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## Alcohol use and interoception – a narrative review

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### Abstract

Interoception, defined as the ability to perceive and interpret body signals, may play an important role in alcohol use disorder (AUD). Earlier studies suggested an association between interoception impairment and known risk factors for AUD (e.g., alexithymia, emotion dysregulation, impulsivity, pain). Neurobiological studies show that the neurotoxicity of alcohol affects various elements of the interoceptive system (especially the insula) at structural and functional levels, with differential short/long term impacts. Conversely, primary interoceptive impairments may promote alcohol consumption and foster the evolution towards addiction. Despite convincing evidence demonstrating that interoception impairment may be an important contributor to the development and course of AUD, only a few studies directly evaluated interoceptive abilities in AUD. The research shows that interoceptive accuracy, the objective component of interoception, is lower in AUD individuals, and is correlated with craving and emotion dysregulation. Interoceptive sensibility is in turn higher in AUD individuals compared to healthy controls. Moreover, there is evidence that therapy focused on improving the ability to sense signals from the body in addiction treatment is effective. However, important methodological limitations in interoceptive measures persist, and it is therefore necessary to further investigate the associations between interoception and AUD.

### Keywords

interoception; interoceptive system; alcohol use disorder; addiction

## 1. INTRODUCTION

Interoception is conceptualized as a combination of processes that reflect the perception of body signals, their processing by the central nervous system, and the development of

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associated mental representations (Craig, 2002; Critchley and Garfinkel, 2017). Deficits in interoception have been well documented in a broad range of psychiatric disorders (Khalsa et al., 2018; Murphy et al., 2017) with some studies notably suggesting the presence of interoception impairments in addictive disorders.

The aim of this review is to present neurobiological and psychological findings indicating the significance of interoceptive processes among problematic alcohol users. This review is organized in two sections: (1) a summary of the current understanding of interoception and of its relevance for psychology and health, with particular emphasis on addictive behaviors (especially alcohol use disorder [AUD] and its risk factors); (2) an overview of the knowledge about the effects of alcohol on various functional elements of the interoceptive system (primarily the insula) and a summary of the existing research on the different domains of interoception among individuals with AUD. The manuscript extends ideas already suggested in previous literature reviews (Herman and Duka, 2019, 2020), with a special focus on severe AUD (while previous reviews mostly focused on subclinical patterns of excessive alcohol consumption).

## PART 1.

### 2. INTEROCEPTION AND RELATED IMPAIRMENTS

**2.1. The concept of interoception**—The view of interoception has changed significantly since 1906, when Sherrington first used this concept by focusing solely on the biological aspects of receiving signals from the body (Sherrington, 1906). More recently, a broader view of this phenomenon emerged following strong evidence indicating the involvement of interoception in psychological processes associated with behavioral regulation (for a review see Ceunen et al., 2016). The link between signals arising from the body and emotional feelings has its origin in the nineteenth century theory of emotions formulated independently by James and Lange (Lang, 1994). They postulated that the experience of emotions is preceded by physiological arousal. In recent years, researchers have studied the role of interoception in the relationship between body and mind. Consequently, the importance of interoception is now recognized in emotion (Critchley and Garfinkel, 2017), cognition (Hafner, 2013; Tsakiris and Critchley, 2016), and self-awareness (embodiment theories; Seth and Friston, 2016). Recent theories suggest a more complex conceptualization of interoception, in which it is defined as the process of *bidirectional* interactions between the brain and other organs that enable sensing, integration, and regulation of internal states (see Chen et al., 2021 for review).

Three basic domains of interoception have been identified in humans: (1) interoceptive accuracy (also known as interoceptive sensitivity) reflects the objective component of interoception; (2) interoceptive sensibility reflects the subjective component, and (3) interoceptive awareness reflects metacognitive confidence in detecting signals from the body (Garfinkel et al. 2015). Importantly, research on anxiety disorders (Domschke et al., 2010) and AUD (Jakubczyk et al., 2019) demonstrates that interoceptive accuracy (sensitivity) is independent of interoceptive sensibility. While interoceptive sensibility is assessed via self-report measures, interoceptive accuracy requires behavioral testing. Given the multimodal nature of interoception and the fact that interoceptive signals likely emerge

from different areas of the body, studies distinguish several modalities of interoception, such as cardiac, gastric, and respiratory. While self-report measures can investigate several modalities simultaneously, behavioral tests examine only one at a time. Cardioception is by far the most studied modality in interoception research, with the most widely used behavioral test being the heartbeat counting task (Schandry Test; Schandry, 1981). The task requires participants to assess their cardiac rhythm (i.e., number of heartbeats) during specific time intervals without relying on external cues. In recent years, however, there has been a discussion regarding the use of heartbeat counting in interoception research, as an increasing number of methodological shortcomings have been noted (see Zamariola et al., 2018 for more details). Despite these limitations the Schandry Test remains the most widely used measure in interoception research (see Zimprich et al., 2020). Nevertheless, given the multidimensional nature of interoception, it is important to note that other behavioral tests have been developed to assess other modalities within the cardiac domain (e.g., Heartbeat Detection Task), as well as the gastric (e.g., Water Load Test and its modifications), respiratory (e.g., Respiratory Detection Task, Respiratory Discrimination Task), and tactile (Soft Touch Task) domains. Yet, these behavioral tests are rarely used, particularly within AUD samples. Given the increased attention on multimodal approaches in the assessment of interoceptive accuracy, future work in this area, especially as it relates to the development of alternative interoception measures (e.g., Van Den Houtte et al. 2021), will significantly advance the field.

## **2.2. Neurobiology of interoception – the interoceptive system—**

Neurobiological knowledge on interoception has expanded recently. Craig (2002) presented a detailed description of the interoceptive pathway, recognizing it as the missing sympathetic afferent pathway of the autonomic nervous system. Commonly found in almost all tissues, small diameter fibers (A- and C-fibers), which are free endings of axons, collect information about the current physiological condition of the body and transmit it to the neurons of the most superficial layer of the spinal dorsal horn (lamina I). In turn, these neurons project to the basal and posterior parts of the ventral medial nucleus of the thalamus. The information is subsequently transmitted to the posterior insular cortex, where the interoceptive representation of the physiological state of the body is built. The re-representation of this region in the right anterior insula is crucial for the subjective awareness of emotion. The insular cortex presents structural and functional specificities. The posterior part of the insula encodes the primary physiological states of the body (homeostatic or allostatic states), while its anterior part is responsible for encoding cognitively and emotionally processed bodily states (Craig, 2009). Previous research has recognized the high importance of the insula in sensorimotor, emotional and cognitive processes, as well as in multi-dimensional models reflecting a combination of these processes, especially with regard to pain or decision making (Uddin et al., 2018). The anatomical basis of interoception is completed by the long-known parasympathetic pathway with its afferents projecting to the anterior insula via the nucleus of the solitary tract in the brainstem. The parasympathetic activity is then re-represented, in contrast to the sympathetic pathway, in the left anterior insula (Craig, 2002, 2003, 2009). Subsequently, the interoceptive signal is transmitted to higher cortical centers of the brain, where integration of internal signals with exteroceptive, cognitive, and emotional information take place (for a review see Chen et al., 2021).

As a whole, efficient interoceptive processes rely on a network of subcortical and cortical areas, below (e.g., the thalamus) and beyond (i.e., anterior cingulate cortex, orbitofrontal and medial prefrontal cortices, but also primary and secondary somatosensory cortex) the insula. Nevertheless, the central role played by the insula in interoception has been largely documented, in healthy populations (e.g., Chen et al., 2021) as well as in clinical samples (e.g., Paulus and Stein, 2010). Accordingly, the insula is widely considered a hub for interoception with insular dysfunction believed to be at the heart of interoceptive deficits among individuals with substance use disorders (e.g., Verdejo-Garcia et al., 2012). In view of this key role, the insula will be the central brain structure considered in the present review, keeping in mind that, as previously, it is part of a larger interoceptive brain network.

**2.3. Interoception and psychopathology related to AUD**—James and Lange hypothesized that emotional stimulus causes various physiological changes in the body that can affect the emotional experience (Lang, 1994). Damasio later stated that these physiological changes must have their neural representations and that “somatic markers” play an important role in generating and carrying emotional states, further affecting cognition and behavior (Damasio et al., 1994). Contemporary embodiment theories refined these views even further by recognizing that conscious experience of emotions requires operating on perceptual symbols (i.e., (re-)representations of the somato-motor and visceral states) that are activated when experiencing a particular emotional feeling or even when thinking about emotions (Niedenthal, 2007). Given that the interoceptive system is paramount in both experiencing the current physiological state of the body and creating its mental representation, which are critical for conscious emotional feelings and emotion regulation, it plays a key role in influencing behavior.

These observations may be important in the context of AUDs. Based on the James-Lang theory of emotions and Damasio’s somatic marker hypothesis, as well as research on addiction in general, it follows that the disturbances in interoceptive processes may be significant in the context of emotional, cognitive, and behavioral alterations associated with alcohol use. Namely, prior work indicates that interoception plays an important role in psychopathological phenomena that are risk factors for AUD such as alexithymia (Murphy et al., 2017), emotional dysregulation (Füstös et al., 2013), impulsivity (Herman and Duka, 2019) and pain (Solca et al., 2020) (Figure 1).

**2.3.1. Alexithymia:** *Alexithymia* is defined as an impairment of recognition and description of one’s own emotional states at the affective and cognitive levels (Taylor et al., 1997). More recent research proposes a broader definition of alexithymia as it can also apply to non-affective interoceptive states (Brewer et al., 2016). Current theoretical models of alexithymia associate difficulties in identifying emotions with reduced interoceptive abilities (Murphy et al., 2017), while psychological and neurobiological empirical studies support a mutual association between these constructs underscoring the link between bodily and emotional awareness. Still, more recent studies suggest that these associations are complex and nonlinear (Aaron et al., 2020). Among findings that offer conflicting evidence regarding the association between alexithymia and interoception (Aaron et al., 2020; Bornemann and Singer, 2017; Brewer et al., 2016; Herbert et al., 2011; Longarzo et

al., 2015; Shah et al., 2016; Zamariola et al., 2018), one meta-analysis concluded that lower interoceptive sensibility is associated with problems in identifying emotions, and that this association is stronger among individuals with co-occurring psychiatric disorders than in healthy participants (Trevisan et al., 2019). These findings suggest that inconsistent results across prior studies may be largely due to differences in assessments. Namely, because alexithymia is only measured via self-report, the association is stronger with self-reported interoceptive sensibility than with the experimentally measured interoceptive accuracy. At the neurobiological level, there are common elements between interoception and alexithymia. New data recently revealed that high alexithymia might be a consequence of a multi-domain failure of interoception related to functional, structural, and neurochemical integrity of the anterior insular cortex (Bird et al., 2010; Murphy et al., 2018). A meta-analytical study on brain's structural abnormalities associated with alexithymia showed smaller grey matter volume of the insula (especially the anterior insula) among participants with alexithymia (Xu et al., 2018). The abnormal function of the insula was also confirmed in meta-analytic neuroimaging studies among individuals with alexithymia (van der Velde et al., 2013).

**2.3.2. Emotion dysregulation:** Interoception is not only a significant prerequisite for emotion identification but also for proper *emotion regulation*. Since body-relevant signals provide information about the organism's arousal, it has been proposed that interoception is crucial for the processing of emotional states and their regulation (Füstös et al., 2013). Greater accuracy in sensing one's bodily state may facilitate the regulation of emotional responses, as ongoing bodily changes can be detected more accurately (Craig, 2002). Greater interoceptive accuracy was found to be a positive precondition for effective self-regulation of emotionally driven behavior in healthy individuals (Füstös et al., 2013). According to Gross, emotion regulation is an adaptive ability to modulate the experience of emotion in order to achieve a specific goal in a specific context (Gross, 1999). Psychological and neurobiological studies indicate that interoception is an important contributor to the process of emotion regulation. The ability to recognize physiological states of the body allows for better emotion regulation accompanying everyday events (Zamariola et al., 2019). Interoceptive accuracy is positively correlated with emotion regulation strategies (cognitive reappraisal and expressive suppression), and individuals with higher interoceptive accuracy are more accurate in matching an effective emotion regulation strategy to a specific context (Kever et al., 2015). For example, they are more likely to choose a cognitive reappraisal strategy (Füstös et al., 2013), which is considered to be more adaptive than available alternatives to regulate emotion (Cutuli, 2014). At the neurobiological level, the important function of the insula in the process of emotion regulation has been established. A recent meta-analysis examining neural activity when adopting different emotion regulation strategies concluded that the insula is one of the three brain regions (along with the ventrolateral prefrontal cortex and the supplementary motor area) that is active across multiple regulation strategies (e.g., cognitive reappraisal, expressive suppression, distraction, detachment; Morawetz et al., 2017). Upon further analysis, it was proposed that the anterior insula controls the activity of other brain regions by acting as an "outflow hub", initiating and adjusting cognitive control mechanisms involved in emotion regulation (Morawetz et al., 2017). Recent research indicates that different parts of the insula may have different

functions in emotion regulation. Primary emotional states activate the posterior part of the insula. As the emotional state is regulated based on additional cognitive information, the frontal parts of the insula become more involved in the process (Zhang et al., 2020).

**2.3.3. Impulsivity:** *Impulsivity*, a multi-dimensional concept, is another risk factor for AUD that is associated with emotional and interoceptive processing. Research distinguishes impulsivity as a personality trait (measured by self-report measures) that increases risk for rapid and unplanned behaviors without considering possible negative consequences (Moeller et al., 2001) from its behavioral representation reflected in the decision-making process: (1) reflection impulsivity (“too fast decision”), (2) motor impulsivity (“too fast action”) and (3) temporal impulsivity (“too long for gratification”) (Herman et Duka, 2019). Due to the multimodal nature of impulsivity, many theories based on neurobiological findings regarding key neural circuits have been proposed. However, it should be noted that in most of these studies a large role is assigned to the central part of the interoceptive system - the insula. Neuroimaging studies confirm the significant role of the insula in motor impulsivity (Dambacher et al., 2015), temporal impulsivity (Frost and McNaughton, 2017), and reflection impulsivity (Furl and Averbeck, 2011). Interestingly, a strong association between the structure of the insula and impulsivity has also been demonstrated in animal studies (Belin-Rauscent et al., 2016). Therefore, it is likely that circuits involved in interoception and impulsivity overlap. Psychological studies investigating the association between impulsivity and interoception indicate that high impulsivity is associated with interoceptive impairment (Herman et al., 2019).

**2.3.4. Pain:** According to Craig’s research, *pain* is an interoceptive feeling that is processed via interoceptive pathways (Craig, 2002), as well as a homeostatic emotion that may motivate behavior (Craig, 2003). Experimental neurobiological research confirms the overlap between brain regions associated with pain and those related to interoception (Bushnell et al., 2002). There is behavioral evidence for impaired interoceptive processing among individuals experiencing chronic pain. Data show that individuals with chronic pain are characterized by decreased interoceptive accuracy (Solca et al., 2020) that correlates negatively with pain severity (Di Lernia et al., 2016). In addition, the positive correlation between interoceptive accuracy and pain sensitivity has been shown among healthy individuals (Pollatos et al., 2012; Weiss et al., 2014). Pain-related negative affectivity may impair interoceptive accuracy, suggesting that the affective aspects of pain influence the perception of internal bodily signals (Borg et al., 2018). Indeed, recent studies highlight the association between pain and emotions at neurobiological and psychological levels (Lumley et al., 2011), suggesting that pain is a more complex construct than just nociception (Gilam et al., 2020).

## PART 2.

### 3. INTEROCEPTION AND ALCOHOL

**3.1. Theoretical accounts**—In recent years, several theories have emerged, indicating the importance of interoceptive signals in addictive behaviors (including those related to AUD). In the context of interoception, three of them seem particularly relevant.

Paulus and colleagues (2009) introduced a model supporting the critical role of the central part of the interoceptive system – the insula – has in addiction. They posit that addiction represents an internal dysregulation caused by a body prediction error alteration (the disparity between anticipated and current interoceptive states) that leads to a disturbance in interoceptive regulatory mechanisms. In this model, drugs of abuse disturb homeostasis through numerous internal body changes. Long-term repeated allostatic dysregulation caused by drugs affect internal states centrally generated in the insula. The abnormal function of the insula leads to maladaptive adjustment of the body prediction error and results in an unstable aversive state of the organism. As a consequence, these changes tend to favor addictive behaviors (Paulus et al., 2009).

The model of allostatic dysregulation proposed by Koob and colleagues is of particular interest in terms of the potential contribution of interoception. In this model, allostatic dysregulation caused by repeated drug use (initially driven by pleasure) leads to the emergence of negative affect (withdrawal symptoms) and consequently converts the use of drugs from an impulsive to a compulsive mode of action (negative reinforcement) (Koob, 2017). The researchers identified three stages of addiction: (1) the binge/intoxication stage, (2) the withdrawal/negative affect stage, and (3) the preoccupation/anticipation stage. They indicate the role of the insula and its connections at every stage (Koob and Volkow, 2016). The peripheral part of the interoceptive system may be of great importance in primary homeostatic dysregulation by establishing new allostatic set points in this model.

The triadic neurocognitive model of addiction presented by Noël and colleagues assumes the impaired functioning of three interrelated neural systems: (1) the impulsive system – amygdala-striatum dependent neural circuits responsible for automatic salient behaviors (traditional reward system), (2) the reflective system – prefrontal cortex dependent system responsible for predicting consequences of a behavior, and (3) the insular cortex – responsible for mental representation of interoceptive states. The authors emphasize the importance of the insula in a disturbed decision-making process leading to the development and maintenance of addiction. During drug use, the insula sensitizes the impulsive system and inhibits the reflective system by altering interoceptive processing to maintain homeostasis through the reduction of conflicting signals associated with motivation (reward) and withdrawal (Noël et al., 2013).

There are several experimental studies that support theories linking addiction with interoception. Naqvi and Bechara noted the importance of interoceptive signals in addictive behaviors. Through their research, they found the critical role of insular damage on the course of nicotine addiction among stroke survivors. Namely, they observed that the urge to smoke was significantly reduced among those whose insula was damaged as a result of a stroke (Naqvi et al., 2007). The results were then reaffirmed in studies on rats whereby animals in which the function of the insula was disturbed demonstrated reductions in drug use behavior that was previously conditioned (Contreras et al., 2007). Based on these observations along with support from other data, the researchers stated that the insula plays a key role in encoding emotional representations from drug-related interoceptive signals (e.g., the taste of alcohol or the sympathomimetic effects of cocaine), which gain positive value through a learning process. According to their hypothesis, these representations may

contribute to the conscious feeling of drug urges and the ultimate decision to use substances when exposed to external drug cues among individuals engaged in problematic substance use (Naqvi and Bechara, 2009). Many studies indicate the dysfunction of the interoceptive system in addiction-related behaviors at the neurobiological level (Verdejo-Garcia et al., 2012). The research focuses primarily on the important role of the insula in these processes (Naqvi et al., 2014). Neurobiological studies on the role of interoception in substance use populations show structural and functional abnormalities of the insula in individuals with amphetamine (Mackey and Paulus, 2013), cocaine (Jia et al., 2011), and cannabis use disorder (Jacobus et al., 2012). In their meta-analysis, Pando-Naude and colleagues (2021) determined that the insula and other brain regions (i.e., anterior cingulate cortex, thalamus, putamen) evidenced the most structural impairment (lower gray matter volume) among individuals with substance use disorders relative to controls. The changes appeared to be mostly independent from the substance used. There is also evidence for shared functional abnormalities of the insula in individuals with substance use disorders that are more substance specific. Namely, reduced insular cortex activity during decision-making tasks was found among those with a methamphetamine or cannabis use disorder, while reduced insular cortex activity during evaluative tasks was found among those with a methamphetamine, nicotine, and alcohol use disorder in comparison to healthy controls (Drouman et al., 2015). Similarly, a recent meta-analysis of neuroimaging studies in substance use disorders (nicotine, cocaine, cannabis, and alcohol) show substance-specific insular function alterations, but the specific results are beyond the scope of this review (see Klugah-Brown et al., 2020 for more details).

These data show that the interoceptive system may play a crucial role in the development and course of addiction. Unfortunately, only a few studies have assessed the multiple domains of interoception (interoceptive accuracy and/or interoceptive sensibility) among individuals with substance use disorder. Preliminary data exist among cocaine users (de la Fuente et al., 2019), nicotine smokers (Hina and Aspell, 2019), and individuals with AUD (Jakubczyk et al., 2019). Recent studies support these observations and suggest differences in interoceptive processing in individuals with substance use disorders relative to healthy controls, such as impaired flexibility (less perceptual sensitivity to the interoceptive signals' modulations) (Smith et al., 2021; Smith et al., 2020). Therefore, interoceptive processing in individuals with substance use disorders warrants further investigation.

**3.2. Neurobiological basis: alcohol**—The link between problematic alcohol use and interoception should be considered at several levels. First, it is important to distinguish between the effects of alcohol intoxication on the perception of bodily signals (e.g., by disrupting the functioning of brain structures important for interoception) and the long-term effects of alcohol use on the interoceptive system (alcohol consumption leads to deficits). Secondly, apart from the changes related to alcohol, it should be noted that some primary interoceptive impairments (e.g., neurobiological changes and psychological characteristics) may promote alcohol consumption leading to addiction (deficits cause alcohol consumption) (Figure 2).

Acute alcohol administration alters interoception. Individuals differ in their subjective assessment of the interoceptive effects associated with alcohol intoxication (Schuckit,



1994). In this context, a group of individuals with a low level of response to alcohol can be identified. Reduced ability to perceive signals from the body caused by alcohol is associated with an increased risk of addiction in the future (Schuckit, 1994). Although this characteristic relates to a specific type of interoception (i.e., the perception of the effects that alcohol has on one's body), it suggests that alcohol modifies the way the internal milieu is recognized. Indeed, research shows that alcohol intoxication changes activity of the insular cortex, but the direction of these changes is not clearly established. Decreased insular activity following acute alcohol intoxication may impair decision-making (Anderson et al., 2011; Sherman et al., 2019) and emotional processing (Padula et al., 2011). Alcohol intoxication may increase risk-taking behavior by activating brain regions including the insula (Gilman et al., 2012).

Long-term excessive alcohol consumption has a more significant influence on the structure and function of the interoceptive system. Current data show that the various structures identified by Craig as key components of the interoceptive system are impaired in individuals misusing alcohol (e.g., Buhler and Mann, 2011). Most of the data involves the insula and the evidence for other components of the interoceptive system is weaker.

Many studies revealed the influence of alcohol use and misuse on the insula, a common element for both the sympathetic and parasympathetic pathways of the interoceptive system (e.g., Chumin et al., 2019; Xiao et al., 2015; Yang et al., 2016). The most significant changes concern individuals with an alcohol use disorder, but they also affect drinkers who do not meet diagnostic criteria. Two meta-analyses performed recently on studies using voxel-based morphometry to assess grey matter abnormalities among alcohol dependent patients confirmed grey matter atrophy in the bilateral insular cortex and its reduction relative to healthy controls (Xiao et al., 2015, Yang et al., 2016). Mackey and colleagues showed lower thickness of the insular cortex in individuals with substance use disorder (alcohol, nicotine, cocaine, methamphetamine, or cannabis) with the most substantial effect associated with AUD (Mackey et al., 2019). It appears that there are no differences in alcohol-induced insular cortex atrophy/insular volume decrease between males and females (Demirakca et al., 2011; Sawyer et al., 2017; Thayer et al., 2016). The right insula volume might be more prone to the synergistic effects of age and alcohol misuse (Thayer et al., 2016). Grey matter atrophy associated with alcohol dependence is partially reversible with abstinence. The insular grey matter volume (Cardenas et al., 2007) and its connectivity (Mueller and Meyerhoff, 2019) partially recovers during both short-term and long-term abstinence (Zou et al., 2018) with some indicating partial recovery within 2 weeks of abstinence (van Eijk et al., 2013). The negative impact of alcohol on insular morphology may occur at an early age. Excessive alcohol use among adolescents not meeting AUD criteria was linked to structural changes (decreased grey matter volume) in the right insula (Heikkinen et al., 2017), and these changes were more substantial than similar changes caused by cannabis use (Infante et al., 2018). Even young adults who have only experienced hangover symptoms in the past may have similar abnormalities (Hua et al., 2020).

Morphological abnormalities related to the toxic effects of alcohol can also affect white matter of the central interoceptive system. There are abnormalities in the microstructure of white matter and structural connectivity of the right insula among individuals with AUD

(Chumin et al., 2019). Namely, among individuals engaging in heavy alcohol consumption, white matter integrity in frontoparietal and corticolimbic networks is negatively correlated with insular activation (Monnig et al., 2014). The white matter volume of the right insula is positively correlated with craving for alcohol (Chung and Clark, 2014).

Functional neuroimaging studies show that both the structure and the functioning of the interoceptive system may be impaired due to alcohol use. That is, increased functional connectivity of the anterior insula may be involved in the maintenance of drinking behavior among individuals with AUD (Helacomb et al., 2019). Activation of brain regions involved in the brain reward system, including the insula, is related to cue-induced alcohol craving among individuals with AUD (Olbrich et al., 2006). In a study conducted by Strosche and colleagues, abstinent individuals with AUD showed increased functional connectivity of the insula during the presentation of alcohol-related cues and these changes correlated with subjective craving and compulsive use of alcohol (Strosche et al., 2021). Sullivan and colleagues postulated that deficits in the insular blood perfusion in individuals with AUD may impair cognitive control over internal urges (Sullivan et al., 2013). Although, the insular response pattern in neuroimaging studies in individuals with AUD is complex, insular activity increases in response to alcohol-related stimuli and decreases when involved in cognitive processes, which is in line with previous observations in other populations with substance use disorder (Paulus and Stewart, 2014). Prior research also supports the influence of alcohol use on the insular function in individuals who do not meet the criteria for AUD (Vergara et al., 2017). The insula is among the main brain areas of the resting state functional network showing connectivity reduction in alcohol users compared to non-substance using controls (Vergara et al., 2017). Resting state insular connectivity patterns also correlate with AUD severity (Claus et al., 2011).

As mentioned before, some abnormalities in the functioning of the interoceptive system in alcohol-misusing individuals are related to factors that may contribute to the development of addiction (e.g., impulsivity, decision-making impairments). Structural changes of the insula are linked to several behavioral consequences. Volume of the anterior insula was shown to be negatively associated with self-reported impulsivity and compulsivity in individuals with AUD (Gordin et al., 2017). Smaller grey volume of the insula may represent genetically conferred risk factors predisposing individuals to use alcohol (Baranger et al., 2020). Furthermore, a negative correlation between insular grey matter volume and alcohol use severity was demonstrated (Betka et al., 2019), especially in relation to the middle insula (Le et al., 2019). The insula is one of the brain regions which abnormal activation during task performance might contribute to impulsive choice (Claus and Hutchinson, 2012), impaired inhibitory control (Claus et al., 2013) and risk-taking decisions (Li et al., 2009) in individuals with AUD. Maurage and colleagues have linked abnormal insular activation in individuals with AUD with interpersonal problems in this group (Maurage et al., 2012). By assessing insular activity while performing a task where inspiratory breathing load was recorded, Berk and colleagues found that adolescents with AUD may be hypersensitive to aversive interoceptive stimuli (Berk et al., 2015). Abnormal insular activity associated with alcohol withdrawal may underlie impaired emotion processing (increased sensitivity to emotional stress) in individuals with AUD (O'Daly et al., 2012). Similar observations were made in healthy controls. That is, greater activation of the anterior insula and other regions

of the frontostriatal circuitry was associated with compulsive alcohol seeking (Grodin et al., 2018) and decision-making (Ames et al., 2014; MacKillop et al., 2014) in heavy drinkers. Similarly, the bilateral activation of the insula was related to decision-making in binge drinkers (Xiao et al., 2013). In addition, frontoinsula activity was associated with response inhibition and cognitive control impairment in binge drinkers (Courtney et al., 2020). Anterior insular cortex activation was linked to risk taking in hazardous drinking individuals (Claus and Hutchison, 2012).

The alcohol-related insular functional activity abnormalities may play an important role in fostering future problem drinking. Lower connectivity between the left nucleus accumbens and other regions, including the left insula, in young male adults was associated with higher lifetime alcohol consumption (Veer et al., 2019). The differences in brain activity in specific regions including the insula between heavy drinkers and non-heavy drinkers exposed to alcohol-related cues may be useful as a pre-diagnostic marker of maladaptive drinking (Dager et al., 2014; Ihssen et al., 2011). Moreover, the specific insular activation to affective faces (Schuckit et al., 2016) or to appetitive cues (Ray et al., 2010) may be used as a predictor of alcohol misuse in the future. Interestingly, family history of alcohol dependence was linked to structural abnormalities among healthy first-degree relatives including abnormalities concerning the insula. Namely, individuals with a positive family history of AUD had smaller grey matter volume of the insula compared to those without a family history of AUD (Filippi et al., 2019; Hill and Sharma, 2019; Sharma and Hill, 2017).

Animal research confirms the important role of the insula in alcohol-related behaviors (see Torrealba et al., 2017 for a review). For example, studies on rats support the role of the insular cortex in alcohol taking behavior (Pushparaj and Le Foll, 2015), compulsive drinking (Darevsky and Hopf, 2020), and context-induced relapse (Campbell et al., 2019).

Another important part of the interoceptive system described by Craig is the ventral medial nucleus of the thalamus. Thalamic shrinkage caused by alcohol misuse was established in both neuropathological (Belzunegui et al., 1995) and neuroimaging studies (Cardenas et al., 2007; Pitel et al., 2015). Despite a significant degree of research investigating alcohol-induced changes in thalamic function and structure, to the best of our knowledge, none described the impact of alcohol use on the nucleus responsible for interoceptive processing. Likewise, there is no research to date concerning the impact of alcohol use on the parasympathetic nucleus of the solitary tract. In turn, there is evidence of alcohol effects on the peripheral components of the interoceptive system for both the sympathetic and parasympathetic paths. Alcohol-related neuropathy was characterized as large-fiber damage caused by nutritional deficiency (especially thiamine), yet Mellion and colleagues (Mellion et al., 2014) described small fiber polyneuropathy in heavy alcohol drinking individuals with normal thiamine status as well. Julian and colleagues (2019) have recently published a meta-analysis on neuropathy among individuals with AUD. They established that neuropathy associated with chronic alcohol use is heterogenous and may involve both large and small fibers, while small fiber loss is generally predominant.

To our knowledge, no studies have been conducted so far on the direct effects of alcohol-induced sympathetic afferent damage on interoceptive processing. Recent work has

established that vagotomy changes alcohol-related behavior in rats (relapse-like drinking) of a high-alcohol-drinking line (Ibanez et al., 2021), suggesting an important role of the peripheral interoceptive system in alcohol use.

Among AUD-related factors, alcohol neurotoxicity is not unique in impacting interoceptive processing at the neurobiological level. There is also evidence that multiple detoxifications following withdrawal during the course of AUD affect the structure and function of the brain. For example, among individuals with AUD experiencing multiple detoxifications, reduction of gray matter volume in cortical brain regions involved in integrating interoceptive signals (e.g., the ventromedial prefrontal cortex and the superior frontal gyrus) was established (Duka et al., 2011). In addition, neuroimaging studies suggest that repeated detoxifications among participants with AUD were associated with decreased insular connectivity with higher cortical brain regions (e.g., anterior cingulate cortex, orbitofrontal cortex) that are involved in interoceptive processing relative to healthy controls (O'Daly et al., 2012). These changes in neural structure and connectivity are associated with emotional impairments, cognitive disabilities, and behavioral deficits that may contribute to relapse (see Duka and Stephens, 2014 for a review).

Together these findings indicate that both short- and long-term alcohol use, as well as multiple detoxifications associated with alcohol withdrawal, may be associated with altered interoceptive processing at the neurobiological level, and have consequences that may contribute to alcohol misuse (Figure 3).

**3.3. Interoception deficits in alcohol-related disorders**—Considering the important function of the insula in processing the interoceptive signals provided by drug taking and addictive behavior, activation of this structure likely promotes alcohol intake (and craving) in order to repeat previously experienced somatic and emotional relief (Naqvi and Bechara, 2009). While some level of alcohol (similar to short-term stress) can be rewarding, repeated alcohol intoxication may initiate neuroadaptations that maintain the allostatic state (Koob and Schulkin, 2019). Findings indicate that a greater discrepancy between interoceptive accuracy and sensibility is associated with symptoms of high arousal (e.g., anxiety; Domschke et al., 2010), and recent results suggest that high alexithymia may increase this discrepancy (Zamariola et al., 2018). In this case, individuals may easily direct their attention to the physical manifestations of emotional arousal instead of the feeling of negative emotion. Although this may serve as a temporary “psychic regulator” to avoid negative emotions, individuals with AUD may choose to use alcohol as an alternative solution to regulate their emotional state. Such conditions may drive alcohol consumption in an effort to regulate one’s emotional state and reset the organism to a more natural hedonic/emotional state (Koob, 2008). Further on, changes caused by alcohol consumption during the course of AUD may exacerbate problems with identifying emotions and regulating them.

Despite growing evidence in the role of interoception in the development and maintenance of addictive behaviors and the multidimensional impact of alcohol on the interoceptive system and associated processes, few studies have directly assessed interoceptive abilities in AUD. Unfortunately, different domains of interoception were not precisely defined in these studies, which in the face of later findings, may cause conceptual confusion.

Additionally, it should be noted that all of the studies mentioned below assessed only the cardiac modality of interoceptive accuracy (cardioception) in individuals with AUD. To our knowledge, there is currently no published research investigating other modalities of interoception (e.g., gastric or respiratory) in individuals with AUD<sup>1</sup>. It is also important to note procedural variations across reviewed studies using the heartbeat counting task (Schandry Task). Namely, differences include: (1) the number of time intervals used during the test, (2) the duration of these intervals, (3) the heart rate measurement methods, and (4) the instructions given to the participant. These differences may affect the results and their comparability across.

Moreover, research on the original version of the heartbeat counting task shows that it may be influenced by non-interoceptive processes (e.g., heartbeat estimation) and evidence that procedural modifications in the adapted version of the test (i.e., participants asked to avoid estimations) resulted in significant changes (Desmedt et. al., 2018). Therefore, future studies should consider more stringent standardization of the heartbeat counting task procedure.

Acute alcohol administration impairs interoceptive accuracy (measured through the Schandry Test) in men who drink alcohol (Abrams et al., 2018; Leganes-Fonteneau et al., 2019) and alters interoceptive awareness (assessed as the correlation between accuracy on the Schandry Test and confidence of responses) among participants who drink alcohol (Leganes-Fonteneau et al., 2019). In addition, in the latter study, researchers established that interoceptive awareness is associated with greater acuity in the perception of alcohol-induced affective and physical changes. On the other hand, Betka and colleagues identified no effect of acute alcohol administration on interoceptive accuracy in non-dependent alcohol drinkers (Betka et al., 2018). The number of studies on this topic is limited, so the evidence remains inconclusive.

To the best of our knowledge, four studies looked at interoceptive processes among individuals with AUD<sup>2</sup>. Schmidt and colleagues did not find an association between interoceptive accuracy and alcohol behavior (self-reported drinking compulsions/obsessions) in individuals with AUD (Schmidt et al., 2013). Yet, they established that interoceptive accuracy was negatively correlated with craving in individuals who had the tendency to decrease negative affect after alcohol use. They also found that deficits in interoception among participants with AUD may increase drinking behavior. Three other studies found that interoceptive accuracy was lower among individuals with AUD in contrast to healthy controls (Ate Çöl et al., 2016; Jakubczyk et al., 2019a; Sönmez et al., 2016). Additionally, Ate Çöl and colleagues found that interoceptive accuracy was negatively correlated

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<sup>1</sup>Searching the PubMed database, we found no studies examining interoceptive accuracy using the previously mentioned tests, such as: (1) the Water Load Test or Water Load Test-II, (2) the Respiratory Detection Task, (3) the Respiratory Discrimination Task, and (4) the Soft Touch Task in participants with AUD. However, one study assessed interoceptive processing in adolescents with Substance Use Disorder [SUD] via the Soft Touch Task, documenting interoceptive impairment in comparison with healthy adolescents (Migliorini et al., 2013).

<sup>2</sup>The following search terms were entered in the PubMed database: (“interoceptive accuracy” OR “interoceptive sensitivity” OR “interoceptive sensibility” OR “interoceptive awareness”) AND (“alcohol use disorder” OR “alcohol dependent” OR “alcohol addicted”). The search revealed six studies. The inclusion criteria were the following: (1) only studies on AUD individuals (meeting the ICD-10 criteria for the diagnosis); (2) only studies, which used the Schandry Task to assess interoceptive abilities. One study was rejected due to the method used to assess interoceptive awareness (i.e., no Schandry Task). Three of them used the same database. One additional study was identified by tracing references from retrieved papers. This search led to the inclusion of four studies.

with alcohol craving (Ate Çöl et al., 2016). In a recent publication, authors observed incongruity between interoceptive accuracy and interoceptive sensibility in individuals with AUD (Jakubczyk et al., 2019a). A negative correlation between interoceptive accuracy and difficulties in emotion regulation among individuals with AUD was found. Moreover, an association between high interoceptive sensibility and problems in controlling impulsive behaviors when experiencing negative emotions in this group was established. These observations led the authors to conclude that individuals with AUD that were more interoceptively accurate were more effective in regulating their emotions (Jakubczyk et al., 2019b). In addition, the authors observed a negative correlation between interoceptive accuracy and pain sensitivity in AUD individuals (Jakubczyk et al., 2021).

Surprisingly, little research thus far has investigated the different dimensions of interoception among individuals with AUD, despite emerging evidence of the effectiveness of therapy focused on improving the ability to sense signals from the body (mindfulness) in addiction treatment. Interoceptive awareness training was shown to be effective in substance use disorder treatment in women (Price et al., 2019). This method has also been associated with better efficiency in substance craving reduction than cognitive behavioral therapy (Garland et al., 2016). There is some evidence for brain stimulation techniques (e.g., transcranial magnetic stimulation [TMS]) targeting the insula in SUD treatment (Ibrahim et al., 2019).

#### 4. CONCLUSIONS

Neurobiological and psychological findings converge to indicate the significance of interoception in homeostatic processes. Herein, the important role of the insula in interoceptive processing has been acknowledged (Paulus et al., 2009). Accordingly, the allostatic dysregulation brought by repeated alcohol administration could plausibly be perpetuated by altered interoceptive regulatory mechanisms that introduces the disparity between the anticipated and the actual interoceptive state. Moreover, emotional dysregulation, alexithymia, impulsivity and pain processes involved in the sequelae of allostatic dysregulation and largely involved in the development and course of AUD, are related to interoceptive processes and functional integrity of the insula. Given existing work, there is convincing evidence demonstrating that impairment in interoception may be a major contributor to the development and course of AUD. Unfortunately, there are only a few studies that directly evaluate various components of interoception among individuals with AUD, and the methods used to detect objective interoceptive impairments are increasingly criticized. Thus, it should be noted that the associations between interoception and AUD require further research. Moreover, it is important to maintain uniform definitions of the different dimensions of interoception in future research to avoid conceptual confusion. It is also important to unify methods of behavioral interoceptive accuracy testing, which will help facilitate the assessment of future results.

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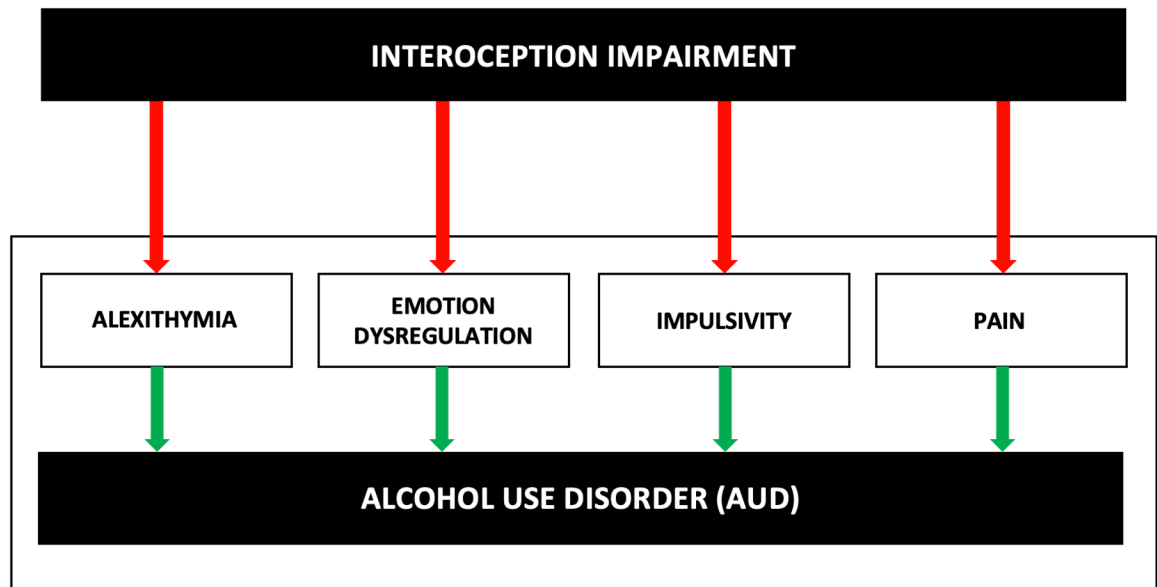
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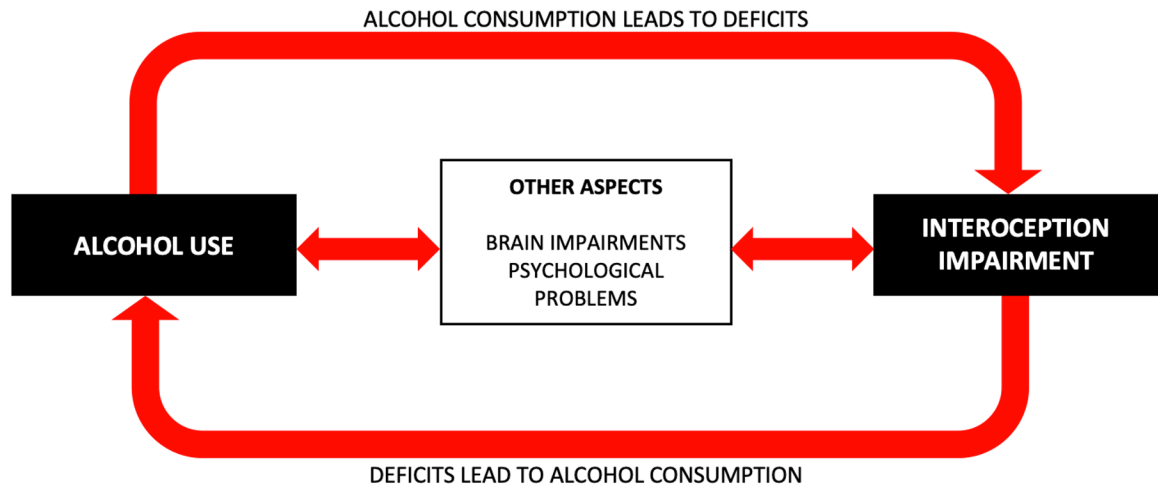
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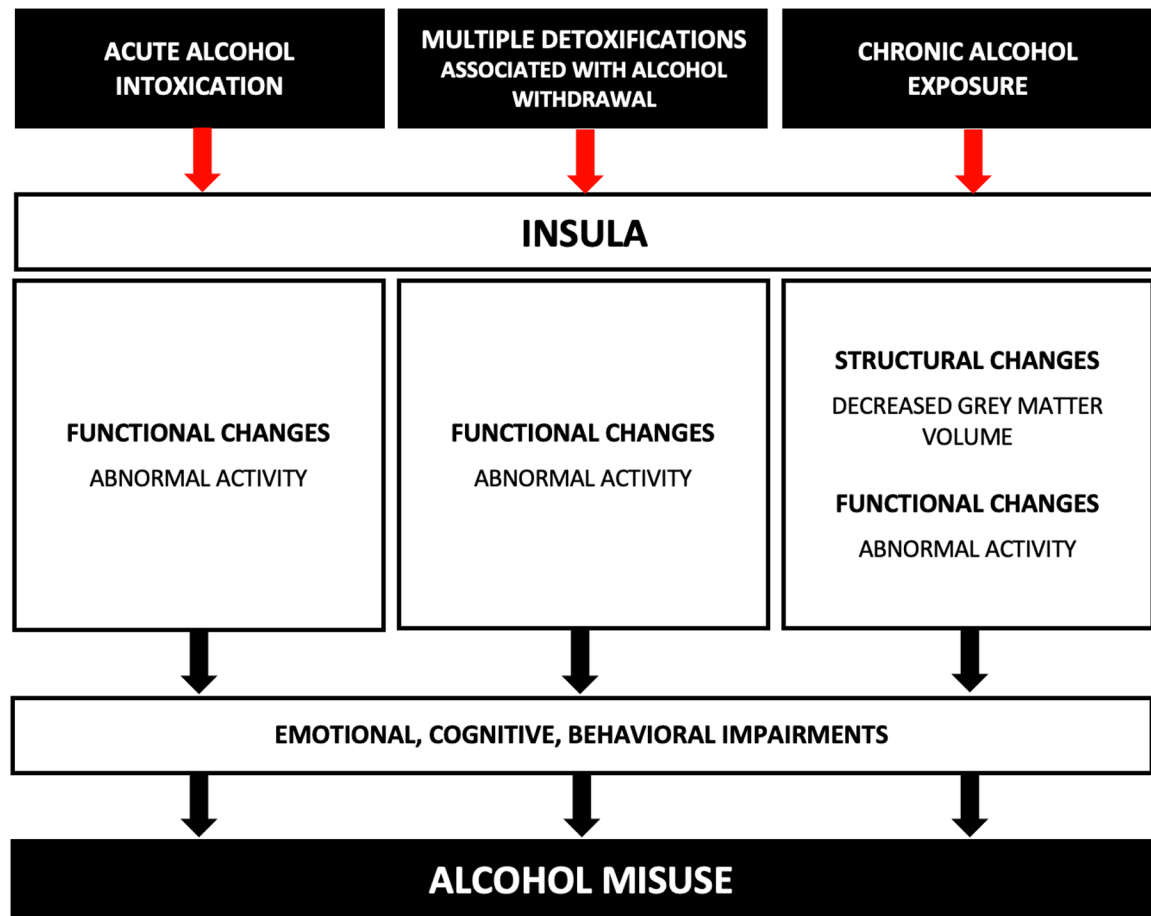
**Figure 1.** Interoception impairment can affect known risk factors for AUD. Primary disturbances in interoceptive processes may affect alexithymia, emotion dysregulation, impulsivity or pain and, as a result, contribute to AUD.





**Figure 2.**

The association between interoception impairment and alcohol use is bidirectional. Interoceptive deficits can lead to alcohol consumption, for example, by influencing factors such as impulsivity and emotional dysregulation. In turn, alcohol consumption can damage the structures of the interoceptive system and interfere with the processing of signals related to the internal environment. Other aspects, such as organic and psychological disorders, can further influence this cyclical relationship.



**Figure 3.** Acute alcohol intoxication, repeated detoxifications during alcohol withdrawal, and chronic alcohol exposure are associated with structural and functional alterations of the insula (and other cortical levels of the interoceptive system) that may contribute to emotional, cognitive and behavioral impairments. These changes may promote alcohol misuse.