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DUAL DIAGNOSIS (RA CHAMBERS, SECTION EDITOR)

Dual Diagnosis of Traumatic Brain Injury and Alcohol Use Disorder: Characterizing Clinical and Neurobiological Underpinnings

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Abstract Recent evidence indicates that TBI can increase the risk of developing AUD. TBI and AUD share common symptoms including cognitive dysfunction. Therefore, it is of interest to better understand how reward-mediated behaviors central to alcohol addiction, such as alcohol craving, may interact with the cognitive dysfunction of TBI both at the behavioral and neurobiological level. We also present a preliminary case series as an illustration of how neural activation to alcohol cues may provide insight into the unique brain state of co-occurring mild TBI and AUD. Treatment implications for TBI and AUD and their co-occurrence are also discussed.

Keywords Alcohol · Traumatic brain injury · Addiction · Neuroimaging

Introduction

Rates of traumatic brain injury (TBI) and alcohol use disorder (AUD) are high in the USA, particularly among military, veteran, and athlete populations at risk for head injury. Among the civilian population, rates of AUD after TBI are as high as 25 % [1]. Among veterans with TBI, rates of AUD range from

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6 to 35 % [2, 3]. Symptoms, cognitive deficits, and neural pathways affected by TBI and AUD often overlap, making these co-occurring conditions challenging to diagnose and treat. This clinical picture is complex because not only is intoxication a risk factor for head injury but also those that experience TBI are at elevated risk for experiencing substance use disorders including AUD [4••, 5••].

In this review, we will describe the clinical picture of co-occurring TBI and AUD, including the overlapping cognitive dysfunction and underlying neurobiological alterations. A neuroimaging case series will be used to illustrate concepts. Finally, we will provide an overview of potential treatments for the co-occurrence of TBI and AUD.

Clinical Picture of Co-occurring TBI and Addiction: From Risk Factor to Vulnerability

Defining TBI and AUD

TBI occurs when a person experiences a physiological disruption of brain function due to an external force. TBI severity is clinically defined by the American Congress of Rehabilitation Medicine [6], the Department of Veterans Affairs/Department of Defense [7], and the Centers for Disease Control and Prevention [8] according to the presence and duration of loss of consciousness (LOC), alteration of consciousness (AOC), and post-traumatic amnesia (PTA). The Glasgow Coma Scale (GCS) score and lesion findings detected by routine structural neuroimaging are also used to characterize TBI severity. Table 1 summarizes how these clinical characteristics define TBI severity into mild, moderate, and severe categories. Mild TBI (mTBI) is defined by a period of LOC lasting less than 30 min or AOC lasting less than 24 h, PTA lasting less than 24 h, a GCS score of 13–15, and an absence of brain lesion findings using standard clinical neuroimaging [6, 9].

AUD ranges in severity from mild to severe and is defined by the American Psychiatric Association in the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [10] by the presence of at least 2 of the 11 symptoms summarized in Table 2 within a 12-month period. Alcohol abuse and alcohol dependence are severity categories used in the DSM-IV [11] and are no longer used with the DSM-5 [10].

Table 2 AUD clinically defined by the DSM-5

Symptoms

1. Alcohol is taken in larger amounts or over a longer period than intended
2. Persistent desire or unsuccessful efforts to cut down or control alcohol use
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol or recover from its effects.
4. Alcohol craving
5. Recurrent alcohol use resulting in failure to fulfill major role obligations
6. Continued alcohol use despite persistent or recurrent social or interpersonal problems due to the effects of alcohol
7. Giving up important social, occupation or recreational activities due to alcohol use
8. Recurrent alcohol use in physically hazardous situations
9. Continued alcohol use despite knowledge of persistent or recurrent physical or psychological problems due to alcohol
10. Tolerance
11. Withdrawal

AUD severity

Mild	Moderate	Severe
2–3 symptoms	4–5 symptoms	≥6 symptoms

Dual Nature of AUD and TBI Risk

It is well known that alcohol intoxication at the time of injury and/or a history of problem alcohol use is associated with increased risk of incurring a TBI [12, 13]. Alcohol use is also known to negatively impact TBI recovery [14]. Furthermore, recent evidence indicates that TBI is a risk factor for subsequent AUD [4••, 5••, 15]. Miller and colleagues reported that active-duty military personnel with mTBI and no prior AUD or SUD showed increased risk of a new alcohol dependence diagnosis relative to a control group with other injuries [4••]. Risk was significantly different, after controlling for relevant demographic and military characteristics, between two large samples of mTBI (n=5065) and non-mTBI (n=44733) active-duty military personnel at all three post-injury time points assessed: 1–30, 31–179, and ≥180 days [4••].

Findings reported by Johnson and colleagues also indicate an increased risk for developing AUD among TBI patients [5••]. In a large sample of active-duty military service members with no prior AUD or SUD, there was an increased

Table 1 Traumatic brain injury (TBI) severity clinically defined

Clinical characteristic	Mild	Moderate	Severe
Loss of consciousness (LOC)	<30 min	30 min to 24 h	>24 h
Alteration of consciousness (AOC)	<24 h	>24 h	>24 h
Post-traumatic amnesia (PTA)	<24 h	1–7 days	>7 days
Glasgow Coma Scale (GCS) score	13–15	9–12	<9
Clinical neuroimaging findings (structural CT/MRI)	Uncomplicated - Normal Complicated - Abnormal	Normal or abnormal	Normal or abnormal

incident rate ratio of AUD diagnosis within 1 year of injury among those that incurred a TBI of any severity (n=53,817) relative to those that did not experience a TBI (n=151,776) after adjusting for covariates including TBI severity, PTSD, other mental health conditions, and relevant demographic factors [5••]. A subgroup analysis revealed that those experiencing a TBI during deployment had a decreased risk of AUD relative to those without TBI and those experiencing a non-deployment-related TBI had an increased risk of AUD relative to those without TBI [5••]. Johnson and colleagues offer a few explanations for this finding including the following: service members deemed fit to deploy have met rigorous pre-deployment screening and therefore may be more healthy and resilient, fewer service members in the deployment TBI group had a history of positive mental health outcomes (19 %) and prior PTSD (3 %) relative to the non-deployment TBI group (25 % for mental health outcomes and 5 % for PTSD), deployed service members may be subject to stricter alcohol availability policies in theater, and deployed service members also have more contact with the medical system providing greater opportunities for identification, treatment, and intervention [5••]. Therefore, the deployed service member subgroup findings may not be representative of the overall trend. This additional analysis of non-deployment-associated TBI makes these findings more generalizable to civilians. These collective findings demonstrate that there is an increased risk of developing an AUD after TBI even for those without an AUD history. This increased risk is independent of TBI severity, and those incurring a TBI outside of deployment may be at greater risk.

It should be taken into consideration that some recent studies have not found that TBI increases risk for AUD [2, 15]. Most recently, Miles and colleagues (2015) found that mTBI did not predict AUD diagnoses for men or women veterans [15]. This study improved on the Miller and Johnson studies by using a mental health evaluation instead of ICD-9 codes for diagnoses, but the sample size was smaller (N=1278). Because separate analyses were conducted for men and women in the Miles study [15], it is unknown whether or not mTBI would predict AUD in a pooled sample of men and women. Furthermore, it is not clear whether pre-injury history of AUD, mTBI, PTSD, or other mental health disorders had an impact on findings as these were not accounted for in the study criteria or analyses [15].

While more research is needed on the topic, the collective evidence suggests that those who have experienced a TBI may be more likely to have a premorbid history of AUD or may be more vulnerable for developing subsequent AUD. The heterogeneous nature of TBI may also affect addiction vulnerability. Lesion severity, location, and focality can differ dramatically across individuals and affect morbidity as well as recovery [16, 17]. Lesions located within reward pathways and regions that modulate them may impact the degree to which individuals with TBI may be more or less susceptible to AUD or addiction in general. Previous reports of stroke-induced damage to the insula and basal ganglia, regions important for reward, inducing smoking cessation support this theory [18–20]. Thus, characterization of the heterogeneous neuropathology of TBI through advanced neuroimaging techniques may provide insight into the level of addiction vulnerability or even protection from addiction. Furthermore, understanding potential behavioral and neurobiological explanations for this increased risk or vulnerability can lead to developing effective treatments.

Impact of TBI on Reward-Mediated Behavior

The increased risk for incurring an AUD among the TBI population may be explained by overlapping cognitive deficits that could impact reward-mediated behavior. Below, we examine recent evidence regarding overlapping cognitive deficits in TBI and AUD in an effort to better understand how cognitive dysfunction induced by TBI may have a profound influence on an individual's reward system and thus how reward-mediated behaviors are expressed for individuals with co-occurring TBI and AUD.

TBI-Induced Cognitive Dysfunction

Cognitive deficits are a hallmark symptom following TBI. Cognitive deficits associated with moderate to severe TBI commonly include memory, executive function, information processing and attention [21]. Cognitive deficits can last for years after significant TBI injury and have a negative impact on life reintegration (i.e., return to work, school, play) [22].

For people with mTBI, cognitive deficits manifest immediately after injury and, for a majority, resolve within 1 to 3 months post-injury [23]. However, for a "miserable minority," symptoms including cognitive deficits may persist [24]. Evidence suggests non-injury-related comorbidities (e.g., demographic, psychosocial, psychiatric factors) may be strong predictors of the persistence of these prolonged symptoms [25]. A recent systematic review published by the International Collaboration on mTBI Prognosis indicates that cognitive impairments in the following domains are reported to occur within the first 2 weeks of injury: distractibility, attention, memory, verbal learning, information processing speed, and impulsivity [26]. Some of the studies included in this systematic review reported persisting deficits in some of these domains lasting up to 6 months post-injury [26]. However, there was less consistency among the persisting cognitive effects and the authors conclude that large-scale, longitudinal confirmatory studies are necessary to elucidate the most common cognitive domain impairments and recovery course following mTBI [26]. Vanderploeg and colleague (2005) [27] presented data on the long-term neuropsychological consequence of mTBI in a sample of over 4000 veterans with an average

post-injury status of 8 years. Theirs was unique in that they had the rare opportunity to match both controls and mTBI groups on preinjury intellectual status. Their findings were consistent with other literature that no adverse long-term neuropsychological effects were present. However, when examining non-traditional ways of characterizing complex attention and working memory, some subtle problems were identified. These findings suggest that while global cognitive functioning recovers in this population, some small alterations may persist.

A recent meta-analysis published by Karr conducted among studies of military blast-induced mTBI corroborates the International Collaboration on mTBI Prognosis systematic review. Karr and colleagues found that the cognitive domains most affected by blast-induced TBI in the post-acute phase were executive function, verbal delayed memory, and processing speed [28]. Notably, the average time post-injury for this mTBI sample was 3.79 years indicating further evidence of persistent cognitive dysfunction [28].

Impulsive behavior is a cognitive domain of interest because of its association with addiction. Studies on impulsivity among mTBI populations are just emerging in the last few years and have included veteran populations with and without co-occurring PTSD. Depue and colleagues report that veterans with co-occurring mTBI and PTSD have reduced anterior amygdala volume relative to controls and that this volume reduction was associated with poor inhibitory control and increased self-reported impulsivity [29]. However, one study demonstrated among veterans with PTSD, mTBI, or co-occurring mTBI and PTSD, those with PTSD self-reported engaging in risky and impulsive behaviors regardless of mTBI diagnosis [30]. Interestingly, no studies to date have examined the cognitive domain of impulsivity using delayed or probability discounting procedures. These procedures classically used in behavioral neuroeconomics may provide additional insight into cognitive dysfunction among the mTBI and co-occurring mTBI and AUD populations. Clearly, further assessments of impulsive behavior among diverse mTBI populations are needed to further understand the potential impact of mTBI on this cognitive domain.

Even in the absence of symptoms including cognitive deficits, experiencing mTBI or even sub-concussive blows alters brain function. This has been determined using multiple neuroimaging modalities including task-based functional magnetic resonance imaging (fMRI), resting state fMRI, and electroencephalography [31••, 32••, 33]. Diffusion tensor imaging (DTI) has also shown some promise in the classification of mTBI and as a potential biomarker of recovery from cytotoxic edema in cerebral white matter [34]. This is relevant because the forces following brain trauma creates a particular mechanical vulnerability for damage to frontotemporolimbic regions, which alters both their function and structure, and thus disrupts cognitive processes mediated by these structures [31••, 35]. Furthermore, alterations in brain function critical to cognitive processes may also be revealed when the body is put under physical stress [36••, 37]. Therefore, it is prudent to use a multi-modal neuroimaging approach to developing biomarkers of the long-term recovery and or sequelae of mTBI [38].

Alcohol Addiction and Reward-Mediated Behavior

In the previous section, AUD was defined with a description of symptoms comprising its diagnosis. Here, we further discuss the processes of alcohol addiction in order to shed light upon how alcohol reward-mediated behaviors may be influenced by TBI-related cognitive dysfunction. There are five classic models of addiction that we will describe here which can be integrated into a framework to understand how reward may be altered with co-occurring TBI and AUD: negative reinforcement [39, 40], positive reinforcement [41], incentive salience [42], impulse control [43, 44], and habit learning [45]. We do not propose one model as a singular explanation of addiction for AUD or co-occurring AUD and TBI. What is presented here and in Fig. 1a is an integration of aspects of these models.

Alcohol addiction is theorized by Koob to be composed of three cyclic phases: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect [39]. In the negative reinforcement model of addiction, drinking behavior occurs in order to remove internal negative affect. This is delineated from more long-term, external negative consequences that can occur among people with AUD (e.g., legal problems). Internal negative affect is prominent during the withdrawal phase. However, it is important to note that in the course of addiction, relapse to drinking behavior occurs outside of acute withdrawal [47, 48] and treating the withdrawal syndrome alone has not proven sufficient.

Alternatively, the positive reinforcement model is that drinking behavior occurs due to the rewarding or euphoric properties of alcohol [41]. That is, in the negative reinforcement model, the drinking response occurs because removing negative feelings is the reinforcing stimulus. In the positive reinforcement model, the drinking response occurs because of the rewarding/euphoric properties of the alcohol stimulus.

In the incentive salience model [42], alcohol and alcohol-related stimuli sensitize reward pathways in the brain such that "wanting" to drink becomes pathological. Alcohol-related contextual cues become increasingly salient. Therefore, alcohol-related stimuli can elicit the response of drinking behavior. Thus, the stimulus/response relationship of the incentive salience model is in the opposite direction as in negative/positive reinforcement described above (Fig. 1a). That is, with negative and positive reinforcement (as well as impulse dyscontrol described below), the response of drinking leads to a stimulus (e.g., euphoria). However, with incentive

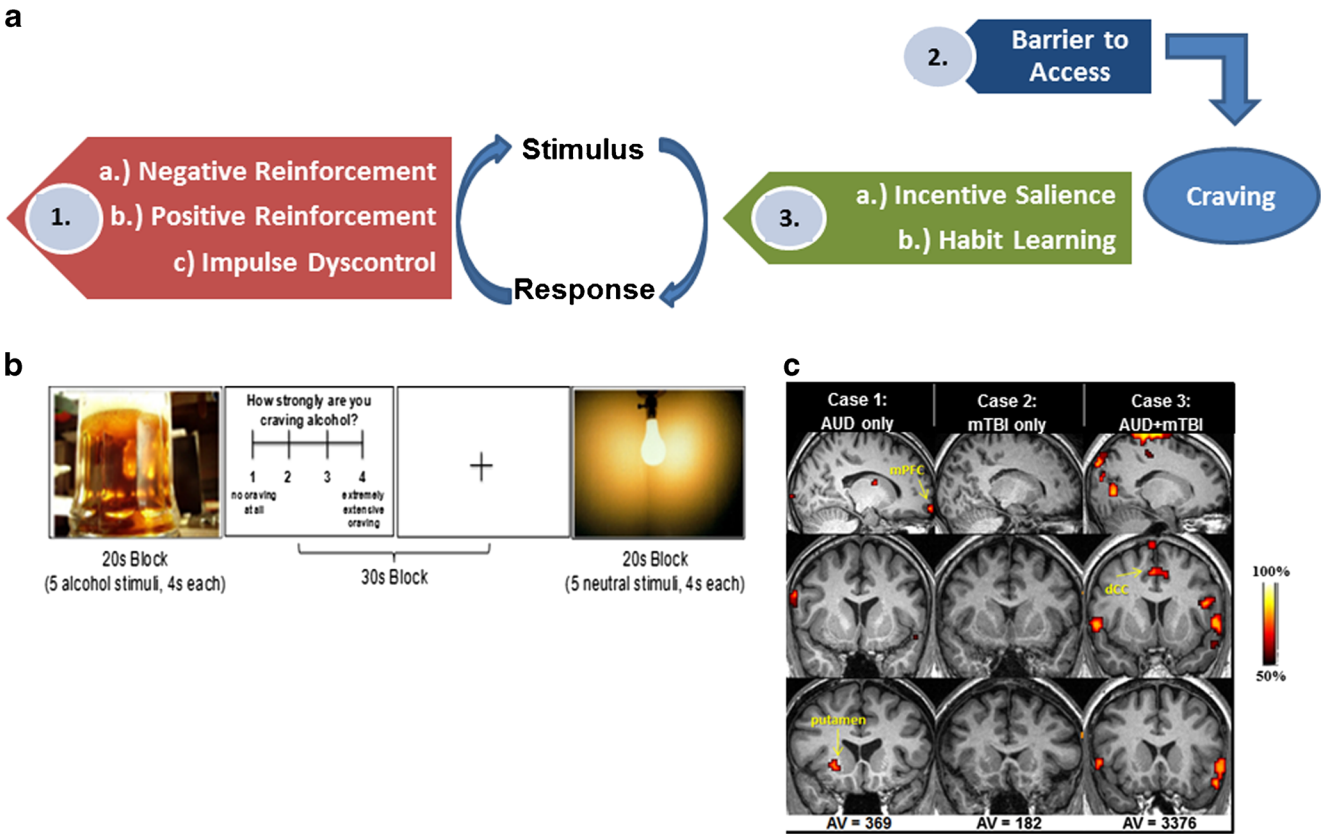

Fig. 1 (*A*) Integrated behavioral/cognitive model of addiction. (*B*) Blocks of alternating visual alcohol, visual neutral cues, and a craving scale followed by a fixation cross were presented. This blocked cue protocol was modified from that of Vollstädt-Klein and colleagues published in 2010 [46]. (*C*) The number of activated voxels (AV) in response to the visual alcohol cues minus the visual neutral cues are displayed. The relative *t* value threshold was set to 50 % of the peak *t* value for each subject independently

salience (as well as habit learning described below), exposure to alcohol-related stimuli leads to a drinking response.

The impulse dyscontrol model includes two systems that are sub-served by defined neural pathways: an impulsive system and a reflective system [43]. The impulsive system transmits immediate signals related to affective or emotional responses. The reflective system transmits long-term signals related to domains such as memory and executive function. Through the reflective system, negative consequences associated with alcohol can be evaluated. Under the impulse dyscontrol model, vulnerability to alcohol addiction can occur when the ability to inhibit the impulsive system is weakened.

The habit learning model builds from the reinforcement and impulse dyscontrol models described above. The habit learning model posits that alcohol use transitions from occurring voluntarily due to largely positive reinforcing experiences to a habitual or compulsive behavior that occurs due to lack of control (e.g., impulse dyscontrol) [45].

Many factors may impact how reward-mediated behaviors are expressed or how drinking behavioral responses occur. Craving, a hallmark symptom of AUD, is one of these factors. Craving is an important symptom to understand because it is a distracting and troubling experience associated with relapse [49] and represents a barrier to recovery. A comprehensive overview of the cognitive perspective on craving is beyond the scope of this review, but has been the subject of previously published reviews [50, 51]. Here, we focus on one perspective craving model, the cognitive processing model developed by Tiffany [52].

The cognitive processing model of craving differentiates itself by viewing alcohol use as a response that can occur in the absence of, or precipitated by, craving [52]. In the cognitive processing model, contextual stimuli can trigger alcohol use through an automatic process in the absence of craving. However, in the nonautomatic process, stimuli trigger behaviors that are met with barriers to drinking, eliciting a craving. Studies in which alcohol related cues slowed reaction time on cognitive tasks support this craving model [50]. People with TBI can experience slowed reaction time among other cognitive dysfunction (described above) as a result of injury. TBI can slow higher cortical function while also disinhibiting motivation and craving associated with addiction. Interestingly, there is some evidence that cognitive rehabilitation treatment administered to people with substance use disorders which is designed to improve cognitive dysfunction can also improve substance use outcomes such as frequency of substance use

and addiction severity index measures [53]. It is important to note that craving can occur outside of the circumstances of encountering a barrier to drug or alcohol access. Small priming doses of abused substances produce robust craving responses [54]. Specifically, there is evidence that priming doses of alcohol induce alcohol craving [55, 56]. Exposure to alcohol-related contextual cues [46, 57] as well as stress [58] is also known to elicit craving as well as activation within reward pathways.

What has not been presented before is the integration of these classic addiction models with that of Tiffany's cognitive processing model in order to provide a framework that may shed light on alcohol addiction for people with co-occurring TBI and AUD. As illustrated in Fig. 1a, (1a) negative and (1b) positive reinforcement as well as (1c) impulse dyscontrol models are illustrated on the left where a behavioral response (i.e., alcohol use) leads to a stimulus (i.e., removal of negative affect/reward). Illustrated on the right are the (3a) incentive salience and (3b) habit learning models in which a generally positive stimulus, such as the rewarding effects of alcohol, leads to a response, such as alcohol use. Thus, the order of response and stimuli is reversed when comparing 1a, 1b, and 1c models relative to 3a and 3b models. This figure illustrates how these models can be used together to provide insight for interpreting reward-mediated behavior in addiction. In situations where automated processes are disrupted by barriers to alcohol access, the link between stimulus and response may be disrupted. This disruption may allow for transitions between phases of these addiction models as well as exacerbation of alcohol craving. For a person with TBI and AUD, negative reinforcement (1a) may be involved due to depression or anxiety symptoms but they may also experience cognitive dysfunction which would create more barriers to alcohol access (2) and perpetuate alcohol craving.

It is important to discuss here that depression and anxiety often co-occur with TBI [59, 60]. Likewise, AUD, depression, and anxiety also co-occur [61, 62]. Alcohol may provide short-term relief from internal negative affective states. However, in the long term, alcohol exacerbates depression and anxiety symptoms which then lead to subsequent relapse [63]. Over time, rewiring of the brain also occurs leading to alterations in how people with addictions perceive reward over time [64]. There is evidence that people with AUD favor smaller immediate rewards over larger delayed rewards [65]. Therefore, the temporal horizon is shortened for people with AUD and it is logical to theorize that a sense of short-term relief of negative affect may be valued more than possible negative long-term consequences that could occur due to drinking.

These circumstantial barriers to alcohol access may stand in for the neurobiological brake that the reflective system provides over the impulsive system drive in the impulse dyscontrol model (1c). However, with a weakened system, the impulsive system may lead to impulsive choices during this period without alcohol access that would increase the likelihood of obtaining alcohol and drinking. These impulsive choices may even result in breaking the law to obtain alcohol. When faced with alcohol-related stimuli during this period where barriers to access are experienced, the drive to obtain alcohol becomes stronger due to the principles of incentive salience (3a). Thus, many principles of these classic addiction models are at play for the person with TBI and AUD. As illustrated in the example above, TBI and associated behavioral sequelae may leave a person more vulnerable to alcohol use or alcohol craving.

The translation of the affective states and craving associated with repeated alcohol use to the engagement in the reward-mediated behavior of relapse for the individual with co-occurring TBI and AUD may be influenced by increased impulsive behavior and decreased executive function. There is evidence that impulsive behavior is associated with the initiation of alcohol use [44], which may help to explain the findings of Miller [4••] and Johnson [5••] that incurring a TBI increases the risk of developing an AUD. Furthermore, self-reported ratings of impulsivity are associated with alcohol use which is described by Lejuez and colleagues to produce a bidirectional relationship between alcohol use and impulsivity [44]. An individual with co-occurring TBI and AUD may be more vulnerable to this bi-directional relationship, thus exacerbating AUD. Individuals struggling with addiction may also experience a hypoactivity of neural systems engaged in top-down inhibitory control involved with decision-making process (i.e., reflective system) or executive function leading to relapse [66]. Thus, executive function, too, may be impaired for the individual with co-occurring TBI and AUD leading to exacerbation of symptoms including alcohol craving and vulnerability to relapse.

Cognitive deficits associated with mTBI overlap with AUD and may explain potential vulnerability of the TBI population to AUD and exacerbation of AUD among individuals with co-occurring TBI and AUD. This exacerbation may include increased craving severity among people with co-occurring TBI and AUD. We have recently reported that veterans with a probable AUD and a combination of mental health disorders with and without mTBI self-reported higher craving levels than veterans with probable AUD alone [67••]. Future studies will determine more specifically the effect of mTBI on alcohol craving levels. Moreover, TBI can have a fundamental impact on experiencing reward. Experiencing a TBI may lead to damages in the brain's reward system leading to compounding these effects and exacerbating the vicious cycle of addiction. For example, TBI can affect naturally occurring intrinsic rewards such as sex. Sexual dysfunction has been reported as occurring in a substantial number of people with TBI [68–70]. Hyposexuality is the most common form of sexual dysfunction following TBI and can occur at all stages

of the sexual response cycle, including arousal, sexual behavior/experience, and orgasm [69]. Hypersexuality or disinhibited sexual behavior can occur following TBI, but it is relatively rare, occurring in less than 10 % of persons with TBI who receive rehabilitation services [71]. Persons with TBI are often socially isolated, and poor social participation is a contributor to sexual impairment in persons with TBI. Consistent with the negative reinforcement model [72], they may drink alcohol to avoid the loneliness and pain associated with social isolation, not being aware that alcohol can have a negative impact on their sexual functioning.

Overlapping Neurobiological Pathways of AUD and mTBI

TBI and associated mental health disorders commonly involve abnormalities within reward pathways that drive both the genesis and continuation of addiction [73–75]. Thus, the increased susceptibility for incurring AUD among people with TBI may be due to an underlying neurobiological phenomenon.

Advanced imaging techniques, such as magnetic resonance imaging (MRI), have been used to study brain volume, neural activation, and neural connectivity of reward pathways. Reward pathways associated with craving and addiction are well-defined for individuals with AUD alone. Comprehensive assessment of reward pathways using structural MRI with advanced morphometric analyses demonstrate that people with AUD have reduced volume relative to control participants in the reward network comprised of the dorsolateral prefrontal cortex, insula, subcallosal, orbitofrontal and cingulate cortices, parahippocampal gyrus, and temporal pole as well as the sub-cortical structures of the nucleus accumbens, amygdala, hippocampus, and ventral diencephalon [76]. Moreover, among the AUD group, decreased reward network volume was significantly associated with decreased working memory scores [76]. Another structural neuroimaging study found that amygdala, hippocampus, and ventral striatum volumes are reduced among individuals with AUD relative to control participants. Increased alcohol craving was significantly associated with reduced amygdala volume among individuals with AUD and this change in volume predicted who would relapse 6 months after an initial 1-week detoxification period [77].

Task-based fMRI protocols in which people are presented with alcohol cues have been repeatedly used to define these pathways [58;78]. For example, brain activation in response to visual alcohol cues within the dorsal striatum is positively associated with craving [46] and within the medial prefrontal cortex (mPFC) is positively associated with relapse [78]. Brain activation in the insula, hippocampus, thalamus, and cingulate cortex is also increased in response to alcohol-related images [78–80]. In addition, mental health disorder symptoms, particularly of depression and anxiety, have been shown to positively correlate with alcohol cue-induced brain activation in the insula, cingulate, striatum, and thalamus among people with AUD [81].

Connectivity between these reward-related brain regions may also be compromised by co-occurring TBI and AUD. Resting state functional connectivity (rsFC) using fMRI is a means by which this can be investigated. Both mTBI [36••, 82–84] and alcohol exposure [85, 86] result in abnormal resting state connectivity in brain networks important for cognition and reward. This is relevant because dysfunction in cognition and reward processing influence craving and relapse. When AUD and TBI co-occur, unique differences in alcohol cue-induced neural activation and connectivity at rest may shed light on their underlying neurobiology and thus dictate development of targeted treatments to reduce alcohol craving and relapse.

Preliminary Case Series

We present here preliminary results from a neuroimaging case series in order to illustrate the effects that co-occurring mTBI and AUD may have on alcohol cue-induced neural activity. Neural activation was compared among three adult males including a civilian with probable AUD only (case 1), a veteran with mTBI only (case 2), and a veteran with co-occurring probable AUD and mTBI (case 3). mTBI was defined using a structured clinical interview based on the American Congress of Rehabilitation Medicine definition of mTBI [6] along with neuropsychological test performance measures [87]. Probable AUD was defined as a positive screen on the alcohol use disorder identification test consumption questions (Audit-C; score of ≥4 for men indicates probable AUD) [88]. fMRI data were acquired in the presence of alcohol cues (Fig. 1b) via a neuroimaging protocol adapted by Volstädt-Klein [46]. The veteran with co-occurring mTBI and AUD (case 3) had the greatest brain activation in response to alcohol cues (Fig. 1c).

Region-of-interest analyses demonstrated that the location of alcohol cue-induced activation within the reward pathway was different for each of the three subjects. Activation for the veteran with mTBI only (case 2) had little to no activation with the alcohol reward pathway as expected. Activation for case 1, with AUD only, was located within multiple regions of the reward pathway (e.g., mPFC, putamen, caudate, and insula), but the majority was located within the mPFC and there was no activation within the dorsal cingulate cortex (dCC). Activation for case 3, the veteran with co-occurring mTBI and AUD, is unique in that the activation to alcohol cues was only located within the dCC of the reward pathway, which plays an important role in executive functioning and error processing [89]. The dCC is also part of a network that processes value or importance of reward (i.e., the salience network) [90]. Activation within the entire cingulate cortex,

in fact, has been associated with alcohol craving and relapse [91•]. These preliminary findings are the first to examine neural activation in response to alcohol cues among an individual with co-occurring mTBI and AUD. Collectively, these findings suggests that the dCC may be more susceptible to responding to alcohol cues for people with co-occurring conditions whereas the mPFC may be more susceptible to responding to alcohol cues for people with AUD alone.

Informing Treatments to Address Co-occurring TBI and Addiction

There are limited treatment options specifically tailored to individuals with co-occurring TBI and AUD. However, our enhanced understanding of behavioral and neurobiological characteristics of TBI and AUD can be used to guide clinicians on the use of existing treatments for individuals with co-occurring TBI and AUD. Below, we discuss potential behavioral, pharmacological, and neuromodulatory treatments for these conditions.

Behavioral

In treating people with co-occurring TBI and AUD, it is important to provide individualized treatment. Behavioral symptoms of alcohol withdrawal, particularly in early abstinence, include impulsivity, anxiety, irritability, dysphoria, insomnia, and impaired concentration [92]. These symptoms overlap with the emotional and cognitive dysfunction resulting from TBI as described above [93]. Implementing multiple treatments to treat an individual's specific symptoms may prove inefficient. Thus, utilizing treatments that target multiple symptoms is important for people with co-occurring conditions. One promising treatment is exercise. Exercise is an established intervention for depression, anxiety, and fatigue and improves global cognitive functioning [94]. Engaging in exercise on a routine basis facilitates neurogenesis and neuroplasticity [94–96]. Neuroplasticity, in particular, decreases neuroinflamation and neurodegeneration that may be contributing to the neurobiological deficits of both AUD and TBI. This patient population has a broad array of symptom complexity and often co-occurring mental health conditions. Therefore, pairing an exercise regimen with effective treatment targeted towards symptom presentation may promote an optimal outcome.

The research on effectiveness of treatment for alcohol abuse following TBI is in its infancy. Due to cognitive dysfunction, people with TBI may have difficulty benefitting from traditional substance abuse treatments, such as 12-step programs. Adaptations to existing treatments may be needed, including repetition, concrete examples, use of visual aids, peer-modeling, and slower pace of instruction. Results of recent studies have indicated that brief interventions combining motivational interviewing with education about the negative impact of substance use on TBI recovery show promise for altering expectations about alcohol use [97••] and for decreasing alcohol use [98] in people with TBI; however, studies are methodologically limited and further research on the effectiveness of these interventions for changing alcohol use is needed.

Pharmacological

There are three FDA-approved medications for alcohol dependence, all of which have good evidence and can be safely used in patients with TBI: disulfiram, acamprosate, and naltrexone. The aversion therapy of disulfiram works for patients committed to complete sobriety. One small study of adolescents shows higher abstinence rates and duration [99]. A disadvantage is that disulfiram does not prevent impulsivity and craving resulting in treatment failures. Acamprosate has few side effects and increases abstinence duration [99]. Acamprosate requires good compliance, is dosed three times daily, and should be avoided in the moderately renal impaired. Naltrexone reduces the number of heavy drinking days [99]. Naltrexone can be dosed once daily orally or once monthly by injection, which is beneficial for patients with problems of compliance, memory, and impulsivity. It has high tolerability but should be avoided in patients with liver dysfunction and those who are also prescribed opiates.

There are a number of potential pharmacological treatments that provide promise for treating AUD. These are briefly reviewed here with consideration for patients with co-occurring AUD and TBI.

High-dose gabapentin, 1800 mg/day, has shown better efficacy for AUD than gabapentin 900 mg/day. Increase in abstinence rates, reduced heavy drinking days, and fewer relapse-related symptoms of insomnia, dysphoria, and cue-induced alcohol craving were reported [100]. Patients taking gabapentin also showed relief of sleep disturbance, irritability, concentration problems, anxiety, and dysphoria during the protracted withdrawal phase [92].

Trials of the combination of naltrexone and gabapentin show superior efficacy to either agent alone for reducing cravings and number of drinking days, increasing time to relapse, and decreasing sleep disruption [92]. Both have good tolerability and safety profiles.

There is good evidence that mirtazapine can be used for treating both behavioral symptoms and cravings. Several studies of mirtazapine indicate it strengthens impulse control, reduces alcohol cravings and consumption, and has positive effects on sleep and mood [101]. Positive results were observed in dose ranges of 30–60 mg in heavy drinking males [102•]. In a 2-year follow-up study, patients with AUD and depression reported longer abstinence and greater remission in mood symptoms with mirtazapine 30 mg relative to placebo [101].

Topiramate has evidence in multiple trials for abstinence and irritability, hostility, and impulsivity. Doses of 100–

300 mg/day improve abstinence up to 6 weeks after detoxification. Patients experienced reduction in anxiety, hostility, and obsessive-compulsivity [103•]. In a study comparing topiramate 300 mg, naltrexone 50 mg, and placebo, patients had longer abstinence and fewer heavy drinking days with topiramate over placebo and no significant difference with naltrexone. Many clinicians may not prefer topiramate for their patients with TBI because (1) it requires long titration to therapeutic dose and (2) has more reported side effects over other agents, including impaired memory and concentration, psychomotor slowing, and dizziness [99], all which can complicate the symptoms of AUD and TBI.

Prazosin has evidence for treatment of hypervigilance and sleep disruption in patients suffering from PTSD. Evidence shows that high doses (16 mg) limits stress-induced cravings and offers control of impulsivity of alcohol consumption [104•] which benefits in the treatment of TBI, as well.

In medications studied thus far, not one single agent has proved effective for all patients with the co-occurring diagnosis of AUD and TBI. Clinical judgment, medical comorbidities, and future trials will guide which agents are used to treat individuals with these chronic co-occurring disorders.

Neuromodulation

Given that TBI and AUD affect overlapping neural pathways, neuromodulatory treatment through non-invasive neural stimulation, such as transcranial magnetic stimulation, may be an ideal treatment for people with co-occurring TBI and AUD. We recently published a review on this topic [105•]. It should also be mentioned that transcranial direct current stimulation is another non-invasive neuromodulatory treatment option that has shown promise for the treatment of alcohol craving and cognitive dysfunction [106–108].

Conclusions

TBI may be a risk factor for developing substance use disorders including AUD. This vulnerability may be explained by overlapping cognitive dysfunction including increased impulsive behaviors and impaired executive function. These cognitive domains engage the same neural pathways integral to reward-mediated behaviors including alcohol craving. This vulnerability may also be altered by the heterogeneous nature of TBI such that lesion properties may dictate whether an individual is more or less susceptible to addiction or if addiction susceptibility is affected at all. Thus, individuals with co-occurring TBI and AUD may have a unique brain state as illustrated in the case series described above (Fig. 1c). The co-occurrence of these conditions, the variance in severity of AUD, as well as the heterogeneity of TBI underscore the need to obtain a comprehensive assessment of this brain state through advanced neuroimaging. A better understanding of this cognitive dysfunction and how reward-mediated behaviors may be exacerbated for the individual with co-occurring TBI and AUD will aid the development of treatments tailored to these individuals.

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Compliance with Ethics Guidelines

Conflict of Interest All authors declare no conflicts of interest.

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- •• Of major importance

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