HHS Public Access

Author manuscript

Neuropharmacology. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Neuropharmacology. 2021 December 01; 200: 108807. doi:10.1016/j.neuropharm.2021.108807.

Interoception and alcohol: Mechanisms, networks, and implications

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Abstract

Interoception refers to the perception of the internal state of the body and is increasingly being recognized as an important factor in mental health disorders. Drugs of abuse produce powerful interoceptive states that are upstream of behavior that drive and influence intake, and addiction pathology is impacted by interoceptive processes. The goal of the present review is to discuss interoceptive processes related to alcohol. We will cover physiological responses to alcohol, how interoceptive states can impact drinking, and the recruitment of brain networks as informed by clinical research. We also review the molecular and brain circuitry mechanisms of alcohol interoceptive effects as informed by preclinical studies. Finally, we will discuss emerging treatments with consideration of interoception processes. As our understanding of the role of interoception in drug and alcohol use grows, we suggest that the convergence of information provided by clinical and preclinical studies will be increasingly important. Given the complexity of interoception processing and the multitude of brain regions involved, an overarching network-based framework can provide context for how focused manipulations modulate interoceptive processing as a whole. In turn, preclinical studies can systematically determine the roles of individual nodes and their molecular underpinnings in a given network, potentially suggesting new therapeutic targets and directions. As interoceptive processing drives and influences motivation, emotion, and subsequent behavior, consideration of interoception is important for our understanding of processes that drive ongoing drinking and relapse.

Keywords

interoception; AUD; addiction; drug discrimination; insula

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Overview

Interoception, the process of sensing, interpreting, and integrating bodily signals, is an important function for maintaining bodily homeostasis. Perception of bodily states such as hunger, pain, thirst, and arousal drive changes in motivational states that influence behavior. As such, interoception plays a critical role in guiding our actions and accordingly, can impact cognitive control, decision-making, reward, emotion and emotional regulation, and conditioning (Bechara et al., 1997; Bevins and Besheer, 2014; Ceunen et al., 2016; Craig, 2003; Critchley and Garfinkel, 2017; Paulus, 2007; Paulus and Stein, 2010; Razran, 1961). Dysregulation of interoceptive processing can contribute to maladaptive behaviors and is posited to be a common feature in several mental health disorders such as anxiety, depression, and addiction (Bevins and Besheer, 2014; Domschke et al., 2010; Harshaw, 2015; Paulus and Stein, 2010; Paulus et al., 2009; Pollatos et al., 2009). To this end, this review conceptualizes the perception of the internal body state induced by alcohol consumption/administration as an interoceptive stimulus capable of guiding behavior. In addition, we discuss how interoceptive states distinct from alcohol may influence alcohol-related behavior.

All drugs of abuse, including alcohol, produce distinct effects. In fact, an individual's sensitivity to the effects of alcohol (e.g., lethargy, lack of coordination, slurring, body sway) has been associated with later alcohol use and misuse, showing that individuals with lower sensitivity to the effects of alcohol have higher susceptibility to later misuse (Schuckit, 1994; Schuckit et al., 2008a; Schuckit et al., 2008b). Self-report questionnaires in which individuals can rate the degree to which they have feelings of "high", "intoxication", "nausea", for example, are important tools to characterize an individual's experience of a particular drug or alcohol effect.

The drug effects associated with alcohol, as well as other drugs (e.g., cocaine, nicotine, amphetamine, caffeine), are perceived as a change in bodily state and can be trained to serve as discriminative stimuli using drug discrimination methods in both humans and non-human animals (Bolin et al., 2016; Kamien et al., 1993; Shoaib and Perkins, 2020; Solinas et al., 2006; Young, 2009). For instance, social drinkers trained to discriminate low doses of alcohol reported using the interoceptive effects of "light-headedness" as the discriminative stimulus (Duka et al., 1998). As such, by serving as discriminative stimuli that guide behavior, these drug effects/states can be conceptualized as interoceptive stimuli (Bevins and Besheer, 2014; Thompson et al., 2019). These tools have been invaluable for our understanding of the underlying neuropharmacology of drugs as will be discussed later in this review. Additionally, the degree to which experimental manipulations (pharmacology, chemogenetics, optogenetics, etc.) produce effects similar to a drug provides insight into the underlying neurobiological mechanisms of that drug's interoceptive state.

Both positive and negative interoceptive states can influence motivated behavior. For example, negative interoceptive states such as anxiety and negative affect from drug withdrawal have potential to drive drinking and relapse behaviors in both rodent models and humans (Hogarth, 2020; Koob et al., 2014). Pursuit of positive effects from alcohol has been observed in the laboratory as drinkers reported an expectation of alcohol to

transform their experience in a positive manner (Brown et al., 1980; Pihl and Smith, 1988). Indeed, enhancing positive affect and reducing negative affect and is proposed to be a major motivator driving alcohol drinking (Cooper et al., 1995; Mun et al., 2008). This has been conceptualized as “liking” vs. “wanting”, respectively, where a positive experience is pursued due to the experience of pleasure (liking), which can be dissociated from incentive salience driving compulsive behavior (wanting; Berridge et al., 2009). In essence, the interoceptive drug state is so salient that it becomes a key factor in homeostatic balance (Paulus et al., 2009; Volkow et al., 2019). The allostasis model of alcohol use disorder (AUD) suggests that positive affect is the primary driver in the beginning stages of AUD, driving drinking through impulsive acts, while in the later stages baseline negative affect is a defining feature of AUD, driving compulsion to drink in order to reduce negative affect characteristic of the withdrawal state (Koob, 2003; Koob and Le Moal, 1997). Current and/or desired interoceptive states underlie these motivations, playing an important role in the guidance of behavior towards alcohol consumption. With growing interest in interoception processes as an important part of mental health and addiction research, the goal of the present review is to 1) discuss interoceptive processes as they relate to alcohol, 2) discuss the interoceptive effects produced by alcohol, and 3) to begin to expand our knowledge related to the brain mechanisms that contribute to these processes.

Interoception and physiological responses to alcohol

Afferent signals from the cardiovascular system are one of the major sources of interoceptive information (Garfinkel and Critchley, 2016; Paciorek and Skora, 2020). There is an extensive literature on bidirectional heart-brain signaling that is critical in regulating blood pressure and heart rate and interoceptive awareness of the cardiovascular state can be modulated by alcohol. For example, individuals with alcohol use disorder (AUD) were found to score higher on interoceptive sensibility (confidence in accuracy of one’s interoceptive observations) but lower on interoceptive accuracy in tasks such as heartbeat tracking/discrimination (Ates Col et al., 2016; Jakubczyk et al., 2019; Schmidt et al., 2013). Interestingly, with acute alcohol consumption, feelings of “light headedness” were associated with increased metacognitive interoceptive awareness, a measure of conscious interoceptive abilities (Garfinkel et al., 2015), in a heart beat discrimination task (Leganes-Fonteneau et al., 2019). In addition, administration of 0.4 g/kg alcohol increased interoceptive accuracy in a heart beat discrimination task, and interestingly expectancies about the valence of the effects of the alcohol correlated with interoceptive accuracy as well (Leganes-Fonteneau et al., 2021). Heartbeat oscillation, termed heart rate variability (HRV), at the 0.1 Hz range carries information about vagus nerve signaling and has been used extensively in the study of interoceptive signaling (Lehrer and Gevirtz, 2014). Measurement of 0.1Hz HRV has proven to be a useful tool in studying alcohol-related perception as changes in HRV were found to correlate with alcohol-related attentional biases after alcohol consumption (Leganes-Fonteneau et al., 2021a), suggesting that alterations to the body state may play an important role in driving alcohol-related behaviors. Further, another study found greater 0.1 Hz heart rate variability signals in subjects with a family history of AUD after they consumed alcohol and were presented with alcohol-related cues, suggesting that the physiological response can contribute to or enhance alcohol-related cognitive

bias (Leganes-Fonteneau et al., 2020). Interestingly, this relationship was weakened with increasing perceived levels of intoxication (Leganes-Fonteneau et al., 2020), which may suggest that cognitive bias for alcohol-related cues is part of an incentive salience process that drives alcohol seeking in a deprived state. These findings underscore the relationship between alcohol, heart rate, and interoception, and highlight how cardiovascular signals can be used to study the cognitive effects of alcohol.

Brain networks and brain regions

The insular cortex, as an integrator of both external and internal (interoceptive) stimuli (Craig and Craig, 2009), is a central hub for interoceptive processing and is anatomically well-positioned to integrate interoceptive information (Naqvi and Bechara, 2010). The insula is critical for translation of sensory and limbic affective information for use in decision-making processes, executive control, and goal-directed behavior via activation of executive control networks (Cloutman et al., 2012; Heilig et al., 2019; Seeley et al., 2007). It is typically co-activated along with the anterior cingulate cortex (ACC) and functions as a major player in transitioning between brain networks, including the default mode network and the salience network, a critical set of interconnected brain regions involved in processing salient stimuli (Chong et al., 2017; Craig, 2002). Stronger connectivity within the salience network is associated with greater accuracy on interoceptive tasks such as heartbeat counting (Chong et al., 2017). In contrast, acute alcohol administration reduces network connectivity (Gorka et al., 2018), and AUD is associated with diminished network connectivity (Sullivan et al., 2013). Subjective feelings of stimulation after consumption of alcohol (0.7-0.8 g/kg) were found to be associated with increased activity in salience network regions including the insular and cingulate cortices as well as the striatum, while notably sedation was not correlated with changes in these brain regions (Weafer et al., 2018). Abstinent alcohol-dependent individuals had greater functional connectivity between the ventral striatum and anterior insula with the dorsolateral PFC during alcohol presentation cues as compared to non-abstinent individuals, suggesting that cognitive control in abstinence may be due in part to the functional connectivity of prefrontal regions with these critical interoceptive brain regions (Strosche et al., 2021). In an experiment where heavy drinkers were conditioned to associate neutral stimuli with an alcohol intoxication state, fMRI scans found increased activity in the insula and ACC as well as executive control networks upon re-exposure to the positively conditioned stimuli (Oberlin et al., 2018), suggesting that stimuli associated with alcohol may drive activity in brain regions related to salience and motivated behavior. Changes in these critical networks and brain regions may manifest as inappropriate emphasis on drug-related states, cues, and behaviors. Indeed, smokers with insula damage were likely to experience a complete disruption of addiction including a complete loss of desire to smoke (Naqvi et al., 2007), suggesting that processing in this region is part of the network encoding the motivation to consume addictive substances. While few studies have directly addressed the neurobiological underpinnings of the contributions of interoception to AUD, the insular cortex and its connections across brain networks are promising targets for future studies.

A number of changes in brain regions associated with processing of interoceptive information have been observed in individuals with AUD. Alcohol-dependent individuals

were found to have smaller insular cortex and ACC volumes which correlated with self-reports of impulsivity and compulsivity (Grodin et al., 2017), as well as enlarged amygdala volume (Senatorov et al., 2015). Similarly, adolescents with AUD had greater white matter volume in the insula which correlated with alcohol preoccupation and craving (Chung and Clark, 2014) and adolescent excessive drinkers had reduced insular gray matter (Heikkinen et al., 2017). Patients with AUD had changes in insular activity levels, showing decreased BOLD signal while performing a visual attention task (Zehra et al., 2019) or cognitive control task (Sullivan et al., 2013). When presented with visual cues related to alcohol, heavy drinkers showed greater BOLD signaling in the insular cortex and the ventral striatum as compared to light drinkers while also having reduced signaling in frontal areas in response to cues related to higher life goals (Ihssen et al., 2011). Further, nontreatment-seeking alcoholics showed increases in ventral striatal dopamine under IV alcohol infusion while social drinkers did not, suggesting a sensitized reward and motivational response in AUD (Yoder et al., 2016). These region-specific enhanced responses to alcohol paired with reduced responses to other salient stimuli are consistent with the idea that heavy alcohol use changes brain network activity resulting in an inappropriate drive, obsessive craving, and focus towards alcohol-related goals to the detriment of alternatives (Addolorato et al., 2005; Koob, 2003).

Interoception and discrimination procedures

Discrimination tasks where subjects identify differing interoceptive states has been an important method for studying interoception. Humans can discriminate between the effects of specific blood alcohol levels (Huber et al., 1976; Lansky et al., 1978; Lipscomb and Nathan, 1980). For example, discrimination of blood alcohol level was used as a potential method by which to moderate alcohol consumption (Lovibond and Caddy, 1970). Individuals were trained to associate internal cues of intoxication with feedback on blood alcohol levels (BALs) to learn to recognize the bodily sensations associated with moderate blood alcohol levels as a strategy to reduce drinking. Drug discrimination procedures have been extensively used in non-human subjects, serving as a model of self-reported effects in humans. In operant drug discrimination methods, animals (most commonly rodents) are trained to respond differently for the same reward (e.g., sucrose, food) after receiving a drug or vehicle. For example, after alcohol administration, responses on a lever (e.g., left) will result in reward delivery, whereas after vehicle administration, responses on a different lever (e.g., right) will result in reward delivery. As such, the drug interoceptive effects serve as a discriminative stimulus to inform the behavioral output (i.e. lever selection). Similar strategies can be employed in Pavlovian drug discrimination procedures (Besheer et al., 2012b; Besheer et al., 2004; Jaramillo et al., 2018a; Palmatier and Bevins, 2008; Randall et al., 2016; Randall et al., 2020a; Randall et al., 2020b; Reichel et al., 2007; Thompson et al., 2019; Troisi II and Michaud, 2019; Wilkinson et al., 2009). In a Pavlovian feature positive occasion setting procedure a sucrose reward is presented into a fluid receptacle following random cue light presentations only after alcohol administration, whereas after vehicle administration the cue light presentations are not followed by sucrose reward. As such, with training, the alcohol interoceptive stimuli come to control anticipatory reward-seeking (goal-tracking) behavior during the light cue. Both training paradigms have been

a tremendous resource in our understanding of the pharmacology and circuitry of alcohol interoceptive effects. For reviews specific to alcohol discrimination in rodents see (Allen et al., 2018; Barry, 1991; Grant, 1994; Hodge et al., 2006; Kostowski and Bienkowski, 1999; Stolerman et al., 2011).

Contribution of preclinical studies to understanding of alcohol interoceptive effects.

Molecular mechanisms and manipulations in preclinical models

Preclinical animal models have been important tools in our understanding of the molecular and neural circuitry mechanisms that underlie the interoceptive effects of alcohol. Both operant and Pavlovian drug discrimination procedures utilize substitution experiments to evaluate the mechanisms underlying the interoceptive effects of alcohol. These experiments train animals to discriminate the interoceptive effects of alcohol from that of vehicle (water), and then test other compounds in place of alcohol for potential alcohol-like stimulus effects (i.e., ability to produce a behavioral response identical to the way in which rats were trained to respond under an alcohol stimulus). Alcohol interoceptive effects appear to be predominantly driven by modulating the balance of excitation and inhibition through inhibition of excitatory (glutamate) neurons and potentiation of inhibitory (GABA) neurons (Grant and Colombo, 1993; Stolerman et al., 2011). Importantly, the biological mechanism for the interoceptive effects of alcohol are dependent on the training dose of alcohol (Stolerman et al., 2011). For example, $GABA_A$ agonists (benzodiazepines, barbiturates, muscimol) fully substitute (produce “alcohol-like” effects) for lower alcohol training doses (e.g., 1 g/kg), indicating that $GABA_A$ agonism is sufficient to produce the interoceptive effects of 1 g/kg alcohol (Grant and Colombo, 1993; Hodge and Cox, 1998). Further, neurosteroids, which potentiate GABA receptors through positive allosteric modulation, also substitute for 1 g/kg alcohol (Bowen et al., 1999b; Hodge et al., 2001). In contrast, as the dose of alcohol increases, there is a shift in the contribution of $GABA_A$ to NMDA receptor involvement (Colombo and Grant, 1992; Grant and Colombo, 1993; Stolerman et al., 2011). That is, at higher doses of alcohol (e.g., ≥ 1.5 g/kg), $GABA_A$ agonists substitute to a lesser degree than NMDA receptor antagonists (MK-801, CGP-40116, and L-701,324) that show full substitution for alcohol at 2 g/kg (Kotlinska and Liljequist, 1997). Again, because alcohol (2 g/kg) diminishes NMDA receptor function, it seems likely that the ability of alcohol to reduce NMDA receptor function gives rise to its interoceptive stimulus effects at this dose (Lovinger et al., 1989).

Data suggest that only specific types of NMDA receptor antagonists are capable of substituting for alcohol. Both MK-801 (non-competitive) and the competitive antagonist CGP-37849 partially substituted for a 1 g/kg alcohol training dose, but a stereoisomer of CGP-37849, CGP-40116 completely substituted for alcohol (Bienkowski et al., 1996). One study that compared different types of NMDA receptor antagonists that bind to different allosteric sites showed that both the glycine-sensitive antagonist L-701,324 and the non-competitive antagonist MK-801 substitute for alcohol, but the polyamine receptor antagonist eliprodil failed to substitute for alcohol (Kotlinska and Liljequist, 1997). Together these data suggest that the interoceptive stimulus effects of alcohol are mediated by some NMDA

receptor antagonists that act on specific allosteric sites. Other studies have demonstrated substitution for alcohol with the competitive NMDA receptor antagonists (Bienkowski et al., 1996). Together, these findings show that some, but not all NMDA receptor antagonists are capable of substituting for the interoceptive effects of alcohol. Similar to preclinical findings, a role for NMDA receptor inhibition in alcohol interoceptive processing has also been identified in humans. For example, detoxified individuals meeting criteria for alcohol dependence reported dose-dependent "alcohol-like" effects following ketamine infusion (Krystal et al., 1998b). Individuals rated these effects as more like the sedative, rather than the stimulant effects of alcohol and because ketamine is an NMDA receptor antagonist (Krystal et al., 1998a). These findings suggest NMDA receptor antagonism is part of alcohol interoceptive effects, consistent with the preclinical literature (Allen et al., 2018; Barry, 1991; Grant, 1994; Grant and Colombo, 1993; Hodge et al., 2006; Kostowski and Bienkowski, 1999; Stolerman et al., 2011).

In addition to GABA and NMDA receptor involvement, serotonin receptors have also been implicated in alcohol interoceptive sensitivity as the 5-HT1B/2C agonist TFMPP was shown to fully substitute for 1 g/kg alcohol (Grant et al., 1997b; Signs and Schechter, 1988). Follow-up studies showed that both 5-$HT_{1B/2C}$ receptor agonists CGS 12066B and mCPP substituted for rats trained at 1 g/kg but not for rats trained at 1.5 or 2.0 g/kg. Furthermore, the 5-$HT_{1A/1B}$ agonist RU 24969 substituted for 1.0, 1.5 and 2.0 g/kg alcohol training doses, but to a lesser extent at 2.0 g/kg. Finally, the 5-HT_{1A} agonist 8-OH DPAT failed to substitute for all training doses of alcohol. Therefore, the authors concluded that substitution for alcohol with serotonin receptor agonists is specific to 5-HT_{1B} receptors and only substitutes for low (1 g/kg) training doses of alcohol (Grant et al., 1997a). Together, these data support a role for neuronal inhibition as a cumulative effect of several receptor systems in the interoceptive effects of alcohol; however, the precise mechanism(s) by which alcohol interacts with brain neurochemistry to give rise to its interoceptive effects are not well understood.

Brain circuitry of alcohol interoceptive effects

The specific brain regions that modulate the expression of alcohol interoceptive effects have also been evaluated with drug discrimination procedures. Consistent with systemic substitution, these studies show a role for GABAergic and glutamatergic involvement in specific brain regions. Studies investigating the anatomical substrates involved in alcohol interoceptive effects have used expression of c-Fos as a proxy measure for neuronal activation in animals trained to discriminate the interoceptive effects of alcohol. In one such study, comparisons were made between an alcohol discrimination trained group (2 g/kg) and an alcohol/behavior-matched control group. This study identified the nucleus accumbens core, the medial septum, and the hippocampus (dentate gyrus and CA3) as important brain regions involved in learning the alcohol discrimination (Besheer et al., 2008). Other studies have shown differential c-Fos response to alcohol vs. water in alcohol discrimination trained animals, potentially implicating corticolimbic circuitry including the nucleus accumbens (core and shell), anterior insular cortex, rhomboid thalamic nucleus, infralimbic cortex, and dentate gyrus (Jaramillo et al., 2016; Randall et al., 2020a). These findings also suggest

differential recruitment of these regions and circuitry depending on the alcohol training dose (Besheer et al., 2008; Jaramillo et al., 2016; Randall et al., 2020a).

We have found that pharmacological inactivation of the mPFC with a baclofen+muscimol cocktail (GABA-A agonist + GABA-B agonist) fully substituted for the interoceptive effects of alcohol (1 g/kg), whereas inactivation of the rhomboid thalamic nucleus produced partial alcohol-like effects (Jaramillo et al., 2016). Interestingly, the same pharmacological inactivation approach in the dentate gyrus disrupted the ability of alcohol to serve as an interoceptive cue, indicating the importance of this region in the expression of the interoceptive effects of a low alcohol dose (0.8 g/kg; Randall et al., 2020a). The NMDAR antagonist MK-801 fully substituted for systemic ethanol when injected into the nucleus accumbens core (AcbC) or the CA1 region of the hippocampus but not when injected into the prelimbic cortex or extended amygdala (Hodge and Cox, 1998), indicating that NMDA antagonism plays an important role in the expression of alcohol interoceptive effects.

In addition to NMDA and $GABA_A$ receptors, metabotropic glutamate receptor-subtype 5 (mGlu5) activity in the accumbens is required for the interoceptive effects of 1 g/kg alcohol (Besheer and Hodge, 2005). Interestingly, this effect may be due to the role of mGlu5 in modulating GABAergic signaling by alcohol (Besheer and Hodge, 2005). Furthermore, mGlu2/3 activation in the amygdala inhibited the discriminative stimulus effects of alcohol (Cannady et al., 2011). Inhibition of ERK(1/2) activity in the amygdala, but not the nucleus accumbens potentiated the stimulus effects of 0.5 g/kg alcohol (Besheer et al., 2012a). These data suggest that the amygdala also plays an important role in alcohol interoceptive sensitivity. Therefore, the interoceptive stimulus effects of alcohol likely involve system-wide adaptations to ethanol, possibly through inhibition of neuronal activity through multiple mechanisms and brain regions.

Studies have also investigated the role of interactions between brain regions in the expression of alcohol interoceptive effects. For example, infusion of MK-801 in the CA1 region of the hippocampus potentiated the ability of MK-801 infused into the AcbC to substitute for alcohol. In contrast, NMDA (which induces agonism of NMDA receptors) injected into the CA1 region of the hippocampus attenuated the ability of MK-801 in the AcbC to substitute for alcohol. The $GABA_A$ agonist muscimol fully substituted for alcohol when administered in the AcbC or the extended amygdala, and co-injection with MK-801 potentiated the substitution effects of muscimol in the AcbC (Hodge and Cox, 1998). Further, concurrent infusion of the $GABA_A$ antagonist bicuculline in the amygdala shifted the muscimol substitution curve in the AcbC to the right. This data pattern indicated a reduction in potency of muscimol to produce alcohol-like effects and suggests the regulation of $GABA_A$ receptor activation in the AcbC by $GABA_A$ receptor activity in the amygdala (Besheer et al., 2003). Together these studies highlight the importance of NMDA and $GABA_A$ signaling in specific brain regions and that crosstalk between brain regions can modulate the interoceptive stimulus effects of alcohol.

As discussed above, pharmacological inactivation (with GABAergic compounds) of the AcbC and many brain regions that project to the AcbC – the prelimbic cortex, insular cortex and thalamus - substitute to some extent for the interoceptive stimulus effects of

alcohol (Jaramillo et al., 2016), reflecting involvement of cortical and thalamic regions in the interoceptive effects of alcohol. Further investigation of circuit manipulations showed that chemogenetic silencing of the IC➔AcbC projections potentiated and produced "alcohol-like" effects (Jaramillo et al., 2018b). Further, in a follow up study investigating the interaction between sensitivity to the interoceptive effects of alcohol and alcohol self-administration, we found that silencing of this IC➔AcbC circuit decreased alcohol self-administration under baseline conditions (Jaramillo et al., 2018b) and potentiated a reduction in self-administration following pre-session treatment with alcohol (showing titration of alcohol drinking in relation to the interoceptive effects) (Jaramillo et al., 2018c). Together, these findings implicate a role for the IC➔AcbC projections as a site of action of alcohol, and we hypothesized that alcohol may reduce IC➔AcbC activity, potentiating the interoceptive effects of alcohol which then in turn affects alcohol self-administration/drinking. However, it is possible that there is a change in the motivation to drink alcohol that is unrelated to the interoceptive effects of alcohol. It is difficult to directly assess the independent contributions of these factors as drinking and interoceptive effects are quantified in separate behavioral procedures. However, we argue that it logically follows that the interoceptive effects of alcohol are an important factor influencing drinking/self-administration and thus should be considered when interpreting changes in drinking/self-administration patterns. Chemogenetic studies have also identified a role for mPFC➔Acb projections in the expression of a compound alcohol+nicotine interoceptive cue. That is, silencing of this circuit decreased sensitivity to the compound interoceptive cue, such that behavior was no longer under the control of the cue. Interestingly, silencing of this circuit potentiated the interoceptive effects of the alcohol component of the compound cue, suggesting a disruption in the balance of the contributions of the nicotine and alcohol components (Randall et al., 2020b). This also further supports a role of suppression of corticolimbic excitatory circuitry may ultimately underlie the interoceptive stimulus effects of alcohol. In addition to CNS mechanisms, the interoceptive effects of alcohol likely also involve peripheral circuitry as previously discussed in the review of the clinical literature. However, to date, this has been under investigated in preclinical models.

Stress and alcohol history modulation of alcohol interoceptive effects: data from clinical and preclinical studies

Interoceptive states distinct from that of the alcohol stimulus, such as those experienced under stress, should also be considered as factors that can impact interoceptive sensitivity to alcohol. The stress response involves a complex cascade of neural and endocrine pathways in response to a potentially harmful stimulus, altering the body state and subsequently interoceptive perception (Schulz and Vögele, 2015). Social drinkers exposed to an acute social stressor prior to alcohol consumption report blunted subjective response to alcohol on ratings of "cheerful", "focused", and "outgoing" (de Wit et al., 2003) and those that report mostly stimulant-like effects from alcohol also report blunted subjective stimulant effects of intravenously administered alcohol (Childs et al., 2011). In preclinical studies the interoceptive effects of alcohol are not altered by an acute stress exposure via restraint (Koros et al., 1999) or foot shock (Bowen et al., 1999a). However, seven days of continuous exposure to corticosterone, the primary output hormone of the stress

responsive hypothalamic-pituitary-adrenal axis, in the home cage drinking water (300 ug/mL) diminished the interoceptive stimulus effects of 1 g/kg (i.g.) alcohol in rats (Besheer et al., 2012c). This attenuated sensitivity to alcohol was restored through systemic activation of mGlu2/3 receptors (Jaramillo et al., 2015) and positive allosteric modulation of mGlu5 in the nucleus accumbens (Besheer et al., 2014), further implicating the importance of glutamatergic signaling in the nucleus accumbens. Together, these data suggest that stress adaptations can attenuate interoceptive sensitivity to alcohol, potentially through glutamatergic adaptations of stress that interact with the ability of alcohol to suppress neuronal activity (Grant and Colombo, 1993; Sanger, 1993).

In addition to stress, alcohol history has been shown to modulate the interoceptive effects of alcohol. Specifically, chronic alcohol vapor exposure shifts the stimulus-response function of alcohol to the right (indicative of reduced sensitivity) in mice and rats previously trained to discriminate alcohol from water in drug discrimination procedures (Crissman et al., 2004; Emmett-Oglesby, 1990; Hodge et al., 2006; Middaugh et al., 2003). Furthermore, the degree to which interoceptive sensitivity to alcohol is attenuated scales as a function of the number and duration of alcohol-vapor exposure (Becker and Baros, 2006). The attenuated interoceptive sensitivity to alcohol observed in animal models with a history of alcohol exposure may result in the animals increasing alcohol intake to achieve the desired interoceptive state as is typically seen with the development of tolerance (Veale and Myers, 1969).

Interestingly, in humans, Silverstein et al. (1974) found that while participants with AUD learned to accurately estimate their BALs, this depended heavily on external feedback in the training setting (e.g., visual feedback or verbal reinforcement from experimenter). That is, in the absence of external feedback, the subjects did not moderate their drinking based on the target BAL. Further work on this topic found that moderate alcohol drinkers were able to accurately estimate BAL after removal of external feedback, suggesting that they were effectively using internal cues (Huber et al., 1976). These findings raised the importance of drinking history as a factor that may make a BAL discrimination strategy relying on internal cues less effective in alcohol dependent individuals in the Silverstein et al (1974) study, who have experienced a variety of internal cues associated with a range of blood alcohol levels as a consequence of tolerance and experience. Indeed, alcohol history has been found to modulate interoceptive perception as interoceptive awareness of heartbeat perception was blunted in individuals with an AUD who abstained from drinking for at least 2 weeks as compared to controls. Furthermore, the reduction in interoceptive awareness was inversely correlated with enhanced alcohol craving (as measured by Penn Alcohol Craving Scale) in the AUD group (Çöl et al., 2016). Together, these studies highlight the potential impact of alcohol history on sensitivity to interoceptive processes.

Sex as a biological variable in interoception research

Sex differences in the rates of AUD and alcohol consumption are well-documented (Erol and Karpyak, 2015; Schulte et al., 2009; White et al., 2015), demonstrating the need to investigate sex differences in the interoceptive stimulus effects of alcohol, as well as how interoceptive states affect alcohol-related behaviors between sexes. Clinical studies

show that acquisition of alcohol discrimination procedures does not vary between men and women, and alcohol-like stimulus effects of lorazepam did not differ between sexes (Duka et al., 1998; Jackson et al., 2005). Historically, in preclinical research examination of sex differences in sensitivity to the interoceptive effects of drugs of abuse has been lacking (Bevins and Charntikov, 2015), though more studies are emerging (Andrade, 2020; Charntikov et al., 2017; Herr and Baker, 2020; Huynh et al., 2020; Troisi II, 2018; Wiley et al., 2021). In our lab, we have recently shown no sex differences in the acquisition of alcohol discrimination (Randall et al., 2020a), corroborating clinical findings. Future work focusing on sex differences will help broaden our understanding of the brain circuits and mechanisms that underlie interoceptive sensitivity to alcohol, interoceptive processing in general, and interoceptive awareness to alcohol.

Emerging treatments

Both behavioral treatments and medications are potential options for use in treating AUD. While research is ongoing to develop novel pharmacological treatments, it is important to consider AUD as a multi-network brain disorder which may be difficult to address using targeted pharmacological manipulations alone. Interventions where patients are encouraged to become more aware of their interoceptive state, or manipulation of brain regions that are known to regulate interoceptive perception, may represent new treatment angles that alter interoceptive states that can contribute to alcohol use disorder. Mindfulness-based treatments, which involve attending to internal/interoceptive experiences and providing a means for patients to evaluate and modify their internal state (Baer, 2003), have been shown to modulate activity in the insular cortex (Gibson, 2019; Santarnecchi et al., 2014). It has also shown some promise as adjunctive treatment resulting in reducing relapse risk, craving, and amount of substance use (for review see Sancho et al. 2018). In smokers, mindfulness training has been shown to result in reductions in smoking likely via reductions in stress reactivity, suggesting that mindfulness involves modulation of relevant brain networks involved in compulsive drug use (Kober et al., 2017). Thus, having patients focus and consciously modulate the internal state through mindfulness training may be a beneficial adjunctive treatment option.

In addition to behavioral treatments, there has been a growing interest in neuromodulation as a treatment option, particularly using methods that are non-invasive. Biofeedback, where information on body or brain activity is provided to a patient in real time, is a non-invasive treatment approach that allows patients to actively train their mind and/or body state, potentially reducing activity related to drugs and craving (Dehghani-Arani et al., 2013; Luigjes et al., 2019). Heart rate variability biofeedback involves the patient attending to the respiratory cycle and heart rate, ultimately modulating the baroreflex which controls vascular tone and blood pressure via involvement of the both the sympathetic and parasympathetic branches of the autonomic nervous system and the vagus nerve (Benarroch, 2008). Patients are able to visualize heart rate deviations on a computer screen and are instructed to breathe at a slow and steady rate that maximizes HRV (termed resonance breathing; (Pagaduan et al., 2019), displayed as positive feedback on the screen (Siepmann et al., 2008). This procedure has been found to reduce negative affect in affective disorders such as major depression and PTSD (Siepmann et al., 2008; Tan et al., 2011), demonstrating

that conscious modulation of the body state can alter affective state. It has also shown promise as an adjunct for inpatient substance use disorder treatment (Eddie et al., 2014) and specifically in subjects with alcohol dependence (Penzlin et al., 2015). Further, a recent study demonstrated a positive relationship between baroreflex function as measured by 0.1 Hz HRV and metacognitive interoception as well as increased interoceptive accuracy during resonance breathing, which may suggest that resonance breathing increases conscious perception of interoceptive information (Leganes-Fonteneau et al., 2021b). There has also been some success with electroencephalogram (EEG) biofeedback, where patients actively modulate their brain state via visual feedback, showing that in some studies patients have had better success remaining abstinent after engaging in a training regimen involving guided imagery related to abstinence (Luigjes et al., 2019; Scott et al., 2005). However, as there are a variety of technical approaches, a general lack of long-term studies, and inconsistency of outcome measurements it is at present difficult to draw strong conclusions (Luigjes et al., 2019). Regardless, there is interest in use of this technology as a means of decreasing drug-related attentional bias and increasing inhibitory control as a supplement to traditional therapeutic treatments (see Billieux and Maurage, 2021).

Transcranial magnetic stimulation (TMS), a clinically approved and growing treatment method for major depressive disorder that uses magnetic fields to drive neuronal activity in targeted brain regions has historically targeted prefrontal areas (Lefaucheur et al., 2014; McClintock et al., 2017) which are also involved in AUD. Notably, TMS has been found to be able to modulate interoceptive accuracy and perception confidence in both directions depending on the specific parameters used (Pollatos et al., 2016). There is considerable interest in determining both potential targets and methodological approaches for treating substance use disorders, including modulation of brain regions involved in drug craving itself. The ACC and medial PFC are activated in response to alcohol, nicotine, and cocaine drug cues (Hanlon et al., 2018a) suggesting a common mechanism in addiction. However, stimulation of the dorsolateral prefrontal cortex has yielded inconsistent results when it comes to drug craving, as some studies have found reductions in drug craving in response to cues (Amiaz et al., 2009) while others have not (Eichhammer et al., 2003). Recent studies have targeted other brain regions such as the ACC, insula, and thalamus (Hanlon et al., 2018b), and the field is growing with effort being invested into developing consensus approaches, refining individualized approaches, and endpoints that will aid future studies for treating both addiction (Ekhtiari et al., 2019; Lefaucheur et al., 2020) and other mental health disorders (Modak and Fitzgerald, 2021; Sonmez et al., 2019). Use of biofeedback and neuromodulation as treatment tools for addiction are still in their early stages, but as methods become refined and standardized and studies continue to show feasibility and promise (Subramanian et al., 2021), these approaches may be a critical piece in advancing both our understanding and treatment of substance use disorders.

Conclusion

Maximizing the advantages of both clinical and preclinical studies will be critical in developing a more thorough understanding of how interoceptive processes contribute to AUD and other drug use disorders. Preclinical studies have elucidated many important mechanisms that contribute to the interoceptive sensitivity to alcohol, and it is important

to consider that the interoceptive effects of alcohol likely are a system-wide/whole brain mechanism. The importance of understanding the interoceptive mechanisms of alcohol lie in its ability to inform therapeutic options for individuals with AUD or those susceptible to the development of AUD. Additionally, negative interoceptive states distinct from alcohol, such as anxiety, have the potential to drive motivation to consume alcohol, demonstrating the importance of studying interoceptive mechanisms that influence alcohol intake and other alcohol-related behaviors. Furthermore, continued drug use can alter interoceptive processing, which is a contributing factor in the maintenance of AUD.

Clinical imaging and connectivity studies have demonstrated that the insular cortex is a critical fulcrum in translating interoception into action, participating in and coordinating transitions between brain networks that ultimately influence and guide motivated behavior. Preclinical animal models have utilized pharmacological and chemogenetic approaches to determine the roles of specific receptor systems and circuits, similarly focusing on corticolimbic connections. However, as is demonstrated across a breadth of literature, brain regions involved in not just sensory information but salience of cues, emotional valence, inhibitory control, and reward all likely play an important role in determining behavioral outcomes. As the study of the role of interoception in drug use disorders matures it will be increasingly important to marry the information provided by clinical and preclinical studies. Given the complexity of information being processed and involvement of multiple brain networks, confidently identifying the role of a given brain region, projection, or network is no small order. An overarching network-based framework can provide context for how focused manipulations modulate interoceptive processing as a whole. Some approaches, such as measurement of physiological responses that correlate with interoceptive changes, may translate well with model organisms. In turn, preclinical studies can systematically determine the roles of individual brain regions and their molecular underpinnings in a given network, potentially suggesting new therapeutic directions. Some preclinical studies have already begun to take this approach, utilizing chemogenetic and rodent fMRI experiments that seek to inform circuit-based neuromodulatory approaches that have shown promise in humans (Haaranen et al., 2020). Studies focused on determining the biological underpinnings of this disconnect will help bridge animal model work with observations from clinicians and may represent a critical path forward for the field towards addressing therapeutics for the treatment of AUD.

Acknowledgements.

Supported by AA011605, AA024095, AA026537, AA025582 (JB). The authors would like to thank Sarah Magee for her contributions to discussions related to this review. The authors have no conflicts of interest to disclose.

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Highlights

- Interoception is a critical contributor to alcohol use disorder
- Alcohol alters peripheral interoceptive information and abilities
- Interoception underlies motivated behavior
- The insular cortex and salience network are important neural underpinnings
- Drug discrimination tasks are powerful tools for exploring interoceptive mechanisms