REVIEW ARTICLE

The Role Of Insular Cortex In Pathogenesis Of Anxiety Disorders, Major Depressive Disorder (MDD), Schizophrenia And Autism Spectrum Disorders (ASD)

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Abstract

Insular cortex (i.e., insula; Latin for "island"), also known as the Island of Riel, represents a still poorly researched part of neural circuitry consisting of anterior and posterior areas divided by the insular central sulcus and surrounded by the peri-insular sulcus. Insula is involved in a variety of functions including gustatory and sensorimotor processing, somatic processing, as well as risk-reward behavior. Insula has been shown to play a major role in socio-emotional processes, such as emotional experience and introspection. Recent comprehensive meta-analysis studies suggest that lesion of the insular cortex can lead to significant psychiatric and neurological disorders as it plays a vital role in human motivation and emotional perception. Therefore, there is a growing interest in the medical community regarding this mostly unknown part of the human brain and the role of insular cortex in the pathogenesis of psychiatric disorders.

Keywords: insula, neocortex, mental disorders.

INTRODUCTION

Paralimbic cortex is a three-layered cortex that consists of piriform, entorhinal and parahippocampal cortex. It lies closely and is directly connected to the adjacent limbic system and its serves as a transitional area between paleocortex and neocortex, incorporating the region of prosiocortex. Being involved in complex cerebral interconnections, it integrates external sensory information with internal emotional and motivational states, among other functions. Insular cortex represents a part of the paralimbic structure situated between paleocortex and neocortex. Phylogenetically, it represents the most primordial part of telencephalon arising from anterior prosencephalon (1). The process of cortical development begins in the inferior cortical regions around the sixth week of fetal development and this particular region will later become, trough the act of folding, limen insulae. Through the disproportionate development of neocortex a horn-like structure is formed with the temporal lobe as its tip. The central window of this spiral opens into the insula. As the development of neurocortex continues, the rotation and compaction of the neural tissue buries the insula beneath the sylvian fissure (2).

The previously mentioned cortical folding does sever the insula's initial connections developed during the neural tube phase, which explains its intracerebral network with other parts of the brain. With the completion of neurological development, the insular cortex becomes fully formed (3). The insula is a highly heterogeneous region with regards to both its anatomical and functional features. Anatomically, the insula is comprised of at least three subregions defined by the presence or absence of granular cortical layer IV neurons, and each subregion has distinct structural connections. Functionally, the insula is implicated in a vast array of behaviors, ranging from experiencing saliency, to social and emotional processing, to interoception.

There is compelling evidence from basic and systems neuroscience research that the insula is altered in a host of psychiatric illnesses, and that the anterior insula in particular may represent a common substrate of psychopathology (4, 5). Yet, recent models have proposed that anterior insula and posterior insula alterations (both in structure and in function) are differentially implicated in multiple symptom profiles of depressive, psychotic, and substance use disorders, among others (6, 7, 8).

Recent research has shed light on the intricate connections between the insula and other brain regions, revealing the crucial role of this area in integrating sensory, emotional, and cognitive information. The unique anatomical position and extensive connectivity allow the insula to serve as a critical hub in the functional network of the brain and the insular involvement in emotional processes, highlighting its implications in psychiatric conditions (9). This paper presents new knowledge about the role of insular cortex in psychological processes, as well as the pathogenesis of psychiatric disorders.

THE INSULAR CORTEX

The insular cortex represents a triangular area of neocortex that forms the floor the Sylvian fissure. It is located deep to the insular operculum, formed by parietal, frontal and temporal lobes. Using axial magnetic resonance imaging (MRI) it can be observed lateral to the extreme capsule, claustrum, putamen and external capsule. Insular cortex primarily consists of two distinct areas: anterior and posterior area separated by the insular central and encompassed by the peri-insular sulcus. Anterior insula composes of anterior, middle and posterior, also known as short gyri, which are separated by two pre-central sulci.

The posterior insula consists of anterior and posterior gyri (short gyri) separated by singular post-central sulcus. Additionally, the insula contains other gyri (accessory gyrus and transverse gyrus), as well as lumen insulae in the anteroinferior apex (9). On the cytoarchitectural level, the insular cortex consists of an anterior dysgranular area and a posterior granular area. The anterior granular area contains pyramidal neurons in layer II and IV, while posterior granular area contains granular cells in layer II and IV. The research conducted by Kurth F. et al. showed that the posterior insula can on the cytoarchitectural level be separated in 3 distinct areas: two granular areas, referred to as Ig1 and Ig2 (insular lobe granular areas), found in dorsal posterior insula, and a dysgranular area (Id1) ("d" for dysgranular area) found in ventral posterior insula. The insular cortex has one unusual feature and that is the presence of large bipolar projection neurons called von Economo neurons (VENs), most common in the frontoinsular cortex (9, 10, 11).

Different parts of the insular cortex correlate with its different cerebral connections. The anterior portion of the insula is primarily connected with anterior cingulate, frontal, orbitofrontal and anterior temporal areas, while the posterior portion connects with posterior temporal, parietal and sensorimotor areas. The insular cortex is a true anatomical integration hub with heavy connectivity to an extensive network of cortical and subcortical brain regions serving sensory, emotional, motivational and cognitive functions. It is not visible on an exterior view of

the brain, as it is fully covered laterally by opercula of the parietal, frontal, and temporal lobes. Directly medial to the insula are the extreme capsule and the claustrum. The central sulcus of the insula is the most inferior extension of the Rolandic fissure (central sulcus) that separates the frontal and parietal lobes. It receives heavy sensory inputs from all modalities. Direct thalamic and horizontal cortical afferents carry information to the insula from outside the body (auditory, somatosensory, olfactory, gustatory and visual information) and from inside the body (interoceptive information).

Several of these inputs project to topographically organized insular sensory regions, giving rise to the 'visceral insular cortex', the 'gustatory cortex' (the primary taste cortex), and the insular auditory and somatosensory fields (11, 12).

FUNCTION OF THE INSULAR CORTEX

The insula's primary role is believed to be that of multimodal integration. With this increased research attention, knowledge regarding the insula's role in clinical syndromes has also increased. Among the first insights into the role of the human insula came from the seminal works and experiments by Penfield and Faulk in the mid-20th century, conducted through intraoperative electro-cortical stimulation on 36 patients with positive results at 82 stimulated points (13). The emergence of new diagnostic techniques, such as neuroimaging in the early 21st century, gave rise to interest and research possibilities regarding the insula's function.

Interest in the function of the insular cortex has increased drastically since the advent of functional neuroimaging techniques, which revealed insular activation in response to a wide variety of stimuli (14).

A meta-analysis of nearly 1,800 functional neuroimaging experiments by Kurth and colleagues suggested the existence of four functionally distinct regions in the human insula: 1) a sensorimotor region located in the mid-posterior insula; 2) a central-olfactogustatory region; 3) a socio-emotional region in the anterior-ventral insula; and 4) a cognitive anterior-dorsal region.

In recent years, tract-tracing studies have supported the view of a central viscero-somatosensory role for the insula, which is now known to receive visceral afferent projections conveying interoceptive information from all over the body (11).

The human insula has emerged as a core region affected across many psychiatric disorders including anxiety disorders, addiction, depression, schizophrenia and autism. Together with the dorsal anterior cingulate cortex, the insula cortex forms a hub that affects the brain's ability to switch between different functional networks according to internal and environmental demands, explaining why insula disturbances may be disproportionally disabling. Given this important role, the insula is one of the most promising targets for brain stimulation treatment of several psychiatric disorders (16, 17, 18).

THE ROLE OF THE INSULA AND PSYCHIATRIC DISORDERS

The insula exhibits altered structure and function across different forms of anxiety disorders, major depressive disorder, schizophrenia and autism spectrum disorders.

ANXIETY DISORDERS

They are the most prevalent mental health condition with a lifetime prevalence of 17%, resulting in significant individual and social impairment and a considerable overall burden of disease. Anxiety can be an adaptive response to unpredictable threats and pathological anxiety disorders occur when symptoms adversely impact daily life. Meta-analyses of functional neuroimaging studies of induced and pathological anxiety were therefore compared.

A systematic search was conducted in June 2019 on the PUBMED database for whole-brain functional magnetic resonance imaging articles. Eligible articles contrasted anxious patients to controls, or an unpredictable-threat condition to a safe condition in healthy participants. Five anxiety disorders were included: post-traumatic stress disorder, social anxiety disorder, generalized anxiety disorder, panic disorder, and specific phobia. 3433 records were identified, 181 met the criteria and the largest subset of task type was emotional (N=138).

Seed-based d-mapping software was used for all analyses. Induced anxiety (n=693 participants) and pathological anxiety (n=2554 patients and 2348 controls) both showed increased activation in the bilateral insula and cingulate cortex/medial prefrontal cortex.

When split by disorders, specific phobia appeared the most, and generalized anxiety disorder the least, similar to induced anxiety.

This meta-analysis indicates a consistent pattern of activation across induced and pathological anxiety, supporting the proposition that some neurobiological mechanisms overlap and that the former may be used as a model for the latter. Induced anxiety might, nevertheless, be a better model for some anxiety disorders than others (19).

Paulus and Stein have proposed that individuals who are more aware or focused on their bodily feelings may exhibit greater interoceptive prediction signals: that is, increased prediction of future aversive physical states may trigger anxiety, worry and avoidance behaviors. Measures of anxiety are correlated with the accuracy of heartbeat detection and activity in the right anterior insular cortex. Changes in insular-mediated anticipation and prediction of future events may lead to heighten anxiety. It may represent a unique opportunity to assess the precise neuronal mechanisms underlying the insula's role in healthy and pathological fear and anxiety. Increasing understanding of the neural correlates of anxiety symptoms in late-life depression (LLD) could inform the development of more targeted and effective treatments. A study that assessed grey matter volume (GMV) with volumetric magnetic resonance imaging in a sample of 113 adults ≥60 years with MDD using the following regions of interest: amygdala, anterior cingulate cortex (ACC), insula, orbitofrontal cortex (OFC), and temporal cortex.

Decreased OFC volumes may serve as a unique biomarker of anxiety symptoms in LLD. Future longitudinal and clinical studies with long-term follow up and more diverse samples will help further elucidate the biological, psychological, and social factors affecting associations between anxiety and brain morphology in LLD (20, 21).

Social anxiety disorder has been described as a persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Neuroimaging of social anxiety disorder has revealed some important findings. However, there has not been enough study on patients with a social anxiety disorder to account for the exact reason for the occurrence of the disorder. The first study on structural brain imaging was done by Potts et al. nearly a quarter-century ago. In that study, it was reported that there was no statistically significant volume difference between patients with a social anxiety disorder and healthy control subjects (22). Kawaguchi et al. measured the insula volumes in patients with a social anxiety disorder in comparison with healthy control subjects and found that insula volumes were significantly reduced compared to those of healthy subjects (16). Atmaca et al. examined twenty-one patients with social anxiety disorder according to DSM-IV and twenty healthy controls. All patients and controls were subjected to magnetic resonance imaging (MRI). Insula volumes were measured by using the manual tracing method in accordance with the standard anatomical atlases and related previous studies on insula volumes. They found that the mean posterior and anterior insula volumes for both sides

of patients were statistically significantly reduced compared to those of healthy control subjects. In the present study, it was found that patients with a social anxiety disorder had reduced insula volumes compared to those of healthy control subjects. However, to build on this finding, novel studies with a larger sample size are required (23, 24).

MAJOR DEPRESSIVE DISORDER (MDD)

The insular cortex is part of a network of highly connected cerebral "rich club" regions and has been implicated in the pathophysiology of various psychiatric disorders, of which major depressive disease is one of the most prevalent. "Rich club" vulnerability can be a contributing factor in disease development. Depression is associated with systemic inflammation, and endotoxin administration, which causes systemic inflammation, elicits mild depressive symptoms, such as fatigue and reduced interest. The neural correlates of depressive symptoms that result from systemic inflammation are poorly defined. Major depressive disorder (MDD) is associated with emotional and cognitive impairments, including negative affect or loss of pleasure. Aberrant anatomy, connectivity and activation of the insula are found in human patients suffering from major depressive disorder. These alterations have been linked with the disease-characteristic anhedonia, the inability to experience pleasure (25, 26). The insula metabolism was altered in depressed patients and the direction of change indicated whether patients would respond better to either one or another of the two major treatment approaches for depression: cognitive behavioural therapy or drug-based therapies. Measuring insula metabolism could thus serve as one of the first neuroimaging biomarkers in the field of neuropsychiatric disorders to guide treatment selection. Hannestad et al. had conducted double-blind, randomized, placebo-controlled, crossover study where 9 healthy subjects received an intravenous dose of endotoxin (0.8 ng/kg body weight) on one day and placebo (saline) on another day, separated by one week. Brain glucose metabolism was measured with FDG-PET, with tracer injection 90 minutes after endotoxin/saline administration, when the systemic immune response peaks. Correlational analyses suggest that the insula may participate in the modulation of systemic levels of inflammatory cytokines, which is consistent with the known functions of the insula; this is a finding with important potential implications for depression that we plan to address in future studies (27).

High-resolution structural subfield analysis of insular volume in combination with cortical thickness measurements and psychological testing might elucidate the way in which the insula is changed in depression. High-resolution structural images of the brain were acquired using a 7T-MRI scanner. The mean grey matter volume and cortical thickness within the insular subfields were analyzed using voxel-based morphometry (VBM) and surface analysis techniques, respectively. The combination of differences in grey matter volume between healthy controls and patients with a positive correlation of cortical thickness with disease severity underscores the insula's role in the pathogeneses of MDD. The connectivity hub insular cortex seems vulnerable to disruption in the context of affective disease (19). Structural alterations of the insula in depression patients (28).

Interoception plays a crucial role in maintaining bodily homeostasis and promoting survival, and is considered the basis of human emotion, cognition, and self-formation. A malfunction of interoception is increasingly suggested to be a fundamental component of different mental health conditions, and depressive disorders have been especially closely associated. Interoceptive signaling and processing depends on a system called the "interoceptive pathway," with the insula, located in the deep part of the lateral fissure, being the most important brain structure in this pathway. Neuroimaging studies have revealed alterations in the structure and function of the insula in a large number of individuals with depression, yet the precise

relationship between these alterations and interoceptive dysfunction remains unclear. Interoceptive dysfunction has been linked to structural or functional impairments of the insula, which plays a central role in processing of interoceptive information. Three aspects of the potential relationship between interoceptive dysfunction and alterations in insular function in people with depression have been assessed, namely clinical symptoms, quantitative measures of interoceptive function and ability, and interoceptive modulation. Firstly, increased severity of somatic symptoms in people with depression was found to be associated with impaired insular function, and among the somatic symptoms, fatigue and pain are the most prominent and have been considered in greatest detail. Secondly, the insula has been demonstrated to be a brain region the function of which is most closely related to the interoceptive ability of an individual. Insular hypo-activation has been reported in people with MDD who were asked to focus on attending to their visceral sensations, indicating a weaker involvement of the insula in processing interoceptive information. Thirdly, interoceptive modulation, produced by various treatments which emphasize attending to bodily sensations and the body–mind connection, produces neuroplastic changes in the insula, restores impaired interoceptive function, rebuilds self-referential thinking and reduces the neural response to pain, and relieves symptoms of depression. Evidence from the existing studies has shown that the insula may be the central structure for the impaired interoceptive function as identified in people with depressive disorder. Future systematic assessments of interoceptive dysfunction and their association with insular function in those with depressive disorder are likely to be highly important in the treatment of MDD (29).

SCHIZOPHRENIA

In schizophrenia, it is evident how difficult the understanding of the specific neurobiological underpinnings of complex phenotypes can be. The positive, negative, and cognitive symptoms of psychosis span a wide variety of experiences and behaviors, and the insula's unique proposed role in integrating sensory information and providing awareness for higher-order social cognition make it a promising candidate for the study of schizophrenia. The anatomical and functional diversity of the insula is further recapitulated in the work investigating its relationship to different symptom profiles in schizophrenia (Stein et al., 2021), as it has been broadly associated with negative symptoms, positive symptoms, and cognitive impairment (30, 31, 32, 33).

Meta-analysis has shown that the bilateral insula is one of the top five most affected brain regions in schizophrenia with regards to reduced cortical thickness and it represents the only brain region whose cortical thickness is associated with earlier age of onset and longer duration of illness (34). Insula grey matter volume is also significantly reduced in chronic schizophrenia, at illness onset and in individuals at ultra-high risk for psychosis who ultimately develop schizophrenia (35, 36). There is additional evidence that insula volume progressively declines after first episode psychosis, particularly in those with non-affective (but not affective) psychotic disorders (37). Functional connectivity of the insula is also abnormal in schizophrenia, with evidence of both reduced and increased connectivity that deviates from normative patterns. Magnetic resonance imaging studies consistently find decreased grey matter volume and reduced cortical thickness in the insula of schizophrenic patients, which progress with increasing disease severity. Functional aberrations observed in schizophrenic patients, which are likely related to altered insula function, include pain insensitivity, deficits in sensory-emotional integration, such as poor recognition of emotions in facial expressions, emotionally blunt speech, impairments in distinguishing self from non-self, and the occurrence of hallucinations (38).

AUTISM SPECTRUM DISORDERS (ASD)

Autism spectrum disorders are complex neurodevelopmental disorders of unknown etiology. The insula has been consistently identified as a locus of hypoactivity and dysfunctional connectivity in ASD, and the pattern of functional connectivity of the insula can be used to discriminate individuals with ASD from typically developing children (39). The insula is essentially involved in multisensory and affective processing, as well as social functions like empathy, all of which are strongly affected in autistic patients and play a key role in the detection of behaviorally relevant stimuli and initiation of dynamic switching between an 'executive control network' of brain regions, which drives externally-oriented attention, and a 'default mode network', which is dedicated to internally oriented cognitive processing. Irregularities in salience-network connectivity are linked to autistic symptom severity. Together, these findings indicate that both functional changes within the insula, as well as in long-range connectivity between the insula and related brain regions, contribute to the behavioral and cognitive symptoms of ASD (40).

There is extensive evidence based on studies with preschoolers, school-age children, and adolescents with autism of altered communication between anterior insula (aINS) and other cortical nodes including those comprising the default mode (DMN) and the frontoparietal (FPN) networks, as well as the amygdala. These alterations include both patterns of hypo- and hyperconnectivity, depending on the region and age. Reduced functional connectivity (FC) between insula and other cortical nodes observed in several studies in children with autism may result in difficulties in transfer and integration of information across these networks, which then could contribute to the impaired processing of social signals (41).

However, given that autism onsets in early childhood and that most FC studies are conducted in older children, it is not clear to what extent the observed differences precede the emergence of symptoms of autism or emerge secondary to the way children with autism experience and interact with their social and nonsocial environment. The study suggests that the circuitry heavily involved in early development of social bonding and motivation may be hypo-connected in those with genetic predisposition for autism by four postnatal weeks and that this hypoconnectivity is linked with later emerging social vulnerabilities. These findings motivate future studies into the development of the networks involved in salience detection and allostatic regulation during the key transition from pre- to postnatal environment and their contribution to later behavioral outcomes relevant to autism (22). Hypoconnectivity between anterior insula and amygdala associates with future vulnerabilities in social development in a neurodiverse sample of neonates (42).

CONCLUSION

The insula is not an isolated 'island' but rather an integral brain hub connecting different functional systems underlying sensory, emotional, motivational, and cognitive processing. It is thus crucial in determining the valence of internal and external stimuli. Together, these features explain the important roles that the insula serves in several forms of reinforcement learning, emotion control, and decision-making. As a salience detector it has further been suggested that the insula marks the most relevant stimuli for further processing in other large-scale brain networks. In addition to these general roles, the insula contains multiple subregions, each characterized by different patterns of connectivity to the rest of the brain and at first sight distinct functional roles. How these different insular regions interact are open questions key to advance our understanding of the insula function. Through this paper, we hope to highlight the importance of the insula as an interface between sensation, emotion, and cognition, and to inspire further research into this fascinating brain region. By recent human neuroimaging stu-

dies, 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. It is important to understand the anatomical and histological features of the human insula, summarize the physiological functions of the insula and underscore its pathological roles in psychiatric and neurological disorders that have long been underestimated. It is crucial to propose possible strategies through which the role of the insula may be further understood for both basic and clinical neuroscience.

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