress-induced immune responses are important in drug seeking and craving: ibudilast blocked stress-induced reinstatement of methamphetamine seeking (116).

Exposure to drug cues (e.g., places and things associated with substance use) is also a powerful trigger of drug craving (117), and there is evidence of conditioned immunologic effects of drug-associated cues. Exposure to cocaine-associated cues elevated plasma tumor necrosis factor α (118), and heroin seeking evoked by exposure to the drug environment was suppressed by the non-opioid TLR4 antagonist (+)-naltrexone (119).

Chronic Effects: Changes in Function of Brain Networks.—Preclinical studies have identified TBI-associated increased network excitability in the cortex that emerges over time, and increased excitatory and decreased inhibitory synaptic inputs have been identified as putative mechanisms of increased excitability of pyramidal neurons (120–122). A rodent model of comorbid TBI and oxycodone abuse identified interactive effects of TBI and drug exposure on increasing widespread connectivity (123), a phenomenon associated with worse TBI outcomes (124,125) and abstinence from prior heroin use (126). The PFC is a region that is highly vulnerable to injury in TBI (127), and the same study found that structural and functional outcomes in the PFC correlated with drug seeking (123).

DISCUSSION

The relationship between TBI and risky substance use is difficult to study, and there is evidence for each to increase the incidence of the other (Figure 1). We have summarized human and animal studies that reflect on the question, does TBI cause risky substance use or SUD? However, there is not sufficient evidence to definitively conclude that TBI can cause such use. In general, preclinical studies outnumber human investigations. Both human and animal studies have identified an association between TBI and risky substance use, although the strength of this association varies. This variability may imply a weak signal or may be due to methodological limitations.

A weak signal also may be due to specific characteristics that modify the presence or strength of relationship. For instance, the relationship between TBI and substance use may vary by the substance studied. Human and animal studies have been almost exclusively about alcohol, although recent studies include other substances. Particularly pertinent may be the sex of the organism, as well as the developmental stage when injury and/or substances are introduced. There are both human and animal studies that suggest that TBI in adolescence shows a greater association to substance use proclivity. It should be noted that prior substance use itself may alter the ability of TBI to increase subsequent risky drug use. A plethora of human studies indicate that pre-injury misuse of substances increases the likelihood of substance misuse after. Similarly, male (but not female) rats with a history of alcohol drinking were found to increase intake following injury (128–130).

Ruling out confounding effects has been more difficult. Human studies controlling for parental and household factors suggest that these factors may not be a source of confound. A human population study using uninjured sibling control subjects to specifically address risky substance use would be a useful addition to these studies. It has been more difficult to rule out personality traits that may be sources of confound. Risk taking, conduct disorders, and childhood traumatization have all been posited. While animal studies could be designed to

test such factors, we are not aware of any that have examined these factors in relationship to the effects of TBI on drug reward or seeking.

Finally, there are several plausible mechanisms of action for TBI to cause a predisposition for risky substance use. Acute and chronic effects of TBI can result in increased CP-AMPARs and decreased mGluR2/3 expression, hallmarks of prior drug exposure. Emerging evidence suggests that microglial priming is a strong candidate for TBI to alter responses to substances in a way that promotes future use. Although research on the immunologic interactions between TBI and drug use is still in its infancy, the therapeutic potential of neuroimmune modulation for the treatment of risky substance use (independent of brain injury) is under investigation (131,132). Another plausible mechanism is by altering the function of brain networks, especially those involving the PFC. The PFC is particularly vulnerable to TBI, and clinical and preclinical studies identify it as a key node in drug craving and seeking (133–135).

The question of whether TBI can cause risky substance use is important for human health: knowledge of prior TBI may be used to guide personalized substance use treatment (136), and there is evidence that prior TBI may change the therapeutic approach for SUD treatment in individuals with comorbid TBI [e.g., dexamethasone reduced cocaine CPP only in TBI animals (43)]. To the extent that childhood TBI may predispose to adult risky substance use, secondary prevention to reduce the likelihood of that outcome could become a target for future research, not unlike adverse childhood experience (137). Future research would benefit from population studies specifically designed to address this question, as well as preclinical studies to test potential therapeutics for substance use in animals with and without brain injuries.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the United States Department of Veteran Affairs (Grant No. RX002931 [to CMO]); National Institutes of Health (Grant No. DA042792 [to CMO]); and the National Institute on Disability, Independent Living, and Rehabilitation Research (Grant No. 90DP0040 [to JDC]).

National Institute on Disability, Independent Living, and Rehabilitation Research is a Center within the Administration for Community Living (ACL), Department of Health and Human Services. The contents of this publication do not necessarily represent the policy of the United States Department of Veteran Affairs; National Institute on Disability, Independent Living, and Rehabilitation Research; Administration for Community Living; National Institutes of Health; or Department of Health and Human Services, and you should not assume endorsement by the Federal Government.

We thank Cole Vonder Haar, Ph.D., and Antje Kroner-Milsch, M.D., Ph.D., for thoughtful comments on prior versions of this manuscript.

Figure 1 was created with BioRender.com.

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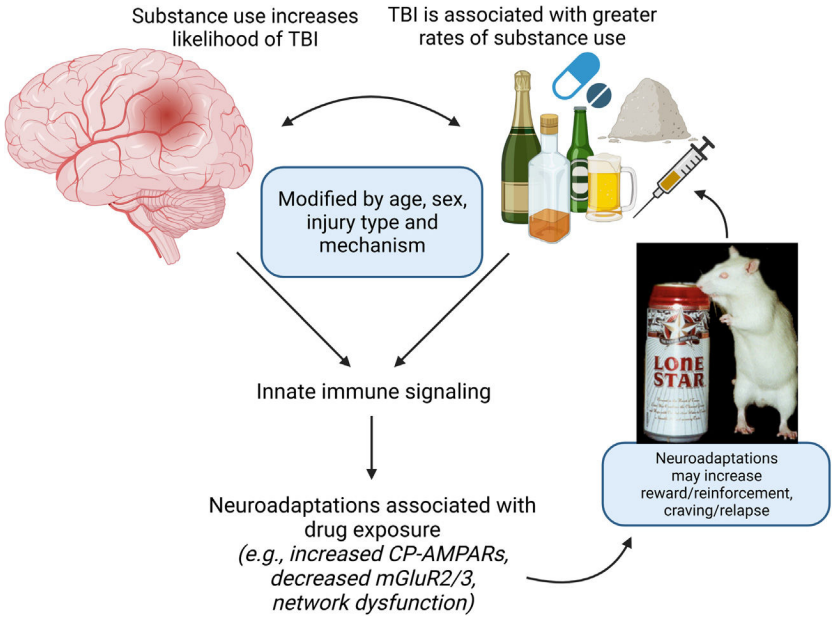

Figure 1.

Theoretical framework of the relationship between TBI and substance use. CP-AMPARs, Ca^{2+}-permeable AMPA receptors; mGluR2/3, metabotropic glutamate 2/3 receptors; TBI, traumatic brain injury.

Table 1.

Human Studies of the Association Between TBI and Risky Substance Use

Study	Sample and Population	Method	Risky Alcohol Use or Alcohol Use Disorder	Use of Other Substances
Corrigan *et al.* (20)	*N* = 4464 adults 1–20 years after acute rehabilitation for TBI and enrolled in TBI model systems	Prospective cohort (retrospective self-report of TBI; past-month [preindex injury] or past-year [postindex injury] use)	Those with history of TBI vs. those without more likely to engage in risky drinking before index injury (42.4% vs. 31.3%) and after index injury (22.8% vs. 13.5%)	Those with history of TBI vs. those without more likely to use illicit drugs before index injury (27.9% vs. 20.3%) and after index injury (17.8% vs. 8.1%)
Dams-O'Connor *et al.* (21)	*N* = 586 adults treated for TBI and enrolled in the TRACK-TBI study	Prospective cohort (retrospective self-report of TBI; past-month use)	Those with history of TBI vs. those without more likely to engage in risky drinking before index injury (56.6% vs. 37.1%)	Those with history of TBI vs. those without more likely to use illicit drugs before index injury (35.3% vs. 14.9%)
Adams *et al.* (22)	*N* = 4645 army soldiers following combat deployment who participated in Army STARRS study	Prospective cohort (retrospective self-report of TBI; past-month drinking) Adjusted for predeployment drinking, predeployment psychiatric diagnosis, combat/deployment stress severity, personal life stress during deployment, PTSD symptoms during deployment, and sociodemographic and military service characteristics	Three months after deployment, lifetime TBI, but not deployment-acquired TBI, associated with increased binge (AOR = 1.39, 95% CI: 1.20–1.60) and heavy drinking (AOR = 1.28, 95% CI: 1.09–1.49). Having both predeployment lifetime history and a deployment-acquired TBI increased heavy drinking 6 months later (AOR = 1.42, 95% CI: 1.03–1.95)	Not studied
Silver *et al.* (23)	*N* = 5034 adults from greater metropolitan New Haven, Connecticut	Population survey (retrospective self-report of lifetime TBI; use disorders from standardized interview) Adjusted for sociodemographics and health-related quality of life variables	Alcohol abuse or dependence (AOR = 2.2, 95% CI: 1.7–2.8)	Drug abuse or dependence (AOR = 1.8, 95% CI: 1.2–2.5)
Anstey *et al.* (24)	*N* = 7485 adults from 2 southeast Australian metropolitan areas	Population survey (retrospective self-report of lifetime TBI; past-month drinking) Adjusted for age group, gender, financial problems, physical health, and psychoticism	No difference for TBI vs. no TBI except young adult females (p = .045)	Not studied
Ilie *et al.* (25)	*N* = 1988 adults in the province of Ontario, Canada	Population survey (retrospective self-report of lifetime TBI; past-month substance use) Adjusted for age, sex, marital status, family income, and education	Not studied	Uses marijuana (AOR = 2.80, 95% CI: 1.79–4.39) Uses nonprescription opioids (AOR = 2.90, 95% CI: 1.50–5.59)
Ilie *et al.* (26)	*N* = 6074 adults in the province of Ontario, Canada	Population survey (retrospective self-report of lifetime TBI; past-month harmful or hazardous drinking)	Of persons with history of TBI, 21.4% reported harmful or hazardous drinking vs. 13.2% of no TBI respondents	Not studied
Whiteneck *et al.* (27)	*N* = 2701 noninstitutionalized adults residing in the state of Colorado	Population survey (retrospective self-report of lifetime TBI history; past-month drinking) Adjusted for place of medical care, age, sex, and race	At-risk alcohol use no more prevalent for persons with history of TBI than general population	Not studied
Bogner *et al.* (28)	*N* = 6996 noninstitutionalized adults residing in the state of Ohio	Population survey Behavioral Risk Factors Surveillance System (retrospective self-report of lifetime TBI; past-month	Binge drinking (AOR = 1.5, 95% CI: 1.1–2.0) Heavy drinking (AOR = 1.7, 95% CI: 1.1–2.6)	Not studied

Study	Sample and Population	Method	Risky Alcohol Use or Alcohol Use Disorder	Use of Other Substances
		alcohol use) Adjusted for age, sex, and race/ethnicity	Those with first TBI before age 15 years: no difference in binge or heavy drinking	
Corrigan *et al.* (29)	*N* = 2935 noninstitutionalized adults with history of TBI with loss of consciousness residing in the state of Ohio	Population survey Behavioral Risk Factors Surveillance System (retrospective self-report of lifetime TBI; past-month alcohol use) Adjusted for age, sex, and race/ethnicity	Those with first TBI before age 20 more likely to binge drink in adulthood (28.5% vs. 20.4%, $p = .003$) Those with first mild TBI before age 20 more likely to binge drink in adulthood (31.9% vs. 19.3%, $p < .001$)	Not studied
Waltzman *et al.* (30)	*N* = 3605 noninstitutionalized adults with history of TBI with loss of consciousness residing in the state of North Carolina	Population survey Behavioral Risk Factors Surveillance System (retrospective self-report of lifetime TBI; past-month alcohol use) Adjusted for sex, age, veteran status, marital status, educational attainment, employment status, and annual income	Those with history of TBI more likely to binge drink (AOR = 1.7, 95% CI: 1.2–2.4) Those with first TBI before age 18: no difference in binge drinking	Not studied
McKinlay *et al.* (138)	*N* = 1265 children born in 1977 in Christchurch, New Zealand	Birth cohort followed to age 25 (TBI from medical record abstraction of prospectively collected medical records; standardized structured interview to determine substance use disorder) Adjusted for sociodemographic factors, early behavioral problems, and parental substance abuse	Alcohol dependence n.s. for each group of age at first injury (0–5, 6–15, 16–21 years old)	Drug dependence for first injury 0–5 years old: AOR = 2.85, 95% CI: 1.11–7.32 Drug dependence for first injury 6–15 years old: AOR n.s. Drug dependence for first injury 16–21 years old: AOR = 2.55, 95% CI: 1.07–6.12
Timonen *et al.* (33)	*N* = 10,934 children born in 1966 in Northern Finland	Birth cohort followed to age 31 (medically diagnosed TBI; heavy drinking defined by diagnosis of alcohol abuse or dependence [DSM-III criteria] or having at least 2 registered drunk driving offenses) Adjusted for mother's marital status and father's social class at time of birth and urban vs. rural residence at approximately age 14	Heavy alcohol use no different for childhood TBI vs. no childhood TBI Among heavy drinkers, children with first TBI before age 12 began heavy drinking 6 years before those with first TBI at 12–15 years old	Not studied
Kennedy *et al.* (34)	*N* = 11,412 children born 1991–1992 in South West region of England (*n* = 800 with mild TBI; *n* = 2305 with orthopedic injury; *n* = 8307 uninjured children)	Birth cohort followed to age 17 (medically diagnosed injuries through age 16; self-reported recent use) Adjusted for prebirth sociodemographic factors, family environment and parenting style, and history of criminal activity	Alcohol use disorder vs. orthopedic injured: AOR = 1.69, 95% CI: 1.17–2.45 Alcohol use disorder vs. general population: AOR = 1.31, 95% CI: 0.94–1.82	Cannabis misuse vs. orthopedic injured (n.s.) Nicotine dependence vs. orthopedic injured (n.s.)

AOR, adjusted odds ratio; CI, confidence interval; n.s., nonsignificant; PTSD, posttraumatic stress disorder; STARRS, Study to Assess Risk and Resilience in Servicemembers; TBI, traumatic brain injury; TRACK-TBI, Transforming Research and Clinical Knowledge in Traumatic Brain Injury.

Table 2.

Summary of Preclinical Studies of TBI and Drug Reward, Reinforcement, and Seeking

TBI Model	Single/ Repeated Injury	Drug of Abuse	Reward/Reinforcement Model	Species/Strain	Sex	Age at Time of Injury	TBI→Testing Delay	Effect of TBI	Reference
TBI→Drug									
CCI (closed head)	Single	Alcohol	Two-bottle choice (drinking in the dark)	Mouse/C57BL/6	M	6–7 wk	4–10 days	Reduced intake	(37)
Weight drop	Single	Alcohol	Two-bottle choice	Mouse/Swiss Webster (selectively bred for stress analgesia)	NS	8 wk	7–19 days	Reduced intake (only in LA mice)	(36)
							62–72 days	No effect	
Blast	Single	Alcohol	Two-bottle choice Two-bottle choice (alcohol deprivation and quinine adulteration tests)	Rat/Sprague Dawley	M	8 wk	1–7 wk	No effect	(38)
							8 wk	Increased 1-hour intake in upper 50% after median split	
							10–24 wk	No effect	
CCI (closed head)	Single	Alcohol	Two-bottle choice	Mouse/Swiss Webster	M	21 days	10–22 days	Increased intake	(40)
CCI (closed head)	Single	Alcohol	Two-bottle choice	Mouse/Swiss Webster	M	21 days	8–9 wk	No effect	(41)
					F	21 days	8–9 wk	Increased intake	
					M	60 days	3–4 wk	No effect	
					F	60 days	3–4 wk	No effect	
CCI (closed head)	Single	Alcohol	CPP	Mouse/Swiss Webster	M	21 days	8–9 wk	No effect	(41)
					F	21 days	8–9 wk	Increased CPP	
Blast	Single Repeated (3×)	Alcohol	Two-bottle choice	Mouse/C57BL/6	M	12–16 wk	4–8 wk	No effect Decreased 24-hour intake Increased 2-hour proportional intake	(39)
CCI (open head)	Single	Cocaine	CPP	Mouse/C57BL/6	M	6 wk	2–3 wk	Increased CPP	(42,43)
CCI (open head)	Single	Cocaine	CPP	Mouse/C57BL/6	M	6 wk	2–3 wk	Increased CPP	(44)
						8 wk	2–3 wk	No effect	

TBI Model	Single/ Repeated Injury	Drug of Abuse	Reward/Reinforcement Model	Species/Strain	Sex	Age at Time of Injury	TBI→Testing Delay	Effect of TBI	Reference
CCI (open head)	Single	Cocaine	CPP	Mouse/C57BL/6	F (E/P)[a] F (M/D)[b]	6 wk	2–3 wk	No effect Increased CPP	(44)
CCI (open head)	Single	Cocaine	SA	Rat/Long-Evans	M	12 wk	2–4 wk	Increased SA	(46)
Blast	Single	Cocaine	SA	Rat/Sprague Dawley	M	8 wk	4–8 wk	No effect on SA	(47)
							10–11 wk	No effect on extinction	
							12–14 wk	No effect on cue- or drug-primed reinstatement	
Blast	Repeated (3×)	Oxycodone	SA	Rat/Sprague Dawley	M	8 wk	4–8 wk	No effect on FR-1 SA	(48)
							5–7 wk	Reduced FR-2 SA; no effect on FR-4 SA	
							7–9 wk	Increased drug seeking in FR-4 extinction sessions	
							10–23 wk	No effect on FR-1 extinction or cue reinstatement of drug seeking	
Blast	Repeated (3×)	Oxycodone	SA	Rat/Sprague Dawley	M	8 wk	6 wk	Increased drug seeking	(123)
Drug→TBI→Drug									
LFP	Single	Alcohol	Operant alcohol SA	Rat/Wistar	F	16 wk	2–10 days	No effect	(128)
LFP	Single	Alcohol	Operant alcohol SA	Rat/Wistar	M	16 wk	9 days	Increased breakpoint for alcohol	(129)
LFP	Single	Alcohol	Operant alcohol SA	Rat/Wistar	M	16 wk	2–15 days	Increased alcohol SA: preinjury intake positively correlated with postinjury increase in intake	(130)

CCI, controlled cortical impact; CPP, conditioned place preference; F, female; FR, fixed ratio; LA, low analgesia; LFP, lateral fluid percussion; M, male; NS, not specified; SA, self-administration; TBI, traumatic brain injury.

[a]Phase at time of injury; E/P, estrus/proestrus.

[b]Phase at time of injury; M/P, metestrus/diestrus.

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Table 3.

Biological Effects of TBI That Are Linked With Neuroplasticity and Plausible Mechanisms by Which These Effects Could Increase Risky Substance Use

Time	Biological Processes	Downstream Effects/ Processes	Link to Neuroplasticity	Plausible Link to Risky Substance Use	Clinical Evidence for Mechanistic Link	References
Immediate	Mechanical deformation/ mechanoporation–induced ion flux: K^+ efflux, Na^+ and Ca^{2+} influx	Membrane depolarization Excitotoxicity	Increased intrinsic excitability of neurons	PFC: increase or decrease in intrinsic excitability during cocaine or remifentanil abstinence (sex and treatment regimen dependent) NAc: decrease in intrinsic excitability during cocaine abstinence VTA: increased intrinsic excitability of dopamine neurons during cocaine abstinence		(54,65,139,140)
Minutes/ Hours	Necrosis	Release of DAMPs/ engagement of TLR2, 3, 4, 7, 9; engagement of purinergic receptors, NLRs, RLRs, ALRs Energy crisis	DAMP-associated TLR4 signaling: increased insertion of CP-AMPARs, increased NMDA-mediated Ca^{2+} flux; decrease in dopamine cell firing rate DAMP-associated TLR3, 7 signaling: growth cone collapse, inhibition of neurite outgrowth, neurodegeneration ATP-associated P2X signaling: release of glutamate from astrocytes NLR signaling: see Downstream Effects/processes/inflammasome activation TLR4 signaling: increased NF-κB → modulation of LTD; antiapoptotic gene regulation TLR4 signaling: increased IL-6 → Short IL-6 exposure: increased intrinsic excitability Long IL-6 exposure: reduced depolarization-induced Na^+ and Ca^{2+} currents, downregulation of presynaptic mGluR2/3	NAc: increase in CP-AMPARs during cocaine abstinence; reduction of NAc CP-AMPARs reduces drug seeking VTA: increase in CP-AMPARs after nicotine, cocaine, amphetamine, morphine, heroin, ethanol, and cannabis Intra-VTA LPS (TLR4 agonist) sufficient to induce reinstatement of cocaine seeking TLR4 agonist sufficient to increase alcohol consumption TLR4 antagonist suppressed incubation of heroin craving Reduction of mGluR2/3 function in mesocorticolimbic brain regions is also observed following exposure to nicotine, cocaine, or alcohol Treatment with mGluR2/3 agonists or positive modulators can reduce the reinforcing effects and seeking of drugs	Lower volumes of gray matter in substance use disorder: largest effects in putamen, thalamus, insula, and anterior cingulate cortex Polymorphisms of human NF-κB1 associated with chronic alcohol use Elevated NF-κB in brains of chronic alcohol users	(64–66,72–76,92,110,119,141–147)
	Axonal injury (shearing, calpain-associated proteolysis of cytoskeletal proteins)	Impaired synaptic transmission, necrosis/ apoptosis	See Downstream Effects/processes/ necrosis/apoptosis	Impaired prefrontal connectivity in TBI and risky substance use	Hypofrontality observed in substance use disorder with many drugs of abuse Axonal injury in polydrug abuse	(148–154)

Time	Biological Processes	Downstream Effects/ Processes	Link to Neuroplasticity	Plausible Link to Risky Substance Use	Clinical Evidence for Mechanistic Link	References
Biphasic: Minutes/ Hours, Then Days and Beyond	Increased BBB permeability	Extravasation of peripheral immune cells and immunogens Activation of the complement system	See Biological Processes/gliosis Complement signaling: synapse loss, neuroprotection against excitotoxicity, increased neurogenesis	Increased alcohol intake following BBB disruption	Reduced BBB integrity in postmortem tissue from risky alcohol use	(36,155–159)
	Generation of reactive oxygen species	Inflammasome activation → generation of IL-1β, IL-18; induction of pyroptosis Inhibition of astrocytic transport of glutamate Decreased NMDA receptor–mediated Ca^{2+} flux Elevated NF-κB	IL-1β: reduction of Nav, L- and N-type Cav, and Kv channel activity; increased NMDA-mediated Ca^{2+} flux; increased or decreased $GABA_A$-mediated Cl^- current (cell-type specific); increased Ca^{2+}-dependent glutamate release, decreased Ca^{2+}-dependent GABA release; inhibition of LTP Pyroptosis: see Biological Processes/apoptosis Elevated extracellular glutamate→promotion of excitotoxicity NF-κB: modulation of LTD; antiapoptotic gene regulation; increase in expression of mu, delta opioid receptors and NK1Rs, increase in expression of β-endorphin and enkephalin propeptides, reduction of dynorphin expression	IL-1β antagonist in VTA reduced cocaine seeking in rats TLR4 antagonist in VTA reduced cocaine-primed drug seeking in rats Intra-NAc NF-κB inhibitor reduced morphine and cocaine CPP NF-κB inhibitor reduced naloxone-precipitated morphine withdrawal severity	Peripheral IL-1β positively correlated with duration of methadone maintenance in former heroin users Peripheral IL-1β elevated in abstinent severe cocaine users with comorbid psychiatric diagnosis Polymorphisms of human NF-κB1 associated with chronic alcohol use Elevated NF-κB in brains of chronic alcohol users	(69,101,110,142,160–165)
Days–Weeks	Gliosis	Potentiation of drug-associated dopamine increase Shift to IDO metabolism Cytokine disruption of tetrahydrobiopterin (BH4) Cytokine increase in levels and activity of SERT Cytokine reduction in DAT Cytokine-induced release of astrocytic glutamate and reduced astrocytic glutamate uptake Cytokine-induced increase in cell surface AMPA and NMDA receptors Cytokine-induced decrease in cell surface $GABA_A$ receptors Cytokine-induced increase in levels and activity of acetylcholinesterase and decrease in acetylcholine release	IDO-biased metabolism reduces serotonin production and produces neuroactive metabolites kynurenic acid (antagonist of AMPA, kainite, and NDMA glutamate receptors) and quinolinic acid (agonist of NMDA receptors) BH4 disruption reduces production of dopamine, norepinephrine, and epinephrine Cytokine-associated changes in glutamate and GABA receptor function produce a net increase in synaptic strength Astroglial scar formation associated with cognitive/motor deficits TNF-α: Involved in synaptic scaling: increases mEPSC frequency and amplitude. Pathological concentrations of TNF-α inhibit LTP Induction of glutamate release from astrocytes and microglia, which acts on extrasynaptic GluN2B	Pharmacological shift of IDO metabolism from quinolinic acid to kynurenic acid pathway abolished the alcohol intake in 2 preclinical models and reduced cue-induced cocaine and alcohol seeking Reduced tonic dopamine and norepinephrine reduces motivational arousal Reduced phasic dopamine in striatum associated with increased cocaine self-administration, reversed by L-Dopa G-CSF increases cocaine self-administration and increases evoked dopamine release TBI-primed immune response may prime immune response to drugs of abuse Dexamethasone reduced TBI-associated increase in cocaine CPP Minocycline reduced TBI-	Lower kynurenic acid in patients with alcohol use disorder Reduced DAT in brain injury and methamphetamine abuse Upregulation of immune-related genes is a consistent finding in postmortem tissue from chronic alcohol users Stress and cue-triggered drug craving elevated plasma TNF-α in cocaine-dependent individuals Microgliosis elevated in orbital frontal cortex, striatum, and midbrain of methamphetamine users, inversely proportional to abstinence duration	(40,55,69,84,91,92,159,166–181)

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Time	Biological Processes	Downstream Effects/ Processes	Link to Neuroplasticity	Plausible Link to Risky Substance Use	Clinical Evidence for Mechanistic Link	References
		Thrombospondin-mediated increase in axonal sprouting Astroglial scar formation	containing NMDA receptors BDNF reduction of inhibitory transmission via decrease of Cl^- transport	associated increase in alcohol drinking		
Weeks	Demyelination	Impaired action potential propagation	See Biological Processes/axonal injury	See Biological Processes/ axonal injury		(54)
Months	Network-level changes	Decreased communication between the default mode network and salience network Widespread elevations in functional connectivity				(56)
	Neurodegenerative processes	Phospho-tau accumulation β-amyloid accumulation	See Downstream Effects/processes/ inflammasome activation	Elevated phospho-tau in rat striatum following heroin self-administration	Elevated phospho-tau in postmortem tissue from heroin abusers Elevated phospho-tau in postmortem tissue from individuals with high levels of prescription opioid use Elevated β-amyloid in polydrug users	(154,182–186)

ALR, AIM2-like receptor; ATP, adenosine triphosphate; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CP-AMPAR, Ca^{2+}-permeable AMPA receptor; CPP, conditioned place preference; DAMP, damage-associated molecular pattern; DAT, dopamine transporter; GABA, gamma-aminobutyric acid; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; LPS, lipopolysaccharide; LTD, long-term depression; LTP, long-term potentiation; mEPSC, miniature excitatory postsynaptic current; mGluR, metabotropic glutamate receptor; NAc, nucleus accumbens; NF-κB, nuclear factor-κB; NK1R, neurokinin 1 receptor; NLR, NOD-like receptor; PFC, prefrontal cortex; RLR, rig-1 like receptor; SERT, serotonin transporter; TBI, traumatic brain injury; TLR, toll-like receptor; TNF-α, tumor necrosis factor α; VTA, ventral tegmental area.