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Review

I Feel, Therefore, I am: The Insula and Its Role in Human Emotion, Cognition and the Sensory-Motor System

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Abstract: Background: The insula is instrumental in integrating the emotional, cognitive, and sensory-motor systems. This manuscript lays a foundational framework for understanding the insula's mechanistic role in moderating brain networks in illness and wellness. Methods: Reviewed here is the select literature on the brain anatomy and function relevant to the insula's role in psychiatrically ill and normative populations. Results: The insula is a hub for moderating social cognition, empathy, reward-driven decision-making, arousal, reactivity to emotional stimuli, and somatic pain processing. Findings indicate a spectrum of increasing complexity in insular function – from receiving and interpreting sensorimotor sensations in the posterior insula to subjective perception of emotions in the anterior insula. The insula plays a key role at the interface of cognitive and emotional domains, functioning in concert with other brain regions that share common cytoarchitecture, such as the ventrolateral prefrontal cortex and the anterior cingulate cortex. Pharmacotherapy and mindfulness-based interventions can alter insular activation. Conclusion: The insula serves as a receiver and interpreter of emotions in the context of cognitive and sensory-motor information. Therefore, insular function and connectivity may potentially be utilized as a biomarker for treatment selection and outcome.

Keywords: insula; emotion; cognition; pediatric bipolar disorder

1. Introduction

As basic and clinical neuroscience advance one another, generating new data from imaging genetics [1] and pharmacological functional magnetic neuroimaging (fMRI) [2,3], the insula is gaining recognition as an instrumental hub in brain networks. The objective of this manuscript is to illustrate the insula's mechanistic role at the interface of emotional, cognitive and sensory-motor brain systems [4].

Functional MRI studies across psychiatric and normative populations where relevant, have shed light on insula-driven mind-body awareness at a subjective level, leading to an action or a reaction at a behavioral level [5,6]. This review accomplishes the following: 1) provides an anatomical and physiological overview; 2) presents the role of the insula in brain networks pertaining to the interfacing emotional and cognitive function, social cognition, empathy, reward-driven decision-making, arousal, reactivity to emotional stimuli, and somatic pain processing; and 3) introduces how insular activity can serve as a biomarker for interventions through pioneering clinical fMRI and positron emission tomography(PET) studies[7].

2. An Anatomical and Physiological Overview

The anatomic, cellular, and physiologic features of the insula offer a context for understanding its functional operations. The insula is an interoceptive cortex at the frontotemporal junction, often termed the fifth lobe of the brain. Hidden by the lid or operculum, it comprises the fundus of the lateral sulcus or the Sylvian fissure [8]. As its name implies, the insular lobe exists as an island, surrounded by the groove of the circular sulcus. The cytoarchitecture is divided into anterior, middle and posterior regions (Figure 1). Based on its cytoarchitecture, connectivity, and function, the insula has also been referred to as the paralimbic or limbic integration cortex [9]. The insula has efferent and afferent projections to the amygdala, lateral orbitofrontal cortex, olfactory cortex, anterior cingulate cortex, and superior temporal sulcus [8].

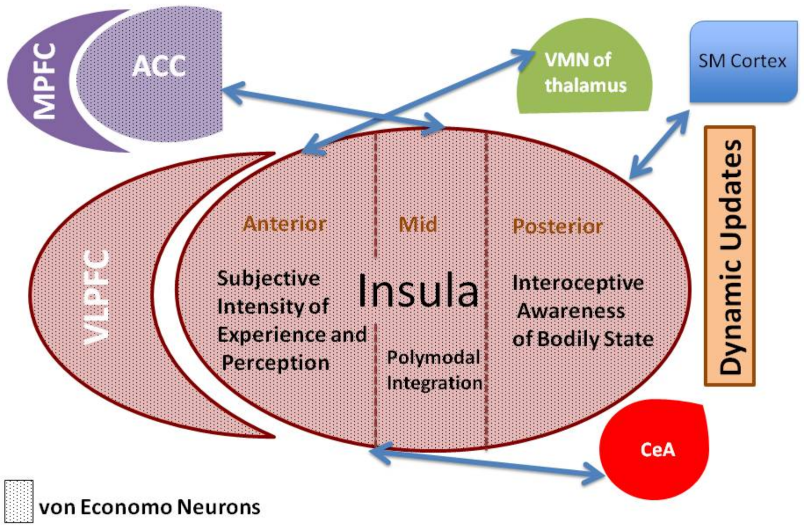

Figure 1. The Insula. Representation of the insula and its cytoarchitectural similarities with the anterior cingulate cortex (ACC) and the ventrolateral prefrontal cortex (VLPFC). Illustrated above are the main connectivities involved in dynamic updates between the following: 1) the posterior insula and the sensory motor (SM) cortex; and 2) the anterior insula and both the central nucleus of the amygdala (CeA) and the ventro-medial nucleus (VMN) of the thalamus. The mid-insula is also connected to the thalamus and is intermediary in translating the somatosensory stimuli to the anterior region where they are perceived and further evaluated in conjunction with the ACC and the medial prefrontal cortex (MPFC).

2.1. The Distinct Anatomy and Physiology of the Posterior, Mid, and Anterior Insular Regions

Anatomical, physiological, or functional connectivity defines the roles of the various insular components, which increase in complexity from the posterior to the anterior region [5]. The anterior insula or anterior insular cortex (AIC) is functionally distinct, with its dorsal part serving a predominantly cognitive role and its ventral part working as a hub for emotional networks[5,10]. The anterior and ventral parts of the insula are well-developed and lie adjacent to the frontal operculum. The AIC in humans consists of densely populated bipolar spindle cells that are distinct from those in the middle and posterior insula. These cells, termed von Economo neurons (VENs), lie on a continuum with similar neurons in the inferior frontal gyrus (IFG) or ventrolateral prefrontal cortex (VLPFC), positioned immediately anterior to the insula [11]. Notably, the VENs are reported to function in mirror self-recognition: to show high immune reactivity to activating transcription factor 3 and interleukin 4; and to generate peptides that are responsible for pain, immune modulation, and interoception of one's own homeostatic condition [12].

PET studies in healthy adults showed that the interoceptive experiences of temperature, sexual arousal, pain and autonomic nervous system changes coincide with the activation of the posterior dorsal insula [13,14]. Subjective experience correlated with polymodal integration in the mid-insula, followed by evaluation at an emotional level associated with activation in the AIC and the MPFC. Craig's work further described this insular posterior-to-anterior gradient [5]. The subjective feelings that follow bodily experiences, as well as emotions such as disgust and social isolation, activate the mid-anterior insula and MPFC. The right insula modulates autonomic arousal such as heart rate and interoceptive awareness of one's body state [5]. The right insula is key in moderating and gauging intense negative emotional experiences while positive emotional experiences activate the left [15–19]. The posterior insular cortex gauges the intensity of the physiological state. The AIC anticipates aversion or pain, and also serves as the "subjective meter" in perceiving the emotion [5].

3. The Functional Role of the Insula

3.1. Integrative Role at the Interface of Cognitive and Affective Domains

Most of the reviews regarding the insula's functionality thus far have been based on findings predominantly from animal or normative human studies. In the current review, we present resting state and task-based findings in frontotemporal dementia, bipolar disorder, major depressive disorder, and attention deficit hyperactivity disorder [3,20–23] in addition to studies on healthy individuals at rest [4,24–26]. The networks consistently involved insular activation or engagement in cortico-cortical and cortico-subcortical networks as follows. The VLPFC is the higher cortical center with dual responsibility for response inhibition in connection with the striatum and for emotional control in connection with the amygdala. Given the anatomical proximity and shared cytoarchitecture, impaired activity was often reported in both the insula and VLPFC as the following clinical examples illustrate.

Frontotemporal dementia (FTD) presents with similar symptoms as bipolar disorder, such as sexual and social disinhibition, as well as impaired emotion recognition, attention, and executive function [27]. Of note, patients with FTD show a 74% reduction in VENs in the insula and VLPFC relative to healthy adults [28].

Using **pediatric bipolar disorder** as a model of affective dyscontrol and attentional problems, we showed that response inhibition and frustration alongside affect dysregulation demonstrated increased activation in the anterior insula and the VLPFC relative to healthy controls [29]. The affective consequence of canceling a motor intention (i.e., frustration) may be associated with interoceptive awareness of heightened autonomic responses during error control [30], thus involving the insula as depicted in Figure 1. Furthermore, our connectivity studies using the stop signal task have illustrated greater insular engagement during response inhibition when treated with risperidone, relative to baseline within patients and healthy controls [29]. This is discussed below as a possible marker of effective intervention.

We also used pediatric bipolar disorder as a model of interfacing affective and cognitive disturbances. We probed these systems with a task of matching colored emotional versus neutral words with colored dots. During negative emotional word matching, these patients showed decreased ability to activate the VLPFC and AIC relative to healthy controls [31]. Our study suggests that the VLPFC and insula work in concert to moderate perceptual experience and decision-making in healthy controls. This function is impaired in disorders involving affect regulation and cognition, as illustrated in pediatric bipolar disorder. Similarly, an fMRI study demonstrated activation in both the AIC and MPFC of **healthy adult participants** when performing a two-choice perceptual task of morphed emotional faces [32].

Not only paradigms, but also affective disorder states evoke emotion. The insula could be moderating negative emotion in the case of a depressive state regardless of the task being cognitive or emotional. Meta-analysis of fMRI studies during working memory tasks in adults with **major depressive disorder (MDD)** compared to healthy controls demonstrated significantly increased activation in the left insula along with DLPFC, parietal regions and the right superior temporal lobe; and there was significantly decreased activation in the right insula, precuneus and precentral gyrus [33]. Additionally, increased cognitive effort was associated with increased left insula activation, while the right insula activation is greater while moderating negative emotional bias in depressed individuals. Conversely, it is possible that the cognitive and emotional duties are predominantly lateralized to the left and the right insula respectively.

Furthermore, the dynamic interaction between the ACC, MPFC and insula is demonstrated in patients with **attention deficit hyperactivity disorder (ADHD)** during response inhibition. While the ACC is engaged during error control relative to healthy controls, insular activation is critical in switching operations from the central executive network involving ACC onto the default mode or a self-reflective network involving the MPFC [8]. The memory of failure or success during response inhibition is processed by the insula as it operates as the common hub in both the executive and default mode networks. This phenomenon potentially underlies the mechanism by which cognitions of self-worth based on task performance outcomes are consolidated.

3.2. Insula's Role in Detecting Salience: Social Cognition and Empathy

Converging evidence indicates that the insula mediates interactions between large-scale networks involved in externally and internally oriented cognitive processes. Therefore, it plays a central role in interoceptive, affective and empathic processes. Interpersonal connectivity appears to be based on the salience network, with the insula as a hub, integrating external environmental cues and the internal sensory-motor, emotional, and cognitive states. In various social cognitive paradigms, individuals with **autism spectrum disorders (ASD)** exhibited hypoactivity of the right anterior insula [8,34]. Due to insular hypoactivity and thus reduced integration of messages from the amygdala and precentral cortex, a reduction in "salience detection" and mobilization of attentional resources necessary for social interaction is hypothesized in ASD [8]. The abnormal development of

VENs that relay the intuitive social nuances in the anterior insula may be at the center of socio-emotional dysfunction in autism [35].

The Salience Network consists of the MPFC, insula, ACC, hypothalamus, and amygdala. Emotional intelligence (EQ) describes the collective ability to perceive, control, and evaluate emotions of the self and others. The triad consisting of the insula (emotion perception), VLPFC (emotion control), and MPFC (emotion evaluation) work together to facilitate empathy, social communication, and conflict resolution. EQ is critical in interpersonal relationships. Neural mechanisms of empathy deficits were demonstrated in **individuals with narcissism**, illustrating persistent activation in the anterior insula during resting state [36]. These findings parallel those seen in pediatric mania manifesting with inflated self-esteem and grandiosity where the right insula showed increased activation [23,29].

3.3. Developmental Differential in Cognitive Flexibility vis-à-vis Reward-Driven Decision Making

A study that contrasted **developing adolescents and healthy adults** revealed increased AIC activity during negative reward predictive error encoding events [37]. Negative prediction or anticipation during a probabilistic reversal-learning task (not the prediction error signals) resulted in increased activation in the insula in adolescents, where they learned quicker than the adults. Affective systems are a major driving force for goal selection and decision-making during adolescence [38]. In contrast, both the risk prediction signals and the risk prediction error signals activated the bilateral AIC in adults [39].

3.4. Arousal and Reactivity: The Insula at the Interface of Biology and Environmental Cues

According to one of the earliest theories of emotion, the James-Lange Theory [40], physiological arousal instigates the experience of a specific emotion, like a reflex reaction. The insula's interoceptive function [14] may explain reactivity to negative visual stimuli often seen in patients with pediatric bipolar disorder [41]. This may explain how reduction of autonomic arousal using propranolol decreases performance anxiety or how alpha-adrenergic agonists reduce hypervigilance symptoms in PTSD [42]. Novel fMRI studies have expanded our appreciation of emotional expression with evaluation of context, prior experience, and social cues via the insula and the MPFC, hippocampus, and face response circuitry respectively [41].

3.5. Somatosensory Networks and the Role of the Insula in Pain Processing

With regards to somatic pain sensation, the insula processes the internal feeling of pain as well as temperature, sensual touch, hunger, and thirst [5]. The fMRI studies in healthy adults suggest that the insula's anterior, mid, and posterior divisions sub serve different functions in pain perception. The anterior insula has predominantly been associated with cognitive-affective aspects of pain, while the mid and posterior divisions have been implicated in sensory-discriminative processing [43]. The imagination or anticipation of pain while looking at depictions of painful events is computed by the insula at the higher order 'meta-representation of the primary interoceptive activity' along with emotional awareness [44,45]. The activation of both the insula and ACC in this study may correspond to the simultaneous generation of a feeling and emotional evaluation because afferents also project to the ACC via the medial dorsal thalamic nucleus [44]. The anterior division of the insula is predominantly connected to the VLPFC (structural and resting state connectivity) and OFC (structural connectivity). In contrast, the posterior insula showed strong connections to the primary somatosensory cortex (structural connectivity) and secondary somatosensory cortex (structural and resting state connectivity). The mid-insula displayed a hybrid connectivity pattern with strong connections to the VLPFC and somatosensory cortex (structural connectivity). Moreover, at resting state strong connectivity of all three insular subdivisions with the thalamus is evident [43]. These findings are consistent with the physiological divisions in insula described above (Figure 1).

Anterior insula structural connectivity was related to the individual degree of pain vigilance and awareness; this positively correlated with anterior insula-amygdala connectivity and negatively correlated with anterior insula-rostral anterior cingulate cortex connectivity [43]. These findings illustrate differential structural and resting state connectivity for the anterior, mid, and posterior insula with other pain-relevant brain regions. This partly explains their various functional profiles in pain processing.

4. Clinical Translation: The Final Frontier Where the Insula Can Serve as a Biomarker for Treatment Selection and Outcome

4.1. Biomarker for Treatment Selection

A PET study identified insular metabolism as a potential neuroimaging biomarker for choosing a treatment modality in major depressive disorder [7]. Differences in the right anterior insula metabolism before the treatment correlated with a differential outcome for medication versus psychotherapy. Specifically, insular hypometabolism was associated with remission from cognitive behavior therapy and poor response to escitolapram pharmacotherapy; insular hypermetabolism was associated with remission on escitalopram treatment and limited response to cognitive behavior therapy [7]. These findings indicate the possibility of an objective approach to guide management based on insular activity in the case of major depression.

4.2. Biomarker of Pharmacotherapy

As a clinical example, fMRI studies of pediatric mania have showen increased insular engagement in the affective and evaluative circuit on treatment with risperidone compared to pre-treatment [20]. In pediatric mania, second generation antipsychotics such as risperidone are often utilized as first-line agents in conjunction with *alpha*-adrenergic agonists to decrease autonomic hyperarousal [46]. Therefore, it is possible that these medications reduce reactivity to negative stimuli and autonomic hyperarousal, respectively. Such an explanation becomes plausible with understanding insular mechanisms of operation. The relevant hypothesis helps construct brain-based treatments and improve clinical outcomes [47].

4.3. Biomarker of Mindfulness-based Interventions

Mindfulness has been shown to reduce depression and stress. A recent study demonstrated that interventions such as breathing exercises led to reduced reactivity to negative stimuli; non-reactivity correlated inversely with activation of the insula [47]. The results suggest that non-reactivity to inner experiences helps protect individuals from the psychological risk for depression by decreasing automatic emotional responses and maintaining a buffer against trait rumination and negative bias [47].

Neuroimaging research in healthy adults has demonstrated that mindfulness training decreases susceptibility to reward-seeking. An fMRI study of healthy adults performing a monetary incentive delay task revealed increased activation in the ventral MPFC with intervention [48]. Furthermore, functional connectivity analyses have shown increased connectivity of the MPFC coupled with the bilateral posterior insula in individuals with mindfulness training relative to the untrained control group. These findings suggest that mindfulness successfully integrates the interoceptive input from the insular cortex with higher cortical control at the MPFC to reduce bias towards immediate gratification [48]. These findings collectively imply that the MPFC and the insula work in concert to moderate reactivity and may serve as biomarkers for assessment of mindfulness-based interventions.

4.4. Attentional Bias and Negative Stimuli

Other interventions capitalize on the connectivity of attentional circuitry with the anterior insula that works in favor of diverting pain perception through distraction from negative stimuli. This approach may be essential for understanding how clinically relevant distraction can serve as a coping strategy when experiencing negative emotions. Increased insular activity has been demonstrated during auditory hallucinations in schizophrenia, similar to the activation during covert speech. At resting-state, the nucleus accumbens is strongly connected to the bilateral insula and parahippocampal regions in patients with audiovisual hallucinations (relative to those experiencing only auditory hallucinations or no hallucinations) [49]. The insula may be more involved in covert multisensory experiences in schizophrenia, given its subjective meta-representation of internal stimuli. Distraction techniques can also help alter insular activation in schizophrenia. These observations support the disrupted salience network hypothesis in schizophrenia.

5. Conclusion

Translating basic science into clinically relevant data enables clinicians to recognize psychopathology linked to insular dysfunction and stratify differential treatments. We must connect the pieces of evidence to understand any brain region, comprehend how the brain operates, and decode clinical manifestations in order to advance our treatments.

The micro-operations of daily life are based on the management of instrumental areas of the brain, such as the insula. The fundamental significance of the insula is its ability to serve as a subjective experiential and feeling center that integrates emotional, sensory, cognitive, and motor functions.

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