



## An insular view of the social decision-making network

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### ABSTRACT

Social animals must detect, evaluate and respond to the emotional states of other individuals in their group. A constellation of gestures, vocalizations, and chemosignals enable animals to convey affect and arousal to others in nuanced, multisensory ways. Observers integrate social information with environmental and internal factors to select behavioral responses to others via a process called social decision-making. The Social Decision Making Network (SDMN) is a system of brain structures and neurochemicals that are conserved across species (mammals, reptiles, amphibians, birds) that are the proximal mediators of most social behaviors. However, how sensory information reaches the SDMN to shape behavioral responses during a social encounter is not well known. Here we review the empirical data that demonstrate the necessity of sensory systems in detecting social stimuli, as well as the anatomical connectivity of sensory systems with each node of the SDMN. We conclude that the insular cortex is positioned to link integrated social sensory cues to this network to produce flexible and appropriate behavioral responses to socioemotional cues.

### 1. Social decision making

It is nearly impossible to overstate the importance of sociality for the survival and success of many species (Wilson, 1992). Social behaviors are tightly interwoven with emotion, and communicating one's emotional state may evoke adaptive behavioral responses from other group members. Animals detect, appraise and respond to others' emotional states with flexible and context-appropriate behaviors through a process called social decision-making. This capacity gives rise to fundamental social actions across species, including parenting, mate selection and aggression (Ranote et al., 2004; Rendon et al., 2015), as well as the more complex and multidimensional facets of human social interactions like empathy, perspective-taking and compassion (Shamay-Tsoory, 2011; Tremblay et al., 2017; Sueur and Pelé, 2016; Marsh, 2018). In humans, impaired emotion recognition and the subsequent inability to generate appropriate social responses may underlie the social impairments characteristic of psychiatric disorders like autism and schizophrenia (Lozier et al., 2014; Edwards et al., 2002). Thus, understanding the neural mechanisms by which social animals detect and respond to socioemotional cues is an important goal of neurobiology.

Emotion, of course, is a complex and multi-faceted construct with varying definitions and applications (Cabanac, 2002). One element of emotion is “core affect,” a moment-to-moment reflection of an individual's arousal level and hedonic state that is influenced by external

stimuli and fluctuations in internal state (Russell, 2003). Core affect falls along two dimensions that span from sedating to arousing and from aversive to pleasing. In humans, emotional labels are used to describe specific combinations along these dimensions. For example, happiness reflects a core affect with modest arousal and pleasure, whereas fear describes a core affect that is aroused and aversive. The ability to communicate one's core affect likely evolved to elicit myriad social actions that promote individual or group survival and so we are able to use a comparative approach to study the mechanisms underlying these social actions. Throughout this review of social decision-making and behaviors observed primarily in rodents, we will use the term “social affect” to describe the expression of an animal's core affect. The behavioral responses that result from appraising another's affective state are considered “social affective behaviors.”

Many species transmit their core affect to other members of the group in expressions that include vocalizations, touch, chemosignals, olfactory cues, and behavioral gestures (Darwin, 1976; Insel, 2010), including facial expressions (Ekman and Oster, 1979; Chevalier-Skolnikoff, 1973; Sotocinal et al., 2011). For example, an infant's cry prompts maternal attention, and a distressed cry or vocalization may elicit help from other members of the species (Marsh, 2018; Ihnat et al., 1995; Brudzynski, 2013). Behavioral responses to social affective cues are generated via social-decision making, defined as the process by which sensory and perceptive systems in the brain appraise and integrate social information, like social affect, with situational factors,

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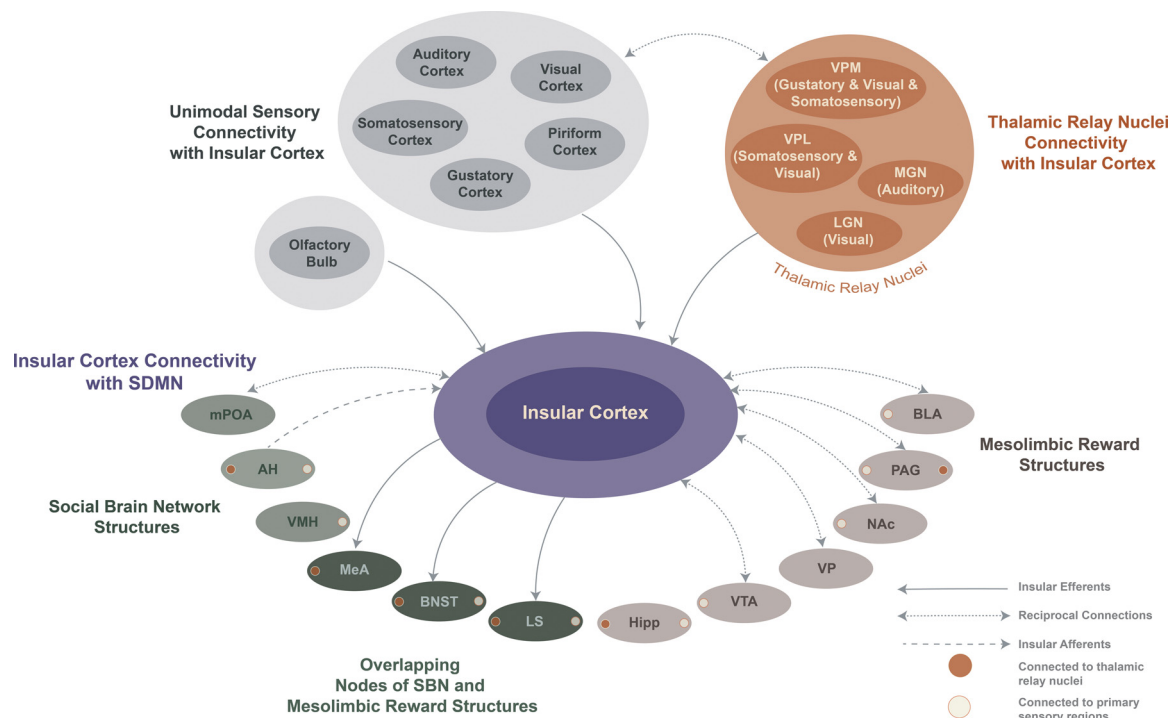
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**Fig. 1.** Schematic of insula connectivity with unimodal thalamic relay nuclei, primary sensory areas, and the social decision-making network. Thalamic nuclei encode and relay sensory information that conveys affect from the external environment to primary sensory areas where sensory information is decoded and assigned meaning. This information is also relayed via parallel projections to the insular cortex, where social cues are contextualized with internal physiology and other factors to produce unique output patterns in insula efferents that influence SDMN network activity and generate flexible behaviors. Few connections exist between thalamic nuclei and SDMN nodes, except for the following: medial geniculate nucleus projects to AH, MeA and PAG; ventroposterior medial nucleus projections to BNST and LS; lateral geniculate nucleus projects to Hipp (orange circles) and, likewise, unimodal cortical connectivity with SDMN is sparse (beige circles; see Section 3.1 for anatomical connections) so sensory information must reach the SDMN via other projections. Insular cortex is well-connected with thalamic relay nuclei, primary sensory areas, and most SDMN structures, suggesting IC is positioned to integrate sensory cues to influence SDMN activity and, therefore, contribute to the integration of socioemotional information with social behaviors. Abbreviations: **MeA**: Medial amygdala; **AH**: Anterior hypothalamus; **VMH**: Ventromedial hypothalamus; **mPOA**: Medial preoptic area; **BNST**: Bed nucleus stria terminalis; **LS**: Lateral septum; **Hipp**: Hippocampus; **VTA**: Ventral tegmental area; **VP**: Ventral pallidum; **NAC**: Nucleus accumbens core; **PAG**: Periaqueductal grey; **BLA**: Basolateral amygdala; **LGN**: Lateral geniculate nucleus; **MGN**: Medial geniculate nucleus; **VPL**: ventroposterior lateral nucleus of the thalamus; **VPM**: ventroposterior medial nucleus of the thalamus.

past experiences and internal physiology to shape specific, context-appropriate social behaviors. One product of integrating and appraising these factors is that an animal can compute the reward value of possible social behavioral responses (Gil et al., 2013; Weiss et al., 2015; Vanderschuren et al., 2016) which may alter the likelihood an animal will execute certain social behaviors (Caldú and Dreher, 2007). In the brain, a “social decision making network (SDMN)” of interconnected brain regions is the central orchestrator of social behavior (O’Connell and Hofmann, 2011; Fig. 1) and this review seeks to understand how social affect might influence this system.

An obstacle to understanding the anatomical correlates underlying social decision-making is its complexity; several parallel neural processes must coordinate across a network of brain regions to produce an observable social behavior. These include salience detection, sensory integration, memory for context and the identity of another individual, motivation, reward, and the motor systems that enable animals to generate social responses to socioemotional cues (Insel and Fernald, 2004; O’Connell and Hofmann, 2011). While these processes are not specific to information processing in the social realm *per se*, they are necessary to generate flexible, nuanced and context-appropriate social actions.

Human neuroimaging already provides some anatomical insight regarding these processes in social decision-making. In the prefrontal cortex (PFC), functional magnetic resonance imaging (fMRI) identified that activity in the dorsolateral, dorsomedial, ventrolateral and ventromedial prefrontal cortices correlated to regulating selfish versus prosocial actions, trust, risk assessment and reward valuation and

emotion recognition, respectively (Rilling and Sanfey, 2011). Beyond PFC, the fusiform face area, anterior cingulate, and ventral striatum and orbitofrontal cortex are implicated in social recognition, inferring others’ intentions, and decoding value signals to inform behavioral responses (Tremblay et al., 2017). Regarding insular cortex (IC), the focus of this review, there is substantial evidence from neuroimaging studies correlating IC activity or connectivity with empathy (Bernhardt and Singer, 2012) and emotion recognition (Green et al., 2016; Yamada et al., 2016). These human neuroimaging studies run parallel to investigations across taxa which investigate the brain systems and neurochemicals that are conserved, or at least have homologs, in mammals, amphibians, reptiles and avian species (reviewed in detail below). These comparative studies, therefore, omit the neocortical structures that are unique to mammals, thus leaving a significant question as to how to relate these lines of research: how do the cortical correlates of social cognition interact with hypothalamic and brainstem systems that we know are essential for many basic social behaviors?

The considerable homology between the rodent and primate brains allows rodent research to identify links between cortical and subcortical brain systems that provide the anatomical basis of social decision-making (Ruff & Fehr, 2014) and in some cases there are examples of functional and anatomical findings in humans that corroborate mechanistic studies in rodents (reviewed in Section 4). However, for rodent research to address the gaps between human and comparative research we must first establish that social decision-making in rodents involves the integration of social affective cues. A number of studies demonstrate that social signals emitted by one animal, referred to as the

“demonstrator,” can elicit behavioral changes in an “observer.” For example, rats will more readily press a lever to release a squealing rat than a toy block from a harness (Rice and Gainer, 1962) and to spare a conspecific from a painful shock (Green, 1969). More recent findings report that rodents transfer negative affective states, including fear, pain, and stress, which elicit social responses. Observer rats (Knapska et al., 2006), mice (Meyza et al., 2015), and voles (Burkett et al., 2016) spend more time exploring a cagemate that underwent tone-shock conditioning, and observers display increased exploration of the demonstrator (Knapska et al., 2010; Mikosz et al., 2015). Further, observer rats that witness or interact with footshocked or fear conditioned demonstrators show observational fear learning, increased sensitivity to pain, and a greater propensity to avoid noxious stimuli (Jeon et al., 2010; Kim et al., 2010). These phenomena highlight the important role of social affect in rodent prosocial behaviors, and we encourage interested readers to read a comprehensive account of this literature by Meyza et al. (2015).

The findings from rodent paradigms are congruent with human work (Von Dawans et al., 2012; Kawamichi et al., 2013; Bouchard et al., 2013; FeldmanHall et al., 2015) which identify that social affective behaviors that result from detecting a stressed demonstrator are influenced by a range of factors including, social rank, age, sex, previous experience with a stressor and familiarity. Regarding age, our lab has reported that adult rats will approach a stressed juvenile, but avoid a stressed adult (Rogers-Carter et al., 2018b). Numerous examples identify familiarity as an important determinant of prosocial behavior in rodent social paradigms: familiarity is either necessary for, or augments, vicarious fear (Jones et al., 2014), pain empathy (Li et al., 2014; Langford et al., 2006), social approach (Rogers-Carter et al., 2018a) and consoling behavior (Burkett et al., 2016). Similarly, rats will work to press a lever to release a restrained conspecific of the same, but not different, strain (Ben-Ami Bartal, Rodgers et al., 2014) but see (Silberberg et al., 2014). Furthermore, several cases of prosocial actions require that the observer had prior exposure to the stressor (Kiyokawa et al., 2014; Ishii et al., 2016; Guzmán et al., 2009), implying a role of mnemonic processes.

While the ability to detect social affective cues is crucial to species success, exactly how this information drives behavioral responses in a social interaction is not completely understood. In the upcoming sections we will articulate how external factors, social cues and physiological state converge to shape social affective behavior from the lens of mechanistic and behavioral studies in rodents. First, we review the existing anatomical models of social behaviors constructed from comparative neurobiology (Newman, 1999; O’Connell and Hofmann, 2011). Next, we discuss the mechanisms by which social affective cues are detected and processed by sensory regions in the rodent brain, while considering the flow of sensory information to social brain structures. We argue that the existing social brain models are incomplete with regard to sensory processing and salience detection. Finally, we synthesize evidence from anatomical, functional and behavioral studies conducted in both humans and rodents that posit the insular cortex (IC) as a site where social sensory stimuli, internal physiological state, and reward value converge. These features position IC to contribute to some of the processes currently unaccounted for in rodent models of social decision-making and bridge findings from human neuroimaging work and mechanistic insights from rodents.

## 2. Anatomical substrates of social decision-making

### 2.1. The social brain network

A network model of brain structures that are able to execute elementary social behaviors in rodents was first introduced in the Social Brain Network (SBN; Newman, 1999). This system includes the LS, mPOA, AH, VMH, PAG, VTA, MeA and BNST (See Fig. 1 caption for list of abbreviations). Homologous networks exist in in birds, bony fish

(Goodson, 2005) and reptiles (Crews, 2003). SBN nodes were included in the network model if they were reciprocally connected with the other regions, contained receptors for gonadal hormones, and were implicated in at least one mammalian social behavior. The SBN model posited that specific social behaviors are not mediated by one specific structure, but rather arise from unique patterns of SBN network activity that are elicited during exposure to certain social stimuli. Accordingly, recent reports support the notion that different patterns of activation across the SBN can give rise to a broad repertoire of social behaviors. For example, in the MeA, GABAergic neurons can produce aggressive, grooming, or mounting behavior depending on the strength of optogenetic excitation (Hong et al., 2014). Consistently, the strength of MeA neural activation during a social interaction varied with conspecific sex (Yao et al., 2017). A similar phenomenon is observed in the VMH where estrogen receptor 1 neurons in the VMH modulate behaviors ranging from investigation to attack (Lee et al., 2014), and in the BLA where inputs to the mPFC have bidirectional control to increase or decrease social investigation (Felix-Ortiz et al., 2016). Moreover, the social cues that drive activity patterns in the SBN may induce long-lasting changes in neurons; progesterone-expressing neurons in the VMH mediate aggression in single-housed, but not socially-housed male mice (Yang et al., 2017). Consistent with the idea presented in the SBN, unique patterns of activity in response to external stimuli are reported in humans (Smith et al., 2009) and in zebrafish during social interactions (Teles et al., 2015).

### 2.2. The social decision-making network

While the SBN captures the essential anatomical loci underlying many social behaviors in non-human mammals, this network lacks the structures needed to detect and appraise potentially rewarding aspects of social interactions. Indeed, reward signaling motivates social interactions, which are then reinforced by the mesolimbic dopamine system in non-human animals (Dölen et al., 2013; Hung et al., 2017; Ramos et al., 2015; Smith et al., 2018) and humans (Chelnokova et al., 2014). To this end, O’Connell and Hofmann (2011, 2012), using an evolutionary biology approach, made the keen observation that anatomical nodes of the mesolimbic dopamine reward system evolved to express many of the same receptors and genes that mediate social behaviors that were used to define the SBN across a range of non-human species, including teleosts, amphibians, reptiles, and avian and mammalian species. To account for the requisite reward signaling in social behavior, O’Connell and Hofmann (2011) merged the SBN with the mesolimbic reward system to form the social decision-making network (SDMN).

The SDMN consists of the SBN structures and the NAc, VP, BLA, Hipp, and VTA, with LS, BNST, and MeA (see Fig. 1 caption for abbreviations) as overlapping nodes in both the mesolimbic reward system and SBN. Each mesolimbic structure executes processes that culminate in an animal’s motivation to respond to their environment. It is not fully understood how social behaviors arise from this coordinated activity, but the known roles of each structure allow for speculation: first, social cues may be detected as salient and trigger the VTA (Root et al., 2018; Bromberg-Martin et al., 2010). This information may be integrated with valence in the BLA (LeDoux, 2000; Beyeler et al., 2018) and then contextualized by Hipp, which can place social information into memory and identify familiar conspecifics (Okuyama, 2018; Kogan et al., 2000), and by the NAc, which computes reward value (Higa et al., 2017). Reward value may be broadcast to SDMN network nodes, including the LS and BNST, both of which are implicated in rodent goal-directed actions (Faser et al., 1991), sexual behaviors (Gulia et al., 2002; Maejima et al., 2015; Petrucci, 2013), and aggression (Wong et al., 2016; Consiglio et al., 2005). Valence is integrated with other information in the SDMN to drive approach or avoidance (Hamel et al., 2017; Hoebel et al., 2007) or other social behavioral responses through connections with limbic and motor structures (Mogenson and Yang,

1991; Smith et al., 2009). Importantly, the mesolimbic system accounts for an animal's ability and motivation to respond to the external environment, whereas the SBN executes specific behaviors in response to mesolimbic inputs.

Mesolimbic structures also express genes associated with dopaminergic signaling, gonadal hormones, and oxytocin (OT) and vasopressin (AVP), all of which regulate behaviors and decision-making across many mammalian species (O'Connell and Hofmann, 2011; Creutz and Kritzer, 2004; Zhang et al., 2008). While sensitivity to OT and AVP were not initial requirements for inclusion in the SDMN, these social nonapeptides are now implicated in myriad social behaviors across species (Donaldson and Young, 2008; Caldwell, 2017) and mechanistic experiments in rodents that causally implicate SDMN nodes to social behaviors have done so via manipulations to, or examination of, OT and AVP signaling (Johnson and Young, 2015; Ophir, 2017). Many social behaviors are age- and sex-specific, which can be explained by differences in OT and AVP activity or receptor expression. For example, in rats, age negatively correlates with propensity to engage in social play, a naturally rewarding behavior, and consistently, juvenile rats have greater OT and AVP receptor binding density in reward-related regions than adults (Smith et al., 2017). Regarding sex, females maintain social recognition longer than males, which is mediated by differences in the AVP system (Bluthé and Dantzer, 1990). Further, the MeA exhibits robust sex differences in AVP binding (DiBenedictis et al., 2017) and promotes maternal behaviors in female rats, but infanticidal behavior in males (Chen et al., 2019). Lesioning AVP cells in the BNST reduced social investigation in males, but increased copulatory behaviors in females (Rigney et al., 2019), and social investigation positively correlated with OT receptor binding in the medial amygdala in males, but not females (Dumais and Veenema, 2016). Further, receptor expression for OT and AVP varies with social experience as pregnant prairie voles exhibited greater AVP receptor expression in the BNST, MeA, VP, NaC and Hipp than non-pregnant voles (Zheng et al., 2013). While not meant to be a comprehensive review of nonapeptides in social behavior, these findings illustrate how investigations of OT and AVP enable causal examination of the SDMN in rodents.

Despite the huge impact of the SDMN on our understanding of the anatomy and signaling systems that underlie social decision-making, this model was developed using a comparative approach and therefore omitted systems that are not conserved widely across species, such as cortical sensory processing regions. However, the SDMN does not capture how social affective sensory cues converge with internal physiology and external environmental factors, or how this information interacts with the neural systems that are directly attributed to social decision-making. Evidence from human studies implicates the cerebral cortex (Adolphs, 2001; Amodio and Frith, 2006b; Hiser and Koenigs, 2018) which receives social information from primary sensory relays (i.e. thalamic nuclei) and integrates this information to produce higher-order representations of sensory information through cortico-cortical network interactions. Anatomists identified the brain regions and tracts by which primary sensory processing structures project to associative “multisensory” structures and ultimately fully integrated structures in the cortex that might serve as the functional anatomic networks that provide the necessary sensory sophistication to inform decision making and cognition (Mesulam, 1998 and see Man et al., 2013, for an historical review of the origins of hypothetical functional networks based on neuroanatomical and mechanistic studies). The next section will review some of the evidence from mammalian research that implicates cortical structures in social decision-making to identify anatomical tracts to connect the cortex to the SDMN.

### 2.3. The cortex in socioemotional behaviors

In humans, the cortex is implicated in myriad social processes: distinguishing self from other, deciding one's motivation to engage in a social interaction, and deciphering the intention of another's motives,

among other social cognitions (Amodio and Frith, 2006a). The specific cortical areas most studied in human social cognition that are also present in rodents are the medial prefrontal cortex (mPFC) the orbito-frontal cortex (OFC), insular cortex (IC), and anterior cingulate cortex (ACC). Other areas, such as the fusiform face area and the extrastriate body area enable face and body detection in humans (Arioli et al., 2018) but will not be discussed here as their rodent homologues are unknown.

While not a complete account of the literature examining the human cortex in social cognition, this subset of findings demonstrates the myriad social processes that have cortical correlates. mPFC activity correlates with social status (Mason et al., 2014), perspective-taking (Frith and Frith, 2003), action-outcome prediction (Alexander and Brown, 2011), pair-bonding (Bales et al., 2007), cooperation, social reward, social punishment, and motivation (Bicks et al., 2015). Similarly, ACC activity correlates with others' social motivation and tracks prediction errors for behavior during a social interaction (Apps et al., 2018; Balsters et al., 2016). Regarding the OFC, activity here correlates with self-other distinction, and OFC neurons preferentially respond to faces and emotional expressions (Barat et al., 2018), signal social reward value, and track if a reward was received by oneself or another (Azzi et al., 2012). In non-human primates, OFC is also implicated in deciphering threatening versus affiliative social cues (Machado and Bachevalier, 2007) and lesions to the OFC reduce freezing to threatening stimuli (Kalin et al., 2007) and produced aberrant social approach and facial expressions (Babineau et al., 2011). Further, OFC can decide behavioral responses to ambiguous contexts based on the reward value of external stimuli (Elliott et al., 2000). Regarding IC, neural activity is correlated with emotion processing (Boucher et al., 2015), emotion recognition (Green et al., 2016; Yamada et al., 2016), cooperation (Rilling et al., 2008), fairness (Gabay et al., 2014; Guo et al., 2013), empathy for pain in others (Bernhardt and Singer, 2012; Gu et al., 2012), social motivation of others (Schreuders et al., 2018) and emotional awareness (Gu et al., 2013). However, IC is one of the most consistently-activated regions in emotion-related neuroimaging research (Phan et al., 2002) and neuroimaging research generally (Kurth et al., 2010) which suggests that IC is engaged by processes that are important for cognition more broadly than socioemotional decision-making.

To determine the extent that the correlates of cortical activity during human social cognition play mechanistic roles in social decision-making (Lee and Harris, 2013) requires translational research in rodent models where circuit-specific tools allow precise investigation of social behaviors. Indeed, recent findings implicate several of these cortical structures in social cognition. In OFC, subpopulations of neurons respond to social cues and inhibit feeding, which demonstrates this region can mediate internally-motivated behaviors in response to external social stimuli (Jennings et al., 2019). Our lab recently reported that approach or avoidance of stressed conspecifics depends on IC (Rogers-Carter et al., 2018a,b), and mPFC neurons show increased firing during social approach (Lee et al., 2016) and strength of synaptic efficacy positively correlates with social rank in mice (Wang et al., 2011). In voles that interact with a recently stressed cagemate, elevated Fos expression is observed in ACC, and ACC activation by oxytocin is necessary for social consoling behavior (Burkett et al., 2016). A common denominator of these findings is that social responses are the product of detecting external stimuli, and as discussed above, existing social brain network models do not account for this prerequisite process. The goal of the next section is to examine how cortical structures are necessary for detecting and responding to social cues, and their anatomical connectivity with the SDMN. This will lay the foundation to speculate how sensory information is conveyed to the SDMN so that behavioral responses are specific to external information.



### 3. Primary loci of sensory processes related to social affect in rodents

#### 3.1. Unimodal sensory processes

##### 3.1.1. Odor and piriform cortex

Odor communication is vital for rodent social behaviors (Johnston, 2003) and olfactory cues and chemosignals communicate one's, species, sex, and reproductive state, social status, sickness, and familiarity (Arakawa et al., 2008; Liberles, 2014). Exposure to specific odors elicits myriad social behaviors in rodents, such as mating (Coria-Avila et al., 2005; Sakuma, 2008), aggression (Stowers et al., 2013), social learning (Choe et al., 2015), maternal behavior (Fleming and Rosenblatt, 1974), and social buffering of fear (Kiyokawa et al., 2012; Takahashi et al., 2013). Odor information is processed in the piriform cortex, which receives primary afferents from the olfactory bulb and amygdala, and it is modulated by cortical structures including the orbitofrontal and entorhinal cortices (Illig and Wilson, 2009). This anatomical arrangement distinguishes piriform from the other unimodal sensory cortices, which are primarily innervated by thalamic relay nuclei. The piriform cortex can distinguish the identity, concentration and intensity of odors (Bolding and Franks, 2017) and accordingly, is implicated in odor-driven social behaviors. Mice that scent-mark in the presence of a conspecific expressed elevated Fos immunoreactivity in the piriform cortex (Borelli et al., 2009), and female mice exposed to juvenile play sessions with a lemon-scented partner later preferred to mate with a lemon-scented male, over an almond-scented male, and expressed greater piriform cortex Fos immunoreactivity than females that underwent the experiment without odor-pairing (Paredes-Ramos et al., 2014). Piriform cortex also receives oxytocinergic inputs from the paraventricular nucleus (Mitre et al., 2016), which contribute to enhanced discrimination and behavioral responses to odors by increasing the signal-to-noise ratio of social olfactory cues and chemosignals (Oettl and Kelsch, 2017). Piriform activation during social tasks likely reflects the detection of social odors specifically, rather than general olfactory information, because piriform can distinguish social from non-social odors; pharmacological and optogenetic inhibition of piriform oxytocin receptors abolished learning of both appetitive and aversive social, but not non-social, stimuli suggesting a role for this region in distinguishing social from non-social odors (Choe et al., 2015).

Piriform cortex has dense reciprocal connectivity with the MeA, BLA, Hipp and the VTA (Cádiz-Moretti et al., 2016; Coolen and Wood, 1998; Johnson et al., 2000; Aransay et al., 2015; Wyss, 1981; De La Rosa-Prieto et al., 2015) but connectivity with other SDMN nodes is sparse since known projections include only the BNST, NAc and Hipp (Weller and Smith, 1982; Brog et al., 1993; Dong and Swanson, 2006), and SDMN inputs to piriform are only found in AH and LS (Roeling et al., 1994; Siegel and Tassoni, 1971). Whether these connections are sufficient to integrate piriform-mediated odor processing to social decision-making is currently unknown. However, several studies demonstrate an interplay between olfactory cues and other sensory inputs in regard to mediating behavior (Rossier and Schenk, 2003; Moyaho et al., 2015), suggesting that separate anatomical regions capable of multimodal integration combine odor with other social stimuli and contextual factors to drive social behaviors.

##### 3.1.2. Tactile contact and somatosensory cortex

Tactile information is represented in the somatosensory cortex. In rodents, the majority of somatosensory information is detected via the whiskers, which relay physical touch to the ventral posterior medial and posterior medial thalamic nuclei (Erzurumlu and Gaspar, 2012; Viaene et al., 2011). These regions send efferents to barrel cortex, a distinct somatosensory cortex subregion that reflects the somatotopic organization of whisker positioning on the face (Li and Crair, 2011). Barrel cortex neurons respond to tactile behaviors observed during rodent social interactions including pinning, anogenital sniffing,

allogrooming, and nape-biting. Following rough and tumble play behavior, juvenile rats express elevated fos immunoreactivity in the barrel cortex (Gordon et al., 2002) and pharmacological blockade of the barrel cortex during social interaction reduced pinning behavior (Charles Lawrence et al., 2008). Rodents also frequently engaged in “social face touch,” a form of head-to-head contact utilizing the whiskers (Wolfe et al., 2011), and the necessity of both whiskers and barrel cortex are well-documented in this behavior. Whisker activity changes as a function of distance from a conspecific (Wolfe et al., 2011), and during bouts of social face touch, at least 40% of barrel cortex neurons increased firing at a rate significantly higher than that observed during contact with non-social stimuli (Bobrov et al., 2014). Moreover, social isolation, and therefore lack of social contact, results in impaired whisker sensitivity and disrupted synaptic plasticity in the barrel cortex (Miyazaki et al., 2012). Neonatal mice with trimmed whiskers performed poorly on a tactile sensitivity assay and displayed aberrant social behaviors in adulthood (Soumiya et al., 2016). Whisker-driven neural activation in barrel cortex was disrupted in NMDA receptor knock-out mice and correlated with social behavioral deficits (Arakawa et al., 2014), and de-whiskered pups were less successful at nursing than whisker-intact littermates, and were less active during social interactions with siblings (Sullivan et al., 2003). These findings signify that somatosensory cortex contains distinct subregions that are capable of uniquely responding to social stimuli.

The somatosensory cortex does not receive inputs from any SDMN structures but projects to several SDMN structures which provide anatomical pathways for tactile experience to shape social behaviors. Projections from somatosensory cortex to the VMH may code tactile events during mating (Stanzani and Russo, 1980; Angoa-Pérez and Kuhn, 2015), whereas projections to NAc and VTA (Tai and Kromer, 2014; Wilson, 2014; Hunnicutt et al., 2016; Lenschow and Brecht, 2018; Faget et al., 2016) may convey information about social contact or position to inform reward value and reinforcement (Báez-Mendoza and Schultz, 2013; Dölen et al., 2013). Sparse somatosensory cortex projections to PAG (Lenschow and Brecht, 2018) may allow social touch to inform adaptive and flexible physical responses in a social interaction (Skuse and Gallagher, 2009). However, none of these tracts have been investigated in rodent social behaviors.

##### 3.1.3. Visible social cues and visual cortex

Rodents display facial and body expressions during social interactions (Brecht and Freiwald, 2012), yet the role of these gestures in coordinating social behavior remains enigmatic. During social interactions and exposure to aversive stimuli, rats displayed tightening of the eyes, welling of the nose and cheeks, and flattening of the ears (Defensor et al., 2012), and changes in ear posture correspond to changes in general arousal state (Lecorps and Féron, 2015). When rats are tickled to induce a positive affect, ears become dark pink and flex at a wider angle (Finlayson et al., 2016), and mice display a “grimace” during negative affective states, like pain (Sotocinal et al., 2011), which correlates to a shorter and more curved spinal stance (Mittal et al., 2016). Facial expressions are observed during social interactions as well. Naked mole rats show aggressive mouth gaping and incisor fencing (Lacey et al., 1991) to establish social dominance (Brecht and Freiwald, 2012), and similarly, mice pluck the whiskers of others, rendering them unable to display aggressive or dominant faces (Sarna et al., 2000). Whisker position also signals if an interaction is aggressive or prosocial: during aggressive bouts, whiskers are protracted and whisk with high amplitude (Wolfe et al., 2011). Moreover, facial displays, like ear wiggling in females, are associated with courting behavior (Vreeburg and Ooms, 1985). Despite a limited understanding of the meaning of rodent visual cues, they appear to be important contributors to social decisions.

To our knowledge there are no neurobiological accounts of visual cortex neural activity during social interaction or exposure to social stimuli, but the importance of social experience on visual cortex

development is fairly well-documented. Rats raised in social isolation displayed increased higher-order dendritic branching (Volkmar and Greenough, 1972) and aberrant expression of dendritic spines in visual cortex pyramidal cells (Connor and Diamond, 1982), whereas rearing in an enriched social environment increased synaptic strength in visual cortex (Mainardi et al., 2010). Lastly, in a murine model of autism, social abnormalities are associated with reduced functional connectivity between visual cortex and other sensory cortical areas (Sforazzini et al., 2016). Visual cortex projections synapse in the PAG, NAc, and VTA (Newman et al., 1989; Wilson, 2014; Dinopoulos and Parnavelas, 1991) but do not receive inputs from the SDMN. This connectivity may provide the anatomical framework for visual information to inform reward valuation during a social interaction, and also suggests that corticocortical interactions are necessary to further process social visual cues and relay them to SDMN.

### 3.1.4. Vocal communication and auditory cortex

Rodents emit audible and ultrasonic vocalizations to convey negative and positive affective states. The acoustic characteristics, functional purpose and neural correlates of ultrasonic vocalizations are reviewed elsewhere (see: Brudzynski, 2013; Portfors and Perkel, 2014). Ultrasonic vocalizations are observed in prosocial (Pultorak et al., 2016; Burke et al., 2017), reproductive (Neunuebel et al., 2015; Matsumoto and Okanoya, 2016) and territorial behaviors (Pasch et al., 2011; Hammerschmidt et al., 2012) and are encoded by auditory cortex. Auditory cortex neurons are active during playbacks of vocalizations (Carruthers et al., 2013). Further, rats expressed elevated Fos in auditory cortex after exposure to recordings of 22 kHz calls (Ouda et al., 2016), and calcium imaging revealed a subset of auditory cortex neurons that respond to the frequency sweep rate of modulating calls (Issa et al., 2017). Ultrasonic vocalizations can modulate social behaviors as well; rats displayed approach behavior when played recordings of 55 kHz calls and expressed Fos in the auditory cortex (Sadananda et al., 2008), and auditory neurons in female dams undergo plasticity to increase the signal-to-noise ratio of pup calls (Tasaka et al., 2018), which drive maternal behaviors (Valtcheva and Froemke, 2018).

Auditory cortex projects to the PAG, BLA, Hipp, and VTA, which may allow acoustic information to be incorporated into context and reward valuation (Lindvall and Stenevi, 1978; Newman et al., 1989; Romanski and LeDoux, 1993; Budinger et al., 2008). Further, projections from auditory cortex to LS (Lindvall and Stenevi, 1978) and BNST (Shin et al., 2008) may integrate vocal cues with emotional (Singewald et al., 2011) and physiological states (Herman et al., 2003), and vocal inputs may evoke oxytocin release via projections to the PVN during social interaction (Peñagarikano et al., 2015). Interestingly, auditory cortex has reciprocal connectivity with NAc, an important hub for vocal song learning in birds (Prather, 2013), and so this pathway may help encode social sounds for later recognition or performance. Moreover, NAc projections in the visual cortex also project to the lateral amygdala, which may allow for the integration of acoustic inputs with emotional or affective state (LeDoux et al., 1991). However, like several other unimodal sensory cortical regions, none of the projections from auditory cortex to SDMN structures have been causally examined in a social behavior.

### 3.1.5. Taste communication and gustatory cortex

Evidence for gustatory communication in social behavior comes from social transmission of food preference. Rats will prefer to consume a certain food if they had recently explored a conspecific that consumed the same food (Galef and Wigmore, 1983; Galef et al., 1985). Similarly, hamsters preferred to consume the diet their mother was fed, but failed to show a preference for a diet fed to either a littermate or a novel conspecific, indicating that the features or relationship of the individual transmitting a food preference are important in determining the observer's behavior (Lupfer et al., 2003). Lastly, in rats, presentation of an olfactogustatory cue prompted nicotine self-administration during

social interaction (Chen et al., 2011). Non-volatile chemosignals are detected through sniffing and licking (Lehman et al., 1980), and so it's possible that chemosensory information involves gustatory processing to some extent. Regarding the SDMN, gustatory cortex is only connected to this network via inputs from the BLA, which may combine taste with emotional state, such as in conditioned taste aversion acquisition (Gallo et al., 1992). However, gustatory cortex is a subregion of IC and anatomical studies of IC may not distinguish gustatory from the broader IC, the connectivity of which with the SDMN will be discussed below.

### 3.2. Multimodal sensory processing of socioemotional cues

Concurrent unimodal sensory information must be integrated to assemble a complete representation of the external environment. To do so requires multisensory convergence and multisensory integration, two processes that are observed in both individual neurons and populations of neurons. Multisensory convergence occurs where inputs from multiple sensory modalities overlap in time, and the resulting neural response is a direct sum of the response that each unimodal input evokes individually. Multisensory integration, however, is identified when the neural response to multisensory inputs is distinctly different (i.e. non-linear) than the sum of the neural responses to converging unimodal signals and, therefore, each individual modality cannot be delineated from the resulting activity (Stein et al., 2014). This binding of information via multisensory integration converts simple sensory representations into higher order abstractions that inform behavioral decisions (Siemann et al., 2014). In animal social behaviors, there are several examples in which concurrent cues take on a unique social meaning (Partan and Marler, 1999). For example, dogs signal threat to one another via growling, but growling in combination with a bowed stance initiates play behavior (Bekoff, 1972). Animals trained to approach a visual cue do so more readily if the cue is paired with an auditory stimulus, which indicates an effect of multisensory presentation on attention (Stein et al., 1989). Furthermore, rat mating behavior (Beach, 1942) and maternal behaviors (Beach and Jaynes, 1956; Smotherman et al., 1974) are mediated by combined olfactory, visual, and tactile cues, do not elicit as robust behavioral responses on their own (but see Stern, 1990).

Only a few studies have examined the neurobiology underlying the integration of multimodal social cues in rodents. In the rat auditory cortex, ultrasonic vocalizations emitted during social interactions evoke fast-spiking neural activity that correspond to the start and end of a bout of tactile contact. However, this activity was inhibited by social face touch, which suggests that the salience of auditory information is modulated by somatosensory information (Rao et al., 2014). Similarly, in lactating female rats, pup odor increases auditory tone-evoked activity of neurons in auditory cortex, which may function to increase maternal attention to pups (Cohen et al., 2011). Consistent with the idea that unimodal sensory cues influence neural responses to stimuli of various modalities, several findings report neural activity that reflects multisensory integration in primary sensory areas in rodents (Duhamel, 2002; Kayser and Logothetis, 2007; Samuelson and Fontanini, 2017; Ma et al., 2016; Maier et al., 2015) which suggests that sensory inputs may already begin to undergo integration in these regions. Second order sensory areas and cortical structures that execute multisensory integration, including the superior colliculus (Stein et al., 1989) and perirhinal (Otto and Eichenbaum, 1992; Furtak et al., 2007), retrosplenial (Vann et al., 2009), orbitofrontal (Schoenbaum et al., 2003), medial prefrontal (Martin-Cortecero and Nuñez, 2016) cortices are also implicated in both multisensory integration and social behaviors. How integrated, multimodal information arrives in the SDMN however, is currently unknown, but the insular cortex (IC) is one region of interest. The next section will discuss how the unique anatomical arrangement and functional role of the insular cortex warrants consideration of this region as a key hub in social decision-making.

#### 4. Insular cortex in social decision-making: evidence from rodents

##### 4.1. The insular cortex integrates external sensory stimuli

The IC is a well-documented site of multisensory processing (Rodgers et al., 2008; Gogolla et al., 2014) and is reciprocally connected with thalamocortical structures (Craig, 2009; Guldin and Markowitsch, 1983), which suggest IC is positioned to integrate sensory information with emotional and motivational states (Damasio and Carvalho, 2013; Krushel and van der Kooy, 1988; Paulus and Stein, 2006). Unimodal visual, sensory, auditory, gustatory and nociceptive inputs first converge in posterior IC by way of dense connections from somatosensory cortices and the supragenulate, posterior intralaminar, peripeduncular nucleus, medial geniculate, and reticular thalamic nuclei, all of which relay sensory information from spinal afferents to the brain (Fig. 1; Shi and Cassell, 1998; Linke and Schwegler, 2000; Hanamori et al., 1998). Posterior IC can then integrate unimodal sensory inputs, which is reflected in supralinear posterior IC activation to multimodal sensory stimuli (Rodgers et al., 2008) mediated, in part, by excitatory inputs from the thalamic reticular nucleus (Hanamori et al., 1998). Similarly, single unit recordings in the insular auditory field show co-responsivity to both forepaw stimulation and white noise bursts (Kimura et al., 2010) and extracellular recordings in posterior IC reveal overlapping neural responses to tail pinch, baroreceptor stimulation, appetitive and aversive tastes, and arterial chemoreceptor stimulation (Hanamori et al., 1998). Human neuroimaging studies identify IC activity in response to facial expressions (Boucher et al., 2015) and voice recognition (Andics et al., 2010). These properties suggest IC has the capacity to encode both internal and external sensory stimuli of various modalities.

##### 4.2. Insular cortex integrates external stimuli with changes in physiological state

In addition to integrating external sensory stimuli, IC is thought to be a locus of interoception because inputs from visceral thalamic nuclei allow IC to detect internal physiological changes (Damasio, 2006; Damasio and Carvalho, 2013; Craig, 2009, 2011; Seth, 2013; Strigo and Craig, 2016). Homeostatic changes profoundly impact brain function, attention, motivation and behavior, and rodent studies of emotion contagion have identified several instances where exposure to a recently stressed demonstrator can cause physiological changes in an observer. In mice, 22 kHz alarm calls emitted by demonstrators activate the sympathetic nervous system of observers (Chen et al., 2009), and after exposure to biting horse flies, demonstrator mice display conditioned analgesia, which is transferred to observers (Kavaliers et al., 2001). Further, both observer and demonstrator voles express elevated plasma corticosterone levels (Burkett et al., 2016), and observer mice display potentiation of corticotropin-releasing hormone neurons in the paraventricular nucleus of the hypothalamus after interaction with a footshocked mouse (Sterley et al., 2018). This begets the question, do observers have a mechanism to detect these bodily changes in order to generate an appropriate social response? Information about internal state is relayed to the brain by visceral afferents via spinal and cranial nerves, which allow the brain to appraise the body's physiological state and generate subsequent behavioral responses (Critchley and Harrison, 2013). These signals are detected by a “general visceral IC” (Ceppetto and Saper, 1987) which receives inputs from ventroposterior medial and ventroposterior parvocellular thalamic nuclei and responds to diverse visceral input from gastric mechanoreceptors, arterial chemoreceptors, cardiovascular baroreceptors, as well as changes in respiration and vagal nerve activity (Barnabi and Ceppetto, 2001). Moreover, IC is known to have top-down control of visceral function via efferent projections to the nucleus of the solitary tract, parabrachial nucleus, and ventrobasal and mediodorsal thalamus (Krushel and van der Kooy, 1988), and stimulation of IC neurons that project to the dorsal vagal

complex or lateral hypothalamic area increases blood pressure and airflow (Bagaev and Aleksandrov, 2006), and sympathetic factors like heart rate, renal nerve activation, and blood pressure (Ceppetto and Chen, 1990), respectively. These findings position the IC to be involved in either the response to, or initiation of, behavioral responses to various stressors and so the IC may detect changes in the internal state caused by exposure to a stressed demonstrator.

Regarding social function, visceral vagal inputs are hypothesized to mediate neurophysiological processes underlying stress and subsequent social behaviors (Porges, 2001) and in IC, exposure to stress increases Fos immunoreactivity (Yokoyama and Sasaki, 1999) and induces hypersensitivity to visceral function (Sun et al., 2016). Further, there may be overlapping neural populations in posterior IC that respond to, and therefore integrate, both internal and external information (Shinder and Newlands, 2014), which may give rise to the “self-other” distinction, and subsequent empathic abilities attributed to the IC in human neuroimaging experiments (Uddin et al., 2008; Singer et al., 2009). Consistent with this thought, prior work suggests IC is the region responsible for transforming internal interoceptive signals into representations of an embodied self (Seth, 2013). Thus, if exposure to a stressed demonstrator induces physiological changes in an observer, IC may integrate visceral information with limbic and motivational states via efferents to PFC (Fujita et al., 2010), amygdala (Shi and Cassell, 1998), hypothalamus (Reep and Winans, 1982) and NAc (Wright and Groenewegen, 1996) all of which are implicated in various social behaviors (Yizhar, 2012; for review). Accordingly, IC is proposed to integrate internal autonomic information with external sensory signals to mediate social learning and inform affective decision-making during neurodevelopment (Quattrocki and Friston, 2014).

##### 4.3. Valence coding in the insular cortex

Decisions are influenced by reward value (Ploeger et al., 1991), and IC is implicated in a number of reward-related tasks in rodents. IC neurons respond to cues that predict a water reward, and increase activity after a negative outcome (Jo and Jung, 2016), suggesting IC encodes stimulus value. Consistently, in a conditioned place preference test, rats favored the maze compartment in which they received electrical stimulation of IC (Hurtado and Puerto, 2018), and unilateral stimulation of pIC was sufficient to induce the conditioned place preference (García et al., 2013). Pattij et al. (2014) demonstrated that pharmacological blockade of IC dopamine receptors impaired performance in a delay-discounting task. In a rat gambling task, infusion of methamphetamine to IC caused rats to opt for a high-risk, high-reward option (Mizoguchi et al., 2015). Congruent with this evidence, Ishii et al. (2012) observed a decrease in risk-taking during a rat gambling task when IC was pharmacologically inactivated. These findings are consistent with human studies in which insular lesions were associated with impaired risky decision-making (Clark et al., 2008).

The foregoing suggests that IC also contributes to value coding in social settings. A major output of the IC is the NAc, with efferents from anterior IC terminating in the dorsomedial portion of NAc, and efferents from mid and caudal IC terminating in the dorsolateral NAc (Wright and Groenewegen, 1996). NAc encodes reward value and decision-making, and, as noted, both IC and NAc are implicated in rodent and human social behaviors (Lamm and Singer, 2010; Trezza et al., 2011; Singer et al., 2006; Lichtenberg et al., 2018). In one experiment investigating this tract, silencing anterior IC→NAc neurons reduced reward seeking behavior (Jaramillo et al., 2018). Interestingly, while glutamatergic inputs to the NAc tend to reinforce instrumental behaviors (Britt et al., 2012), the consequence of NAc glutamate is a product of interactions between glutamate and co-transmitters like dopamine and oxytocin (Dölen et al., 2013), and the specific postsynaptic NAc cell types (Tye, 2012). Accordingly, glutamatergic inputs to NAc might contribute to both rewarding and aversively motivated social behaviors.



#### 4.4. The insular cortex, rodent social behaviors, and connectivity with SDMN

In light of the description of the sensory connectivity of IC, recent findings implicate IC as a mediator of social behavior in rodents. Our lab has reported that OT receptors in IC mediated both approach toward stressed juvenile rats and avoidance of stressed adult rats (Rogers-Carter et al., 2018b). Further, aberrant GABAergic circuit maturation is observed in the IC of several strains of autism-model mice with known social impairments (Gogolla et al., 2014) and IC microinfusions of a NMDA receptor antagonist are sufficient to decrease wrestling, social exploration, and ultrasonic vocalizations in male rats exposed to alcohol during development (Bird et al., 2017). Regarding social memory, dopaminergic, adrenergic, and serotonergic receptors in IC are involved in social recognition memory (Cavalcante et al., 2017).

These social roles for IC may result from its extensive circuitry with SDMN structures, a feature that is not observed in other higher-order sensory processing sites in the cortex. IC is reciprocally connected with the VTA, BLA, VP, NAc, MeA and PAG (Faget et al., 2016; Reep and Winans, 1982; Dong and Swanson, 2006; Shi and Cassell, 1998; Reynolds and Zahm, 2005; Groenewegen et al., 1993; Wright and Groenewegen, 1996; Cádiz-Moretti et al., 2016; Pardo-Bellver et al., 2012; Neafsey et al., 1986; Herrero et al., 1991), projects to LS, BNST and mPOA (Dong and Swanson, 2004, 2006; Simerly and Swanson, 1986) and receives afferents from AH (Reep and Winans, 1982). The only SDMN structures with which IC lacks connectivity are Hipp and VMH (Fig. 1). These connections position IC to integrate internal visceral changes with external sensory information from primary sensory inputs in order to influence SDMN activity, providing the anatomical framework by which external sensory stimuli can drive patterns of activity across the SDMN to elicit specific behavioral responses as hypothesized by Newman (1999). In addition to the anatomical connectivity, Seeley et al. (2007) demonstrated that IC is functionally connected to most of the deep brain structures of the SDMN. Specifically, insula BOLD signals were strongly correlated with a “salience network” of ROIs including the ACC, amygdala, VP, thalamus, hypothalamus, PAG, and VTA. This pattern is remarkably congruent to both the rodent anatomy reviewed here and primate insular anatomy (Mesulam and Mufson, 1982; Ongur and Price, 2000). Subsequent neuroimaging research has found that this salience network is involved in many cognitive functions, including socioemotional processes (Toller et al., 2018) and autism (Uddin and Menon, 2009). However, no mechanistic studies of the connections between insula and the SDMN in the context of social affective behavior exist, making this a particularly rich area for discovery.

#### 4.5. Insular cortex in social decision-making

In the foregoing sections we presented the anatomical foundation to think about the contributions of IC to social cognition in rodents and other non-human mammals. In the extant research, IC activity is correlated with many aspects of social stimuli and behavioral responses possibly because it is positioned to integrate multisensory social stimuli with internal state. In an attempt to place the IC in the information processing stream for social affective behaviors, here we suggest where and how social affect is detected and integrated, leading to social affective behaviors. First, social affective cues from a demonstrator in a negative affective state, that is after a stressor, elicits physiological changes in an observer which reach the IC via thalamic relay nuclei and primary sensory regions. Concurrent input from IC afferents from the basolateral amygdala may convey the valence associated with the cues. IC then binds valence and sensory information to produce a multimodal sensory representation of the social stimulus. It is at this point that IC may attribute affect to the demonstrator. This assessment enables IC to convey information to SDMN structures to generate social behavioral responses. This view leads to the prediction that removing either the

BLA or sensory inputs to the IC would render social behavior insensitive to the emotional states of others whereas removal of specific IC projections might selectively impair certain social affective behaviors. In support of this view, network analyses of IC activity and connectivity with somatosensory cortex revealed that the integrity of this circuit is important for social behavior. In healthy mice, somatosensory and IC activity correlated with sociability but in mice treated with valproic acid, a model of autism, decreased functional connectivity associated with social avoidance (Cho et al., 2017). With regard to IC outputs, we found that IC projections to the NAc are selectively active during encounters with stressed juveniles and are necessary for social approach (Rogers-Carter et al., 2019). We demonstrated that modulating IC activity in the absence of socioemotional manipulations was sufficient to recapitulate either approach or avoidance behaviors (Rogers-Carter et al., 2018b) which suggests that within IC, ensembles of neurons must contribute in some way to selecting a social behavioral response (i.e. approach or avoid) and this occurs after sensory information arrives.

The anatomical and behavioral evidence reviewed thus far make a strong case that the IC is important to social affective behavior, but does not address *why* it is important in terms of information processing. Prevailing views of the insular cortex from human neuroimaging studies argue that IC is a locus of salience detection (Seeley et al., 2007 and for review see Menon and Uddin, 2010, 2015) and empathic cognition (Bernhardt and Singer, 2012). Considering the IC as a waypoint for multisensory integration likely accounts for the range of cognitive processes that are associated with this region. With regard to salience detection, IC is positioned to respond to meaningful or surprising combinations of internal and external stimuli, and because of its efferent connectivity, the salient events can profoundly shape the locus of neural circuit activity. This is well elaborated and supported by studies wherein salient stimuli trigger a shift from resting state functional connectivity to executive circuit function (Menon and Uddin, 2012). This might be why IC is important to empathy and other social emotional processes: they involve salience detection. In contrast, if the IC is uniquely engaged by social affect or, in other words, plays a unique role in empathic cognition, then one would predict that unique ensembles of IC neurons are active according to specific affective states of other individuals. To better understand what the IC contributes to information processing, future studies should be designed to untangle salience from empathy-specific cognition. Here we suggest a synthesis of the salience and empathy views; perhaps, in response to social affect, the IC may also toggle neural circuit control within the SDMN? The anatomical and behavioral evidence reviewed suggests that IC is engaged during seemingly opposite social behaviors such as both approach and avoidance (Rogers-Carter et al., 2018a,b) but the IC is not needed for typical social behavior between naïve rats (Christianson et al., 2011). Therefore, the sensory social information that precedes these behaviors might drive IC only when it is salient. Specifically, social encounters that involve stress, sex, food might trigger the IC, via its efferents to the SDMN, to toggle network control to yield different social behaviors: avoidance to approach, aggression to submission, and so on.

## 5. Conclusion

Across species, social decision-making allows for navigating the social world with behavioral flexibility. Behavioral reactions in a social situation reflect the convergence of social information, external stimuli and physiological state to produce appropriate responses. Multimodal sensory integration and convergence allow socioemotional cues to be bound with relevant external cues and internal states. We argue this function is uniquely attributed to IC, which is anatomically positioned to serve as a waypoint for social information to influence activity patterns in the SDMN. From this view, we can better understand why abnormal IC function and connectivity are correlates of a broad range of neuropsychiatric symptoms and should be seen as a focal point for research efforts to better treat, diagnose and prevent mental illness.



## Conflicts of interest

The authors have no competing financial conflicts of interest to declare.

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