

Opinion

The Insula: An Underestimated Brain Area in Clinical Neuroscience, Psychiatry, and Neurology

Ho Namkung,^{1,2} Sun-Hong Kim,¹ and Akira Sawa^{1,2,3,*}

Supported by recent human neuroimaging studies, the insula is re-emerging as an important brain area not only in the physiological understanding of the brain, but also in pathological contexts in clinical research. In this opinion article, we briefly introduce the anatomical and histological features of the human insula. We then summarize the physiological functions of the insula and underscore its pathological roles in psychiatric and neurological disorders that have long been underestimated. We finally propose possible strategies through which the role of the insula may be further understood for both basic and clinical neuroscience.

Introduction: It Is Time to Pay Attention to the Insula

The human insula was first described as an 'island' of cortex by Johann-Christian Reil in 1796 ('insula' is Latin for island). Since then, the insula has long been neglected. The insula re-emerged from this dearth of interest in 1994 when Antonio Damasio formulated the 'somatic marker hypothesis' that rational thinking is inseparable from feelings and emotions represented in the brain as body states [1]. Recent human neuroimaging studies have pointed out the significance of the insula in many brain disorders [2,3].

The aim of this opinion article is to highlight the role of the insula, particularly in conjunction with psychiatric and neurological disorders. Keeping this purpose in mind, we start by briefly introducing the anatomical and histological features of the human insula. We then provide significant insights into the physiological functions of the insula and its pathological roles. Finally, we propose promising strategies in which causal roles of the insula in brain function and dysfunction can be better understood.

Anatomy and Histology of the Human Insula

The human insular cortex is bilaterally located deep within the lateral sulcus or the fissure that separates the temporal lobe from the parietal and frontal lobes, at the bottom of the lateral cerebral fossa (Figure 1) [4]. It can be roughly subdivided into posterior and anterior sections, and each section has different cytoarchitectonic features, connectivity, and therefore functions [4–7]. The posterior regions [granular regions (see Glossary)] of the insula receive ascending sensory inputs from the spinal cord and brainstem via the thalamus, in addition to inputs from parietal, occipital, and temporal association cortices. Thus, these posterior regions have a role in somatosensory, vestibular, and motor integration. The anterior regions (agranular regions) have reciprocal connections to limbic regions such as the anterior cingulate cortex, the ventromedial prefrontal cortex, the amygdala, and the ventral striatum. The anterior regions

Trends

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The anterior insula has a core role in supporting subjective feeling states. It can also regulate the introduction of feelings into cognitive and motivational processes.

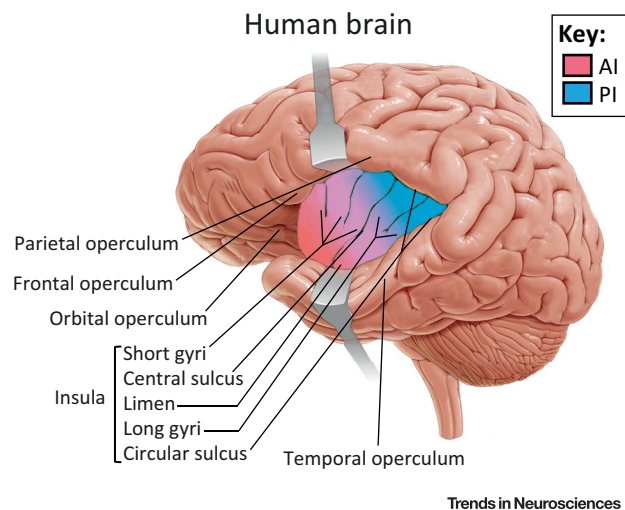
Understanding of mental conditions through multiple distinct dimensions of function associated with the insula may be important.

To overcome the limitations in human neuroimaging studies, computational and statistical efforts in human brain image processing and analysis are expected.

With recent technological advances in preclinical studies using rodents, we expect a better understanding of causal roles for the insula in higher brain function. Such understanding consists of the information at multiple levels spanning from the gene, molecule, cell, circuitry, physiology to behavior.

¹Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

²Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA



³Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

*Correspondence: asawa1@jhmi.edu (A. Sawa).

Figure 1. Anatomy of the Human Insula. The human insular cortex is bilaterally located deep within the lateral sulcus separating the temporal lobe from the parietal and frontal lobes. The insula is covered with folds of the adjacent frontal, parietal, and temporal opercula. The circumference of the insula is outlined by the circular sulcus, and the deep central sulcus of the insula separates the anterior and posterior parts. Three short insular gyri are found in the anterior insula (AI), whereas two long insular gyri lie in the posterior insula (PI). Cytoarchitecturally, the insula is roughly divided into anterior agranular and posterior granular sections with a transitional dysgranular mid-section.

have been implicated in the integration of autonomic and visceral information into emotional, cognitive, and motivational functions.

The anterior insula is among the most differentially expanded neocortical regions in humans compared with those in other primate species [8]. It has strong structural and functional connections with the anterior cingulate cortex, and thus the anterior insula can be considered as a ‘limbic sensory area’ connected with the anterior cingulate cortex, a ‘limbic motor area’ [9,10]. Interestingly, the anterior insula contains a high density of large spindle-shaped neurons among the pyramidal neurons in layer 5, called von Economo neurons, which has a structural architecture similar to that of the anterior cingulate cortex at the cellular level [11]. While exactly what von Economo neurons are doing within the circuit is not yet known, considerable evidence suggests that von Economo neurons, with their large diameter axons, facilitate rapid long-range information integration [12].

Physiological Functions of the Human Insula

The myriad sensory functions of the insula have been unified under the concept of **interoception** [13]. Interoception is called the **neural mapping of body states** that have special relevance for the maintenance of homeostasis. A posterior-to-anterior progression of interoception through the insula has been proposed [14]: first, primary (objective) interoceptive signals arrive in the posterior insula where low-level sensory features are processed. Then, this information is passed to the anterior insula where the re-represented interoceptive signals are integrated with emotional, cognitive, and motivational signals collected from other cortical and subcortical regions, such as the amygdala, the anterior cingulate cortex, the dorsolateral prefrontal cortex, and the ventral striatum (Figure 2).

The anterior insula has a core role in supporting **subjective feeling states** [15]. It is well known that sensory signals map onto primary sensory cortices such as the primary visual cortex [16]. Similarly, primary interoceptive signals map onto specific subregions in the posterior insula [13,17]. Importantly, posterior-to-anterior remapping of interoceptive signals enables conscious perception of interoceptive information [14]. Therefore, the anterior insula constitutes

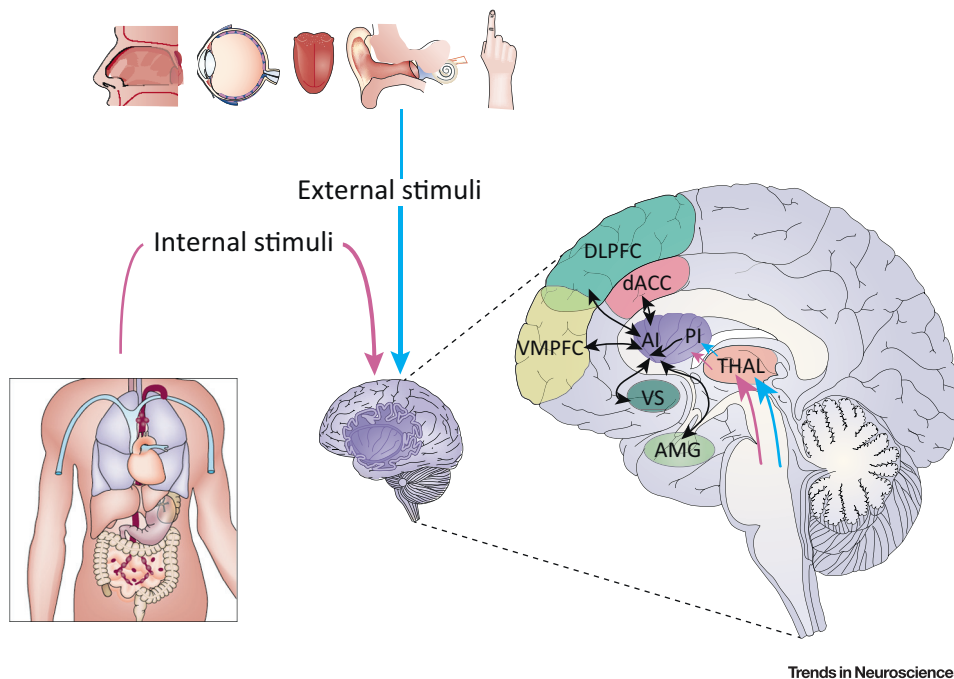


Figure 2. Interoceptive Information and Its Integration with Emotional, Cognitive, and Motivational Signals from an Array of Cortical and Subcortical Regions. Interoceptive information of constantly changing body states arrives in the posterior insula by ascending sensory inputs from dedicated spinal and brainstem pathways via specific thalamic relays. This information is projected rostrally onto the anterior insula, where it is integrated with emotional, cognitive, and motivational signals from an array of cortical and subcortical regions. As a result, the anterior insula supports unique subjective feeling states. The anterior insula regulates the introduction of subjective feelings into cognitive and motivational processes by virtue of its cortical location at the cross-roads of numerous pathways involved in higher cognition and motivation. Abbreviations: AI, anterior insula; AMG, amygdala; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PI, posterior insula; THAL, thalamus; VMPFC, ventromedial prefrontal cortex; VS, ventral striatum.

the neural basis of subjective feeling states [13–15]. The subjective feeling states arising from the insula might also provide a basis for the ‘self’: several investigators have proposed the idea that interoceptive representation in the anterior insula provides an awareness of the physical self as a feeling (sentient) entity, which may constitute a basis of selfhood [10,14,18].

The insula has been shown to play a significant role in cognition [19,20]. Multiple lines of evidence imply that feeling states arising from the insula influence cognition [20,21]: feeling states influence and possibly determine the relative salience of competent stimuli, which then prioritizes stimuli for **cognitive resources**. We pay attention to and remember salient events that are associated with feelings of joy, sorrow, pleasure, and pain [22,23]. Feeling states also influence reasoning, which contributes to the fixation of belief [22]. Taken together, the anterior insula marks salient information by referring to subjective feelings states, and therefore initiates cognitive processes for further processing the salient information [20,21].

The insula also plays an important role in motivation, particularly in explicit motivation [24,25]. Explicit motivation is the conscious or subjective desire to engage in behaviors, whereas implicit motivation is the unconscious desire to engage in behaviors. Converging evidence implies that the insula encodes **incentive values** of stimuli by evaluating the stimuli-eliciting subjective feeling states [24–26]. Rewarding stimuli evoke feelings of pleasure, which in turn drive conscious desires for deciding to take particular actions, whereas aversive stimuli evoke feelings of pain, which lead to conscious aversions for avoiding particular behaviors. In this regard, feelings arising from the insula mediate human behaviors [22].

Glossary

Agranular region (cortex): an isocortical region with a relatively undifferentiated layer II and layer III, and lack of layer IV.

Central executive network: a brain network that includes the dorsolateral prefrontal cortex and the posterior parietal cortex, which is responsible for high-level cognitive functions, such as attention and working memory.

Cognitive resources: a set of all mental abilities and resources related to knowledge (e.g., attention, memory, working memory, reasoning).

Default mode network: a brain network including the ventromedial prefrontal cortex and the posterior cingulate cortex, which is responsible for self-related activities such as autobiographical processing and self-monitoring.

Granger causality analysis: an approach to explore causal interactions between neural activities from time-series functional magnetic resonance imaging data. It implements a statistical, predictive notion of causality whereby causes precede and help predict their outcomes.

Granular region (cortex): an isocortical region with six differentiated layers, including a well-defined layer IV that contains many stellate granule cells receiving thalamocortical inputs.

Incentive values: appetitive or aversive values assigned to stimuli that underlie particular behaviors. For example, appetitive incentive value is anticipated pleasure in particular behaviors, such as eating foods and drinking water.

Interoception: the perception and integration of autonomic, hormonal, visceral, and immunological homeostatic signals that collectively describe the physiological state of the body. A posterior-to-anterior progression of neural processing through the insula has been proposed: the posterior insula supports primary (objective) mappings of interoceptive signals, whereas the anterior insula supports its secondary re-representations and integration with emotional, cognitive, and motivational signals.

Neural mapping of body states: the process of mapping body states topographically onto the central

The dynamic interactions of feelings with cognition and motivation are realized by the unique anatomical position of the anterior insula. The anterior insula by itself has a key role in subjective feelings. Furthermore, the anterior insula is connected with subregions of the prefrontal cortex, such as the dorsolateral prefrontal cortex and the ventromedial prefrontal cortex. Recent studies have suggested that the dorsolateral prefrontal cortex collects salient information from the anterior insula, and then controls cognitive processes such as attention and working memory [20], whereas the ventromedial prefrontal cortex collects information on past behavioral outcomes in the current context from the anterior insula on the basis of subjective feelings, and then formulates goals to make decisions on future actions [27,28].

These functions involving the anterior insula are reminiscent of those mediated by the amygdala. The amygdala also by itself has a key role in emotional processing. However, these two brain areas play distinct roles in the context of the emotional dimension: the amygdala plays a role in automatic (implicit) responses, whereas the anterior insula in subjective (explicit) experiences (i.e., subjective feelings) [22]. Therefore, while the amygdala is considered as an impulsive system, the insula is regarded as a reflective one [29]. Taken together, beyond being the center of interoception, the anterior insula stands at a 'hub' position to regulate the introduction of subjective feelings into cognitive and motivational processes.

Pathological Roles of the Insula in Psychiatric and Neurological Disorders

Human behaviors involve dynamic interactions of feelings with cognition and motivation, and their dysfunction underlies many psychiatric disorders. Indeed, recent comprehensive meta-analyses of structural and functional neuroimaging studies suggest that the insula is a 'common core' that is affected in many psychiatric disorders [2,3].

Recent genomic studies have revealed the highly polygenic nature of psychiatric disorders [30]. Furthermore, such studies have provided a new insight that genetic risk factors are shared among different diseases (pleiotropy), which challenges the biological validity of existing diagnostic categories. Although the classic categorical approach is still useful in clinical settings where reliability and quick utility are appreciated, understanding of mental illnesses via multiple dimensions of function associated with the corresponding brain circuits is becoming important in brain science [31]. As described earlier, the insula by itself has a role in subjective feelings in the emotional dimension. Furthermore, the insula plays roles in cognitive and motivational dimensions by connecting with the prefrontal subregions such as the dorsolateral prefrontal cortex and the ventromedial prefrontal cortex, respectively. Accordingly, dysfunction of the insula disturbs not only the emotional dimension, but also the cognitive and motivational dimensions in a wide range of psychiatric disorders.

First, dysfunction of the insula leads to abnormal subjective feeling states for multiple mental disorders. Structural neuroimaging studies of voxel-based morphometry have detected significant reduction in gray matter of the insula in patients with major depressive disorder [32,33]. In functional magnetic resonance imaging (fMRI) studies, the insular activity was significantly increased during emotional processing [34,35], whereas the insular activity was decreased in resting-state paradigms in patients with major depressive disorder [36,37]. Structural and functional abnormalities of the insula have also been observed in patients with bipolar disorder: in structural neuroimaging studies, gray matter of the insula was consistently reduced in patients with bipolar disorder, including altered developmental trajectories of the insular volume [38–40]. In functional MRI studies, no consistent insular activity has been thus far detected in patients with bipolar disorder [41,42]. Beyond mood disorders, the insula deficits in abnormal subjective feelings seem to underlie many other conditions that include mood-associated dimensions in their pathologies. For example, structural and functional deficits in the insula have been implicated in anxiety disorders [43,44], in schizophrenia for disturbed affective processing

nervous system, particularly on the upper brainstem and cerebral cortex including the insula. For example, body responses elicited by thermal or visceral stimulation are mapped on subregions of the insula. Changes in these neural maps are constantly monitored and regulated for maintenance of the body's physiology within an optimal homeostatic range.

Salience network: a brain network that includes the anterior insula and the anterior cingulate cortex, which is responsible for identifying salient stimuli and coordinating cognitive resources, such as attention and working memory, between the central executive network and the default mode network.

Self: the conscious perception of one's own being. Subjective feeling states constantly updated by body states enable an awareness of the physical self.

Subjective feeling states: the conscious perception of body states elicited by interoceptive stimuli (e.g., thirst, dyspnea, air hunger, sensual touch, itch, penile stimulation, sexual arousal, coolness, warmth, exercise, heartbeat, wine tasting, distension of the bladder, stomach, and so on).

[45], in psychopathy for abnormal social emotion processing such as empathetic pain processing [46], and in anorexia nervosa for distorted subjective feelings of one's body [47]. Insula pathology has also been implicated in neurological disorders, including Huntington's disease and multiple sclerosis for impaired processing of facial emotions [48], and Alzheimer's disease for the loss of sense of self [49].

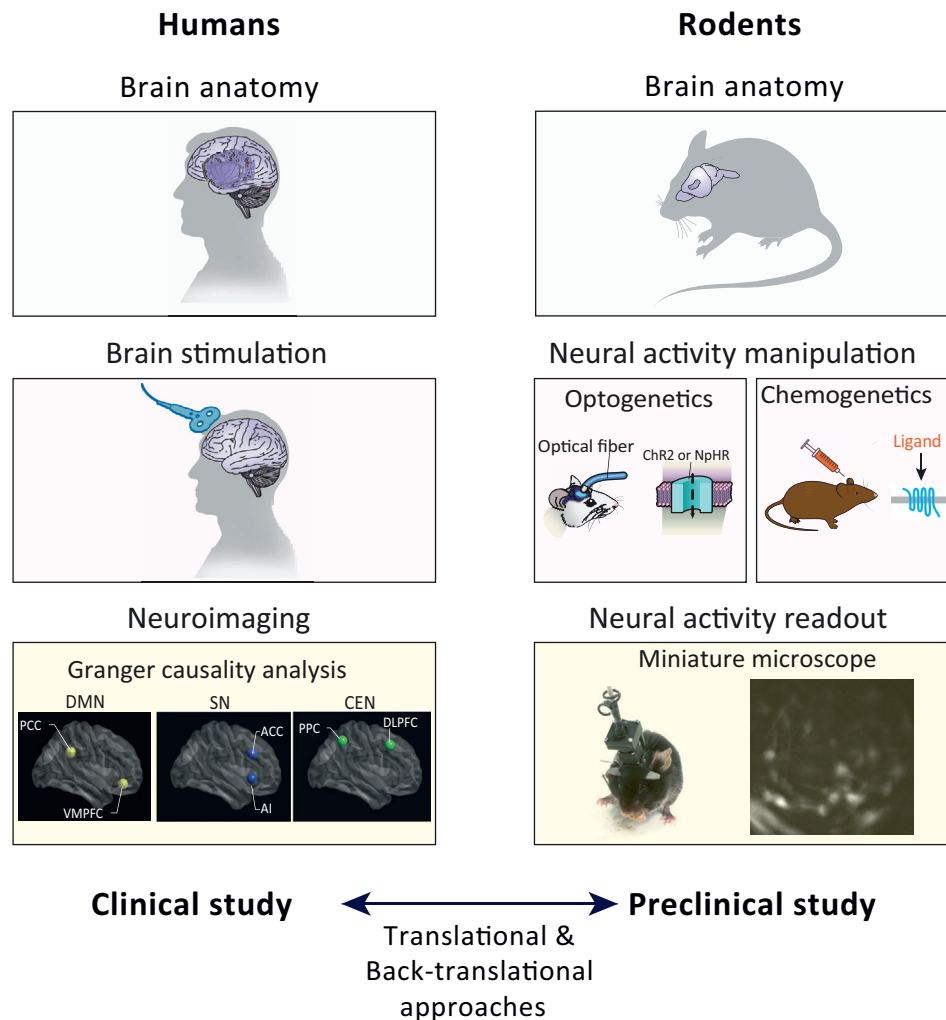
Dysfunction of the insula also underlies cognitive deficits in a wide range of mental disorders. Functional neuroimaging studies using **Granger causality analysis** have discovered, in patients with schizophrenia, a reduction in the strength of the causal influences from the insula-centric **salience network** on the **central executive network** and the **default mode network** [50,51]. The insula-mediated dynamic switching between the central executive network and the default mode network facilitates access to cognitive resources, such as attention and working memory, when a salient event is detected [20]. Thus, altered strength in the connectivity in these networks affects cognitive deficits in some cases of schizophrenia [51]. This network deficit is also reported in some patients with autism spectrum disorder [52], which may be consistent with the shared genetic and biological risks between autistic spectrum disorder and some cases of schizophrenia [53]. The pathological role of the insula in abnormal fixation of belief has also been implicated in delusion [54,55].

Dysfunction of the insula also underlies motivational deficits, such as in drug addiction. A number of meta-analyses of functional imaging studies have shown that drug-associated cues can elicit the insular activity in individuals with substance abuse [56,57]. Based on the physiological function of the insula in motivation as discussed earlier, it is likely that drug-evoked hedonic feelings may influence motivational salience associated with drug-related cues, which in turn would affect decision-making behaviors. Motivational deficits in individuals with anhedonia may also be related to dysfunction of the insula. Recent evidence implies that structural and functional alterations of the insula can be associated with impaired effort-based decision making in individuals with anhedonia [58,59]. At the molecular level, variability in dopamine responses in the bilateral insula in humans has been reportedly correlated with willingness to expend effort for rewards [60,61].

Toward Better Understanding of the Physiological and Pathological Roles of the Insula

Human neuroimaging studies have provided insights into the physiological and pathological roles of the insula. However, it is difficult to address causal roles in biology from neuroimaging. Signals of human brain imaging are limited in spatial and temporal resolution. Furthermore, the physiological basis underlying neuroimaging signals (such as the blood oxygen level-dependent signals in functional MRI) is only partly understood. To overcome these limitations, computational and statistical efforts in human brain image processing and analysis should be made. For example, Granger causality analysis may be useful in studying causal relationships that may exist across networks [62]. In addition, recent advances in noninvasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation, may be useful in providing causal insights into the insula without major ethical constraints [63].

Animal studies provide a great opportunity to understand causal roles of the insula by back-translating the observations in humans. Furthermore, animal models are useful in overcoming limitations in spatial and temporal resolution that are present in human brain imaging studies. Comparative functional anatomy is important for linking human and animal observations. Given the corresponding cytoarchitecture and connectivity, we can identify the homology between the human and rodent insula [64,65]. Animal studies allow us to conduct invasive brain manipulations, which are critical to address causations without the major ethical constraints in human studies. Recent technological advances in preclinical studies using mice are

Key Figure**Strategies for Better Understanding the Causal Roles of the Insula in Brain Function**

Trends in Neurosciences

Figure 3. Computational and statistical efforts in human brain image processing and analysis, as well as recent advances in noninvasive brain stimulation techniques, may be useful in providing causal insights into the insula without major ethical constraints in human studies. Given the corresponding cytoarchitecture and connectivity, the homology between the human and rodent insula has been identified. Taking advantage of mice may provide a great opportunity for better understanding causal roles of the insula as it allows for invasive brain manipulations that are ruled out by ethical constraints in human studies. Recent technological advances in preclinical studies using mice allow us to acquire a sophisticated understanding of neuronal circuit architecture and activity information in behaviorally relevant contexts. The anatomically and genetically defined neural circuitry elements or connectivity can be interrogated with activity readouts and/or activity manipulations in behaviorally relevant contexts. Exploiting translational and back-translational approaches between clinical and preclinical studies would finally enhance our understanding of the causal role for the insula in higher brain function at multiple levels spanning from the gene, molecule, cell, circuitry, physiology to behavior. Abbreviations: ACC, anterior cingulate cortex; AI, anterior insula; CEN, central executive network; ChR2, channelrhodopsin-2; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; NpHR, halorhodopsin; PCC, posterior cingulate cortex; PPC, posterior parietal cortex; SN, salience network; VMPFC, ventromedial prefrontal cortex.

beginning to allow neuroscientists to acquire a sophisticated understanding of neuronal circuit architecture and activity information in behaviorally relevant contexts. Above all, neural circuitry elements and connectivity can be anatomically and genetically defined at high resolution, based on a combination of genetic engineering techniques such as Cre-based cell type-specific targeting of input/output-defined circuit elements [66]. Then, the anatomical and genetic targeting of neural circuitry elements or connectivity can be combined with activity readouts and/or activity manipulations in behaviorally relevant contexts to form a complete picture of causal circuitry functions in relation to behavior. *In vivo* neural activity imaging in freely behaving mice using miniature microscopes for activity readouts [67] and optogenetic/chemogenetic approaches for activity manipulations [68,69] are representative tools that are currently available (Figure 3, Key Figure).

Clinically detectable molecular signatures resulting from disease-perturbed biological networks may be captured with advanced measurement techniques such as next-generation sequencing and single-cell approaches [70,71]. Then, causal roles of these molecular clues in the pathophysiology of mental illnesses can be interrogated at multiple levels spanning from the cell, circuitry, physiology to behavior by generating relevant mouse models such as transgenic and gene knockout/knockin mouse models. Taken together, we optimistically propose the significance of exploiting translational and back-translational approaches between clinical and preclinical studies, to achieve a comprehensive understanding of the insula (see Outstanding Questions).

Acknowledgments

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Outstanding Questions

What are the neural substrates of feeling states and other key features/functions associated with the insula at the microscopic level (e.g., neurons and glia, synapses, and their molecular mediators)?

How do specific neural circuitries and pathways regulate the introduction of the insula-mediated feelings into cognitive and motivational processes in behaviorally relevant contexts?

How do genetic factors of neuropsychiatric conditions affect the functions of the insula? How are these insula pathologies implicated in each domain of brain dysfunction?

What are the technical limitations in human neuroimaging studies that we should overcome to acquire causal insights into the insula?

How can animal studies enhance our understanding on the causal roles of the insula in brain function and dysfunction with advanced techniques that include *in vivo* neural activity imaging, optogenetic/chemogenetic approaches, genetic engineering, and computational neural network modeling?

What kind of clinical observations and questions can be further interrogated in animal models? What are the limitations of animal studies? How can clinical and preclinical investigations complement each other?

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