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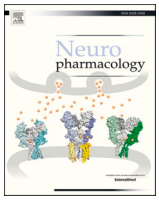

Better living through understanding the insula: Why subregions can make all the difference

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ABSTRACT

Insula function is considered critical for many motivated behaviors, with proposed functions ranging from attention, behavioral control, emotional regulation, goal-directed and aversion-resistant responding. Further, the insula is implicated in many neuropsychiatric conditions including substance abuse. More recently, multiple insula subregions have been distinguished based on anatomy, connectivity, and functional contributions. Generally, posterior insula is thought to encode more somatosensory inputs, which integrate with limbic/emotional information in middle insula, that in turn integrate with cognitive processes in anterior insula. Together, these regions provide rapid interoceptive information about the current or predicted situation, facilitating autonomic recruitment and quick, flexible action. Here, we seek to create a robust foundation from which to understand potential subregion differences, and provide direction for future studies. We address subregion differences across humans and rodents, so that the latter's mechanistic interventions can best mesh with clinical relevance of human conditions. We first consider the insula's suggested roles in humans, then compare subregional studies, and finally describe rodent work. One primary goal is to encourage precision in describing insula subregions, since imprecision (e.g. including both posterior and anterior studies when describing insula work) does a disservice to a larger understanding of insula contributions. Additionally, we note that specific task details can greatly impact recruitment of various subregions, requiring care and nuance in design and interpretation of studies. Nonetheless, the central ethological importance of the insula makes continued research to uncover mechanistic, mood, and behavioral contributions of paramount importance and interest.

1. Overview

The insular cortex is an expansive brain area spanning the anterior/posterior gradient of the brain in humans and animals. The insula has emerged as central in numerous subfields of neuroscience, where it seems to be an integral component of behavior in many disease and non-disease states. In recent years, clinical research of insula subregions has exploded, leading to identification of between 2 and 13 insula subregions based on anatomic and/or functional information used in the parcellation technique (Wager, 2004; Deen et al., 2011; Cauda et al., 2012; Chang et al., 2013; Uddin et al., 2014; Alcauter et al., 2015; Droutman et al., 2015; Glasser et al., 2016; Ghaziri et al., 2018). At the simplest level, the insula can be anatomically segmented into anterior and posterior insula lobes by the central insular sulcus (Faillenot et al., 2017). Both human and non-human primate work shows that these lobes have distinct cytoarchitecture and connectivity patterns (Mesulam and Mufson, 1985; Augustine, 1996; Taylor et al., 2009), with the anterior more connected with frontal and limbic structures (Carmichael and Price, 1994; Cauda et al., 2011), and the posterior more connected with motor and sensory areas (Cerliani et al., 2012; Jakab et al., 2012). These coincide with functional distinctions, with anterior lobe associated more with emotion and cognition and posterior linked with sensory processes (Craig, 2010) (detailed below). Dividing the insula into two lobes represents one of the largest and easiest to define functional distinctions

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within the insula. However, these lobes can be further parsed based on gross anatomy, cytoarchitecture, and fiber tracing (Faillenot et al., 2017), which align with functional meta-analyses identifying four subregions; dorsal anterior (dAINS), ventral anterior (vAINS), middle (MINS), and posterior insula (PINS). On a cytoarchitectural level, the insula is characterized as agranular, dysgranular, or granular where granular refers to the presence of all six cortical layers, dysgranular a small layer IV, and agranular lacking a layer IV altogether.

The emergence of the insula as integral for a number of behavioral functions, coupled with its large size, has led to numerous nomenclature systems, with differential anatomical delineation between insula subregions (based on cytoarchitecture, afferents/efferents, behavior, etc). Moreover, species differences in all these factors have complicated comparisons of studies in humans with those in rodents, and mice with rats. As the insula continues to gain popularity for its role in attention, motivation, mood disorders, addiction, and higher order cognitive functioning and consciousness in humans, there is an increasing need to centralize what we know about the insula and its subregions, especially to define commonalities (and differences) between human, non-human primate, and rodent studies to guide more accurate subregion delineation based on a number of factors collectively.

The goal of this review is to provide a thorough overview of the insula as studied in human and animal literature, with a focus on insular subdivisions where possible. This review will compare functions, behaviors, and afferents/efferents across species, with the hopes of drawing a holistic map of the insula to guide future insula research. In setting out to achieve this goal, this review will highlight the historical disconnect between clinical and preclinical insula research, in an attempt to facilitate future coordinated efforts to bridge this gap and delineate this integral brain area and its role in guiding interoceptive behaviors.

2. The human insula

Unbiased clinical neuroimaging studies have long identified the insula as significantly involved in numerous behaviors, disorders, and related dysfunctions. However, many of these earlier human imaging studies failed to report specific subregions of the insula, complicating generalizable interpretations for the insula's many roles in human behavior. As will be discussed below, different subregions of the insula can have dramatically different-even seemingly diametrically opposed-roles in specific behaviors. With that caveat in mind, the following section will provide an overview of the insula literature and the major conclusions deduced, while in some cases refraining from attempts to tie together and overinterpret disparate findings.

Several seminal clinical neuroimaging studies provided much insight into the insula's roles in regulating behavior. For example, stroke damage to the insula decreases the urge to smoke in long-term tobacco smokers, resulting in easier smoking cessation (Naqvi et al., 2007), while greater insula reactivity to smoking stimuli in anatomically-intact individuals is linked with larger likelihood of relapse to smoking (Janes et al., 2010, 2017). These findings support the concept that the insula sits at the convergence of interoception (bodily urges) and drive for action, which is important in many motivated behaviors. However, it is not always apparent how insula subregions play a distinct role, as stroke-induced lesions typically involve widespread damage, and task-related activation often co-activates different subregions. One influential model describes a caudal to rostral flow of information, where PINS encodes more somatosensory information, which is passed forward and integrated with emotional information in MINS, that in turn projects to AINS where sensory/limbic input is integrated with cognition and planning (Craig, 2009; Kurth et al., 2010; Cauda et al., 2012; Droutman et al., 2015). Indeed, using autonomic regulation as an example, the AINS and PINS show similar changes when parasympathetic arousal increases attention and cognitive function (Barber et al., 2020), and may work together when salient stimuli recruit autonomic responses to promote stronger behavioral performance (Schmidt et al., 2009). Conversely, reduced AINS and PINS activity are both associated with disrupted working memory in those with an alcohol use disorder (AUD) (Sullivan et al., 2021). However, as detailed below, there are also clear divergences in function. Thus, it is likely that subregions make differential contributions, but still often work together in a larger integrative role. There are several candidate avenues for dividing the insula (e.g., function, circuitry, cytoarchitecture) that could dramatically increase consistency and interpretability of future insula research. Unfortunately, several earlier neuroimaging studies simply implicated insula involvement in a behavior and did not report specific insula-centric circuitry and how it relates to function. As the literature stands, anatomically subdividing the insula is currently the most consistent method, therefore the following sections will review the anterior (AINS), middle (MINS), and posterior (PINS) insula.

2.1. The human anterior insula

2.1.1. Suggested roles for the AINS in regulating behavioral action

Before considering possible functional differences between dorsal and ventral AINS, we first address AINS as one functional unit, since AINS is often described this way. The AINS is the anterior-most portion of the insula's anterior lobe, and has received considerable attention due to its association with a range of processes including emotion, attention, working memory, bodily awareness, autonomic functions, pain, taste, and olfaction (Davis et al., 1998; Coghill et al., 1999; Craig, 2002, 2009, 2010; Rolls, 2016). More specifically, the AINS is thought to integrate cognitive, emotional, and sensory processes, giving rise to subjective feelings and awareness of emotional states (Wager, 2004; Craig, 2002; Gu et al., 2013). For example, greater right AINS activity is linked to better awareness of heartbeat and greater emotional experience (Critchley et al., 2004). Similarly, greater explicit awareness of fear increases behavioral and autonomic responses, which are mediated by AINS (Tabbert et al., 2011). Such findings not only support AINS contributions to bodily awareness, but also fit with Damasio's somatic marker theory, where bodily physiological signals influence the richness of perceived emotions, and, importantly, can be used to guide decision making (Damasio, 1996).

Another related conceptualization addresses AINS importance for expectation, anticipation, and awareness (Sarinopoulos et al., 2006; Gu et al., 2016; Addicott et al., 2017; Arulpragasam et al., 2018). Thus, AINS activity has been linked to expectation of, and empathy for, pain (Fazeli and Buchel, 2018; Fallon et al., 2020) (although also pain sensation, see below), and to anticipating both social rewards and social punishment avoidance (Martins et al., 2021). Also, when imagining a large future payoff, left AINS is more active when imagining future versus present value (Benoit et al., 2011). Further, AINS processes errors in order to alter responding, but especially for errors that one is aware of (reviewed in Ullsperger et al., 2010), and AINS activity correlations with autonomic indicators are related to a greater neural control state (and readiness to act) for aware (versus unaware) errors (Harsay et al., 2018). Thus, in this conception, AINS may simulate interoceptive feeling states associated with future states (as directly shown in rodent, Livneh et al., 2020) and possible course of actions, which helps determine whether to recruit cognitive and physical resources needed to act (Damasio, 1996; Craig, 2009).

When generating expectations, one may need to process unsureness before identifying the best response option. A number of studies find AINS activity under different forms of uncertainty, including ambiguity, skew rather than variability, and novelty (reviewed in Preuschoff et al., 2008). Right AINS activity is linked to unpredictability of preferred rewards (rather than reward encoding per se) (Berns et al., 2001). An interesting recent study also found that L-dopa, which increases dopamine, changes the exploration/exploitation trade-off (Chakroun et al., 2020), which is the choice between choosing either an uncertain, potentially higher value option (exploration) versus choosing a familiar

option with a known outcome (exploitation) (Cohen et al., 2007). L-dopa decreased exploration, which is associated with reduced uncertainty representation in AINS (and dorsal anterior cingulate cortex, dACC) (Chakroun et al., 2020). Also, AINS activation before uncertain feedback relates to greater arousal (Critchley et al., 2001) and regulation of attendant emotions (Mohr et al., 2010), and where uncertain conditions are likely of greater salience (with potential to be highly significant) and thus require greater attention and effort for accurate processing. Indeed, AINS activity can spike at the moment of recognition, when a solution suddenly comes to mind when mulling over a problem (see Craig, 2009). Similarly, greater AINS activity under higher potential risk/uncertainty has been considered readiness to make predictions when information becomes available (Preuschoff et al., 2008). Thus, AINS likely sits at the confluence of identifying important situations and processing unsureness to identify better response options.

Similar to an AINS role in estimating the best response plan, the AINS is considered critical for different aspects of behavioral control. For example, encoding of the main task plan (across a series of behavioral paradigms) was best represented by activity in AINS and dACC (Dosenbach et al., 2006, 2007, 2008; Nelson et al., 2010). This can be conceptualized as keeping the main, overarching task plan in mind, as a sustained control network (Krug and Carter, 2012), a multiple-demand network (Chong et al., 2017), and maintaining the overall reward value of an environment (Wittmann et al., 2020) to prevent errors (Eichele et al., 2008). AINS is also implicated in aspects of proximal behavioral control. While there are some mixed findings, suggesting little AINS role in basic inhibitory control (Cai et al., 2014), greater AINS activity is specifically linked to greater withholding of "no-go" responses (in a go/no-go task) after a salient stimulus, which is associated with AINS attentional processing (Happer et al., 2021). Also, thinner AINS in humans (Lopez-Larson et al., 2012), and thinner or inactivated AINS in rats (Pattij et al., 2014; Belin-Rauscent et al., 2016) is associated with higher impulsivity, while, in humans, greater AINS activity predicts less impulsivity (Kayser et al., 2012) and larger AINS predicts better attentional control (although not suppressing inappropriate behaviors) (Nouchi et al., 2016). In contrast, more AINS activity is linked to greater impulsivity in people with AUD (Lim et al., 2017); greater AINS activity in SUD humans may reflect larger cognitive effort (sometimes unsuccessful) to achieve the same outcome (e.g. Suarez-Suarez et al., 2020). Other findings suggest regulation of behavioral control by regions other than AINS. Left AINS and right MINS are active when suppressing conscious thoughts (clearing mind of all thoughts) (Wyland et al., 2003), and bilateral MINS is active when suppressing urges to blink (Lerner et al., 2009). Also, suppressing attentional interference is associated with greater AINS activity (Bunge et al., 2002), although actual response inhibition does not involve AINS but instead the adjacent ventrolateral PFC. Further, other work finds greater AINS activity for unsuccessful versus successful no-go trials, suggesting a role in evaluating the effectiveness of action rather than implementing control per se (Ghahremani et al., 2015). This is similar to AINS encoding of prediction errors in risk (e.g. Preuschoff et al., 2008), and right AINS activity when using information to improve decision making (Krawitz et al., 2010). Thus, AINS clearly can regulate behavioral expression, with both global and proximal contributions, while the exact contribution may vary with task conditions (addressed further below).

AINS processing of uncertainty, expectation, and control may come together to support the ability to maintain responding in the face of challenge. Some studies directly implicate AINS in compulsion-like responding for alcohol (Arcurio et al., 2015; Grodin et al., 2018), where adverse consequences must be ignored to continue drinking, a major obstacle to clinical treatment (discussed further below). If AINS helps overcome challenges to receive rewards, one would predict greater activation under higher challenge. Higher AINS activity is seen with increasing response control requirements (Dodds et al., 2011; Wu et al., 2019) and hard versus easy attentional demands (Deary et al., 2004; Brooks et al., 2017), while insula lesion reduces cognitive function under high load (Wu et al., 2019). Further, several studies show greater right AINS activity concurrent with decreased PINS, observed with harder memory demands (Jansma et al., 2007) and greater attentional load (Alnaes et al., 2014), which may reflect AINS suppression of potentially disruptive physiological signals from PINS. Further, greater AINS activity is associated with less behavioral interference from conflict (Bunge et al., 2002; Krug and Carter, 2012), better behavioral control under emotion (Shafritz et al., 2006; Levens and Phelps, 2008) but not non-emotion (Shafritz et al., 2006), and preventing intrusive memories from disrupting working memory (Nee et al., 2013), especially memory maintenance (D'Esposito et al., 1998). Further, imagining a large future reward reduces temporal discounting (decreased value when a reward is distant in time) (Benoit et al., 2011), one of many studies associating AINS with ignoring costs to gain rewards (further addressed in Supplemental Discussions in Darevsky et al., 2019; Darevsky and Hopf, 2020). AUD subjects may provide insights into how negative information can be ignored (Zilverstand et al., 2018). In AUD women, higher AINS activity under high-risk drinking situations is associated with DMN activation and greater AINS resting state functional connectivity (rsFC) with cue (hippocampus) and value (mPFC) areas (and PINS) (Arcurio et al., 2015). Similar AUD findings (mostly in males) found greater AINS rsFC with PINS and value-related areas (hippocampus and mOFC), but decreased rsFC with frontoparietal control regions (Halcomb et al., 2019). Further, inaccurate self-knowledge about memory disruptions in AUD is associated with greater right vAINS functional connectivity (FC) with DMN and weaker FC with dACC (salience network) (Le Berre et al., 2017). Taken together, these studies suggest that risk/consequence-resistant responding in AUD could reflect AINS-related inability to switch away from internal alcohol cue value representations, or other impaired state transitions , accompanied by decreased top-down control and impaired insight about impaired memory. Similarly, AINS can mediate pro-risk responding (Ayton et al., 2004; Xue et al., 2010), especially in people with higher urgency (Xue et al., 2010), and over-attributions that contribute to gambling, including "near-win" increases in drive to gamble and the "gambler's fallacy" (Clark et al., 2014; Pushparaj et al., 2015a). Thus, under some conditions including addiction, AINS can encode expectations, whether adaptive or maladaptive, which helps decrease the impact of conflict and allows behavior to continue.

It is important to note that AINS is also important for avoiding negative situations, rather than overcoming or ignoring negativity. A number of studies implicate AINS in risk aversion and avoidance learning (Knutson et al., 2008; Palminteri et al., 2012; Norbury et al., 2018; Nash et al., 2021), including rejection of options devalued by cognitive or physical effort (Benoit et al., 2011) or unfairness in an economic game (Sanfey et al., 2003). Further, AINS lesion in humans can lead to lack of response to pain or threat (Berthier et al., 1988), and reduced avoidance of the worst choices (Palminteri et al., 2012) (see also Clark et al., 2008). Similarly, AINS lesion in monkey prevents the normally decreased responding for a devalued reward (Machado and Bachevalier, 2007). Also, in a task where possibility of loss increases across time, AINS activity reflects this loss possibility and the drive to stop (Meder et al., 2016). As with many aspects of insula, there is some nuance to AINS negativity processing. Viewing unpleasant scenes under threat of shock increases defense reactivity, with AINS (and ACC) mediating the greater arousal by shock threat, rather than encoding negativeness per se (Sambuco et al., 2020). Similarly, under conditions with two aversive stimuli, AINS activity is specific for the more salient negative outcome (Fazeli and Buchel, 2018). Thus, AINS can encode motivationally-salient aversiveness, including avoidance of costs considered not worth it.

2.1.2. The AINS and large-scale brain networks

Another model describes AINS as a central node in the Salience Network, a core neurocognitive brain network involved in processing potentially important stimuli and situations (Seeley et al., 2007;

Sridharan et al., 2008; Menon and Uddin, 2010). For example, right AINS contributes to fast attentional capture (Happer et al., 2021), particularly for behaviorally relevant and novel stimuli (Downar et al., 2002), which potentially allows for imminent behavioral changes (Craig, 2010; Menon and Uddin, 2010) needed for action (Jansma et al., 2007; Eichele et al., 2008; Sterzer and Kleinschmidt, 2010) (see also Wen et al., 2012). Salience-driven attention shifts may relate to AINS importance for switching between large-scale brain networks (Sridharan et al., 2008; Goulden et al., 2014) (see also Corbetta et al., 2008), especially between the default mode network (DMN) and frontoparietal network, which support internally-focused cognition and top-down, goal-directed processes, respectively (Sridharan et al., 2008; Spreng et al., 2010).

2.1.3. Von Economo neurons: a cellular basis for higher order cognitive function?

The AINS may manage network control due to the presence of von Economo neurons (VENs), large bipolar neurons located within AINS and dACC (Allman et al., 2005, 2010). VENs are thought to quickly send basic information from insula to other regions, allowing for rapid information processing for cognitive and emotional decision making. In agreement, VEN disruption is noted in disorders such as fronto-temporal dementia, characterized by emotional and cognitive impairments (Seeley et al., 2006). Also, VENs are more prevalent in right versus left hemisphere, which fits with Craig's homeostatic model where right insula processes sympathetic activation, negative emotions, and pain, while the left insula is associated with parasympathetic engagement, positive emotions, and calming responses (Craig, 2005, 2009, 2011) (addressed further below). Allman and colleagues (Allman et al., 2011) suggest that greater right VENs may represent the evolutionary need to more quickly process threatening stimuli. However, brain structures in the right and left hemisphere are often co-active (e.g. Toro et al., 2008; Duerden et al., 2013), making it difficult to unequivocally define the relative contribution of each hemisphere. It is also important to note that VENS have been identified in a number of large mammals such as elephants, whales, and larger primates (reviewed in Cauda et al., 2014) suggesting a potential role for these neurons in long-range signaling. While VENS have not been observed in rodents, a subset of insula pyramidal neurons in mice expressing similar VEN-specific proteins may fulfill the VEN role in rodents (Butti et al., 2013). Regardless, the apparent absence of true VENS in rodents can confound any cross-species parallels in insula subregion functions, which would be separate from VEN contributions.

2.2. Psychopathologies and emotional (mis)regulation in the AINS

With AINS's critical role in cognition, emotion, and large-scale network dynamics, it comes as no surprise that this region is also implicated in a range of psychiatric disorders, including schizophrenia (Wylie and Tregellas, 2010), anxiety (Paulus and Stein, 2006, 2010, 2010; Baur et al., 2013), autism (Di Martino et al., 2009), and substance use disorders (SUDs) (Naqvi et al., 2007, 2014; Janes et al., 2010, 2017, 2020; Sutherland et al., 2013a, 2013b; Lerman et al., 2014; Fedota et al., 2016, 2018). Increased opioidergic tone in AINS may enhance negative affect in depressed individuals (Lutz et al., 2021), while greater AINS-amygdala FC is linked with more state and trait anxiety (e.g. Baur et al., 2013), but AINS is hypoactive in autism during social processing (Di Martino et al., 2009). In addition, therapy efficacy may be indicated by AINS changes, e.g. where greater symptom reduction after exposure-based psychotherapy for post-traumatic stress disorder (PTSD) correlates with larger decreases in FC between insula and other attention regions (Fonzo et al., 2020)

2.2.1. The AINS and substance use disorders

For SUDs, greater relapse vulnerability is linked both with enhanced AINS reactivity to drug-associated cues, including for cocaine (Prisciandaro et al., 2013; Hanlon et al., 2018), nicotine (Brody et al., 2002; McBride et al., 2006; Gloria et al., 2009; Janes et al., 2010, 2017), and alcohol (Claus et al., 2011; Schacht et al., 2013), and with blunted AINS reactivity during cognitive tasks such as risk evaluation (Gowin et al., 2015), decision making (Paulus et al., 2005), and working memory (Sullivan et al., 2021), which may impair top-down control. Reduced AINS volume has also been linked to addiction severity, with some recovery of AINS size with protracted abstinence (Chanraud et al., 2007). Further, in alcohol drinkers, AINS activation by negative stimuli correlates with negative urgency (impulsivity driven by negative affect) (Cyders et al., 2015), and right AINS activity best connects negative urgency and real-world alcohol drinking (Chester et al., 2016). Interestingly, while stimulant use overall decreased M/AINS FC with other regions, greater insula-striatal FC predicted resilience against developing SUD (Ersche et al., 2020). In addition, the GABAB receptor activator baclofen, which can reduce alcohol drinking, reduces threat cue-mediated activation of AINS in drinkers with comorbid anxiety (Morley et al., 2021). Also, while AINS activity can mediate where negative emotional states increase drive to drink alcohol (Seo et al., 2011; Cyders et al., 2015; Chester et al., 2016), one metanalysis found inconsistent emotion-related AINS activation in males with SUD, suggesting that greater emotionality might not underlie addiction-related drives (Wilcox et al., 2016). In contrast, women with SUD show greater insula activation by emotional stimuli (Potenza et al., 2012), suggesting possible sex differences in emotion-addiction interactions.

Thus, insula is deeply tied to many psychopathologies, and perhaps treatment success; the nature of such plasticity is a very interesting future question. However, insula involvements may not simply relate to ubiquitous increases or decreases in insula function. For instance, substance use relapse is related to both increased insula activation to drug stimuli and decreased activation during other cognitive processes. Thus, structural and/or functional disruptions could reduce cognitive control (akin to hypofrontality) and also cause insufficient local regulation that allows greater insula activation by salient cues. This is one of several cautionary notes against an overly simplistic view of the insula, and, instead, indicates the need for caution and nuance.

2.2.2. The AINS and affective state

One widespread thread centers around AINS-related (mis)regulation of emotional state. Indeed, AINS is considered to represent salience at an interoceptive/feeling level (which recruits autonomic and cognitive resources in case action is needed), and AINS mediation of anxiety and stress could contribute broadly across adaptive and pathological conditions (Gogolla, 2017; Zhang et al., 2021). While AINS activity and FC with DMN can be associated with better self-control and emotional regulation (Li et al., 2021), excessive AINS activity is widely linked to anticipation and expression of anxiety (Critchley et al., 2004; Carlson et al., 2011; Terasawa et al., 2013; Adhikari, 2014), including worrying about negative self-relevant events like job loss (Hoehn-Saric et al., 2004), and during provoked symptoms in those with phobias, PTSD, and obsessive-compulsive disorder (OCD) (Rauch et al., 1997). Paulus and Stein (2006, 2010) suggest that AINS contributions to anxiety reflect overinterpretation of negative stimuli, giving them more value and impact (Etkin and Wager, 2007), which may involve greater insula-amygdala FC (Baur et al., 2013; Jung et al., 2018). Greater AINS encoding of anxiety can impair learning (e.g. Nash et al., 2021), although behavioral impairments under higher anxiety can be associated with less AINS activity (Krug and Carter, 2012), suggesting inefficient management of challenge.

Other work may clarify AINS contributions to emotional reactivity under anxiety. People with anxiety disorders show greater AINS and autonomic changes to aversive cues under conditions of uncertainty (Hiser et al., 2021), suggesting that unpredictability enhances aversive events in anxiety through AINS circuitry. AINS also activates for unexpected stimuli, which is transient for emotion-neutral but sustained for emotion-laden stimuli (Han et al., 2019). Further, since greater AINS

activity correlates with greater heartbeat detection as well as trait anxiety (Critchley et al., 2004), one speculation is that, since we have limited control over the outside world, greater awareness leaves one open to the unpredictable possibility that negative events will occur and be experienced. In this model, accurate cognizance involves rational greater anxiety (reasonable anticipation that negative outcomes would occur at some point), which can easily become pathological.

AINS links to emotional regulation are paralleled by modulation of autonomic states (Craig, 2002, 2005, 2009; Oppenheimer and Cechetto, 2016; Rolls, 2016; Roquet and Conti, 2021). AINS activity mirrors skin conductance responses during arousal (Nagai et al., 2004), and AINS stimulation modulates cardiac function in humans (Sanchez-Larsen et al., 2021) and rodents (discussed in Funk and Stewart, 1996). Also, arousing pictures lead to more physical force and lower effort sensation when responding for reward, with greater AINS activity related to arousal level, reward magnitude, and effort generated (Schmidt et al., 2009). Others emphasize AINS interactions with the noradrenergic system, a known regulator of autonomic function, including for attention (Ullsperger et al., 2010). Activity of dAINS, recorded with intracranial electrodes in human, mediates the ability of salient cues to increase pupil diameter (Kucyi and Parvizi, 2020), which can reflect noradrenergic function (Oppenheimer et al., 2016), while noradrenergic inhibition in rodent AINS reduces autonomic responses to stress (Funk and Stewart, 1996; Alves et al., 2009, 2014). Thus, autonomic regulation is likely a critical mechanism by which AINS integration of emotional and cognitive inputs (in concert with other salience-processing regions) facilitates rapid decision-making under salient conditions.

2.2.3. Distinct roles for dorsal and ventral AINS

AINS has been functionally subdivided into dorsal and ventral components. Original meta-analyses implicated vAINS in emotional processing, with dAINS more cognitive (Wager, 2004; Deen et al., 2011). However, when comparing emotion and attention-switching tasks (Wager, 2004), vAINS activates more during emotional tasks, while dAINS activates for both task types. However, eliciting emotion likely also involves attention redirection. Thus, for many tasks, it has been challenging to definitively parse the functional roles of dAINS and vAINS. More recently, it has been hypothesized that dAINS and vAINS contributions may relate more to external and internal processing, respectively, rather than emotion versus cognition per se. This fits with AINS acting as a "causal outflow hub" which facilitates switching between large-scale brain networks subserving internal processing or goal-directed cognition (Uddin et al., 2011) (described above). Wang, Zhu, and colleagues (Wang et al., 2018b) took this a step further by showing vAINS FC with limbic and DMN structures, which subserve emotional processing and internally-focused cognition, with dAINS more connected with attention and goal-directed networks. Indeed, a recent connectivity study confirmed vAINS interactions with autonomic and emotional regions, and dAINS with more cognitive areas, across humans and rodents (Tsai et al., 2020). However, other studies have somewhat different findings: using a simple gambling task to dissociate presence of risk (uncertainty of outcome) from risk prediction error (how risk prediction changes with new information), right dAINS activity reflects risk presence, while right vAINS reflects prediction error (Preuschoff et al., 2008), and both risk presence and risk changes occur in the external world and likely lead to internal affective changes.

2.2.4. Dorsal and ventral AINS, laterality, and addiction

As described above, the AINS is intricately involved in many aspects of addiction. Recent neuroimaging studies have begun to further parse apart the AINS to account for potential differences within the AINS. For instance, Wang and colleagues (Wang et al., 2018a) linked externally- and internally-oriented systems with the dorsal dAINS and vAINS respectively. This distinction was replicated by our group when studying nicotine dependent smokers where the dAINS show more functional connectivity with an externally oriented system including aspects of the fronto-parietal network, while the vAINS is more connected with the internally-oriented DMN (Janes et al., 2019). These systems also were specifically linked with internally versus externally generated craving. In a double dissociation, baseline craving (internally generated) relates to greater rsFC of vAINS, while cue-induced brain activation (externally generated) relates to greater dAINS rsFC. Considering baseline craving as driven by internal physiological urges, and cue-related craving from external stimuli, our results support vAINS and dAINS links to internal- and external-localized triggers for craving to smoke. One other speculation of interest is that the greater dAINS-rACC rsFC occurs before presentation of the smoking cue, suggesting that this greater basal dAINS-rACC FC leads to greater focus on external factors and thus greater rACC cue activation and cue-induced craving. In addition, these rsFC patterns of vAINS and dAINS might serve as biomarkers for susceptibility to baseline and cue-related cravings (Dunbar et al., 2014).

Fedota et al. (2018) examined insula rsFC patterns after 48 h abstinence, where withdrawal symptoms would be much stronger than 1 h after smoking as in the study described above (in Janes et al., 2019). Interestingly, after longer abstinence, right dAINS (and PINS) showed increased FC to DMN areas, and greater PINS FC with dACC and other regions, while there was reduced FC between right vAINS and executive control areas (whose level correlated with craving). The authors note that this doesn't match a simple model of AINS for switching between external and internal perspectives. Instead, the ostensibly external dAINS shows greater connectivity to internalizing DMN, with vAINS detached from some cognitive control areas, which together may increase adversity during abstinence and activate aversion-driven urges for intoxicants that characterize negative reinforcement (Koob, 2013). In addition, the implication of right AINS after abstinence (Fedota et al., 2018) and left AINS in more sated smokers (Janes et al., 2019) could support the speculation that left AINS activity mediates anticipated positive effects under conditions where cravings are present but more manageable, while right AINS regions dominate when aversive affect is much stronger. For example, left AINS FC with nucleus accumbens (NAcb) mediates pleasure from the violence of mixed martial arts (Porges and Decety, 2013), and left MINS FC with NAcb is greater when overcoming disgust to enjoy watching pimple popping videos (Wabnegger et al., 2021). In contrast, other conditions could be considered "management of negative emotions," such as FC of right AINS and NAcb relating to subjective and objective compulsivity for alcohol in heavy human drinkers (Grodin et al., 2018) (described above). Thus, one future hypothesis worthy of testing is whether right-versus left--dominant AINS activity (and in dAINS vs vAINS) reflects the attempt to mitigate negative emotions, which may depend on the level of adversity of the situation.

2.3. The human posterior and middle insula

2.3.1. Suggested roles for the PINS and MINS in regulating behavioral action

While the AINS has received significant focus due to its role in higher-order functions, the AINS likely relies on interoceptive signals from caudal insula areas. As noted above, one central hypothesis involves a posterior-to-anterior flow of information, where sensory information within PINS is passed anteriorly, via dense anatomical connections (Mesulam and Mufson, 1982), to allow for awareness of interoceptive states and integration of sensory/limbic information with cognition and planning (Craig, 2002, 2009; Critchley et al., 2004; Cauda et al., 2012; Droutman et al., 2015). However, caudal insula areas also likely play important roles in their own right. MINS has been linked to important aspects of interoceptive processing, including interoceptive attention (Kurth et al., 2010; Schulz, 2016), interoceptive recall (DeVille et al., 2018), and other interoceptive signals (Avery et al., 2015). Further, a longitudinal study in adolescents who gain body fat maintain MINS responses to cues predicting milkshake delivery, while non-fat-gainers have reduced MINS cue-related activation (Stice and

Yokum, 2016). Also, dissonant smokers (who dislike their smoking) have stronger responses to smoking cues in right MINS and left PINS (Stippekohl et al., 2012). MINS is also beginning to emerge as critical in the pathology of depression and anxiety, where MINS activity during a cardiac attention task relates to state and trait anxiety (Tan et al., 2018). However, major depressive disorder is linked with reduced dorsal MINS activity during interoceptive attention (Avery et al., 2014) and interoceptive recall (DeVille et al., 2018), leading Avery et al. (2015) to suggest that enhanced signals from the amygdala are being sent to MINS. This fits with the theory proposing that noisy interoceptive signals play a primary role in anxiety and depression, making it difficult to use interoceptive information to predict the influence of environmental stimuli (Paulus and Stein, 2010).

The model linking sensory PINS to limbic MINS and then cognitive AINS would be supported by evidence implicating both anterior and caudal insula for a particular condition. Many such studies relate to autonomic function. AINS and PINS show similar changes in activity under conditions involving parasympathetic arousal which increases attention and cognitive function (Barber et al., 2020). In addition, stimulating AINS or PINS leads to similar slowing of heart rate (Sanchez-Larsen et al., 2021). Further, AINS and PINS may work together to allow salient stimuli to recruit autonomic responses to promote greater behavior (Schmidt et al., 2009). Similar AINS/PINS activity changes are also seen when tasting pleasant or unpleasant foods (Small et al., 2003). In addition, AINS is active for anticipated touch, which correlates with experienced touch intensity and also PINS activation, suggesting that AINS helps drive PINS activity and touch experience (Lovero et al., 2009). Also, decreased AINS and PINS activity in problem alcohol drinkers correlates with disrupted memory (Sullivan et al., 2021). Further, AINS and MINS are active for both social cognition and music perception (with PINS also in the latter) (Van 't Hooft et al., 2021). In contrast, other work dissociates insula subregion contributions to interoception, exteroception (attention and cognitive control), and affective processing (emotional awareness) (Simmons et al., 2013a); MINS and PINS are more active for interoception, with dAINS for exteroception and vAINS for anxiety (see also Farb et al., 2013). Similarly, MINS is more linked to interoceptive attention (attending to heartbeat), while right dAINS is related to interoceptive accuracy (correctly counting heartbeats) (Haruki and Ogawa, 2021). However, Simmons et al. (2013a) note many similarities in rsFC of different insula subregions with other brain areas, consistent with insula integrating information across other systems. Thus, it is likely that subregions make differential contributions, but still often work together in a larger integrative role.

Another possible conception focuses on AINS importance under uncertain or ambiguous situations, while MINS/PINS could mediate salient but well-defined or at least subjectively certain situations. At a simpler level, MINS activity relates to the pleasantness of chocolate (Small et al., 2001), PINS FC to NAcb at rest and for food rewards is greater when hungry (Charroud et al., 2021), and dorsal MINS processes gustatory signals and visceral interoception (Avery et al., 2015). Also, left MINS is related to love under long-term romantic conditions (including greater subjective and autonomic activation) (Bartels et al., 2000). Further, MINS/PINS are active when learning an intuition-based coordination task; while this would seem to involve uncertainty, insula activity is related to subjective effortlessness (Kuo et al., 2009), suggesting that the subjective relationship to the task may lead to certainty that the game is solvable. Perhaps in agreement, rats can perform complex and challenging but well-learned tasks without AINS (Ragozzino and Kesner, 1999). Thus, the subjective relationship to an event (certainty vs uncertainty) may be what recruits particular insula subregions. Further, studies noted above implicate MINS/PINS for interoception and interoceptive attention (Farb et al., 2013; Simmons et al., 2013a; Haruki and Ogawa, 2021), requiring simple attention to internal states. These could be more subjectively certain (simply attending to internal state) relative to dAINS encoding of exteroceptive signals (Simmons et al., 2013a) or interoceptive accuracy (counting heartbeats) (Haruki and Ogawa, 2021), or vAINS encoding of anxiety (Simmons et al., 2013a). Finally, in studies of insula encoding of salience (most intense conditions, whether good or bad), bilateral PINS is active in relation to salience but not value (e.g. strongly- vs weakly-liked good-tasting food) when choosing food to eat later (Litt et al., 2011). Similarly, in a risk task, AINS correlates with amount of risk, with maximal AINS activation with high or low reward probability (Preuschoff et al., 2008), more like a salience than value signal. In these studies, PINS encoded salience for a condition where an individual is certain (liked and disliked foods), versus AINS for uncertainty/risk. While speculative, these findings lend support for a caudal/rostral insula divergence for subjectively certain/uncertain events.

2.3.2. MINS and PINS in affective state

Some M/PINS responses link to important subcortical regions which regulate negative affect. For example, alcohol-dependent individuals exhibit greater PINS activation in response to negative/threatening images compared to healthy controls (Gilman et al., 2008a, 2008b). Furthermore, when PTSD patients anticipate aversive stimuli, MINS shows early hyperactivation along with amygdala, while AINS showed sustained increases in activity along with bed nucleus of the stria terminalis (BNST), a component of the extended amygdala involved in sustained anxiety (Brinkmann et al., 2017). Further, MINS/AINS rsFC with BNST is low in controls but higher in PTSD patients (Rabellino et al., 2018). In contrast to BNST, central nucleus of the amygdala (CeA), another component of the extended amygdala involved in acute stress and anxiety, shows rsFC with AINS, MINS, and PINS in healthy controls (Gorka et al., 2018). Thus, compared to the PTSD findings, other studies show different patterns in healthy controls. Only PINS shows rsFC with BNST in controls (Torrisi et al., 2015; Gorka et al., 2018), with AINS/MINS activation with a threat of shock. However, controls only show increased BNST-AINS FC and CeA-M/PINS FC under safe conditions (Torrisi et al., 2018). There are some mixed findings, as another study found BNST and CeA FC with both AINS and PINS (Berry et al., 2021), where differences among studies may reflect challenges in imaging such small regions. Nonetheless, these studies highlight the important influence of caudal insula pathways on acute and sustained threats, including for PTSD.

2.4. Comparing anterior, mid, and posterior insula function

Subregion differences in experience and expectation can be more complex under negative events. PINS activity for anticipation of loss predicts aversion to loss, with AINS for anticipating gain (Canessa et al., 2013). However, pain anticipation and experience can be represented in both PINS (Bitar et al., 2020; Brenner et al., 2021; Fu et al., 2021), and AINS (Makovac et al., 2020), with similar AINS findings for aversive images (Nitschke et al., 2006a,b). In youth with anxiety, actual but not anticipated pain relates to larger PINS activity (Abend et al., 2021), and PINS is linked to innocuous and noxious stimulation of the colon (Brenner et al., 2021). Also, a recent study compared pain experience and empathy, and found AINS activity for both experience and empathy, with PINS only for pain (Fallon et al., 2020). One challenge is that insula may embody the actual sensory experience, even when that experience is modified by expectations (which could occur through other brain areas). For example, under reduced expectation of pain (where distracted attention produces analgesia), PINS/MINS activity relate to the level of pain actually experienced (Brooks et al., 2017). Similarly, when expecting a bad taste to be less aversive, there is less taste-related MINS/PINS activity (Nitschke et al., 2006a,b). Some conditions are more nuanced, e.g. where PINS/MINS activate for touch and anticipation of touch, with AINS activating more for anticipated touch (Lovero et al., 2009).

Other findings challenge the PINS-MINS-AINS sensation-emotion-cognition model as too simplistic, since functions attributed to AINS (expectation, awareness, integration) can also occur in caudal insula.

Some studies implicate M/PINS in awareness, where PINS activity relates to imagining (and consuming) food (Frank et al., 2013; Wright et al., 2016), MINS/PINS are implicated during interoceptive recall (conscious remembering of internal states) (DeVille et al., 2018), and MINS activity during conscious cardiac attention is related to anxiety (Tan et al., 2018). Also, since AINS is considered to integrate more abstract processing with homeostatic information, AINS should reflect greater activity to food images when blood glucose is low. However, while AINS and dorsal MINS both activate for food taste and food images, only dMINS activity integrates dropping blood glucose levels (homeostatic state) with food stimuli (Simmons et al., 2013b). Perhaps in agreement, AINS inhibition in rats decreases palatable food intake in freely-feeding rats, but does not alter food consumption in food-deprived animals (Baldo et al., 2016) (implicating the importance of MINS). Further, as noted above, caudal insula activates for some aspects of expectation. Indeed, stronger confirmation bias (accepting or rejecting information that agrees or disagrees, respectively, with a predetermined belief) is associated with greater M/PINS white matter connectivity with a large subcortical network (Moutsiana et al., 2015). A final caveat to AINS mediating higher-order functions is where electrical stimulation of AINS in monkey leads to disgust and ingestive actions, but more social affiliative responses occur when stimulating MINS (Caruana et al., 2011) or PINS (Jezzini et al., 2012). In an interesting convergence, PINS inhibition in rats reduces social interaction (Rogers-Carter et al., 2018, 2019). Further, implicit (unaware) social judgements activate right MINS for untrustworthy and left MINS for trustworthy (with AINS for explicit judgements) (Winston et al., 2002). There are also mixed findings, with PINS linked to positive social evaluations (and AINS to negative) (Dricu et al., 2020), while others (Fallon et al., 2020) find AINS rather than PINS in empathy for pain; these differences could relate to the modality of the negative condition. Thus, more caudal insula regions can contribute to higher-level processes.

In addition to sensory perception and negative valence, insula subregion circuitry can regulate aspects of addiction. People with SUD (Volkow et al., 2010) or food cravings (Wang et al., 2009) who exert cognitive effort to decrease craving, and are successful, show less PINS activity, although success in smoking cessation is linked to greater PINS FC with several areas which may reflect better behavioral control (Addicott et al., 2015). Moreover, in a gambling task study of loss aversion (dislike of loss), right PINS activity reflected the magnitude of anticipated loss (with deactivation for gains) and the behavioral expression of loss aversion, while left AINS activation increased with anticipated gain (and deactivated with loss), but also correlated with loss aversion (Canessa et al., 2013). Therefore, while PINS activity related to loss and aversion to loss, AINS reflected something more complicated, maintaining information about anticipated gain even when behavior was driven more by aversion to loss. Thus, anterior and caudal insula areas can mediate negative expectation and experience under some conditions, although overall the AINS seems more associated with expectation.

2.5. Other considerations for interpreting human insula studies

The above studies describe examples from a rich and diverse literature relating different insula subregions to proposed mechanistic roles. Taken together, it is clear there is still much to learn about differences across insula subregions. This can be facilitated by task designs which better dissociate different aspects of interoception, emotion, cognition, etc. within the same study. This is consistent with the recently-developed Research Domain Criterion (RDoC) approach, where different basic components of motivation and behavior are compared in a systematic and delineated manner. There are also other challenges to defining insula roles. While some core models are of great heuristic value, other studies suggest such models may be too simplistic. Importantly, small differences in task demands could significantly alter the subjective relationship to a task and insula regions recruited, and overly simplistic considerations may lead to misdirected conclusions about core insula functions. Further, the correlational nature of many human studies, and the imprecision and often broad localization of human lesions, makes animal studies of great value, since these preclinical methods allow precise mechanistic interventions to delineate specific functional contributions. Most importantly, having the greatest precision in terminology when describing which insula subregions examined will also greatly aid identification of the functions of insula subregions.

One larger challenge comes from case studies from people with lesion in insula (and other areas) which find intact interoception, emotion, and self-awareness (Khalsa et al., 2009; Philippi et al., 2012; Pedrazzini and Ptak, 2019; Damasio et al., 2013). Although recovery of function in remaining brain areas may occur, these seem to challenge some basic core functions proposed for insula. One possibility is that insula is not central to emotional experience per se, but mediates "more complex elaboration of emotional stimuli and in the production of appropriate responses" (Caruana et al., 2011) and/or "relat[ing] feeling states to cognitive processes such as decision-making" (Damasio et al., 2013). Thus, insula areas may always activate during emotion and awareness (to prepare for responding) but not be necessary for such experiences per se. For example, AINS lesion in monkeys does not change preference for palatable foods (Machado and Bachevalier, 2007), although modulating AINS in rats can alter hedonic processing (Castro and Berridge, 2017). Similarly, while AINS and PINS in mice mediate many responses to sweet/bitter stimuli (Peng et al., 2015), decerebrated animals still exhibit sweet attraction and bitter aversion. In addition, there are difficult human tasks which can be solved solely by perceptual information in stimuli and do not recruit AINS (Dubis et al., 2016), again perhaps dissociating insula when more primary information (even under challenge) is sufficient to act.

Another central consideration is that insula recruitment may depend on the exact task conditions. For example, AINS activity (and subjective distress) are greater when watching videos of suffering in related (versus unrelated) people. However, when people imagine (rather than view) suffering, AINS is activated equivalently irrespective of relatedness, and does not relate to subject distress (Wever et al., 2021 and references therein). Thus, AINS contributions vary dramatically for external versus internal stimuli. Similarly, bilateral AINS activates for internal (recall) but not external (video) generated sadness (Reiman et al., 1997), and personal recall of a negative and positive events activate AINS (e.g. Lane et al., 1997a, 1997b), while passive viewing of images of positive or negative emotions activates AINS only for disgust (with PINS for appetite or disgust) (Britton et al., 2006). AINS importance may also vary with response requirements. Studies requiring rapid responses find AINS activation when stopping action under high effort (Croxson et al., 2009). In contrast, when there is time for consideration, AINS activates for both anticipated reward and attentional demands, and only if reward-directed action occurs (Stoppel et al., 2011), suggesting that AINS minimizes the impact of cost in order to allow action. Similarly, in a challenging task where performance is not devalued by cost, AINS activity increases as task difficulty increases (Engstrom et al., 2014), and in a physical effort task where high responding is not reduced by effort cost, bilateral AINS activity corresponded to expected reward (with other regions encoding reduced reward value due to effort) (Croxson et al., 2009). However, when physical effort is high enough to reduce responding, left AINS activity actually decreases as reward value decreases (Prevost et al., 2010). Thus, AINS contributions under high effort may depend on whether a reward is deemed worth it or not, including whether there is time for consideration or responding is rushed. Task demand differences may also contribute under more complex emotional conditions. Bilateral AINS activity during active lying predicts subsequent attitude change (a shift to greater acceptance/comfort with the lie position) (van Veen et al., 2009). However, under conditions of more passive cognitive dissonance (where choosing one of two names leads to greater liking of the chosen name), and less overall conflict than in van Veen et al. (2009), reduced bilateral AINS activity is associated with

attitude change (Jarcho et al., 2011). Thus, even in somewhat complex emotional behavior (rationalization), AINS can promote avoidance under simpler conditions, while AINS activity can help overcoming conflict in conditions with greater challenge, complexity, and/or awareness. Furthermore, AINS activity and importance for risk processing is observed in many human (above) and rodent (below) studies. However, there is little AINS activation in a risk task with known probabilities of gain and loss (where PINS/MINS processes risk) (Purcell et al., 2021), and, in a rat gambling task with probabilistic but otherwise predictable reward delivery, AINS inhibition has no effect (St Onge and Floresco, 2010). See also (Dodds et al., 2011) for discussion of differential AINS findings across behavioral control tasks related to task details. A final important consideration is where, under more ethological conditions, threat- or value-related stimuli would usually be associated with action, while insula contributions might be harder to disambiguate under more artificial laboratory conditions (where stimuli can occur without need for action). Thus, these examples provide important illustration of the need to carefully consider task details, in relation to subjective sense of certainty and impact of reward and cost, when designed and interpreting insula studies.

Finally, there may be important sex differences in insula, although there are many challenges when interpreting such studies, including where it can be quite difficult to disentangle biological versus social influences. Better emotional regulation is related to positive rsFC between amygdala and AINS and PINS in females, but with a negative FC in males (Wu et al., 2016). Greater emotional regulation is also associated with larger volume of PINS in females but not males (Kong et al., 2014). Thinner right AINS is associated with cigarette craving only in women (Perez Diaz et al., 2021). Further, stress cues activate across the insula in both sexes, with women having greater PINS (Seo et al., 2017), while alcohol drinkers have AINS activation to stress and alcohol cues, but with greater PINS in men to stress cues (Seo et al., 2011). Altered MINS/PINS activation to emotional pictures also occurs in relation to menstrual phases and hormone replacement therapy (Protopopescu et al., 2005; Shafir et al., 2012). However, while women exhibit greater disgust sensitivity (and greater AINS activation), sex differences in brain activity are not different when normalized for experienced disgust (Caseras et al., 2007). Indeed, a recent large metanalysis suggests that, when corrected for brain size, there are few consistent structural and functional sex differences (Eliot et al., 2021), although others find sex differences including larger insula in females (Liu et al., 2020). In addition, many studies assess emotion regulation through self-report, which can be strongly influenced by cultural expectations. Thus, while females but not males show greater AINS activity when viewing emotional pictures, and males show greater AINS-dACC FC when rating arousal level (with no sex differences in self-reported emotional arousal) (Moriguchi et al., 2014), this could reflect a stereotypical male expectation to not feel emotions (externalizing), rather than an "intrinsic biological" sex difference. Long-term integration of cultural expectations could even impact autonomic and other more automatic, unconscious levels of responding. Culturally learned patterns would still be very relevant for people's lived experiences, both adaptive and pathological, and for therapeutic approaches. However, such possibilities again reinforce the importance of not having too simplistic conceptions of underlying mechanisms, and underscore the importance of well-controlled preclinical studies to explore insular sex differences.

3. The rodent insula

3.1. Rodents and humans: promise and pitfalls of translation

Behavioral parallels between species (i.e. rodents and humans) are of particular translational value, and similarities in anatomical and functional connectivity also enhance the relevance of rodent findings to humans. However, connectivity needn't be identical between human and rodents since related regions could have similar anatomical compositions and neural circuitry that gives rise to similar behavioral functions. While rodent work holds3promise for understanding insula function, there are significant difficulties in translation related to species-specific anatomic differences (e.g. VENs), the difficulty in measuring and quantifying emotional and interoceptive behavioral differences across species, and the differing methodologies used to study brain function between rodents and humans. Despite these difficulties, rodents allow for mechanistic investigations and functional dissections that cannot be ethically performed in human. Advanced techniques in the rodent such as viral vector-assisted circuit tracing, optogenetics and chemogenetics to manipulate synaptic transmission, and methods to sample neuronal firing such as fiber photometry and microendoscopy offer a high-resolution look into insula subregions currently unavailable in humans. Current and future rodent studies may form the de facto foundation for defining the anatomy and function of insula subregions, especially in the pre-clinical literature, due to the use of these rodent-centric techniques, yet validating this work in the human is a critical step that must be done to avoid pitfalls in bringing insula findings from bench to bedside. Below we will discuss areas of overlap between humans and rodents and point out limitations requiring further investigation.

A recent study used fMRI in rats to examine rsFC patterns across insula subregions (Tsai et al., 2020). In line with the human anatomic distinctions described above, unbiased analyses in rodent models found that insula sorted into three modules: dAINS, vAINS, and PINS. Importantly, rat findings overall parallel rather well with human patterns, where vAINS connects to dAINS, OFC, mPFC, and other Salience Network regions, and PINS connects with sensorimotor, visual/auditory, and parietal cortices. Importantly, analogous insula subregions showed generally similar FC patterns across rat, mouse, monkey, and human. Another recent study from mice systematically examined connectivity of insula subregions with other regions. Insula was divided into three equally sized regions, AINS, MINS, and PINS (Gehrlach et al., 2019, 2020). Interestingly, MINS and PINS were overall more similar in their connectivity, with AINS different. However, mouse MINS and PINS did show some differences (e.g. with amygdala subregions). The authors also note that mouse MINS has been identified as gustatory cortex, which in rat seems to fall within regions with more AINS connectivity in Tsai et al., 2020) (detailed more below). Thus, while there is overall agreement between rat and mouse regarding AINS differences from caudal insula, there may also be some species differences, especially in central insula. Resolving this will in part require detailed connectivity maps in rat.

Traditional anatomical studies support an overall cross-species convergence. Anterior areas that constitute rodent AINS/OFC resemble posterior OFC and adjacent AINS in primates (Preuss, 1995; Dalley et al., 2004; Wise, 2008), with distinctive projection patterns conserved across species (Ongur and Price, 2000). Also, PINS in human and rodent both connect to more sensory areas, and lack higher-order connections such as AINS bidirectional projections with mPFC (Markowitsch et al., 1980; Cechetto and Saper, 1987; Shi and Cassell, 1998; Vertes, 2004). Further, the gustatory/visceral cortex is part of the AINS in rats (Krushel and van der Kooy, 1988) and primates and humans (Ongur and Price, 2000; Small, 2006; Price, 2007) (but see Nitschke et al., 2006a,b), including converging limbic and primary sensory inputs not present within other cortical areas (Saper, 1982); the possible distinction in mice described above is thus interesting and needs further understanding. AINS also has interactions with higher-order thalamic regions in rodents and humans (Krettek and Price, 1977; Van der Werf et al., 2002; Matyas et al., 2014), although, based on these thalamic inputs, rodents dAINS has been proposed to represent primate prefrontal cortex (Markowitsch et al., 1980; Van De Werd and Uylings, 2008). Other insula projections are also similar across rodents and primates/humans, including some linked to avoiding food paired with sickness (Barbier et al., 2020).

Even with these convergences, there are clear anatomical differences

between rodents and humans. In addition to rodents seemingly lacking VENs (see above), Tsai et al. (2020) found that rat dAINS had connections to all three insula areas and sensory cortical areas, but lacked the strong connections with frontal cortical regions present in human dAINS. Similarly, mouse AINS and ACC have modest connections (Qadir et al., 2018), which are robust in humans. Also, the orientation of rat and human insulae are rotated relative to each other, e.g. leading to human agranular being both anterior and ventral to granular zones (reviewed in Castro and Berridge, 2017).

3.2. Rodent studies: importance of precise description of insula subregions, and examining across subregions within the same study

Assessing different functional contributions of rodent insula subregions would be aided by examining across subregions in the same study, removing possible differences in task design, strain, and other factors across published findings. Thus, our discussions below begin from the limited rodent studies which directly compared the functional contribution across subregions. Also, while there is some diversity in terms describing subregions, here we will use two terminologies. One is simply AINS and PINS, where exact coordinates are less defined. The second anatomical designation we use here for rodent studies measures how far the brain region is anterior or posterior (AP) relative to Bregma, a widely used landmark on the surface of the skull where AP = 0. For rats, regions are centered on rostral AINS (rAINS, AP∼+2.8 and forward), gustatory cortex part of the AINS (GC-AINS, AP∼+1.2 to+2.0), rostral PINS (rPINS, primary interoceptive posterior, centered at AP ∼ -0.5, Casanova et al., 2016), and caudal PINS (cPINS, centered at AP ∼ -2.3, Benison et al., 2011). Table 2 of (Bales et al., 2015) is a particularly good resource for rat insula subregion landmarks, where middle cerebral artery is AP+1.0. Recent studies from Gerlach and colleagues (Gehrlach et al., 2019, 2020) are particularly useful for delineating insula subregions in mouse (see also Gogolla, 2017); mouse AINS extends across AP∼+2.5 to +1.2, MINS from AP+1.19 to +0.1, with PINS from AP+0.09 to ∼ -0.7. For both rat and mouse studies, we provide coordinates as much as possible. Also, very few rodent studies have compared dorsal and ventral AINS, but will be noted when relevant.

Importantly, one of the main purposes for writing this review is to encourage researchers to be more precise in their description of insula regions under study. Further, we hope the previous paragraph can serve a central reference point for anatomically defining insula subregions based on the corresponding coordinates. There are several cases where insula studies from AINS and PINS are combined as insula references, and even where subregions are misattributed. Insula areas are receiving ever-increasing attention, and we feel it imperative, as a field, to be more careful in how we describe and think about insula subregions, similar to how the rodent medial prefrontal cortex is now distinguished by prelimbic and infralimbic subregions. This will allow our collective work, and the larger neuroscience field, to have the greatest confidence and clarity in proposed insula contributions, which is already made quite challenging given the large number of sensory, emotional, behavioral, and cognitive functions insula regions are implicated in (see above).

3.3. Insula subregions and learning

Many studies have examined the importance of insula regions for avoidance learning, such as conditioned taste aversion (CTA, where LiCl sickness is paired with sweet taste). Nerad and colleagues (Nerad et al., 1996) provide evidence that different AINS regions can have different behavioral contributions in rats. Using lesions centered at rAINS (AP+3.7), GC-AINS (AP+1.7), or rPINS (AP-0.3), rat CTA learning is disrupted by removing GC-AINS but not by rAINS or rPINS. Similarly, inhibiting central rat insula (AP ∼+1.0 to −0.5) disrupts CTA learning, while disrupting regions anterior (to AP+2.0) or posterior (to AP-1.2) does not consistently alter CTA (Schier et al., 2014, 2016). Thus, even though rAINS and GC-AINS show similar FC patterns (Tsai et al., 2020), different parts of AINS can differentially impact CTA behavior. In contrast, electrolytic lesions (which disrupt fibers of passage as well as local neurons) of rAINS or GC-AINS (but not PINS) disrupt odor-based CTA learning, while a different aversion learning paradigm, where a compound odor/taste is paired with aversion, requires rAINS but not GC-AINS or PINS (Lasiter et al., 1985). Some differences among studies could reflect different task details, and lesion type, although acute pharmacological inhibition of GC-AINS disrupts CTA learning (e.g. AP+2.0, Bermudez-Rattoni et al., 1991, AP+1.2, Ramirez-Lugo et al., 2016; see Arguello et al., 2017). Nonetheless, it is clear that AINS subregions can contribute differentially to aversion learning, despite ostensibly similar brain connectivity.

AINS is also implicated in other types of learning, with some mixed results. Learning in the water maze spatial task is disrupted by GC-AINS and rPINS but not rAINS lesion (Nerad et al., 1996). However, rAINS lesions do not impair performance in a go/no-go version of the spatial radial maze (Ragozzino and Kesner, 1999). AINS inhibitions can also disrupt reward learning (e.g. Di Pietro et al., 2004; Kesner and Gilbert, 2007), including Pavlovian reward learning (AP+2.8, Nasser et al., 2018).

3.4. Insula subregions and "simpler" negative and positive processing

While different AINS subregions may vary in contributions to aversion learning, further studies suggest a similar rAINS and GC-AINS contribution during other negative conditions. One study (Mendez-Ruette et al., 2019) used the anxiety-related elevated plus maze to examine the impact of activating (GABAR blocker bicuculline) and inhibiting (AMPAR blocker) four subregions: rAINS (AP+2.8), GC-AINS (AP+1.2), rPINS (AP-0.5), or cPINS (AP-2.3). Anxiety decreases when inhibiting rAINS or GC-AINS, and is elevated by activating rAINS or GC-AINS (although GC-AINS lesion did not alter EPM in Rotge et al., 2017). There were no locomotor changes, suggesting a specific impact on emotional processing. In addition, cPINS modulations have opposite effects to AINS/GC-AINS changes, with no effects in rPINS. Thus, both AINS regions promoted expression of anxiety, with cPINS actually decreasing anxiety in this rat paradigm.

Interestingly, studies of hedonic reactivity (facial reactions showing like or dislike during sugar or other intake) in rats seem to show similar regional influences. Local activation across rat anterior to middle insula (AP +3.5 to −1) leads to disgust-like reactions, while PINS (AP ∼ -0.5 to −3) activation lead to hedonic, positive facial reactions (Castro and Berridge, 2017). Thus, rat AINS can mediate negative hedonia and greater anxiety, with the converse for PINS. Also, inhibiting rat AINS decreases autonomic responses to stress (Alves et al., 2009, 2014), and inhibition of noradrenergic function in GC-AINS (AP+1.2) reduces avoidance of novel taste under high arousal (without changing total intake) (Rojas et al., 2015). Further, inactivating rat rPINS (AP-0.36) but not GC-AINS (AP+1.2) disrupts acquisition of morphine CPP, while inactivating either subregion impairs naloxone-induced CPA in morphine-exposed rats (Li et al., 2013), suggesting that negative but not positive learning occurs in GC-AINS, with rPINS for both. An interesting recent study (Wu et al., 2020) shows lateralization of AINS effects. Aversive visceral stimuli (but not shock) increase activity in right, but not left, mouse GC-AINS (AP+0.5), and stimulating right (but not left) GC-AINS suppresses feeding, causes place avoidance (with inhibition having the opposite effects), and mediates avoidance of sickness paired food, without changing drinking, bitter sensitivity, mating, or anxiety. Thus, these studies concur with human findings that the right rather than left AINS is important for negative processing, the only study we are aware of demonstrating such lateralization in rodent insula. Also, stimulating mouse rAINS (AP+1.6) or cPINS (AP-1.06) has no behavioral effects, providing additional evidence that different AINS subregions can have varied behavioral effects, even with largely similar brain connectivity (see above). However, another recent study showed

that AINS (AP+1.78) inhibition in mice decreases anxiety and fear (Shi et al., 2020).

While these studies link AINS to negative events, other findings implicate AINS for positive responses. At the simplest level, sweet taste in mice is encoded in AINS (AP+1.6), with bitter linked to PINS (AP-0.3) (Peng et al., 2015); AINS stimulation also leads to CPP and greater licking, while PINS stimulation leads to CPA and decreased licking, and bitter quinine taste increases cFos expression, a proxy for neuronal activation, at AP-0.3 but not +0.7/+1.5. Also, inhibiting AINS prevents sweet but not bitter taste discrimination (and vice versa for PINS), and stimulating AINS substitutes for sweet taste during taste-cued go/nogo (with related effects for PINS and bitter as cue). Together, these provide strong evidence implicating AINS and PINS for positive and negative processing, respectively. A recent mouse study concurs, where stimulating mouse AINS (AP+1.7) induces pleasure-like facial responses, while stimulating PINS (AP-0.35) induces disgust (Dolensek et al., 2020). In addition, human studies support AINS importance for some aspects of positive processing, where AINS activity corresponds with maternal affiliation, pleasant voices, and music chills (Fig. 2 of Craig, 2009), and AINS seizures can elicit intense feelings of well-being (Picard and Craig, 2009). Similarly, mouse AINS lesions (AP+1.98) impair nicotine CPP (reward) but not withdrawal CPA (Scott and Hiroi, 2011).

These findings indicate that AINS and PINS can both mediate positive or negative situations in rats and mice, as is observed in humans, with the potential for both divergent and similar contributions across subregions and perhaps species. Thus, it will be important and interesting in future rodent work to understand which task details lead to particular subregion involvement under given conditions, especially to compare different conditions systematically within the same study (including direct mouse-rat comparisons).

3.5. Insula subregions and risk, emotion regulation, and management of adversity

Given the importance of human insula for emotion-related decision making (see above), similar affective findings in rodent would provide cross-species validity. Risk-related behaviors are an interesting example. For example, when rats choose between four options differing in magnitude and probability of rewards and penalties, inactivating rAINS (AP+2.8) shifts preference toward greater reward and less punishment, while inhibiting cPINS (AP-3.8) slows responding but has no other effects (Pushparaj et al., 2015a). This rAINS modulation does not alter many other behaviors (trials, omissions, latency, premature or perseverative responses), suggesting that rAINS specifically promotes risk taking. However, other AINS-risk studies have mixed results, which may reflect different task details. Pushparaj et al. (2015a) involved well-trained 4-choice responding, while another study utilized a 4-choice gambling task with learning better and worse options in a single session, and AINS lesion (AP+1.4) impairs performance in optimally-performing rats but actually improves performance in poorer performers (Daniel et al., 2017); AINS lesion did not impact simple learning, reversal, or progressive ratio, again suggesting a more specific AINS contribution to risk assessment. Further, studies using only two options (risky vs safe) find that AINS inactivation has no effect (St Onge and Floresco, 2010) or reduces risk taking (Ishii et al., 2012). Thus, complexity, subjective certainty, and prevalence of favorable options could all influence AINS contributions to risk (discussed in Daniel et al., 2017). Human studies implicate AINS in risk aversion, but also some pro-risk responding (see above). These risk findings align with AINS importance for encoding expectations, whether adaptive or maladaptive.

Findings of individual differences in AINS lesion on risk behavior (Daniel et al., 2017) suggest that the insula may support action that a given individual's brain thinks is important, i.e. the basal bias in that individual. In support, AINS (+3.2)/adjacent OFC inhibition reduces avoidance in rats with high freezing to fear stimuli, but induces avoidance in naturally low-freezing rats (Rodriguez-Romaguera et al., 2016). Individual differences are also seen in (Pushparaj et al., 2015a). Thus, task parameters likely strongly contribute to subjective responses, and, unless tuned to be near a decision point across which subjects naturally segregate, most individuals in a given study will act in a similar manner. This might lead to an incorrect conclusion that AINS performs a particular function (e.g. driving risk avoidance) rather than a more nuanced perspective.

The Hopf lab is particularly interested in maladaptive forms of emotional regulation that contribute to addiction, in particular the circuitry that supports compulsion-like responding, where the drive for intoxicant persists even in the face of known negative consequences, since this is a strong contributor to human addiction (see above), and is likely to evoke strong affective states that need regulating (Naqvi et al., 2014; Darevsky et al., 2019; Darevsky and Hopf, 2020). Rat and mouse studies concur that AINS circuits are critical for responding for alcohol despite aversive challenge (Seif et al., 2013; Chen and Lasek, 2019; De Oliveira Sergio et al., 2021). Further, AINS outputs to NAcb are critical for aversion-resistant alcohol intake in rats (Seif et al., 2013), and, in heavy human drinkers, AINS-NAcb FC is related to both aversion-resistant responding for alcohol and subjective sense of compulsivity (Grodin et al., 2018) (see also Cardenas et al., 2011). Further, context-related punishment in rats greatly reduces alcohol responding, which partially recovers after 30 days of abstinence, and rAINS (AP+2.8) mediates alcohol relapse after 30 days but not 1 day of abstinence (with low responding) or in an unpunished context (with high responding), and with greater AINS cFos related to higher responding in the punished context (Campbell et al., 2019). Thus, AINS promotes alcohol responding despite acute adversity (Seif et al., 2013; Chen and Lasek, 2019) or memory of punishment (Campbell et al., 2019). Furthermore, AINS inhibition does not disrupt unpunished, alcohol-only behaviors in several studies (Seif et al., 2013; Campbell et al., 2019; Chen and Lasek, 2019; Haaranen et al., 2020a), suggesting a specific AINS role under higher challenge and affect levels. In contrast, we recently showed that globally inhibiting AINS with the alpha1-noradrenergic receptor blocker prazosin or with GABA receptor activators does significantly reduce both compulsion-like alcohol drinking and alcohol-only intake (De Oliveira Sergio et al., 2021). Interestingly, inhibition of compulsion-like intake does not correlate with reduction in alcohol-only, suggesting that different pathways within AINS mediate the two forms of alcohol drinking. Combined with specific regulation of compulsion-like alcohol consumption by AINS projections (to NAcb, Seif et al., 2013; to brainstem, De Oliveira Sergio et al., 2021) and putative regulators of AINS GABAergic interneurons (Chen and Lasek, 2019; De Oliveira Sergio et al., 2021), these results suggest that AINS contains separable populations of neurons that regulate compulsion-like intake (via local interneurons and subcortical projections) and alcohol-only (identity unknown at present). However, we also note that Jaramillo and colleagues find that chemogenetic inhibition of AINS-NAcb projections reduces self-administration of sweetened alcohol (Jaramillo et al., 2018b) or unsweetened alcohol (Jaramillo et al., 2018c), with no aversive consequences to overcome, and without changing locomotion or sucrose responding, in concert with AINS and AINS-NAc inhibition increasing sensitivity to alcohol's interoceptive effects (Jaramillo et al., 2018a). Additional work should address such differences, including different alcohol procedures (weeks of two-bottle intake before operant training in Seif et al., 2013; sucrose-fade and only operant in Jaramillo et al., 2018b, 2018c), as well as strain differences and other potential factors.

Nonetheless, the importance of AINS projections in conflict-resistant responding for alcohol is consistent with ideas proposed by clinical researchers that compulsion-like responding in humans reflects responding despite conflict, and that it is the conflict that recruits cortical areas (Tiffany and Conklin, 2000; Naqvi and Bechara, 2010; Naqvi et al., 2014). Indeed, in women with AUD, seeing alcohol cues when imagining high-risk drinking situations activates bilateral AINS and other Salience

Network areas more than under low-risk conditions (Arcurio et al., 2015); reaction time also slows specifically for alcohol cues under high-risk, suggesting processing of conflict. Differential circuitry of challenge-resistant and ostensibly unchallenged responding is also supported by the observation that punishment-resistant responding (Campbell et al., 2019) is not predicted by many other behavioral measures, including home-cage drinking, self-administration, or basal sensitivity to punishment, suggesting a specific AINS contribution to overcoming negativity to allow responding. In contrast, shock-resistant alcohol responding does correlate with progressive ratio for access to alcohol in (Giuliano et al., 2018), similar to cocaine (e.g. Deroche-Gamonet et al., 2004), although shock-resistance does not relate to alcohol-only intake. Thus, similar to risk, the AINS contribution may focus on negativity processing to facilitate responding.

However, while AINS can allow overcoming challenge to maintain responding, AINS is also important for some avoidance responses, as in humans (above). In addition to AINS mediating avoidance learning, AINS is important for goal-directed responding rather than habitual resistance to reward devaluation (Geddes et al., 2008; Parkes and Balleine, 2013; Parkes et al., 2015), and AINS neuronal activity is associated with resistance to maladaptive persistence during overtraining (Martinez-Rivera et al., 2020). Also, more inhibitory firing in AINS (AP+3.7 to +1.7) correlates with less motivation for, and intake of, cocaine under cocaine-paired aversion (Moschak et al., 2018). As noted elsewhere, it is likely that differences in task demands are central for defining the specific contribution of AINS.

3.6. AINS-specific studies: importance for drug intake under ostensibly non-conflict conditions

Different aspects of AINS signaling seem critical for alcohol responding despite adverse consequences versus alcohol-only intake, and AINS-dependent responding for other drugs is observed under conditions without overt negative consequences. Cue-induced reinstatement of cocaine and nicotine seeking and context reinstatement of cocaine seeking are all reduced by AINS inhibition, without impacting drug-primed reinstatement or food seeking (Cosme et al., 2015; Pushparaj et al., 2015c; Arguello et al., 2017). AINS disruption also decreases intake of highly palatable food, without changing locomotion or water intake (Baldo et al., 2016). Further, inhibition of AINS (AP+2.8) reduces methamphetamine seeking (Venniro et al., 2017). Any differences from alcohol might reflect where nicotine and psychostimulants have strong negative as well as positive effects during acute exposure, although this remains speculation without clear methods to directly assess animal affective state. Adding an additional wrinkle, intermittent access to chocolate induces an addiction-like phenotype in a subset of female rats, with greater progressive ratio and shock-resistant responding. However, inhibiting AINS (AP+2.8) projections to NAcb reduces progressive ratio responding (without impacting simple fixed-ratio responding) but actually enhances compulsion-like responses (Spierling et al., 2020). Although several studies implicate greater progressive ratio responding and shock-resistance as an addicted state for cocaine and alcohol (Deroche-Gamonet et al., 2004; Giuliano et al., 2018), other studies dissociate circuitry for punishment-resistance and progressive ratio responding (e.g. Radke et al., 2015). Spierling and colleagues (2020) propose an interesting resolution, where AINS encodes the most relevant interoceptive state, appetitive for progressive ratio and aversive for punishment resistance. Thus, AINS-NAc inhibition could lead to "greater release from shock suppression." Under this model, primary alcohol reward may actually contain some level of aversiveness (e.g. bad taste or physiological withdrawal) which is not present for palatable food (also suggested by De Oliveira Sergio et al., 2021). While speculative, this reinforces the idea of motivational context being critical for AINS contributions.

Drug studies also find interesting differences when AINS is disrupted before or after drug learning occurs. GC-AINS lesions before drug intake training increase cocaine seeking (Pelloux et al., 2013; Rotge et al., 2017) while post-training lesions decrease it (similar to acute inactivation), with related findings for OFC lesions (Fuchs et al., 2004). In contrast, GC-AINS lesion (AP+1.4) does not alter heroin intake when performed pre-training, but actually increases intake and relapse post-training (Joshi et al., 2020). The authors note the possibility of cocaine having mixed acute interoceptive effects (both good and bad), unlike heroin, and also links between AINS and impulsivity for cocaine but not heroin. These data again underscore where AINS contributions likely depend on specific aspects of motivational and contextual state (in this case, drug history).

We also note that there are some mixed findings. AINS inhibition can increase responding for alcohol (AP+3.2, Jaramillo et al., 2018b) and heroin (Joshi et al., 2020). While the reasons remain unclear, AINS projections to different target regions (addressed below) could have different behavioral effects, yielding different and even seemingly paradoxical effects under global AINS inhibition. In a related vein, activating rAINS can increase (Jaramillo et al., 2018b) or suppress (Haaranen et al., 2020a, 2020b) alcohol drinking, and decrease sucrose (Haaranen et al., 2020b) and food intake (Price et al., 2019), without producing freezing or escape reactions (Baur et al., 2013) or altering locomotor activity or water drinking (Haaranen et al., 2020a, 2020b). With AINS important for emotion and stress regulation, AINS activity may have an inverted U-shaped contribution, with too much or too little impairing certain motivated behaviors.

3.7. Rodent AINS subregions and expectation rather than primary sensation

Human studies suggest AINS importance for expectation, rather than primary sensation per se, and some rodent studies concur. Reinstatement of drug seeking by cues or context are considered driven by more abstract learned associations; thus, it is interesting that many forms of cue/context reinstatement require AINS, while seeking instigated by a drug prime, even though interoceptive, does not require AINS (see above). Further, GC-AINS (AP+1.2) lesion disrupts extinction and devaluation when driven from memory, but not when rats can taste the reward (Balleine et al., 2000). Also, in a reward contrast task, where 2% sucrose signals that 32% sucrose will be available right after, there is greater intake of 32% sucrose compared with 32% sucrose presented alone; AINS lesion (AP+4.9 to +2.9) removes this reward anticipation effect, while not changing the higher 32% or lower 2% intake levels when either concentration is presented alone (Kesner and Gilbert, 2007). On the negative side, AINS inactivation (AP+2.65) does not alter pressing of a punished lever, but does increase pressing on previously punished lever when no punishment is delivered (Jean-Richard-Dit-Bressel et al., 2016), implicating AINS in aversion avoidance based on predicted (learned) rather than primary aversion.

In a related vein, while GC-AINS neurons fire for different tastants in rats (e.g. Yamamoto et al., 1989; MacDonald et al., 2009), mice (Levitan et al., 2019), and monkeys (Rolls, 2000), AINS inhibition does not impair many aspects of primary taste discrimination (see Bales et al., 2015; Mendez-Ruette et al., 2019). Also, rAINS lesion (AP+4.9 to 3.9) disrupts the ability to use different sugar concentrations as cues for withholding action under "no-go" conditions, without impacting taste-cued go responses, suggesting impairment in behavioral control rather than taste discrimination per se (Ragozzino and Kesner, 1999; see also Neill, 1976). Further, while GC-AINS neurons fire for primary taste properties, they also encode subjective, hedonic taste palatability (Jezzini et al., 2013), including decreased activity with satiety (O'Doherty et al., 2000; Rolls, 2000). Importantly, a recent study (Levitan et al., 2019) found that mouse GC-AINS firing for tastes is overall similar to previous reports in rat, with many neurons responding to multiple taste modalities; in addition, neurons code taste type first, then hedonic palatability, suggesting transformation from primary sensory to motivational relevance.

One simpler aspect of expectation is the processing of reward-predictive cues. Inhibiting AINS (AP+0.98) (Vincis et al., 2020) or MINS (AP+0.28) (Kusumoto-Yoshida et al., 2015) in mouse impairs cue-driven approach to reward. Further, AINS firing in rats reflects reward value, anticipation, and context (AP+1.5, Pribut et al., 2021; AP+3.2, Jo and Jung, 2016), and one study suggested that expectation increases the ability to process stimuli, e.g. where taste-predictive cues in rat increase GC-AINS (AP+1.4) firing to help rapidly discriminate tastes (Samuelsen et al., 2012). Also, disrupted AINS firing in rats after chronic cocaine is associated with greater attraction to immediate reward (Pribut et al., 2021). Finally, while MINS/PINS neuronal activity in mouse is greater when hungry but not sated (Livneh et al., 2017), this activity is influenced by food cues in a way that suggests integration of internal state and cues to predict future homeostatic state (Livneh et al., 2020). Further, AINS (AP+3.0) activation decreases lever pressing for cues paired with high-fat-food (HFF), but not pressing for HFF itself, even under progressive ratio, in food-deprived rats, supporting AINS importance for responding from learned hedonic associations, rather than homeostatic feeding (drive to eat when hungry) (Price et al., 2019). In contrast, AINS inhibition decreases HFF intake in freely-fed rats, suggesting a role in desire for high-calorie food when not hungry, and perhaps the speculation that this is driven as much by HFF memories as by HFF itself. Similarly, while shock-resistant, compulsion-like responding for alcohol only persists if alcohol is present (unpublished observations), we have suggested that AINS contributions to compulsion-like responding involves internal, prediction-related processes. In particular, based on detailed analyses of licking microstructure, we propose a "head down and push" model, where rats adopt a more automatic response strategy which allows continued responding for a desired reward while ignoring (as best as possible) associated negative consequences (Darevsky et al., 2019; Darevsky and Hopf, 2020). These studies all converge on AINS being important for behaviors driven by learned, expectation-related factors, and detached from primary sensory experience.

However, there is some nuance to these possibilities. AINS processes primary disgust (see above), and extensive GC-AINS lesions in rat reduce taste sensitivity to bitter tastes (although higher concentrations are detectable), while sucrose taste is not impacted (Bales et al., 2015). In addition, rAINS inhibition in rat directly regulates autonomic responses (Funk and Stewart, 1996; Alves et al., 2009, 2014), reduces hyperalgesia and anxiety induced by pancreatitis (AP+2.16, Bai et al., 2019), and elicits analgesia (Jasmin et al., 2003) (and from GC-AINS in Jung et al., 2016). Also, AINS inactivation inhibits rat cocaine reinstatement driven by drug-paired olfactory but not auditory cues (Di Pietro et al., 2006). Olfactory cues may elicit a particular interoceptive state as part of a multi-cue, contextual state (and multi-modal stimuli elicit stronger insula activation and greater urge to smoke in humans, McClernon et al., 2016). Further, while electrical stimulation of AINS in monkeys reduces approach to rewards and increases avoidance, effects are greater during approach-avoid conflict, compared to conditions with approach or avoid alone (Saga et al., 2019). Thus, AINS can process primary negative events and interoceptive signals, although usage of this information for behavior can be modulated by contextual factors. One speculation is that AINS contributions to primary sensory conditions such as disgust may reflect the brain's attempt to distance awareness of the experience, "retreating" to an internal perspective. This is the core of our "head down and push" model of compulsion-like responding described above, where AINS processes strong primary negative experiences with the goal of mitigating their impact.

3.8. The rodent PINS and MINS

As in humans, there are challenges when trying to develop a singular theory about the functional importance of caudal insula regions in rodent, since PINS has been implicated in both negative and positive processing. In mice, PINS stimulation induces freezing, anxiety, and avoidance behavior, and mediates bitter taste (Peng et al., 2015; Schiff et al., 2018; Wang et al., 2018a; Gehrlach et al., 2019). Further, mouse PINS but not AINS may mediate visceral pain (Brenner et al., 2021). However, PINS activation in rats decreases anxiety (Mendez-Ruette et al., 2019) and increases positive facial reactions (Castro and Berridge, 2017), although inhibiting cPINS in rat reduces both amphetamine CPP and aversion to LiCl-paired cues, implicating PINS for positive and negative learning (Contreras et al., 2007). Mouse studies have generally involved simpler behaviors and primary reactivity to positive or negative stimuli, while rats have often been used for more complex behaviors. One exception is where MINS-CeA in mice regulates taste-guided go/no-go responses (Schiff et al., 2018) (see below). Thus, when accounting for mixed findings, it remains unclear whether there are species differences or not (especially since FC patterns of AINS versus PINS are conserved across rats, mice, and humans, Tsai et al., 2020), and this remains a critical area for future work.

One central unanswered question is the nature of the rodent MINS. Human MINS can activate without PINS, suggesting the potential for a different functional contribution. Detailed anterior-posterior mapping in rat (Castro and Berridge, 2017; Mendez-Ruette et al., 2019) find that AINS/GC-AINS have opposing influences as cPINS, while the "rPINS" (centered around AP~0) is more varied, showing no net effect. However, across individual animals, different subjects increase or decrease anxiety when modulating rPINS, leading (Mendez-Ruette et al., 2019) to suggest that anterior and posterior insula have opposing effects on anxiety, with the boundary varying across individuals rather than having a distinct central insula region. However, anatomical studies suggest somewhat different connectivity of mouse MINS versus PINS, although MINS/PINS have many similarities that are different from AINS (Gehrlach et al., 2020). In addition, recent work from our group demonstrated increased cFos activation in the mouse MINS (AP+0.02) 15 days into protracted alcohol withdrawal, and, furthermore, inactivating the MINS is sufficient to decrease anxiety-like behavior (Centanni et al., 2019), with the importance of other insula subregions of great interest. In contrast, inactivating MINS prior to acute restraint stress has no effect on subsequent anxiety, although activating MINS-BNST increases anxiety-like behavior after restraint stress (Luchsinger et al., 2021). These studies suggest MINS recruitment only during specific negative affect-inducing behaviors, but not others. Also, prolonged periods of negative affect, such as those induced during drug and alcohol abstinence may engage the MINS to drive cravings and relapse-like behavior, in essence inducing a "hyperawareness" of the negative internal state that can be alleviated by drug relapse (first proposed in Naqvi et al., 2014).

Another recent study (Girven et al., 2021) showed that PINS (−0.8 AP) projects to ventral BNST cells that input to VTA, and that activating PINS-BNST is reinforcing (causes place preference and self-stimulation for PINS-BNST activation) in a dopamine-dependent manner, while inhibiting this pathway leads to place aversion and anxiety without altering locomotor activity. Interestingly, short-term alcohol drinking and abstinence increases glutamatergic strength in PINS cells projecting to vBNST in both females and males, while alcohol exposure increased PINS cell firing only in females, with actually decreased firing in abstinence in females but not males (Marino et al., 2021). The authors propose that this pathway mediates identification of particular inputs as positive and worthy of approach, and has interesting and sexually dimorphic plasticity as a result of alcohol intake and abstinence.

An important and poorly understood question is the interaction between AINS and PINS. AINS and PINS differently impact anxiety, hedonic expression, and basic taste processing, a strong wrinkle for theories where PINS relays interoceptive information to AINS to guide responding, which predict similar behavioral contributions of AINS and PINS. However, some studies support similar AINS/PINS roles. Most simply, AINS activation increases PINS activity (Haaranen et al., 2020b). Further, amphetamine CPP memory in rat is disrupted by inhibiting protein synthesis in rAINS (AP+2.8) or rPINS (AP-0.5) (Contreras et al.,

2012). Inhibiting AINS (Jaramillo et al., 2018c) or rPINS (−0.5) (Pushparaj and Le Foll, 2015) in rat reduces operant responding for alcohol, while nicotine but not food self-administration in rat is reduced by inhibiting PINS (AP-0.4) (Forget et al., 2010) or GC-AINS (AP+1.2) (Hollander et al., 2008). It is also interesting that different basic emotion states can be discerned from mouse facial expression (Dolensek et al., 2020), and while stimulating mouse AINS leads to pleasure-like responses, and stimulating PINS induces disgust, the individual PINS neuron activity encodes different facially-expressed emotions, including pleasure. Thus, while macroscopic activation of PINS yields aversion, more physiological conditions may allow PINS-mediated expression of pleasure which could require PINS-to-AINS projections. Clearly, there is still much to learn about AINS/PINS interactions in rodents, including where PINS activation effects require AINS or vice versa.

3.9. Importance of specific insula projections

As we have seen, there are significant challenges when trying to develop a central conception for the respective contributions of different insula subregions. The exact details of a given situation are likely critical, including the level of reward versus cost, the subjective sense of certainty or uncertainty, and an individual's basal biases. It is also likely that different insula projections have divergent and sometimes even opposite contributions (e.g. as seen in mPFC, Siciliano et al., 2019). This is one area which highlights the great strengths of rodent studies, where mechanistic interventions targeting specific projections are possible. We are still at a very early stage of understanding the contributions of specific insula outputs, but the present findings are already interesting and valuable. Taken together, existing studies implicate a number of insula projections in specific aspects of alcohol-related behaviors, and these likely make related contributions to other important intoxicant, anxiety, and motivated responses.

3.9.1. Insula projections to amygdala, BNST and hypothalamus

A number of studies have examined insula projections to amygdala regions. AINS-basolateral amygdala (BLA) in mice is linked to sweet tastes and appetitive drives (Wang et al., 2018a) and pleasure-related facial expressions (Dolensek et al., 2020). In contrast, PINS-CeA activity is related to bitter/aversion (Wang et al., 2018a) and anxiety- and fear-related avoidance (Gehrlach et al., 2019). Similarly, inhibiting MINS (AP-0.1) projections to CeA in mice impairs taste-guided behavioral control (go and no-go responses), while activation induces aversion and suppresses licking (Schiff et al., 2018). Also, inhibiting MINS-CeA reduces avoidance of bitter quinine but does not impact sucrose licking (Schiff et al., 2018), consistent with caudal insula in mice for bitter but not sweet processing. Furthermore, (Ponserre et al., 2020) used an elegant synaptic tracing strategy to characterize downstream targets of MINS (AP-0.5 to +1.0) projections to CeA, and identified that most CeA neurons impacted by MINS in turn project to the lateral hypothalamus (LH). Since right GC-AINS-to-LH projections in mice are linked to suppression of feeding and place aversion (Wu et al., 2020), these findings together could suggest that caudal insula outputs to amygdala may act through LH to mediate aversion.

However, other studies have different findings. Some link AINS-amygdala outputs with negative rather than positive processing, where mouse AINS-BLA contributes to fear learning (Matyas et al., 2014), CTA retrieval (Abe et al., 2020, AP+1.0) and taste aversion (Kayyal et al., 2019). In the latter, inhibiting AINS (+0.86) projections to BLA reduces aversive taste memory acquisition and retrieval (but not maintenance), while activation along with a neutral taste induces CTA, implicating AINS-BLA when associating taste stimuli with negative body states. An additional study finds increased postsynaptic (AMPA receptor) function in mouse AINS (AP+2.70) projections to BLA in alcohol withdrawal (McGinnis et al., 2020), which could promote aversive withdrawal symptoms. Providing additional wrinkles, and in contrast to AINS-BLA/PINS-CeA dissociations described above, both AINS (AP+1.70) and PINS (AP-0.35) in mice project to both BLA and CeA (Ju et al., 2020; but see Shi et al., 2020), with somewhat broad insula-amygdala projections also in rats (Shi et al., 1998). Indeed, inhibiting vAINS-CeA in rat prevents methamphetamine reinstatement after abstinence (Venniro et al., 2017). It is also important to note that insula-amygdala projections are bidirectional, where BLA-AINS maintains cue representation (Samuelsen et al., 2012) and reward memory (Gil-Lievana et al., 2020), and BLA-MINS mediates hunger signals (Livneh et al., 2017).

In addition to amygdala, negative affective processing involves MINS/PINS projections to the BNST, a component of the extended amygdala heavily implicated in prolonged anxiety and negative affect (Lebow and Chen, 2016, and references therein). Chemogenetically inactivating the MINS (AP+0.14) during protracted alcohol withdrawal reduces anxiety-like behavior (Centanni et al., 2019), and, using a transsynaptic anterograde cell tagging approach, we established a specific role for BNST cells receiving MINS projections in generating anxiety-like behavior during alcohol withdrawal (see also (Flook et al., 2021a; Flook et al., 2021b) for human AINS and BNST connectivity during alcohol withdrawal). MINS has a dense, unidirectional projection to BNST, which can also collateralize to the CeA (Reynolds and Zahm, 2005), underscoring the potential central influence of MINS on subcortical areas that regulate mood and emotional state. Moreover, a subsequent study from our group (Luchsinger et al., 2021) used retrograde viral mapping to determine that the densest projection of insula neurons into the BNST is centered around AP ~+0.02 (MINS) in the mouse. This study also used monosynaptic rabies tracing (TRIO) to map upstream afferents onto MINS neurons that project to the BNST and identified dense inputs from motor, premotor, and somatosensory cortices, as well as amygdala. Further, this study showed a unique role for the motor cortex-to-MINS neurons in regulating struggling behavior during restraint stress. This unique motor cortex-to-MINS-to-BNST circuit could represent a feedforward pathway by which information relevant to physical activity can directly regulate affective circuitry. This fits with the concept of efference copy (Wolpert and Miall, 1996; Blakemore et al., 2000; Whitford et al., 2017), a collateralized circuit mechanism through which the brain can compare predicted actions (through insula regulation of emotional states) to resultant outcomes and sensations.

3.9.2. Insula projections to striatal regions

Insula also projects to striatal areas, with the potential to control expression of motivated behavior. As described above, inhibiting AINS-NAcb core in rats reduces compulsion-like alcohol drinking, with no effect on alcohol-only consumption, which was observed for both operant and two-bottle choice drinking methods (Seif et al., 2013). Another group also found no effect of inhibiting AINS (AP+3.0)-to-NAcb core (or AINS-CeA or -BLA) on alcohol-only two-bottle-choice drinking, although activating some projections reduced consumption (Haaranen et al., 2020a). On the other hand, DREADD inhibition of AINS-NAcb did decrease operant responding for alcohol in (Jaramillo et al., 2018c). As described above, it will be critical to understand whether mixed findings reflect specific procedural differences or other factors. Further, in addition to AINS, PINS (AP ~ -0.5) also projects to NAcb, and PINS-NAcb projections in mice mediate reduced feeding under physical sickness, different from PINS-CeA which mediates anxiety- and fear-related avoidance (Gehrlach et al., 2019), allowing PINS to mediate different types of aversive state. However, PINS-NAcb core in rats regulates social interaction with stressed juvenile rats (Rogers-Carter et al., 2019), which may reflect an empathy-like behavior. Thus, there are potentially divergent functional insula contributions depending on behavioral context.

Also, while much of the AINS projection-specific literature currently focuses on NAcb and amygdala, monosynaptic retrograde rabies viral tracing in mouse AINS (AP+2.4) finds major projections to lateral striatum, thalamus, and midbrain regions that are currently

understudied and emerging areas of research (Gehrlach et al., 2020) (see also Hunnicutt et al., 2016). For example, AINS (AP+2.4) has functional projections to dorsolateral striatum (DLS) in mice. Interestingly, one week of alcohol drinking or single injections specifically disrupts mu opioid receptor mediated long-term depression in these AINS-DLS projections (Munoz et al., 2018), suggesting that acute alcohol exposure may lead to hyperexcitability of AINS-DLS synapses via loss of presynaptic modulation of AINS inputs. While the behavioral effects of modulating these AINS inputs remain unknown, they could contribute to more habit-like drive for alcohol, given the DLS importance for habitual responding. Also, the magnitude of LTD across DLS cells has been remarkably consistent, suggesting impacts on AINS inputs to both D1-and D2-type MSNs (Atwood et al., 2014; Munoz et al., 2018), and anatomical tracing finds that insular cortex equally innervates both types of MSNs (Wall et al., 2013).

3.9.3. Insula projections to brainstem regions

Insula regions have strong projections to several brainstem regions, including those regulating autonomic function. For example, MINS/PINS neurons project to prodynorphin-containing mouse brainstem neurons, which are also in humans (Agostinelli et al., 2021). We also recently showed that AINS projections to the Locus Coeruleus area regulate compulsion-like but not alcohol-only drinking (De Oliveira Sergio et al., 2021). Given the importance of AINS and brainstem areas for autonomic and behavioral regulation, this is an area of critical importance for future work.

4. Conclusion

This review was designed to comprehensively consider the functional roles of different insula subregions, comparing examples from the extensive human literature with the more limited work in rodents. Even with important species differences, there seems to be meaningful parallels between human and rodent insula contributions. Indeed, insula subregions likely play central roles for many emotion- and motivation-related behaviors, and may be particularly important for integrating sensory, interoceptive, emotional, and cognitive inputs into a singular representation to help guide decision making and behavior. In addition, the specific details of a given situation, including task demands, subjective certainty, and the balance between desire for reward and level of cost, can strongly impact how the different insula subregions may be recruited. For example, under some conditions, AINS regions may be more important for prediction and expectation, while caudal insula subregions may mediate more concrete aspects of sensory and limbic experience. Most importantly, one central purpose of this review is to emphasize and encourage the importance, in all studies, of carefully and accurately delineating the different insula subregions under examination, to counter where the term “insula” might be used too broadly and thus potentially lead to incorrect interpretations. Together, we believe that these strategies will help future investigations provide clear models of what these highly relevant insula areas and the larger insula-centric circuitry are designed to accomplish.

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