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Anxiety during abstinence from alcohol: A systematic review of rodent and human evidence for the anterior insula's role in the abstinence network

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Abstract

Alcohol Use Disorder (AUD) is a chronic, relapsing disease that impacts almost a third of Americans. Despite effective treatments for attaining sobriety, the majority of patients relapse within a year, making relapse a substantial barrier to long-term treatment success. A major factor contributing to relapse is heightened negative affect that results from the combination of abstinence-related increases in stress-reactivity and decreases in reward sensitivity. Substantial research has contributed to the understanding of reward-related changes in AUD. However, less is known about anxiety during abstinence, a critical component of understanding addiction as anxiety during abstinence can trigger relapse. Most of what we know about abstinence-related negative affect comes from rodent studies which have identified keys brain regions responsible for abstinence-related behaviors. This abstinence network is comprised of brain regions that make up the extended amygdala: the nucleus accumbens (NAcc), the central nucleus of the amygdala

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(CeA), and the bed nucleus of the stria terminalis (BNST). More recently, emerging evidence from rodent and human studies suggests a fourth brain region, the anterior insula, might be part of the abstinence network. Here, we review current rodent and human literature on the extended amygdala's role in alcohol abstinence and anxiety, present evidence for the anterior insula's role in the abstinence network, and provide future directions for research to further elucidate the neural underpinnings of abstinence in humans. A better understanding of the abstinence network is critical towards understanding and possibly preventing relapse in AUD.

Keywords

Abstinence; Addiction; Alcohol Use Disorder; Anterior Insula; Anxiety; Extended Amygdala

Introduction

In American adults, Alcohol Use Disorder (AUD) has a lifetime prevalence of over 29%.[1] Despite effective treatments for attaining sobriety, relapse occurs in the majority of patients, creating a barrier to long-term abstinence.[2,3] Decades of research have shown that chronic alcohol exposure causes the brain to undergo neuroadaptation, contributing to allostasis. Following these neural changes, abstinence from alcohol creates a new state of imbalance, leading to symptoms of increased negative affect, including anxiety, depression, and stress-reactivity, coined the "dark side of addiction" (for review see Koob[4]). Anxiety during abstinence often triggers relapse because alcohol can quickly alleviate anxiety and negative affect.[2,5–7] Anxiety during abstinence results from the dysregulation of brain regions involved in reward and anxiety[8–10] (for review see Koob[11]). Namely, the brain experiences decreased reward sensitivity,[12] increased anxiety,[13] heightened stress-reactivity,[14] and increased expression of anxiogenic hormones.[15,16]

Although much alcohol research has focused on reward-related changes, a number of studies have investigated the neurobiological basis for negative affect during abstinence. The extended amygdala is a network of brain regions with a role in both anxiety-related and addiction-related behaviors, making the extended amygdala a promising network to examine. In a substantial body of work, Koob and others identified the extended amygdala as a critical network responsible for negative affect during abstinence (e.g. Koob and Volkow[17]). Neuroimaging advancements have allowed for evaluation of the extended amygdala in humans, and early studies have begun to validate rodent findings in humans (e.g. Avery et al[18]). Another brain region with contributions to both anxiety-related and addiction-related behavior is the anterior insula, leading to the possibility that the anterior insula could also contribute to negative affect during abstinence.

The goal of this review is to systematically examine rodent and human evidence from the alcohol literature to consider the anterior insula as an additional part of the abstinence network (Figure 1). The first section summarizes the role of the extended amygdala in abstinence and anxiety. The second section introduces the anterior insula as a brain region with potential to be included in the abstinence network. The systematic investigation of whether the anterior insula is part of the abstinence network is guided by the following

questions: (1) Are the anterior insula and extended amygdala connected? We posit that if the anterior insula is critical for abstinence, then it should have robust structural and/or functional connections to the extended amygdala; (2) Does the anterior insula have a role in abstinence and anxiety? The abstinence network mediates negative affect during abstinence. To be considered a component of the abstinence network, the anterior insula must have a demonstrated role in both anxiety and abstinence; and (3) Is anterior insula-extended amygdala connectivity altered in abstinence and anxiety? During abstinence, anxiety- and addiction-related changes should be reflected by alterations in structural or functional connectivity between the anterior insula and existing abstinence network.

This review will integrate findings from both rodent and human literature; however, combining research into a translational model can cause confusion from species-specific differences. Here we clarify important differences between rodent and human research and establish the terms used throughout this review. First, the rodent insula is often classified by its cytoarchitecture, but the human insula is more often described by its location. The cytoarchitecture of the rodent anterior insula is predominantly agranular (described in more detail below), so we included rodent studies of the agranular insula unless the study specifies that results are from the posterior agranular insula. For simplicity, both rodent and human studies will use the term “anterior insula”. Second, rodent studies infer anxiety from behaviors, and consequently use terms such as “anxiety-related behaviors” or, more generally, “negative affect”. In this review, we will use “negative affect” when discussing rodent literature. In contrast, human studies typically use self-reports of anxiety symptoms or physiological assessments of anxiety. The term negative affect can be used in humans, but often refers to negative emotions more broadly, including: sadness, anger, and guilt, in addition to fear and anxiety; for this reason, we will use the more precise term “anxiety” when discussing human literature. Anxiety often refers to a feeling that can occur in both healthy and pathological states; alternatively, anxiety can be used to indicate a clinical diagnosis for which we will use “anxiety disorder”, or specify a disorder (e.g. Social Anxiety Disorder). Third, in rodent research, circuits are structurally and functionally interconnected populations of neurons whereas, in humans, circuits typically refer to brain regions with highly correlated activity. Due to these differences, we will refrain from using the term “circuit”. Fourth, “reinstatement” refers to reinitiating alcohol use in rodents and is equivalent to the term “relapse” in humans. In keeping with the literature, we will use reinstatement when discussing rodent research and relapse when discussing human research.

Methods

The role of the extended amygdala in anxiety or abstinence has previously been reviewed in both rodents and humans (for examples see Koob and Volkow[17], Avery et al.[19], Shackman and Fox[20]). Likewise, the anterior insula’s role in anxiety and negative affect has previously been reviewed.[21–23] To our knowledge, the human literature supporting a role for the anterior insula in abstinence has not been systematically reviewed.

Here we will provide a comprehensive review of the abstinence (post-detoxification) studies examining the anterior insula in individuals with AUD. Abstinence can encompass a number of stages from detoxification to prolonged abstinence; we include studies of abstinence from

any stage past detoxification. We avoided studies with detoxification because detoxification symptoms (i.e. seizures, tremors, hallucinations, autonomic instability, etc.) are volatile but short-lived whereas other abstinence symptoms (including negative affect and anxiety) are more stable and can persist for weeks or months.[24] The alcohol literature includes a variety of populations, including occasional drinkers, heavy drinkers, binge drinkers, and patients with AUD. The ability to control alcohol intake and maintain abstinence is a defining principle that distinguished drinkers with and without pathology. In this review, we are most interested in brain mechanisms related to these issues with maintaining abstinence. For this reason, only studies of individuals with a diagnosis of AUD (or the older terms alcohol dependence or alcoholism) are included.

To identify human abstinence studies with anterior insula changes in patients with AUD, the following search terms were used in Web of Science: *TOPIC: ("Alcohol" OR "Ethanol" OR "Alcoholism") AND TOPIC: ("Abstinence" OR "Withdrawal" OR "Sober" OR "Abstinent" OR "Detox*") AND TOPIC: ("Insula" OR "Insular Cortex") AND TOPIC: ("MRI" OR "functional imaging" OR "functional connectivity" OR "DTI" OR "structural connectivity" OR "brain imaging" OR "VBM" OR "Voxel based morphometry")*. The search resulted in 43 studies. Of these, 31 met at least one of our exclusion criteria. First, review papers (n = 2) and treatment studies (n = 1) were excluded. Second, studies were excluded if the participants did not include a group of abstinent patients with AUD. Abstinence was defined as >7 days sobriety or >3 days sobriety if the study also specified that participants had no withdrawal symptoms. We excluded studies with substances other than alcohol (n = 13); participants that did not have AUD (n = 3); AUD patients that were in withdrawal (n = 1); and species other than humans (n = 1). Third, many studies did not specify if insula results were anterior or posterior (n = 10), so studies were only included if they specifically referred to the anterior insula, specified peak voxels that were within the anterior insula, or had figures indicating the anterior insula. The anterior insula was defined as anterior to the central insula sulcus. We also reviewed the references cited by and citing the studies found by our search and added the references that met inclusion criteria (n = 8). Table 1 presents the final list of the included studies (n=20).

Because we review human neuroimaging studies in detail, we provide some basic definitions of imaging methods here. Structural MRI assesses gray matter volume and cortical thickness. Diffusion tensor imaging (DTI) measures the Brownian motion, or diffusion, of water molecules in the brain which can be used to identify white matter tracts structurally connecting different brain regions. Functional MRI (fMRI) uses blood-oxygenation-level-dependent (BOLD) signal to measure blood flow changes as a proxy for neuronal activity.[25] BOLD signal can be evaluated at rest (resting-state fMRI) or in response to a task (task-based fMRI). Functional connectivity studies use BOLD signal to identify increases or decreases in synchronous activity between brain regions either at rest or during different tasks or conditions. Although functional connectivity can be useful for determining coordinated activation between regions, functional connectivity does not imply direct communication between the regions. Structural connectivity is able to identify connections between regions; thus, in combination functional and structural connectivity provide evidence for direct communication with functional significance between regions and establish evidence for the formation of networks.

The extended amygdala

The extended amygdala consists of the bed nucleus of the stria terminalis (BNST), central amygdala (CeA), and shell of the nucleus accumbens ($NAcc_{shell}$). The BNST is a small region located at the end of the stria terminalis, a white matter tract connecting the BNST and amygdala. The CeA is a nucleus of the amygdala in the deep, medial temporal lobe. The NAcc is part of the ventral striatum and can be divided into the core and shell, of which only the $NAcc_{shell}$ is considered part of the extended amygdala.[26]

Seminal findings from rodent research have shown that the extended amygdala modulates behavioral responses to emotionally salient stimuli particularly associated with negative affect or reward. Specifically, the BNST is a central hub of anxiety-related behaviors[27] and plays a role in stress-induced alcohol reinstatement.[28] The CeA regulates fear processing, mediates the stress response, and contributes to anxiety-related behaviors during abstinence.[28,29] A recent comprehensive review summarizes contributions of the CeA and BNST to negative affect during alcohol abstinence.[30] The $NAcc_{shell}$ is involved in reward processing and motivated behaviors, which contribute to its role in aversion behaviors,[31,32] and drives compulsive drug seeking during abstinence.[33] Together, the BNST, CeA, and $NAcc_{shell}$ act to promote negative affect behaviors during abstinence and trigger stress-induced reinstatement.

Human imaging research of the extended amygdala recapitulates findings from rodent research, including preliminary support for a role in anxiety during abstinence. Importantly, due to resolution constraints associated with human imaging research, subcortical structures are rarely subdivided. Thus, addiction and anxiety literatures reviewed here will be of the amygdala and NAcc, unless the CeA or $NAcc_{shell}$ is specifically referenced. Much less research has been conducted on the BNST as methodological advancements of resolution and newly developed and validated BNST masks have only recently allowed for investigation of the BNST in humans, and the field is still in its infancy (for example see Avery et al.[19]).

Extended amygdala studies in humans have predominantly focused on anxiety, with less research in addiction. Evidence for increased BNST or amygdala activity in patients with anxiety disorders and in anxiety- or fear-provoking tasks has been aggregated in a number of systematic reviews (e.g. Avery et al[19], Shackman and Fox[20]). Less is known about the NAcc in anxiety, but evidence has demonstrated NAcc activation during avoidance of anxiety-provoking situations.[34]

Altered extended amygdala activity has been shown in AUD, though the results are varied. In general, the extended amygdala shows increased activation in response to alcohol cues in abstinent patients with AUD.[35] In addition, decreased amygdala volume is seen in patients with AUD who relapse compared to healthy controls and patients who remain abstinent.[36] The NAcc has increased resting-state connectivity with many cortical regions in patients with AUD who remain abstinent after six months compared to those who relapse.[37] A handful of studies have investigated the interaction of negative affect and addiction. One study found increased BNST-amygdala connectivity during fearful face viewing in abstinent

patients with a history of multiple relapses of AUD.[38] Overall, these studies support rodent findings by providing evidence for the extended amygdala's role in anxiety- and addiction-related neural processes.

The Insula

In addition to the well-characterized roles of extended amygdala in anxiety and addiction, converging evidence suggests a potential role for the anterior insula in anxiety during abstinence. The insula is a large and heterogeneous brain region, located deep to the lateral sulcus. In most mammals, including humans, the insula has a varied cytoarchitecture (agranular, dysgranular, and granular cortex), where 'granular' refers to the presence of cortical layer IV. Importantly, the spatial organization of these regions varies between species (for review see Gogolla[39]). Humans have a rostroventral agranular zone, a caudodorsal granular zone, and an intermediate dysgranular zone (Figure 2). Compared to humans, the rodent insula has a proportionately larger agranular zone, which comprises most of the anterior insula but extends into the posterior insula.[40] Due to differences in cytoarchitectural organization and relative size, direct comparisons between human and rodent insula findings are difficult. In addition, rodent studies typically segment the insula cytoarchitecturally, whereas typical human neuroimaging studies either 1) consider the insula as a single brain region; 2) create anterior and posterior insula subregions; or 3) further divide the anterior insula into dorsal and ventral subregions. Thus, human studies generally do not reflect underlying cytoarchitecture, further complicating direct comparisons with rodent studies. These limitations are an important caveat in translating findings between rodent and human literatures, suggesting the need for a more standard insula partition with translational validity.

Most commonly, human studies divide the insula into anterior and posterior subregions (Figure 2) separated by an anatomical landmark: the central insula sulcus. The anterior and posterior insula have overlapping but separate structural and functional connections.[41,42] The anterior insula is generally involved in emotional and cognitive processes;[43–46] the posterior insula is involved in sensory processing, including interoception, and sensorimotor integration.[43,47] When considered a distinct brain region, the anterior insula's functions make it an attractive region for evaluating perturbations in reward-related processes such as addiction and emotion-related processes including anxiety (for reviews see Naqvi and Bechara[48], Paulus and Stein[22]).

Rodent Studies

Are the anterior insula and extended amygdala connected?—Many preclinical studies have demonstrated largely unidirectional connections from the anterior insula to the BNST, CeA, and $NAcc_{shell}$[49–53] with a small number of reciprocal connections from the BNST to the anterior insula reported.[54] The anterior insula also has substantial connections to other subregions within amygdala and NAcc (e.g. Jasmin et al[55], Shi and Cassell[56]). Additionally, the amygdala and NAcc subregions are highly interconnected,[57,58] suggesting that the exchange of information between the anterior insula and extended amygdala could be direct and indirect. Methodological advancements in tracer studies, such as the ability to

map multisynaptic pathways, will be critical for confirming and extending what is known about the anterior insula connections to the extended amygdala.

Does the anterior insula have a role in abstinence?—The anterior insula has increased activity during abstinence, and connections between the anterior insula and extended amygdala are implicated in reinstatement and compulsive alcohol consumption in rodents. Following chronic alcohol intake, rodents have increased neuronal activity in the anterior insula during abstinence.[50] The BNST has increased neuronal activity during abstinence which attenuates with inhibition of anterior insula inputs to the BNST.[50] Inhibition of the anterior insula also prevents stress-induced reinstatement, providing evidence for the anterior insula's role in maintaining abstinence.[59] In a model of compulsive drinking, inhibiting insula inputs to the NAcc decreased alcohol seeking behavior.[60] More specifically, inhibiting anterior insula projections to the NAcc decreased alcohol consumption, yet silencing the whole insula increased alcohol self-administration, highlighting the need to examine the insula as distinct subregions.[61] Notably, these NAcc studies were core projections, indicating anterior insula projection studies specific to the shell. Overall, abstinence from alcohol increases neuronal activity in the anterior insula, and projections from the anterior insula alter extended amygdala activity and alcohol seeking behavior.

Does the anterior insula have a role in negative affect behaviors during abstinence?—Rodent studies investigating the role of the anterior insula in negative affect during abstinence are limited, but preliminary work is promising. A recent study showed BNST cells receiving anterior insular inputs drive negative affect behaviors during abstinence and inhibiting the anterior insula decreased the negative affect phenotype.[50] Given the limited rodent evidence, further dissection of anterior insular projections to the extended amygdala in addiction will likely provide valuable information about negative affect during abstinence.

Summary of rodent studies.—The anterior insula projections to the extended amygdala can alter neural activity and negative affect during abstinence. Anterior insula projections to the BNST reduce abstinence-related increases in BNST neuronal activity and decrease negative affect seen during abstinence. Further, anterior insula projections to the CeA and NAcc drive alcohol-seeking behaviors during abstinence, creating a link between negative affect and relapse.

Human Studies

Are the anterior insula and extended amygdala structurally connected?—Human DTI studies recapitulate much of the rodent research demonstrating structural connections between the anterior insula and the extended amygdala. Structural connectivity between the anterior insula and the amygdala has been reported by three studies,[62–64] with a fourth showing connectivity with a large "limbic" region of interest that included the amygdala.[41] To better characterize a more specific structural connectivity pattern, Ghaziri et al[63] divided the insula into 19 subregions and showed that the amygdala and NAcc had the strongest connectivity with the anteroventral insula, which is the location of agranular

cortex. Thus, the amygdala and NAcc are likely the most connected with the agranular insula, as seen in rodents. NAcc-anterior insula structural connectivity was also reported in an earlier study but did not specify a region within the anterior insula.[65] To date, no research has reported anterior insula-BNST structural connectivity, likely because few BNST structural connectivity studies exist.

Are the anterior insula and extended amygdala functionally connected?— Resting-state functional connectivity has been reported between the anterior insula and the extended amygdala, but findings are mixed. Multiple studies report connectivity between the whole insula and the BNST, amygdala, or NAcc (e.g. Roy et al[66], Robinson et al[67], Cauda et al[68]); however, few studies have specifically investigated the anterior insula. Of the studies describing anterior insula resting-state connectivity, the most consistently reported finding is amygdala connectivity.[64,69,70] However, one study only found amygdala connectivity with the posterior insula.[42] Several studies have specifically investigated the central nucleus of the amygdala (CeA) and report resting-state connectivity with both the anterior and posterior insula.[66,71] Of the studies looking at NAcc connectivity, two found anterior insula connectivity.[42,70] Another study reported anterior insula connectivity with the ventral striatum but did not specify the NAcc.[69] As with structural connectivity, few BNST resting-state connectivity studies exist. BNST studies to date have not shown connectivity with the anterior insula.[18,71,72] In summary, very few studies have specifically addressed whether the anterior insula has resting-state connectivity with the extended amygdala in humans; existing resting-state fMRI studies have mixed results, suggesting the need for future studies specifically examining anterior insula connectivity.

Does the anterior insula have a role in abstinence?—The anterior insula has a well-established role in abstinence, with structural and functional changes associated with substance use and relapse (for review see Garavan[73]). Structural differences have been observed in gray matter volume and cortical thickness. Compared to healthy controls, abstinent patients with AUD have smaller anterior insula volumes.[74–80] Smaller anterior insula volume is associated with higher impulsivity and compulsivity[81] and lower cognitive flexibility[82] in abstinent patients with AUD. Further, in abstinent AUD patients, thinner cortex in the anterior insula was associated with greater personal distress.[83] Decreases in volume reverse with longer lengths of abstinence,[74,84] suggesting that anterior insula volume may normalize over time of abstinence.

Studies of anterior insula function show that abstinent patients with AUD have heightened anterior insula activity during anticipation and presentation of drug-related cues, known as cue-reactivity. Heightened cue-reactivity has been shown in abstinent patients with recent history of alcohol dependence[85,86] although exceptions exist (e.g. Huang et al[87]). In abstinent AUD patients, insula activation to alcohol cue presentation was also positively correlated with faster reaction times.[85]

Abstinence from AUD also impacts anterior insula function during other emotional and cognitive processes. For example, during explicit social exclusion abstinent patients with AUD demonstrated heightened anterior insula activity compared to healthy controls and degree of insula activity correlated positively with subjective feelings of exclusion.[88] In

abstinent adolescent patients with AUD, greater total number of lifetime drinks correlated to decreased anterior insula activity during a spatial working memory task.[89] In a task probing metamemory, the awareness of episodic memory ability, the abstinent AUD group showed a positive correlation between anterior insula activation and metamemory. Anterior insula functional connectivity was weaker with the dorsal anterior cingulate cortex but stronger with the left lingual gyrus and the ventromedial prefrontal cortex in the AUD group. However, in the AUD group stronger insula-ventromedial prefrontal cortex connectivity was correlated with lower metamemory scores.[90]

Is anterior insula-extended amygdala connectivity altered in abstinence?—To our knowledge, there are not yet any human studies of alcohol abstinence demonstrating connectivity changes between the anterior insula and extended amygdala. One study reported greater structural connectivity between the anterior insula and striatum in abstinent patients with AUD;[91] however, the study did not specify regions within the striatum, making it impossible to discern whether the connection was observed in the NAcc. Likewise, another study found reduced resting-state connectivity between the basolateral amygdala and anterior insula in abstinent patients with AUD.[92] This study did not investigate anterior insula connectivity with the central amygdala or the whole amygdala, making conclusions about the extended amygdala impossible. Future studies are needed to explicitly test for altered insula-extended amygdala connectivity during abstinence.

Does the anterior insula have a role in anxiety?—Decades of research have characterized the anterior insula's role in emotional processing and regulation (for reviews see Craig[93], Lamm and Singer[46]). Specifically, the anterior insula has a role in both normative and pathological levels of anxiety. A common neuroimaging approach to studying anxiety is to examine threat anticipation, where participants learn to associate a cue or context with an upcoming aversive stimulus. During threat anticipation, healthy controls show increased anterior insula activation.[94–100] Anterior insula activation correlates with trait anxiety during both predictable[101] and unpredictable[102] threat anticipation. Further, during unpredictable threat, patients with anxiety disorders have greater anterior insula activation relative to controls.[98,103] Anterior insula activation also correlates with worry symptoms in healthy individuals during unpredictable threat[95] and when viewing negative emotional faces in patients with social anxiety disorder[104] and anxiety-prone individuals.[105] Anxiolytic medication attenuates anterior insula activity in both healthy controls during threat presentation[106,107] and patients with an anxiety disorder during both neutral and threatening stimulus presentation.[108] Together these studies demonstrate the anterior insula is involved in normative anxiety processes, has heightened activity in individuals with an anxiety disorder, and is modulated by anxiolytics.

Is anterior insula-extended amygdala connectivity altered in anxiety?—Three types of studies have been used to evaluate anterior insula connectivity with the extended amygdala in anxiety: anxiety tasks in healthy controls and patients with an anxiety disorder and resting-state studies in patients with an anxiety disorder. The most well-studied connection is between the anterior insula and amygdala. In anxiety tasks, stronger anterior insula-amygdala connectivity was observed in response to conditioned fear stimuli relative

to generalized stimuli in both healthy controls and patients with generalized anxiety disorder (GAD).[109] When viewing aversive stimuli, patients with GAD have increased anterior insula-amygdala connectivity compared to both healthy controls and GAD patients following treatment.[103] Interestingly, a meta-analysis of general emotion-related fMRI studies did not find anterior insula-amygdala connectivity,[110] suggesting the connection may not generalize to all emotions. In resting state studies, anterior insula-amygdala connectivity is stronger in patients with social anxiety disorder compared to healthy controls.[111] Less has been shown about anterior insula-BNST and anterior insula-NAcc connectivity. In one study, anterior insula-BNST connectivity was heightened during threat in healthy controls.[112] Although there is compelling theoretical evidence for an anterior insula-NAcc connection associated with anxiety and negative affect (for examples see Knutson et al[113], Porter et al[114], Lago et al[115]), this connection has not yet been shown. Overall, connectivity between the anterior insula and extended amygdala is stronger during rest in patients with anxiety disorders and is stronger during task-induced anxiety in healthy controls and in patients with anxiety disorders.

Is there evidence for a role of the anterior insula in anxiety during abstinence?—To our knowledge, only two studies have examined the anterior insula's role in anxiety during abstinence. During threat anticipation, higher scores of early life adversity correlated with decreased anterior insula activity in abstinent AUD patients.[116] In abstinent AUD patients, anterior insula had decreased activity across conditions of stress induction and craving induction.[117] Future studies will be critical to replicate and expand on these findings.

Summary of Human Studies.—In summary, the evidence demonstrates that the anterior insula is: 1) altered during abstinence in AUD as evidenced by smaller anterior insula volumes and heightened anterior insula activation to alcohol cues; 2) engaged by anxiety-provoking tasks in healthy controls; 3) more responsive to anxiety tasks in patients with an anxiety disorder; 4) functionally connected with the amygdala and BNST, particularly in patients with anxiety disorders; and 5) more strongly connected to the amygdala at rest in patients with anxiety disorders. Preliminary evidence also suggests a role for the anterior insula in anxiety during abstinence.

Conclusions and Future Directions

This review has examined evidence to consider the anterior insula as an additional part of the abstinence network. The evidence shows that the anterior insula demonstrates connectivity with the established abstinence network, with structural and functional connectivity to the extended amygdala in rodents and to the amygdala and NAcc in humans. Based on converging rodent and human evidence, the anterior insula has a role in both abstinence and anxiety, and in humans, anterior insula connections with the amygdala and BNST strengthen during anxiety. A role for the anterior insula in anxiety-like behaviors during abstinence has been supported by rodent research and preliminary human findings. Further, in rodents, connections between the anterior insula and extended amygdala are critical for expression and maintenance of negative affect during abstinence. Considering the evidence from both rodents and humans, we propose the anterior insula as a core brain

region involved in anxiety during abstinence and should be considered part of the abstinence network.

Known functions of the anterior insula could contribute to its role in anxiety during abstinence. One possible role for the anterior insula in anxiety during abstinence is to initiate alcohol seeking in response to anxiety-provoking stimuli. The anterior insula is thought to integrate sensory information from the posterior insula with memory and context to elicit emotion and motivate a behavioral response (e.g. Craig[45], Craig[93]). We propose that during abstinence the posterior insula interprets stress-related autonomic signals from interoception and other sensory inputs, which combines with context cues to elicit anterior insula hyperactivity and results in downstream activation of the extended amygdala. The activated extended amygdala then produces anxiety behaviors through outputs from the amygdala and BNST. The anterior insula and extended amygdala activation will also produce exaggerated responses to anxiety-provoking or alcohol-related cues, triggering alcohol seeking through connections with the NAcc. Thus, in response to stressors, connections from the anterior insula to the extended amygdala could increase both anxiety and alcohol-seeking behavior.

Based on the evidence presented in this review, we propose that the anterior insula be considered, along with the extended amygdala, part of the abstinence network. However, many important questions remain unanswered; it will be critical for future research to thoroughly test this expanded network in both animal and human studies. We propose the following initial future research directions:

Conduct rodent studies that further delineate anterior insula effects on negative affect during abstinence.

Current methods that manipulate specific projections *in vivo* could be used to investigate the effect of anterior insula projections; for example: Does input from the anterior insula alter interactions between amygdala, BNST, and NAcc?; Can anterior insula inputs to the extended amygdala alter the extended amygdala response to other abstinence-related inputs?; and How do anterior insula inputs to the extended amygdala alter abstinence-related behaviors that are driven by the extended amygdala?

Translate rodent findings of connections between the anterior insula and extended amygdala to humans.

A seminal study has identified the major structural connections of the human BNST.[18] More targeted studies are needed to test specific connections observed in rodents. Functionally, rodent studies have begun to investigate the influence of negative affect on the anterior insula in abstinence. Human neuroimaging studies using anxiety-inducing tasks to investigate the effect of anxiety on the abstinence network in abstinent patients with AUD will provide greater insight into the functional role of these connections.

Evaluate the influence of sex in the abstinence network.

Stress and negative affect are more likely to coincide with a new AUD diagnosis in women, and negative affect and alcohol-related measures are more strongly correlated in women (for review see Peltier[118]). Women also have increased risk of stress- or anxiety-induced relapse

and greater negative affect during abstinence (for review see Becker and Koob[119]). In addition, sex differences in brain structure and function, including in the anterior insula and extended amygdala, are widespread. To date, very few studies have investigated sex differences in the abstinence network in humans, particularly in studies of anxiety during abstinence. Future studies could help establish if epidemiological differences in anxiety during abstinence are driven by sex-based differences in the abstinence network.

Explore the interaction between craving and anxiety.

Craving and anxiety are both known to trigger relapse and likely interact to increase risk of relapse (e.g. Sinha et al[120]). Treatment studies have shown that some medications that decrease anxiety during abstinence also decrease craving (e.g. Bruno[121], Gimeno et al[122]). Studies have also identified the anterior insula as a critical brain region mediating craving, suggesting that the anterior insula could play a role in understanding the interaction between anxiety and craving. Important future questions should include whether the abstinence network contributes to craving as a network, or if the intersection of craving and anxiety during abstinence is limited to the anterior insula. Further, are there individual differences in anxiety during abstinence that could explain why some can abstain from drinking when experiencing craving compared to others who relapse? Are these differences reflected by activation or connectivity differences in the anterior insula?

Extend findings to other substances.

This review focused on alcohol, but negative affect during abstinence has been described in other substances of abuse. It will be important to determine the generalizability of the anterior insula's role in abstinence-induced anxiety. Do CNS depressants have similar brain changes in abstinence as CNS stimulants? Can our findings from abstinence in AUD help tackle the opioid epidemic or rising rates of e-cigarette use in adolescence? Studies of other substances have also shown a role for the anterior insula in abstinence. For example, a number of nicotine studies in humans suggest involvement of the anterior insula in anxiety during abstinence. Currently most only investigate short-term abstinence (~24 hrs) (for examples see Froeliger et al[123], Sutherland et al[124]), making withdrawal and abstinence more difficult to differentiate. Thus, future studies will be critical to determine how the abstinence network contributes to anxiety during abstinence for other substances.

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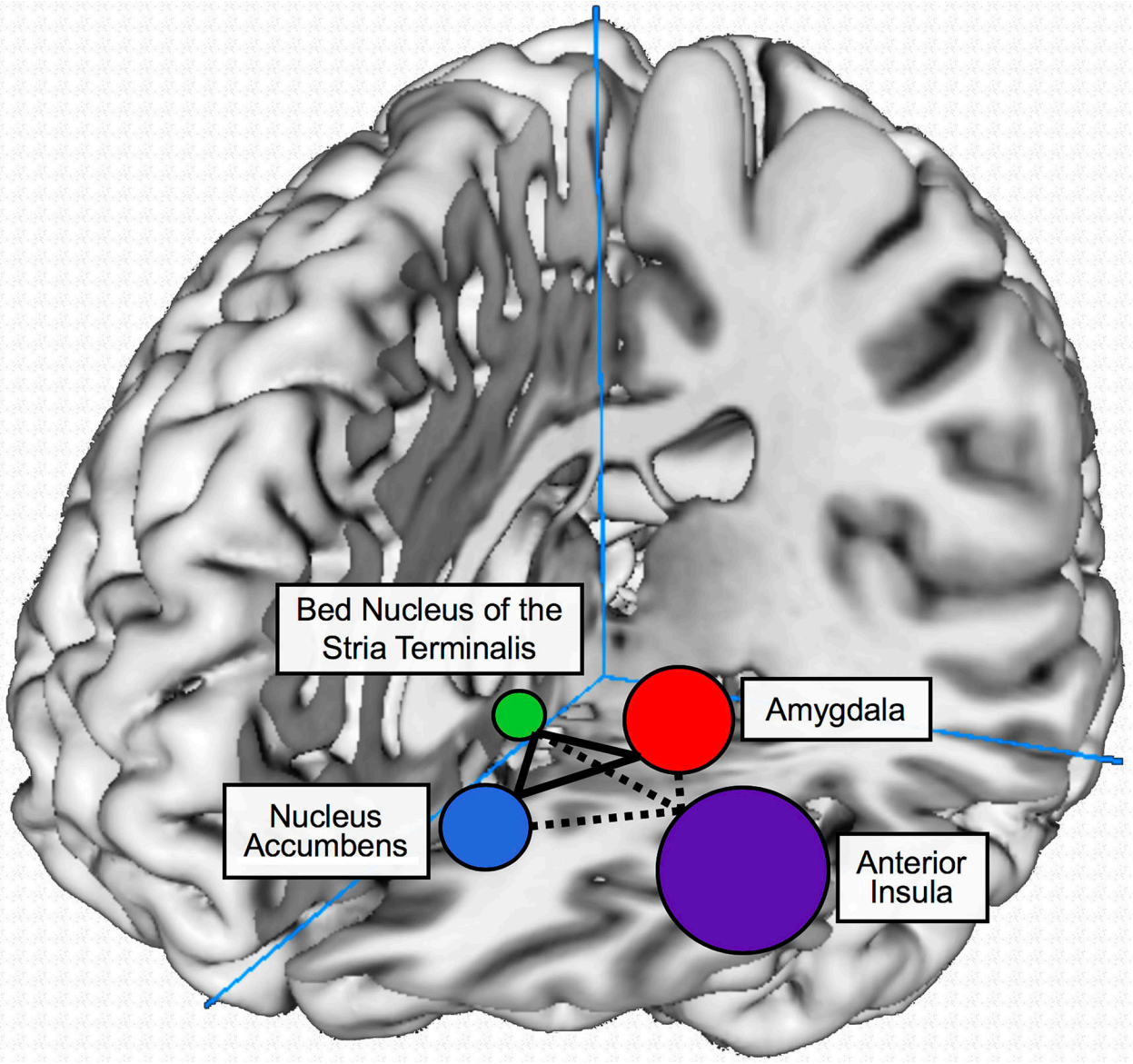

Figure 1:
The abstinence network. Solid lines: current model; extended amygdala. Dotted lines: proposed model; with the addition of the anterior insula.

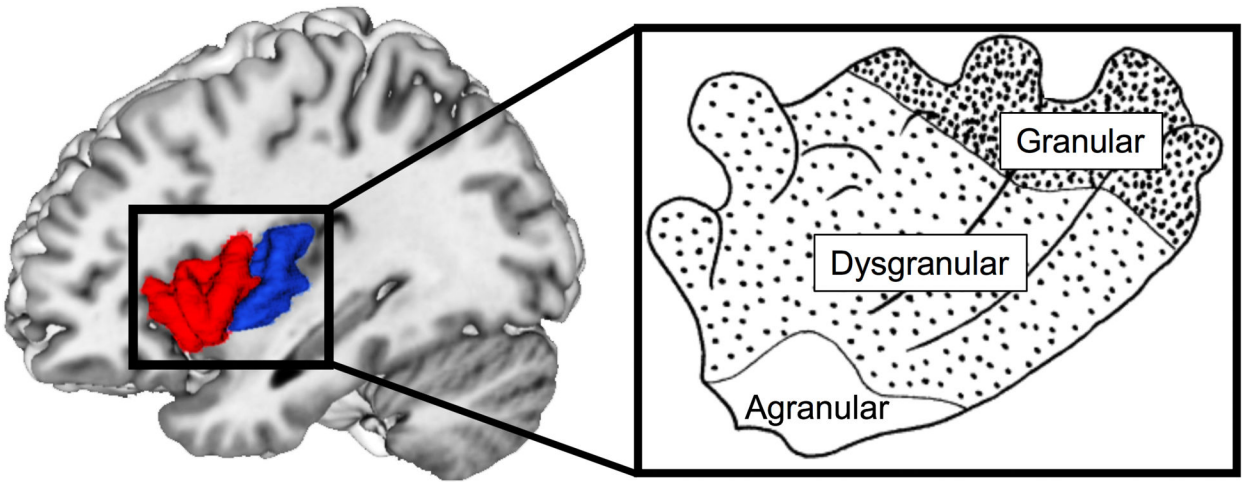

Figure 2:
Subregions and cytoarchitecture of the human insula. Left: common anterior and posterior division of the human insula. Red, anterior insula; blue, posterior insula. Right: cytoarchitectural regions of the human insula (image adapted from Nieuwenhuys 2012).

Table 1:

Human imaging studies of abstinence in patients with AUD

Brain Morphometry

Study	Participants	Method	Findings in AUD
Cardenas 2007	25 AUD 8 HC	GMV	Abstinent participants recovered tissue in anterior insula faster than relapsed participants
Chanraud 2007	31 AUD 38 HC[a]	GMV	Correlation between volume of anterior insula and a measure of cognitive flexibility, speed, and shifting ability
Mechtcheriakov 2007	22 AUD 22 HC	GMV	Reduced left anterior insula volume
Makris 2008	21 AUD 21 HC[a]	GMV	Decreased NAcc, amygdala, and anterior insula volume, NAcc and anterior insula volume loss reverses with length of abstinence
Demirakca 2011	50 AUD 66 HC	GMV	Decreased anterior insula right hemisphere volume
Van Holst 2012	36 AUD 54 HC	GMV	Reduced right anterior insula volume
Trick 2014	29 AUD 31 HC	GMV	Decreased anterior insula volume
Senatorov 2015	26 AUD 24 HC	GMV	Decreased anterior insula volume, increased amygdala volume
Zois 2017	95 AUD 87 HC	GMV	Decreased anterior insula volume
Grodin 2017	60 AUD 49 HC	GMV and Cortical Thickness	Anterior insula volume and cortical thickness decreased, anterior insula volume negatively correlates with self-reported impulsivity and compulsivity
Schmidt 2017	13 AUD 20 HC 14 HR	Cortical Thickness	Decreased anterior insula cortical thickness in AUD compared to both HR and HC; higher “personal distress” correlated with reduced CT in anterior insula

Functional MRI

Study	Participants	Task	Findings in AUD
Task-Based fMRI			
Tapert 2004a	8 AUD 9 HC[b]	Alcohol cue reactivity	Heightened anterior insula activity to cue reactivity
Tapert 2004b	15 AUD 19 HC	Working Memory	Greater lifetime alcohol drinks consumed correlated to decreased spatial working memory
Maurage 2012	22 AUD 22 HC[a]	Social exclusion task	Social exclusion increased anterior insula activity
Seo 2013	45 AUD 30 HC	Craving and stress induction	Decreased anterior insula activity across stress, alcohol, and neutral cues
Yang 2015	15 AUD 15 HC[a]	Anticipatory anxiety	During anticipatory anxiety, negative relationship between childhood adversity interview and anterior insula BOLD signal

Le Berre 2017	24 AUD 26 HC	Episodic memory and Metamemory	Metamemory accuracy correlated with anterior insula activity. Connectivity between anterior insula and ventromedial prefrontal cortex during task associated with worse metamemory and memory performance
Schulte 2017	26 AUD 26 HC	Stroop match-to-sample with alcohol-related pictures	Anxiety correlated with craving scores; alcohol craving correlated with behavioral cue reactivity to alcohol pictures, behavioral cue reactivity correlated with anterior insula activity; reaction time to alcohol cues correlated to anterior insula activity
		Resting-State fMRI	
Orban 2013	29 AUD 22 HC[b]	Resting state	Significantly reduced positive synchrony between left BLA and left anterior insula
Kohno 2017	43 AUD 26 HC	Resting state	Greater striatum – anterior insula connectivity

[a]All male participants

GMV = Grey Matter Volume

AUD = Patients with Alcohol Use Disorder

HC = Healthy Controls

High Risk = family history of AUD

[b]All female participants