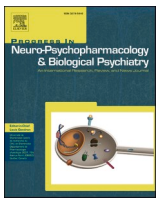
Progress in Neuropsychopharmacology & Biological Psychiatry 111 (2021) 110397

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



Alcohol use and interoception – A narrative review

Paweł Wiśniewski [a,*], Pierre Maurage [b], Andrzej Jakubczyk [a], Elisa M. Trucco [c,d], Hubert Suszek [e], Maciej Kopera [a]

[a] Department of Psychiatry, Medical University of Warsaw, Warsaw, Poland
[b] Louvain Experimental Psychopathology research group (LEP), Psychological Sciences Research Institute, UCLouvain, Louvain-la-Neuve, Belgium
[c] Department of Psychology, Center for Children and Families, Florida International University, Miami, FL, USA
[d] Department of Psychiatry, Addiction Center, University of Michigan, Ann Arbor, MI, USA
[e] Department of Psychology, University of Warsaw, Warsaw, Poland

ARTICLE INFO

Keywords:
Interoception
Interoceptive system
Alcohol use disorder
Addiction

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.

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 associated mental representations (29, 32). Deficits in interoception have been well documented in a broad range of psychiatric disorders (79, 101) 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 [57,63,64], 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 (129). More recently, a broader view of this phenomenon emerged following strong evidence indicating the involvement of interoception in psychological processes

* **Corresponding author at:** Department of Psychiatry, Medical University of Warsaw, 27 Nowowiejska St., 00-665 Warsaw, Poland.
E-mail address: wisniewski.lek@gmail.com (P. Wiśniewski).

https://doi.org/10.1016/j.pnpbp.2021.110397
Received 21 February 2021; Received in revised form 31 May 2021; Accepted 29 June 2021
Available online 3 July 2021

associated with behavioral regulation (for a review see 20). 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 (85). 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 (32), cognition (58, 140), and self-awareness (embodiment theories; 125). 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 21 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 (50). Importantly, research on anxiety disorders (42) and AUD (73) 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; 121). 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 154 for more details). Despite these limitations the Schandry Test remains the most widely used measure in interoception research (see 157). 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., 142), will significantly advance the field.

2.2. Neurobiology of interoception – The interoceptive system

Neurobiological knowledge on interoception has expanded recently. Craig (29) 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 (31). Previous research has recognized the high importance of the insula in sensorimotor, emotional and cognitive processes, as well as in multidimensional models reflecting a combination of these processes, especially with regard to pain or decision making (141). 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 (29-31). 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 21).

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.,21) as well as in clinical samples (e.g., 112). 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., 146). 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 (85). 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 (35). 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 (106). 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-Lange 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 (101), emotional dysregulation (49), impulsivity (62) and pain (132) (Fig. 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 (136). More recent research proposes a broader definition of alexithymia as it can also apply to non-affective interoceptive states (15). Current theoretical models of alexithymia associate difficulties in identifying emotions with reduced interoceptive abilities (101), 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 (1). Among findings that

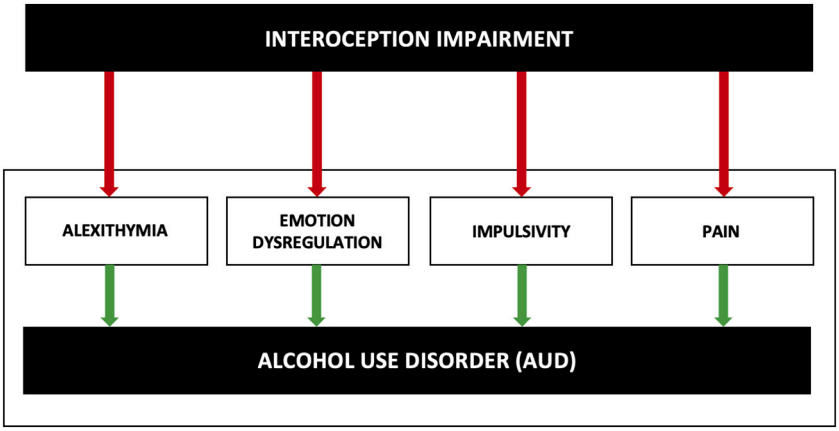


Fig. 1. Interoception impairment can affect known risk factors for AUD. Primary disturbances in interoceptive processes may affect alexithymia, emotion dysregulation, impulsivity or pain and, as a result, contribute to AUD.

offer conflicting evidence regarding the association between alexithymia and interoception (1,14,15,61,89,126,155), 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 (139). 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 (12,102). 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 (151). The abnormal function of the insula was also confirmed in meta-analytic neuroimaging studies among individuals with alexithymia (143).

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 (49). Greater accuracy in sensing one's bodily state may facilitate the regulation of emotional responses, as ongoing bodily changes can be detected more accurately (29). Greater interoceptive accuracy was found to be a positive precondition for effective self-regulation of emotionally driven behavior in healthy individuals (49). 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 (56). 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 (153). 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 (78). For example, they are more likely to choose a cognitive reappraisal strategy (49), which is considered to be more adaptive than available alternatives to regulate emotion (33). 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; 99). 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 (99). 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 (156).

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 (97) 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") (62). 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 (36), temporal impulsivity (47), and reflection impulsivity (48). Interestingly, a strong association between the structure of the insula and impulsivity has also been demonstrated in animal studies (7). 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 (62).

2.3.4. *Pain*

According to Craig's research, *pain* is an interoceptive feeling that is processed via interoceptive pathways (29), as well as a homeostatic emotion that may motivate behavior (30). Experimental neurobiological research confirms the overlap between brain regions associated with pain and those related to interoception (17). 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 (132) that correlates

negatively with pain severity (41). In addition, the positive correlation between interoceptive accuracy and pain sensitivity has been shown among healthy individuals (116, 148). Pain-related negative affectivity may impair interoceptive accuracy, suggesting that the affective aspects of pain influence the perception of internal bodily signals (13). Indeed, recent studies highlight the association between pain and emotions at neurobiological and psychological levels (90), suggesting that pain is a more complex construct than just nociception (52).

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 (114) 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 (114).

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) (82). 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 (84). 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 (107).

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 (105). 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 (27). 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 (103). Many studies indicate the dysfunction of the interoceptive system in addiction-related behaviors at the neurobiological level (146). The research focuses primarily on the important role of the insula in these processes (104). Neurobiological studies on the role of interoception in substance use populations show structural and functional abnormalities of the insula in individuals with amphetamine (92), cocaine (76), and cannabis use disorder (72). In their meta-analysis, Pando-Naude and colleagues (111) determined that the insula and other brain regions (i.e., anterior cingulate cortex, thalamus, putamen) evidenced the most structural impairment (lower grey 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 (43). 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 80 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 (38), nicotine smokers (66), and individuals with AUD (73). 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) (130,131). 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 lead to alcohol consumption) (Fig. 2).

Acute alcohol administration alters interoception. Individuals differ in their subjective assessment of the interoceptive effects associated with alcohol intoxication (123). 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 (123). 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

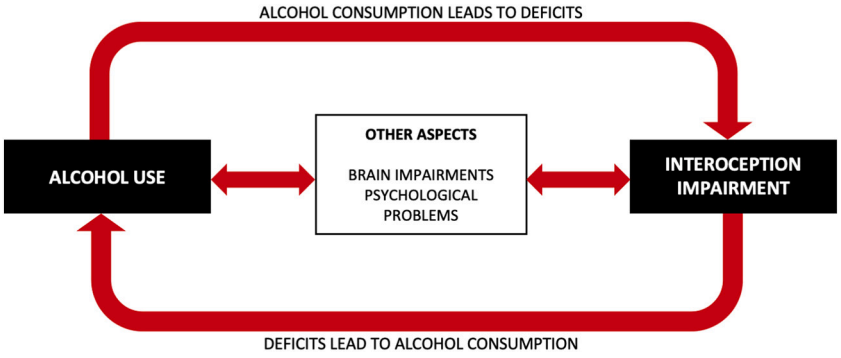


Fig. 2. The association between interoception impairment and alcohol use is bidirectional. Interoceptive deficits can lead to alcohol consumption, for example, by influencing factors such as impulsivity and emotional dysregulation. In turn, alcohol consumption can damage the structures of the interoceptive 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.

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 (4,128) and emotional processing (110). Alcohol intoxication may increase risk-taking behavior by activating brain regions including the insula (53).

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., 16). 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., 22,150,160). 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 (150,152). 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 (91). It appears that there are no differences in alcohol-induced insular cortex atrophy/insular volume decrease between males and females (39,120,137). The right insula volume might be more prone to the synergistic effects of age and alcohol misuse (137). Grey matter atrophy associated with alcohol dependence is partially reversible with abstinence. The insular grey matter volume (19) and its connectivity (100) partially recovers during both short-term and long-term abstinence (158) with some indicating partial recovery within 2 weeks of abstinence (144). 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 (60), and these changes were more substantial than similar changes caused by cannabis use (71). Even young adults who have only experienced hangover symptoms in the past may have similar abnormalities (67).

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 (22). Namely, among individuals engaging in heavy alcohol consumption, white matter integrity in frontoparietal and corticolimbic networks is negatively correlated with insular activation (98). The white matter volume of the right insula is positively correlated with craving for alcohol (23).

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 (59). Activation of brain regions involved in the brain reward system, including the insula, is related to cue-induced alcohol craving among individuals with AUD (109). 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 (134). Sullivan and colleagues postulated that deficits in the insular blood perfusion in individuals with AUD may impair cognitive control over internal urges (135). 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 (113). Prior research also supports the influence of alcohol use on the insular function in individuals who do not meet the criteria for AUD (147). 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 (147). Resting state insular connectivity patterns also correlate with AUD severity (24).

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 (54). Smaller grey volume of the insula may represent genetically conferred risk factors predisposing individuals to use alcohol (6). Furthermore, a negative correlation between insular grey matter volume and alcohol use severity was demonstrated (11), especially in relation to the middle insula (86). The insula is one of the brain regions which abnormal activation during task performance might contribute to impulsive choice (26), impaired inhibitory control (25) and risk-taking decisions (88) in individuals with AUD. Maurage and colleagues have linked abnormal insular activation in individuals with AUD with interpersonal problems in this group (94). 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 (9). Abnormal insular activity associated with alcohol withdrawal may underlie impaired emotion processing (increased sensitivity to emotional stress) in individuals with AUD (108). 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 (55) and decision-making (3,93) in heavy drinkers. Similarly, the bilateral activation of the insula was related to decision-making in binge drinkers (149). In addition, frontoinsular activity was associated with response inhibition and cognitive control impairment in binge drinkers (28). Anterior insular cortex activation was linked to risk taking in hazardous drinking individuals (26).

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 (145). 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 (34,70). Moreover, the specific insular activation to affective faces (124) or to appetitive cues (119) 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 (46,65,127).

Animal research confirms the important role of the insula in alcohol-related behaviors (see 138 for a review). For example, studies on rats support the role of the insular cortex in alcohol taking behavior (118), compulsive drinking (37), and context-induced relapse (18).

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 (8) and neuroimaging studies (19,115). 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 (95) described small fiber polyneuropathy in heavy alcohol drinking individuals with normal thiamine status as well. Julian and colleagues (77) 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 (68), 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 grey matter volume in cortical brain regions involved in integrating interoceptive signals (e.g., the ventromedial prefrontal cortex and the superior frontal gyrus) was established (45). 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 (108). These changes in neural structure and connectivity are associated with emotional impairments, cognitive disabilities, and behavioral deficits that may contribute to relapse (see 44 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 (Fig. 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 (103). While some level of alcohol (similar to short-term stress) can be rewarding, repeated alcohol intoxication may initiate neuroadaptations that maintain the allostatic state (83). Findings indicate that a greater discrepancy between interoceptive accuracy and sensibility is associated with symptoms of high arousal (e.g., anxiety; 42), and recent results suggest that high alexithymia may increase this discrepancy (155). 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 (81). 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.[1] 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 (40). 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 (2,87) and alters interoceptive awareness (assessed as the correlation between accuracy on the Schandry Test and confidence of responses) among participants who drink alcohol (87). 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 (10). The number of studies on this topic is limited, so the evidence remains inconclusive.

[1] 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 (96).

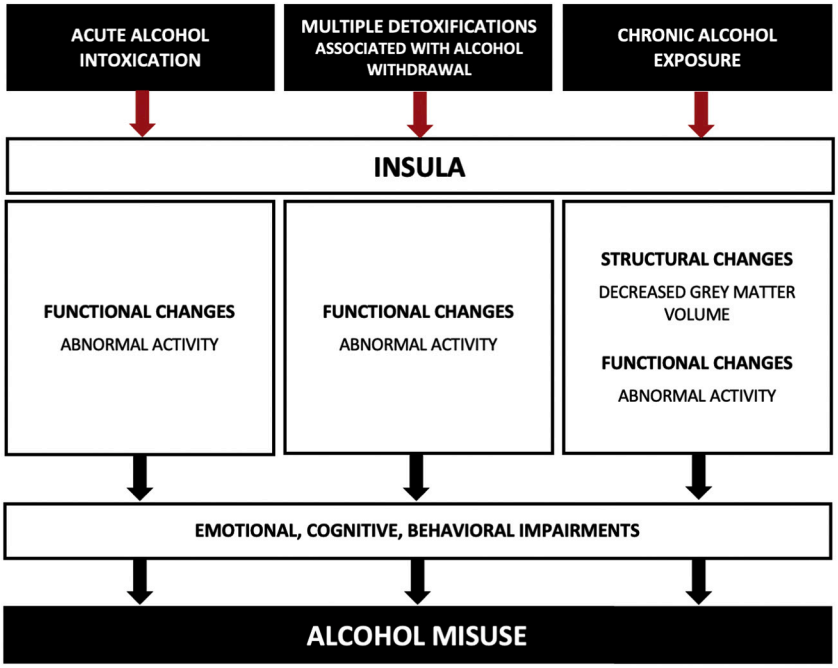


Fig. 3. Acute alcohol intoxication, repeated detoxifications during alcohol withdrawal, and chronic alcohol exposure are associated with structural and functional alterations of the insula (and other cortical levels of the interoceptive system) that may contribute to emotional, cognitive and behavioral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

To the best of our knowledge, four studies looked at interoceptive processes among individuals with AUD.[2] Schmidt and colleagues did not find an association between interoceptive accuracy and alcohol behavior (self-reported drinking compulsions/obsessions) in individuals with AUD (122). 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 (5,73,133). Additionally, Ateş Çöl and colleagues found that interoceptive accuracy was negatively correlated with alcohol craving (5). In a recent publication, authors observed incongruity between interoceptive accuracy and interoceptive sensibility in individuals with AUD (73). 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 (74). In addition, the authors observed a negative correlation between interoceptive accuracy and pain sensitivity in AUD individuals (75).

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 (117). This method has also been associated with better efficiency in substance craving reduction than cognitive behavioral therapy (51). There is some evidence for brain stimulation techniques (e.g., transcranial magnetic stimulation [TMS]) targeting the insula in SUD treatment (69).

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 (114). 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 sequalae 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.

Funding: This study was supported by the National Science Centre grant (2017/25/B/HS6/00362; PI: Jakubczyk), the National Institute on Alcohol Abuse and Alcoholism (K08 AA023290; PI Trucco), and the National Institute on Minority Health and Health Disparities (U54

[2] 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 accuracy (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.

MD012393; Sub-Project ID:5378; Co-PIs Trucco and Matthew Sutherland). Pierre Maurage (Senior Research Associate) is supported by the Belgian Fund for Scientific Research (F.R.S.-FNRS).

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1 Aaron, R.V., Blain, S.D., Snodgress, M.A., Park, S., 2020. Quadratic relationship between alexithymia and interoceptive accuracy, and results from a pilot mindfulness intervention. Front Psychiatry 11, 132.
2 Abrams, K., Cieslowski, K., Johnson, S., Krimmel, S., La Rosa, G.B., Barton, K., Silverman, P., 2018. The effects of alcohol on heartbeat perception: implications for anxiety. Addict. Behav. 79, 151–158.
3 Ames, S.L., Wong, S.W., Bechara, A., Cappelli, C., Dust, M., Grenard, J.L., Stacy, A. W., 2014. Neural correlates of a go/NoGo task with alcohol stimuli in light and heavy young drinkers. Behav. Brain Res. 274, 382–389.
4 Anderson, B.M., Stevens, M.C., Meda, S.A., Jordan, K., Calhoun, V.D., Pearlson, G. D., 2011. Functional imaging of cognitive control during acute alcohol intoxication. Alcohol. Clin. Exp. Res. 35 (1), 156–165.
5 Ateş Çöl, I., Sönmez, M.B., Vardar, M.E., 2016. Evaluation of interoceptive awareness in alcohol-addicted patients. Noro Psikiyatr Ars 53 (1), 17–22.
6 Baranger, D.A.A., Demers, C.H., Elsayed, N.M., Knodt, A.R., Radtke, S.R., Desmarais, A., Few, L.R., Agrawal, A., Heath, A.C., Barch, D.M., Squeglia, L.M., Williamson, D.E., Hariri, A.R., Bogdan, R., 2020. Convergent evidence for Predispositional effects of brain Gray matter volume on alcohol consumption. Biol. Psychiatry 87 (7), 645–655.
7 Belin-Rauscent, A., Daniel, M.L., Puaud, M., Jupp, B., Sawiak, S., Howett, D., McKenzie, C., Caprioli, D., Besson, M., Robbins, T.W., Everitt, B.J., Dalley, J.W., Belin, D., 2016. From impulses to maladaptive actions: the insula is a neurobiological gate for the development of compulsive behavior. Mol. Psychiatry 21 (4), 491–499.
8 Belzunegui, T., Insausti, R., Ibáñez, J., Gonzalo, L.M., 1995. Effect of chronic alcoholism on neuronal nuclear size and neuronal population in the mammillary body and the anterior thalamic complex of man. Histol. Histopathol. 10 (3), 633–638.
9 Berk, L., Stewart, J.L., May, A.C., Wiers, R.W., Davenport, P.W., Paulus, M.P., Tapert, S.F., 2015. Under pressure: adolescent substance users show exaggerated neural processing of aversive interoceptive stimuli. Addiction 110 (12), 2025–2036.
10 Betka, S., Gould Van Praag, C., Paloyelis, Y., Bond, R., Pfeifer, G., Sequeira, H., Duka, T., Critchley, H., 2018. Impact of intranasal oxytocin on interoceptive accuracy in alcohol users: an attentional mechanism? Soc. Cogn. Affect. Neurosci. 13 (4), 440–448.
11 Betka, S., Harris, L., Rae, C., Palfi, B., Pfeifer, G., Sequeira, H., Duka, T., Critchley, H., 2019. Signatures of alcohol use in the structure and neurochemistry of insular cortex: a correlational study. Psychopharmacology 236 (9), 2579–2591.
12 Bird, G., Silani, G., Brindley, R., White, S., Frith, U., Singer, T., 2010. Empathic brain responses in insula are modulated by levels of alexithymia but not autism. Brain 133 (Pt 5), 1515–1525.
13 Borg, C., Chouchou, F., Dayot-Gorlero, J., Zimmerman, P., Maudoux, D., Laurent, B., Michael, G.A., 2018. Pain and emotion as predictive factors of interoception in fibromyalgia. J. Pain Res. 11, 823–835.
14 Bornemann, B., Singer, T., 2017. Taking time to feel our body: steady increases in heartbeat perception accuracy and decreases in alexithymia over 9 months of contemplative mental training. Psychophysiology 54 (3), 469–482.
15 Brewer, R., Cook, R., Bird, G., 2016. Alexithymia: a general deficit of interoception. R. Soc. Open Sci. 3 (10), 150664.
16 Bühler, M., Mann, K., 2011. Alcohol and the human brain: a systematic review of different neuroimaging methods. Alcohol. Clin. Exp. Res. 35 (10), 1771–1793.
17 Bushnell, M.C., Villemure, C., Strigo, I., Duncan, G.H., 2002. Imaging pain in the brain: the role of the cerebral cortex in pain perception and modulation. Journal of Musculoskeletal Pain 10 (1–2), 59–72.
18 Campbell, E.J., Flanagan, J.P.M., Walker, L.C., Hill, M., Marchant, N.J., Lawrence, A.J., 2019. Anterior insular cortex is critical for the propensity to relapse following punishment-imposed abstinence of alcohol seeking. J. Neurosci. 39 (6), 1077–1087.
19 Cardenas, V.A., Studholme, C., Gazdzinski, S., Durazzo, T.C., Meyerhoff, D.J., 2007. Deformation-based morphometry of brain changes in alcohol dependence and abstinence. Neuroimage 34 (3), 879–887.
20 Ceunen, E., Vlaeyen, J.W., Van Diest, I., 2016. On the origin of Interoception. Front. Psychol. 7, 743.
21 Chen, W.G., Schloesser, D., Arensdorf, A.M., Simmons, J.M., Cui, C., Valentino, R., Gnadt, J.W., Nielsen, L., Hillaire-Clarke, C.S., Spruance, V., Horowitz, T.S., Vallejo, Y.F., Langevin, H.M., 2021. The emerging science of Interoception: sensing, integrating, interpreting, and regulating signals within the self. Trends Neurosci. 44 (1), 3–16.
22 Chumin, E.J., Grecco, G.G., Dzemidzic, M., Cheng, H., Finn, P., Sporns, O., Newman, S.D., Yoder, K.K., 2019. Alterations in White matter microstructure and connectivity in young adults with alcohol use disorder. Alcohol. Clin. Exp. Res. 43 (6), 1170–1179.
23 Chung, T., Clark, D.B., 2014. Insula white matter volume linked to binge drinking frequency through enhancement motives in treated adolescents. Alcohol. Clin. Exp. Res. 38 (7), 1932–1940.
24 Claus, E.D., Ewing, S.W., Filbey, F.M., Sabbineni, A., Hutchison, K.E., 2011. Identifying neurobiological phenotypes associated with alcohol use disorder severity. Neuropsychopharmacology 36 (10), 2086–2096.
25 Claus, E.D., Feldstein Ewing, S.W., Filbey, F.M., Hutchison, K.E., 2013. Behavioral control in alcohol use disorders: relationships with severity. J Stud Alcohol Drugs 74 (1), 141–151.
26 Claus, E.D., Hutchison, K.E., 2012. Neural mechanisms of risk taking and relationships with hazardous drinking. Alcohol. Clin. Exp. Res. 36 (6), 932–940.
27 Contreras, M., Ceric, F., Torrealba, F., 2007. Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium. Science 318 (5850), 655–658.
28 Courtney, K.E., Infante, M.A., Bordyug, M., Simmons, A.N., Tapert, S.F., 2020. Prospective associations between BOLD markers of response inhibition and the transition to frequent binge drinking. Alcohol. Clin. Exp. Res. 44 (2), 463–469.
29 Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev. Neurosci. 3 (8), 655–666.
30 Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurobiol. 13 (4), 500–505.
31 Craig, A.D., 2009. How do you feel–now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10 (1), 59–70.
32 Critchley, H.D., Garfinkel, S.N., 2017. Interoception and emotion. Curr. Opin. Psychol. 17, 7–14.
33 Cutuli, D., 2014. Cognitive reappraisal and expressive suppression strategies role in the emotion regulation: an overview on their modulatory effects and neural correlates. Front. Syst. Neurosci. 8, 175.
34 Dager, A.D., Anderson, B.M., Rosen, R., Khadka, S., Sawyer, B., Jiantonio-Kelly, R. E., Austad, C.S., Raskin, S.A., Tennen, H., Wood, R.M., Fallahi, C.R., Pearlson, G.D., 2014. Functional magnetic resonance imaging (fMRI) response to alcohol pictures predicts subsequent transition to heavy drinking in college students. Addiction 109 (4), 585–595.
35 Damasio, A.R., Tranel, D., Damasio, H.C., 1991. Somatic Markers and the Guidance of Behavior: Theory and Preliminary Testing, Frontal Lobe Function and Dysfunction. Oxford University Press, New York, NY, US, pp. 217–229.
36 Dambacher, F., Sack, A.T., Lobbestael, J., Arntz, A., Brugman, S., Schuhmann, T., 2015. Out of control: evidence for anterior insula involvement in motor impulsivity and reactive aggression. Soc. Cogn. Affect. Neurosci. 10 (4), 508–516.
37 Darevsky, D., Hopf, F.W., 2020. Behavioral indicators of succeeding and failing under higher-challenge compulsion-like alcohol drinking in rat. Behav. Brain Res. 393, 112768.
38 de la Fuente, A., Sedeño, L., Vignaga, S.S., Ellmann, C., Sonzogni, S., Belluscio, L., García-Cordero, I., Castagnaro, E., Boano, M., Cetkovich, M., Torralva, T., Cánepa, E.T., Tagliazucchi, E., Garcia, A.M., Ibañez, A., 2019. Multimodal neurocognitive markers of interoceptive tuning in smoked cocaine. Neuropsychopharmacology 44 (8), 1425–1434.
39 Demirakca, T., Ende, G., Kämmerer, N., Welzel-Marquez, H., Hermann, D., Heinz, A., Mann, K., 2011. Effects of alcoholism and continued abstinence on brain volumes in both genders. Alcohol. Clin. Exp. Res. 35 (9), 1678–1685.
40 Desmedt, O., Luminet, O., Corneille, O., 2018. The heartbeat counting task largely involves non-interoceptive processes: evidence from both the original and an adapted counting task. Biol. Psychol. 138, 185–188.
41 Di Lernia, D., Serino, S., Riva, G., 2016. Pain in the body. Altered interoception in chronic pain conditions: a systematic review. Neurosci. Biobehav. Rev. 71, 328–341.
42 Domschke, K., Stevens, S., Pfleiderer, B., Gerlach, A.L., 2010. Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clin. Psychol. Rev. 30 (1), 1–11.
43 Droutman, V., Read, S.J., Bechara, A., 2015. Revisiting the role of the insula in addiction. Trends Cogn. Sci. 19 (7), 414–420.
44 Duka, T., Stephens, D.N., 2014. Repeated detoxification of alcohol-dependent patients impairs brain mechanisms of Behavioural control important in resisting relapse. Current Addiction Reports 1 (1), 1–9.
45 Duka, T., Trick, L., Nikolaou, K., Gray, M.A., Kempton, M.J., Williams, H., Williams, S.C., Critchley, H.D., Stephens, D.N., 2011. Unique brain areas associated with abstinence control are damaged in multiply detoxified alcoholics. Biol. Psychiatry 70 (6), 545–552.
46 Filippi, I., Hoertel, N., Artiges, E., Airagnes, G., Guérin-Langlois, C., Seigneurie, A. S., Frère, P., Dubol, M., Guillon, F., Lemaître, H., Rahim, M., Martinot, J.L., Limosin, F., 2019. Family history of alcohol use disorder is associated with brain structural and functional changes in healthy first-degree relatives. Eur Psychiatry 62, 107–115.
47 Frost, R., McNaughton, N., 2017. The neural basis of delay discounting: a review and preliminary model. Neurosci. Biobehav. Rev. 79, 48–65.
48 Furl, N., Averbeck, B.B., 2011. Parietal cortex and insula relate to evidence seeking relevant to reward-related decisions. J. Neurosci. 31 (48), 17572–17582.
49 Füstös, J., Gramann, K., Herbert, B.M., Pollatos, O., 2013. On the embodiment of emotion regulation: interoceptive awareness facilitates reappraisal. Soc. Cogn. Affect. Neurosci. 8 (8), 911–917.

50 Garfinkel, S.N., Seth, A.K., Barrett, A.B., Suzuki, K., Critchley, H.D., 2015. Knowing your own heart: distinguishing interoceptive accuracy from interoceptive awareness. Biol. Psychol. 104, 65–74.
51 Garland, E.L., Roberts-Lewis, A., Tronnier, C.D., Graves, R., Kelley, K., 2016. Mindfulness-oriented recovery enhancement versus CBT for co-occurring substance dependence, traumatic stress, and psychiatric disorders: proximal outcomes from a pragmatic randomized trial. Behav. Res. Ther. 77, 7–16.
52 Gilam, G., Gross, J.J., Wager, T.D., Keefe, F.J., Mackey, S.C., 2020. What is the relationship between pain and emotion? Bridging constructs and communities. Neuron 107 (1), 17–21.
53 Gilman, J.M., Smith, A.R., Ramchandani, V.A., Momenan, R., Hommer, D.W., 2012. The effect of intravenous alcohol on the neural correlates of risky decision making in healthy social drinkers. Addict. Biol. 17 (2), 465–478.
54 Grodin, E.N., Cortes, C.R., Spagnolo, P.A., Momenan, R., 2017. Structural deficits in salience network regions are associated with increased impulsivity and compulsivity in alcohol dependence. Drug Alcohol Depend. 179, 100–108.
55 Grodin, E.N., Sussman, L., Sundby, K., Brennan, G.M., Diazgranados, N., Heilig, M., Momenan, R., 2018. Neural correlates of compulsive alcohol seeking in heavy drinkers. Biol Psychiatry Cogn Neurosci Neuroimaging 3 (12), 1022–1031.
56 Gross, J.J., 1999. Emotion regulation: Past, present, future. Cognit. Emot. 13 (5), 551–573.
57 Haaranen, M., Scuppa, G., Tambalo, S., Järvi, V., Bertozzi, S.M., Armirotti, A., Sommer, W.H., Bifone, A., Hyytiä, P., 2020. Anterior insula stimulation suppresses appetitive behavior while inducing forebrain activation in alcohol-preferring rats. Transl. Psychiatry 10 (1), 150.
58 Häfner, M., 2013. When body and mind are talking. Interoception moderates embodied cognition. Exp. Psychol. 60 (4), 255–259.
59 Halcomb, M.E., Chumin, E.J., Goñi, J., Dzemidzic, M., Yoder, K.K., 2019. Aberrations of anterior insular cortex functional connectivity in nontreatment-seeking alcoholics. Psychiatry Res. Neuroimaging 284, 21–28.
60 Heikkinen, N., Niskanen, E., Könönen, M., Tolmunen, T., Kekkonen, V., Kivimäki, P., Tanila, H., Laukkanen, E., Vanninen, R., 2017. Alcohol consumption during adolescence is associated with reduced grey matter volumes. Addiction 112 (4), 604–613.
61 Herbert, B.M., Herbert, C., Pollatos, O., 2011. On the relationship between interoceptive awareness and alexithymia: is interoceptive awareness related to emotional awareness? J. Pers. 79 (5), 1149–1175.
62 Herman, A.M., Duka, T., 2019. Facets of impulsivity and alcohol use: what role do emotions play? Neurosci. Biobehav. Rev. 106, 202–216.
63 Herman, A.M., Duka, T., 2020. The role of impulsivity facets on the incidence and development of alcohol use disorders. Curr. Top. Behav. Neurosci. 47, 197–221.
64 Herman, A.M., Rae, C.L., Critchley, H.D., Duka, T., 2019. Interoceptive accuracy predicts nonplanning trait impulsivity. Psychophysiology 56 (6), e13339.
65 Hill, S.Y., Sharma, V.K., 2019. DRD2 methylation and regional grey matter volumes in young adult offspring from families at ultra-high risk for alcohol dependence. Psychiatry Res. Neuroimaging 286, 31–38.
66 Hina, F., Aspell, J.E., 2019. Altered interoceptive processing in smokers: evidence from the heartbeat tracking task. Int. J. Psychophysiol. 142, 10–16.
67 Hua, J.P.Y., Piasecki, T.M., McDowell, Y.E., Boness, C.L., Trela, C.J., Merrill, A.M., Sher, K.J., Kerns, J.G., 2020. Alcohol use in young adults associated with cortical gyrification. Drug Alcohol Depend. 209, 107925.
68 Ibañez, C., Vicencio, S., Quintanilla, M.E., Maldonado, P., 2021. Interoception and alcohol addiction: Vagotomy induces long-lasting suppression of relapse-type behavior. Addict. Biol. 26 (1), e12836.
69 Ibrahim, C., Rubin-Kahana, D.S., Pushparaj, A., Musiol, M., Blumberger, D.M., Daskalakis, Z.J., Zangen, A., Le Foll, B., 2019. The insula: a brain stimulation target for the treatment of addiction. Front. Pharmacol. 10, 720.
70 Ihssen, N., Cox, W.M., Wiggett, A., Fadardi, J.S., Linden, D.E., 2011. Differentiating heavy from light drinkers by neural responses to visual alcohol cues and other motivational stimuli. Cereb. Cortex 21 (6), 1408–1415.
71 Infante, M.A., Courtney, K.E., Castro, N., Squeglia, L.M., Jacobus, J., 2018. Adolescent brain surface area pre- and post-Cannabis and alcohol initiation. J Stud Alcohol Drugs 79 (6), 835–843.
72 Jacobus, J., Goldenberg, D., Wierenga, C.E., Tolentino, N.J., Liu, T.T., Tapert, S.F., 2012. Altered cerebral blood flow and neurocognitive correlates in adolescent cannabis users. Psychopharmacology 222 (4), 675–684.
73 Jakubczyk, A., Skrzeszewski, J., Trucco, E.M., Suszek, H., Zaorska, J., Nowakowska, M., Michalska, A., Wojnar, M., Kopera, M., 2019. Interoceptive accuracy and interoceptive sensibility in individuals with alcohol use disorder-different phenomena with different clinical correlations? Drug Alcohol Depend. 198, 34–38.
74 Jakubczyk, A., Trucco, E.M., Klimkiewicz, A., Skrzeszewski, J., Suszek, H., Zaorska, J., Nowakowska, M., Michalska, A., Wojnar, M., Kopera, M., 2019. Association between Interoception and emotion regulation in individuals with alcohol use disorder. Front Psychiatry 10, 1028.
75 Jakubczyk, A., Wiśniewski, P., Trucco, E.M., Kobyliński, P., Zaorska, J., Skrzeszewski, J., Suszek, H., Wojnar, M., Kopera, M., 2021. The synergistic effect between interoceptive accuracy and alcohol use disorder status on pain sensitivity. Addict. Behav. 112, 106607.
76 Jia, Z., Worhunsky, P.D., Carroll, K.M., Rounsaville, B.J., Stevens, M.C., Pearlson, G.D., Potenza, M.N., 2011. An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. Biol. Psychiatry 70 (6), 553–560.
77 Julian, T., Glascow, N., Syeed, R., Zis, P., 2019. Alcohol-related peripheral neuropathy: a systematic review and meta-analysis. J. Neurol. 266 (12), 2907–2919.
78 Kever, A., Pollatos, O., Vermeulen, N., Grynberg, D., 2015. Interoceptive sensitivity facilitates both antecedent- and response-focused emotion regulation strategies. Personal. Individ. Differ. 87, 20–23.
79 Khalsa, S.S., Adolphs, R., Cameron, O.G., Critchley, H.D., Davenport, P.W., Feinstein, J.S., Feusner, J.D., Garfinkel, S.N., Lane, R.D., Mehling, W.E., Meuret, A. E., Nemeroff, C.B., Oppenheimer, S., Petzschner, F.H., Pollatos, O., Rhudy, J.L., Schramm, L.P., Simmons, W.K., Stein, M.B., Stephan, K.E., Van den Bergh, O., Van Diest, I., von Leupoldt, A., Paulus, M.P., 2018. Interoception and mental health: a roadmap. Biol Psychiatry Cogn Neurosci Neuroimaging 3 (6), 501–513.
80 Klugah-Brown, B., Di, X., Zweerings, J., Mathiak, K., Becker, B., Biswal, B., 2020. Common and separable neural alterations in substance use disorders: a coordinate-based meta-analyses of functional neuroimaging studies in humans. Hum. Brain Mapp. 41 (16), 4459–4477.
81 Koob, G.F., 2008. Hedonic homeostatic dysregulation as a driver of drug-seeking behavior. Drug Discov Today Dis Models 5 (4), 207–215.
82 Koob, G.F., 2017. The dark side of addiction: the Horsley Gantt to Joseph Brady connection. J. Nerv. Ment. Dis. 205 (4), 270–272.
83 Koob, G.F., Schulkin, J., 2019. Addiction and stress: an allostatic view. Neurosci. Biobehav. Rev. 106, 245–262.
84 Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 3 (8), 760–773.
85 Lang, P.J., 1994. The varieties of emotional experience: a meditation on James-Lange theory. Psychol. Rev. 101 (2), 211–221.
86 Le, T.M., Zhornitsky, S., Wang, W., Zhang, S., Li, C.R., 2021. Problem drinking alters gray matter volume and food cue responses of the lateral orbitofrontal cortex. Addict. Biol. 26 (1), e12857.
87 Leganes-Fonteneau, M., Cheang, Y., Lam, Y., Garfinkel, S., Duka, T., 2019. Interoceptive awareness is associated with acute alcohol-induced changes in subjective effects. Pharmacol. Biochem. Behav. 181, 69–76.
88 Li, C.S., Luo, X., Yan, P., Bergquist, K., Sinha, R., 2009. Altered impulse control in alcohol dependence: neural measures of stop signal performance. Alcohol. Clin. Exp. Res. 33 (4), 740–750.
89 Longarzo, M., D'Olimpio, F., Chiavazzo, A., Santangelo, G., Trojano, L., Grossi, D., 2015. The relationships between interoception and alexithymic trait. The Self-Awareness Questionnaire in healthy subjects. Front Psychol 6, 1149.
90 Lumley, M.A., Cohen, J.L., Borszcz, G.S., Cano, A., Radcliffe, A.M., Porter, L.S., Schubiner, H., Keefe, F.J., 2011. Pain and emotion: a biopsychosocial review of recent research. J. Clin. Psychol. 67 (9), 942–968.
91 Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., Allen, N.B., Alia-Klein, N., Batalla, A., Blaine, S., Brooks, S., Caparelli, E., Chye, Y.Y., Cousijn, J., Dagher, A., Desrivieres, S., Feldstein-Ewing, S., Foxe, J.J., Goldstein, R. Z., Goudriaan, A.E., Heitzeg, M.M., Hester, R., Hutchison, K., Korucuoglu, O., Li, C. R., London, E., Lorenzetti, V., Luijten, M., Martin-Santos, R., May, A., Momenan, R., Morales, A., Paulus, M.P., Pearlson, G., Rousseau, M.E., Salmeron, B.J., Schluter, R., Schmaal, L., Schumann, G., Sjoerds, Z., Stein, D.J., Stein, E.A., Sinha, R., Solowij, N., Tapert, S., Uhlmann, A., Veltman, D., van Holst, R., Whittle, S., Wright, M.J., Yücel, M., Zhang, S., Yurgelun-Todd, D., Hibar, D.P., Jahanshad, N., Evans, A., Thompson, P.M., Glahn, D.C., Conrod, P., Garavan, H., 2019. Mega-analysis of Gray matter volume in substance dependence: general and substance-specific regional effects. Am. J. Psychiatry 176 (2), 119–128.
92 Mackey, S., Paulus, M., 2013. Are there volumetric brain differences associated with the use of cocaine and amphetamine-type stimulants? Neurosci. Biobehav. Rev. 37 (3), 300–316.
93 MacKillop, J., Amlung, M.T., Acker, J., Gray, J.C., Brown, C.L., Murphy, J.G., Ray, L.A., Sweet, L.H., 2014. The neuroeconomics of alcohol demand: an initial investigation of the neural correlates of alcohol cost-benefit decision making in heavy drinking men. Neuropsychopharmacology 39 (8), 1988–1995.
94 Maurage, P., Joassin, F., Philippot, P., Heeren, A., Vermeulen, N., Mahau, P., Delperdange, C., Corneille, O., Luminet, O., de Timary, P., 2012. Disrupted regulation of social exclusion in alcohol-dependence: an fMRI study. Neuropsychopharmacology 37 (9), 2067–2075.
95 Mellion, M.L., Silbermann, E., Gilchrist, J.M., Machan, J.T., Leggio, L., de la Monte, S., 2014. Small-fiber degeneration in alcohol-related peripheral neuropathy. Alcohol. Clin. Exp. Res. 38 (7), 1965–1972.
96 Migliorini, R., Stewart, J.L., May, A.C., Tapert, S.F., Paulus, M.P., 2013. What do you feel? Adolescent drug and alcohol users show altered brain response to pleasant interoceptive stimuli. Drug Alcohol Depend. 133 (2), 661–668.
97 Moeller, F.G., Barratt, E.S., Dougherty, D.M., Schmitz, J.M., Swann, A.C., 2001. Psychiatric aspects of impulsivity. Am. J. Psychiatry 158 (11), 1783–1793.
98 Monnig, M.A., Thayer, R.E., Caprihan, A., Claus, E.D., Yeo, R.A., Calhoun, V.D., Hutchison, K.E., 2014. White matter integrity is associated with alcohol cue reactivity in heavy drinkers. Brain Behav 4 (2), 158–170.
99 Morawetz, C., Bode, S., Derntl, B., Heekeren, H.R., 2017. The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: a meta-analysis of fMRI studies. Neurosci. Biobehav. Rev. 72, 111–128.
100 Mueller, S.G., Meyerhoff, D.J., 2021. The gray matter structural connectome and its relationship to alcohol relapse: reconnecting for recovery. Addict. Biol. 26 (1), e12860.
101 Murphy, J., Brewer, R., Catmur, C., Bird, G., 2017. Interoception and psychopathology: a developmental neuroscience perspective. Dev Cogn Neurosci 23, 45–56.
102 Murphy, J., Catmur, C., Bird, G., 2018. Alexithymia is associated with a multidomain, multidimensional failure of interoception: evidence from novel tests. J Exp Psychol Gen 147 (3), 398–408.
103 Naqvi, N.H., Bechara, A., 2009. The hidden island of addiction: the insula. Trends Neurosci. 32 (1), 56–67.

104 Naqvi, N.H., Gaznick, N., Tranel, D., Bechara, A., 2014. The insula: a critical neural substrate for craving and drug seeking under conflict and risk. Ann. N. Y. Acad. Sci. 1316, 53–70.
105 Naqvi, N.H., Rudrauf, D., Damasio, H., Bechara, A., 2007. Damage to the insula disrupts addiction to cigarette smoking. Science 315 (5811), 531–534.
106 Niedenthal, P.M., 2007. Embodying emotion. Science 316 (5827), 1002–1005.
107 Noël, X., Brevers, D., Bechara, A., 2013. A neurocognitive approach to understanding the neurobiology of addiction. Curr. Opin. Neurobiol. 23 (4), 632–638.
108 O'Daly, O.G., Trick, L., Scaife, J., Marshall, J., Ball, D., Phillips, M.L., Williams, S.S., Stephens, D.N., Duka, T., 2012. Withdrawal-associated increases and decreases in functional neural connectivity associated with altered emotional regulation in alcoholism. Neuropsychopharmacology 37 (10), 2267–2276.
109 Olbrich, H.M., Valerius, G., Paris, C., Hagenbuch, F., Ebert, D., Juengling, F.D., 2006. Brain activation during craving for alcohol measured by positron emission tomography. Aust N Z J Psychiatry 40 (2), 171–178.
110 Padula, C.B., Simmons, A.N., Matthews, S.C., Robinson, S.K., Tapert, S.F., Schuckit, M.A., Paulus, M.P., 2011. Alcohol attenuates activation in the bilateral anterior insula during an emotional processing task: a pilot study. Alcohol Alcohol. 46 (5), 547–552.
111 Pando-Naude, V., Toxto, S., Fernandez-Lozano, S., Parsons, C.E., Alcauter, S., Garza-Villarreal, E.A., 2021. Gray and white matter morphology in substance use disorders: a neuroimaging systematic review and meta-analysis. Transl. Psychiatry 11 (1), 29.
112 Paulus, M.P., Stein, M.B., 2010. Interoception in anxiety and depression. Brain Struct. Funct. 214 (5–6), 451–463.
113 Paulus, M.P., Stewart, J.L., 2014. Interoception and drug addiction. Neuropharmacology 76 Pt B(00), 342-350.
114 Paulus, M.P., Tapert, S.F., Schulteis, G., 2009. The role of interoception and alliesthesia in addiction. Pharmacol. Biochem. Behav. 94 (1), 1–7.
115 Pitel, A.L., Segobin, S.H., Ritz, L., Eustache, F., Beaunieux, H., 2015. Thalamic abnormalities are a cardinal feature of alcohol-related brain dysfunction. Neurosci. Biobehav. Rev. 54, 38–45.
116 Pollatos, O., Füstös, J., Critchley, H.D., 2012. On the generalised embodiment of pain: how interoceptive sensitivity modulates cutaneous pain perception. Pain 153 (8), 1680–1686.
117 Price, C.J., Thompson, E.A., Crowell, S., Pike, K., 2019. Longitudinal effects of interoceptive awareness training through mindful awareness in body-oriented therapy (MABT) as an adjunct to women's substance use disorder treatment: a randomized controlled trial. Drug Alcohol Depend. 198, 140–149.
118 Pushparaj, A., Le Foll, B., 2015. Involvement of the caudal granular insular cortex in alcohol self-administration in rats. Behav. Brain Res. 293, 203–207.
119 Ray, S., Hanson, C., Hanson, S.J., Bates, M.E., 2010. fMRI BOLD response in high-risk college students (part 1): during exposure to alcohol, marijuana, polydrug and emotional picture cues. Alcohol Alcohol. 45 (5), 437–443.
120 Sawyer, K.S., Oscar-Berman, M., Barthelemy, O.J., Papadimitriou, G.M., Harris, G. J., Makris, N., 2017. Gender dimorphism of brain reward system volumes in alcoholism. Psychiatry Res. Neuroimaging 263, 15–25.
121 Schandry, R., 1981. Heart beat perception and emotional experience. Psychophysiology 18 (4), 483–488.
122 Schmidt, A.F., Eulenbruch, T., Langer, C., Banger, M., 2013. Interoceptive awareness, tension reduction expectancies and self-reported drinking behavior. Alcohol Alcohol. 48 (4), 472–477.
123 Schuckit, M.A., 1994. Low level of response to alcohol as a predictor of future alcoholism. Am. J. Psychiatry 151 (2), 184–189.
124 Schuckit, M.A., Smith, T.L., Paulus, M.P., Tapert, S.F., Simmons, A.N., Tolentino, N. J., Shafir, A., 2016. The ability of functional magnetic resonance imaging to predict heavy drinking and alcohol problems 5 years later. Alcohol. Clin. Exp. Res. 40 (1), 206–213.
125 Seth, A.K., Friston, K.J., 2016. Active interoceptive inference and the emotional brain. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371 (1708).
126 Shah, P., Hall, R., Catmur, C., Bird, G., 2016. Alexithymia, not autism, is associated with impaired interoception. Cortex 81, 215–220.
127 Sharma, V.K., Hill, S.Y., 2017. Differentiating the effects of familial risk for alcohol dependence and prenatal exposure to alcohol on offspring brain morphology. Alcohol. Clin. Exp. Res. 41 (2), 312–322.
128 Sherman, L.E., Rosenbaum, G.M., Smith, A.R., Botdorf, M.A., Fettich, K., Patrianakos, J.L., McCloskey, M., Steinberg, L.D., Chein, J.M., 2019. The interactive effects of peers and alcohol on functional brain connectivity in young adults. Neuroimage 197, 264–272.
129 Sherrington, C.S., 1906. The Integrative Action of the Nervous System. Yale University Press, New Haven, CT, US.
130 Smith, R., Feinstein, J.S., Kuplicki, R., Forthman, K.L., Stewart, J.L., Paulus, M.P., Khalsa, S.S., 2021. Perceptual insensitivity to the modulation of interoceptive signals in depression, anxiety, and substance use disorders. Sci. Rep. 11 (1), 2108.
131 Smith, R., Kuplicki, R., Feinstein, J., Forthman, K.L., Stewart, J.L., Paulus, M.P., Khalsa, S.S., 2020. A Bayesian computational model reveals a failure to adapt interoceptive precision estimates across depression, anxiety, eating, and substance use disorders. PLoS Comput. Biol. 16 (12), e1008484.
132 Solcà, M., Park, H.D., Bernasconi, F., Blanke, O., 2020. Behavioral and neurophysiological evidence for altered interoceptive bodily processing in chronic pain. Neuroimage 217, 116902.
133 Sönmez, M.B., Kılıç, E.K., Ateş Çöl, I., Görgülü, Y., Çınar, R.K., 2017. Decreased interoceptive awareness in patients with substance use disorders. J. Subst. Abus. 22 (1), 60–65.
134 Strosche, A., Zhang, X., Kirsch, M., Hermann, D., Ende, G., Kiefer, F., Vollstädt-Klein, S., 2021. Investigation of brain functional connectivity to assess cognitive control over cue-processing in alcohol use disorder. Addict. Biol. 26 (1), e12863.
135 Sullivan, E.V., Müller-Oehring, E., Pitel, A.L., Chanraud, S., Shankaranarayanan, A., Alsop, D.C., Rohlfing, T., Pfefferbaum, A., 2013. A selective insular perfusion deficit contributes to compromised salience network connectivity in recovering alcoholic men. Biol. Psychiatry 74 (7), 547–555.
136 Taylor, G.J., Bagby, R.M., Parker, J.D.A., 1997. Disorders of Affect Regulation: Alexithymia in Medical and Psychiatric Illness. Cambridge University Press, New York, NY, US.
137 Thayer, R.E., Hagerty, S.L., Sabbineni, A., Claus, E.D., Hutchison, K.E., Weiland, B. J., 2016. Negative and interactive effects of sex, aging, and alcohol abuse on gray matter morphometry. Hum. Brain Mapp. 37 (6), 2276–2292.
138 Torrealba, F., Madrid, C., Contreras, M., Gómez, K., 2017. Plasticity in the interoceptive system. In: von Bernhardi, R., Eugenín, J., Muller, K.J. (Eds.), The Plastic Brain. Springer International Publishing, Cham, pp. 59–74.
139 Trevisan, D.A., Altschuler, M.R., Bagdasarov, A., Carlos, C., Duan, S., Hamo, E., Kala, S., McNair, M.L., Parker, T., Stahl, D., Winkelman, T., Zhou, M., McPartland, J.C., 2019. A meta-analysis on the relationship between interoceptive awareness and alexithymia: distinguishing interoceptive accuracy and sensibility. J. Abnorm. Psychol. 128 (8), 765–776.
140 Tsakiris, M., Critchley, H., 2016. Interoception beyond homeostasis: affect, cognition and mental health. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 371 (1708).
141 Uddin, L.Q., Nomi, J.S., Hébert-Seropian, B., Ghaziri, J., Boucher, O., 2017. Structure and function of the human insula. J. Clin. Neurophysiol. 34 (4), 300–306.
142 Van Den Houte, M., Vlemincx, E., Franssen, M., Van Diest, I., Van Oudenhove, L., Luminet, O., 2021. The respiratory occlusion discrimination task: A new paradigm to measure respiratory interoceptive accuracy. Psychophysiology 58, e13760. https://doi.org/10.1111/psyp.13760.
143 van der Velde, J., Servaas, M.N., Goerlich, K.S., Bruggeman, R., Horton, P., Costafreda, S.G., Aleman, A., 2013. Neural correlates of alexithymia: a meta-analysis of emotion processing studies. Neurosci. Biobehav. Rev. 37 (8), 1774–1785.
144 van Eijk, J., Demirakca, T., Frischknecht, U., Hermann, D., Mann, K., Ende, G., 2013. Rapid partial regeneration of brain volume during the first 14 days of abstinence from alcohol. Alcohol. Clin. Exp. Res. 37 (1), 67–74.
145 Veer, I.M., Jetzschmann, P., Garbusow, M., Nebe, S., Frank, R., Kuitunen-Paul, S., Sebold, M., Ripke, S., Heinz, A., Friedel, E., Smolka, M.N., Walter, H., 2019. Nucleus accumbens connectivity at rest is associated with alcohol consumption in young male adults. Eur. Neuropsychopharmacol. 29 (12), 1476–1485.
146 Verdejo-Garcia, A., Clark, L., Dunn, B.D., 2012. The role of interoception in addiction: a critical review. Neurosci. Biobehav. Rev. 36 (8), 1857–1869.
147 Vergara, V.M., Liu, J., Claus, E.D., Hutchison, K., Calhoun, V., 2017. Alterations of resting state functional network connectivity in the brain of nicotine and alcohol users. Neuroimage 151, 45–54.
148 Weiss, S., Sack, M., Henningsen, P., Pollatos, O., 2014. On the interaction of self-regulation, interoception and pain perception. Psychopathology 47 (6), 377–382.
149 Xiao, L., Bechara, A., Gong, Q., Huang, X., Li, X., Xue, G., Wong, S., Lu, Z.L., Palmer, P., Wei, Y., Jia, Y., Johnson, C.A., 2013. Abnormal affective decision making revealed in adolescent binge drinkers using a functional magnetic resonance imaging study. Psychol. Addict. Behav. 27 (2), 443–454.
150 Xiao, P., Dai, Z., Zhong, J., Zhu, Y., Shi, H., Pan, P., 2015. Regional gray matter deficits in alcohol dependence: a meta-analysis of voxel-based morphometry studies. Drug Alcohol Depend. 153, 22–28.
151 Xu, P., Opmeer, E.M., van Tol, M.J., Goerlich, K.S., Aleman, A., 2018. Structure of the alexithymic brain: a parametric coordinate-based meta-analysis. Neurosci. Biobehav. Rev. 87, 50–55.
152 Yang, X., Tian, F., Zhang, H., Zeng, J., Chen, T., Wang, S., Jia, Z., Gong, Q., 2016. Cortical and subcortical gray matter shrinkage in alcohol-use disorders: a voxel-based meta-analysis. Neurosci. Biobehav. Rev. 66, 92–103.
153 Zamariola, G., Frost, N., Van Oost, A., Corneille, O., Luminet, O., 2019. Relationship between interoception and emotion regulation: new evidence from mixed methods. J. Affect. Disord. 246, 480–485.
154 Zamariola, G., Maurage, P., Luminet, O., Corneille, O., 2018. Interoceptive accuracy scores from the heartbeat counting task are problematic: evidence from simple bivariate correlations. Biol. Psychol. 137, 12–17.
155 Zamariola, G., Vlemincx, E., Corneille, O., Luminet, O., 2018. Relationship between interoceptive accuracy, interoceptive sensibility, and alexithymia. Personal. Individ. Differ. 125, 14–20.
156 Zhang, Z., Guo, T., Fan, J., Wu, X., Tan, T., Luo, J., 2020. Dissociable posterior and anterior insula activations in processing negative stimulus before and after the application of cognitive reappraisals. Front. Psychol. 11, 268.
157 Zimprich, D., Nusser, L., Pollatos, O., 2020. Are interoceptive accuracy scores from the heartbeat counting task problematic? A comment on Zamariola et al. (2018). Biol. Psychol. 152, 107868.
158 Zou, X., Durazzo, T.C., Meyerhoff, D.J., 2018. Regional brain volume changes in alcohol-dependent individuals during short-term and long-term abstinence. Alcohol. Clin. Exp. Res. 42 (6), 1062–1072.