The Role of the Insula in Schizophrenia

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27.1 Introduction

Affecting approximately 1% of the population worldwide [1], schizophrenia (SZ) is a rare but devastating neuropsychiatric disorder characterized by broad cognitive and functional impairments. The symptoms of SZ are typically categorized into positive and negative symptoms. Positive symptoms include sensory hallucinations, delusional thinking, grandiosity, paranoia, disorganized thinking, and hostility [2]. Negative symptoms, by contrast, include blunted affect (affective flattening), amotivation, social withdrawal, and a poverty of speech [2, 3]. The broad cognitive impairments related to SZ yield problems in social cognition, sensory processing, verbal semantic processing, and executive attention, to name a few [4–6].

Cognitive deficits are present at the earliest stages of SZ [6, 7] but may manifest long before disease onset. Motor and neurological deficits, including deficits in attention, verbal memory, and motor skills [8, 9], and deficits in social competence [10, 11] are prospective indicators of SZ. A 48-year longitudinal study showed that teacher ratings of interpersonal deficits within school-age children were significantly related to the later development of SZ [12]. This suggests that rather than interpersonal deficits arising as a product of disease onset, such deficits may instead represent the earliest manifestation of neurodevelopmental alterations.

Cognitive functioning in SZ patients is associated with negative symptom severity [6, 13] and overall functional outcome [14]. Working memory, verbal memory and processing speed, and attentional and perceptual processing account for 52% of all variance in the 9-month return to school or work following recent first-episode psychosis (FEP) [15].

Understanding the neural correlates of SZ has been a focus of extensive research. The insular cortex undergoes significant alterations in structure and connectivity over the course of the disease. With participation across broad cognitive domains, damage to the insular cortex may be involved in many observed disease deficits. We will herein discuss the structural and functional alterations undergone by the insula over the course of SZ.

27.2 Morphometric Changes of the Insula

SZ induces regional structural alterations within the brain, driving reductions in gray matter (GM), white matter (WM), cortical surface area, and corresponding ventricular enlargement [16–19]. The insula is one such region, exhibiting significant reductions in GM, WM, and cortical

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surface area over the course of the disease [20–23].

The literature reveals variability regarding the lateralization of insular structural alterations. Reductions in insular GM have been reported to be lateralized to both the left [19, 21, 24–26] and right [27–29] insula. Reductions in insular cortical surface area have also been observed in the left [25, 30] and right insula [31]. However, the preponderance of literature reveals bilateral insular reductions [18, 23, 32–39].

It is important to consider the localization of insular reductions, given the unique functional connectivity of insular subregions. Functional connectivity studies have parcellated the insula into three distinct subregions: the posterior insula (PI), dorsal anterior insula (dAI), and ventral anterior insula (vAI) [40]. The PI is most significantly connected to the pregenual anterior cingulate cortex (ACC), supplementary motor area (SMA), and somatosensory cortex and is involved in the processing of pain, sensorimotor stimuli, and language [40–42]. The dAI is connected to the dorsal ACC (dACC) and dorsolateral prefrontal cortex (DLPFC), demonstrating involvement in executive control and tasks of higher cognition [40–42]. The vAI is connected to the amygdala, ventral tegmental area (VTA), superior temporal sulcus, and the posterolateral orbitofrontal cortex and is associated with emotion, chemosensation, and autonomic function [40].

The subregional localization of disease-related structural alterations is unclear in the literature. While GM reductions are commonly found to span the entire insular cortex [23, 34, 43], greater relative reduction has been reported in both the anterior [22–24, 44] and posterior [27, 43] aspects of the insula. Using a region-of-interest (ROI) based approach, Saze et al. showed global insular reductions in SZ patients [43]. However, a separate subdivisional analysis revealed the right PI as the only subregion with significant volume difference. Recent work has further parcellated the insular cortex, suggesting the structure to contain six functionally unique subregions [42].

Still other studies have failed to find reductions of insular GM or cortical surface size in SZ [16, 45]. Of 14 papers in a voxel-based morphometry (VBM) meta-analysis, only seven found reductions in insular GM and WM [16]. Of the seven studies, reductions were bilateral in four, localized to the left insula in two, and localized to the right insula in one [16]. In 2000, Crespo-Facorro et al. conducted a ROI analysis on 25 drug-naïve first-episode schizophrenia (FES) patients, finding significant reductions in cortical surface size and GM volume in the left insular cortex [25]. However, attempts to replicate these findings in a new study population 10 years later were unsuccessful [46]. Upon controlling for sociodemographic and clinical characteristics in a subsequent ROI analysis of drug-naïve FES patients, Crespo-Facorro and colleagues found no significant difference in insular volume between patients and healthy controls. In fact, patients exhibited non-significantly larger insular volumes.

27.2.1 Gender Effects

It has been suggested that SZ exhibits a gender-specific pathology. Duggal et al. conducted an ROI study on an equal number of male and female FES patients [47]. Significant GM reductions were found solely in the right insula of female patients [47]. Elsewhere, SZ-related morphometric changes were confined to the left insula of male patients [25, 48]. Other studies have failed to find any gender-morphometry interaction [46] and a recent meta-analysis of 15 ROI studies found no evidence for a gender effect [22].

27.2.2 Treatment Effects

Evidence suggests that antipsychotic treatment may influence structural alterations in SZ [45, 49, 50]. However, heterogeneity in study populations, imaging modalities, and analysis techniques has challenged the development of a proper understanding of this potential confound.

One such point of heterogeneity lies in the pharmacological differences between typical (first generation) and atypical (second generation) antipsychotics. In a longitudinal ROI study,

Lieberman et al. demonstrated significant differences in the progression of global GM changes between patients treated with haloperidol (typical) and olanzapine (atypical) [51]. Haloperidol-treated patients exhibited a loss of global GM, appearing to peak within the first 12 weeks of treatment, while the olanzapine-treated patients did not experience significant global GM loss. In contrast, other studies assert no difference exists between typical and atypical antipsychotics regarding their effects on global GM [52, 53]. Despite these conflicting results, converging evidence from recent meta-analyses reveals a regionally-specific effect of antipsychotic type on GM and WM loss, such that less progressive loss occurs in SZ patients treated exclusively with atypical (versus typical) antipsychotics [17, 54].

As with whole-brain analyses, studies investigating the treatment effects of antipsychotics upon the insula have been mixed. Pressler et al. found no significant difference in insular volume between SZ patients and matched controls, but patients were found to have a positive correlation between typical neuroleptic exposure and insular volume [45]. Of interest, compared to healthy controls, patients exhibited non-significantly larger insular volumes, but smaller cortical surface area. Elsewhere, authors have failed to find any correlation between daily dose or antipsychotic medication type and insular GM volume [23, 43, 44].

Antipsychotic treatment has been correlated with insular activation [55]. During an overt verbal fluency task, functional magnetic resonance imaging (fMRI) of FEP patients exposed to early atypical antipsychotic treatment demonstrated a negative correlation between medication exposure and activation of the left insula [55]

Though differences have been attributed to medication effects, genetics, or, the course of the disease, meta-analyses support the presence of bilateral insular reductions, independent of confounds [22, 33]. Fusar-Poli et al. conducted a voxel-wise analyses of 14 VBM studies of antipsychotic-naïve FEP patients [33]. Compared to healthy controls, FEP patients showed consistent GM reductions in the bilateral insula. While genetics may play a role in the heterogeneity of insular defects, Borgwardt et al.'s imaging of monozygotic twins discordant for SZ demonstrated significant bilateral GM reductions in the affected twins [56].

27.2.3 Progression of Structural Changes

SZ patients experience a regionally-specific temporal pattern of neural tissue loss [16, 17, 57, 58]. Whole-brain tissue loss is greatest during the initial phases of the disease (i.e., early years following the onset of psychosis), slowing down over subsequent time periods as patients settle into the chronic phase of the disease [17, 44]. The trajectory of this tissue loss is temporally- and regionally-specific [17, 57]. Of 14 VBM studies, 11 examined chronic patients, while three examined first-episode patients [16]. Reduced volume in the left medial frontal gyrus was reported in seven (64%) chronic patient studies, while not found in any of the three first-episode studies. Conversely, reductions in the volume of the right ACC were reported in all three first-episode patient studies, while in only 27% of the chronic patient studies.

The insula undergoes a similarly progressive deterioration of GM over the course of SZ. Compared to controls, FES patients have significantly greater reductions in bilateral insular GM over time [44]. Along with several other select regions, the insula experiences the greatest relative GM loss during the initial phases of psychosis [44]. The rate of this GM loss abates in later stages of SZ. Once in the chronic stage of the disease, greater reductions in right insular GM, relative to FES patients, are observed [28].

The insula may serve as a neuroanatomical correlate underlying the transition to psychosis [33, 48]. Fusar-Poli et al. examined structural differences between high-risk (HR) and antipsychotic-naïve FEP individuals [33]. Their voxel-wise meta-analysis revealed the onset of psychosis was characterized by significant reductions in, among other regions, insular GM. FEP subjects exhibited significant GM reductions in

the bilateral insula compared with healthy controls and significant GM reductions in the left insula compared to HR subjects. These findings suggest insular reductions may reach a critical point that marks the onset of SZ symptomology.

Insular morphology also serves as an indicator of disease risk, with HR individuals exhibiting reductions in insular GM prior to disease onset [28, 33, 59]. Takahashi et al. found significantly greater volume reductions in the bilateral insula of HR patients who later developed psychosis, compared to those who did not [23]. Additional studies have demonstrated an association between HR subjects who later develop SZ and reduced GM in the right insula [59, 60]. Between ultra-high-risk patients who later developed psychosis (UHR-P) and those who did not (UHR-NP), UHR-P patients had significantly reduced bilateral insular GM compared to UHR-NP patients, and exhibited significantly reduced right insular GM compared to controls [61]. While individuals at an enhanced clinical risk for psychosis exhibit bilateral insular GM reductions, it appears individuals at an enhanced genetic risk display greater left-sided insular GM reductions [60].

27.2.4 Clinical Correlations

The insula is a broadly connected neural region. It is therefore not surprising that reductions in insular GM and cortical surface size have been associated with various symptom dimensions. Several studies report a negative correlation between the severity of positive symptoms in SZ and insular morphometry (GM volume and cortical surface area) [24, 25, 33, 45]. This correlation has been elsewhere disputed [43, 46].

Crespo-Facorro et al. found insular cortical surface area and GM volume to be negatively correlated with positive symptoms in drug-naive FES patients [25]. No such correlation existed with negative symptomology. Other research has demonstrated an association between right insular cortical surface area and hallucination severity [45]. In this study, left insular cortical surface area and bilateral GM volumes showed similar but non-significant trends. No correlations were found between delusions and insular morphology. UHR patients who later developed psychosis have been found to exhibit significant GM reductions in the right PI that correlated with negative symptom severity at baseline [61]

It is important to remember the limitations of all imaging modalities and analysis techniques, as well as the heterogeneity of study populations, as these methodological differences likely account for many observed discrepancies.

27.3 Functional Role of the Insula

The insula is involved in a broad range of functions including autonomic control, executive control, social cognition, interoception, and emotional and sensorimotor processing [62–64]. Interoception, emotional processing, and sensory processing represent three domains that underlie many cognitive and behavioral deficits in SZ. See Uddin et al. [42] for a review of insular function.

Successful social interaction hinges on social cognition, in turn served by the processes of interoception and emotional processing [64]. Dysfunction in these domains, a hallmark of SZ, can explain much of the impaired social functioning in SZ [65, 66].

27.3.1 Interoception

Interoception describes one's sensitivity to internal body states [67]. A state of interoceptive awareness is achieved upon the successful integration of current internal stimuli to form a present sense of self. Interoceptive processing requires the allocation of attention to particular internal body states and valuation of the attended-to stimulus. Craig proposes a central role for the anterior insula (AI) in these processes [64].

In line with this assertion, broad evidence supports a role for the AI as an integration hub of internal sensory information and higher-order cognitive predictions to create this state of awareness within an individual [68, 69]. The insula

plays a critical role in attention to and awareness of visceral internal responses [70, 71]. Activation of the right AI predicts interoceptive accuracy in patients asked to judge the timing of their own heartbeats [70]. The same study demonstrated right AI GM volume to be directly associated with interoceptive accuracy and patient's subjective reports of interoceptive awareness [70]. Interoceptive accuracy holds significant influence over decision-making processes [72] and autonomic regulation in social situations [73]. The insula is also involved in the affective processing of anticipatory stimuli [74]. It has been suggested this anticipatory processing serves to allow the AI to assign a valuation to the anticipated stimulus and regulate the sensitivity of the PIs subsequent processing of said stimulus [74].

Interoceptive accuracy is compromised in SZ, reflected in the loss of a patient's ability to detect internal stimuli and accurately identify said stimuli as internally-generated [75]. Poor insight, characterized by impaired awareness and attribution of the origin of mental events, is common in SZ [76]. Right PI cortical surface size and WM volume have been correlated with lack of insight [76], while left insular WM abnormalities have been associated with symptom unawareness [77]. Further highlighting the effects of abnormal insular functioning on interoception, SZ patients demonstrate reduced insular response to aversive stimuli (electric shock), with insular response correlating to positive symptom severity [78].

27.3.2 Emotional Processing

Interoception is intricately intertwined with emotional processing [79]. The James-Lange theory of emotion states that emotional feelings result from internal body sensations evoked by emotional stimuli [80]. Craig similarly posits a central importance of interoception in facilitating subjective feeling, emotion, and self-awareness [67]. Accordingly, interoceptive accuracy correlates with negative emotional experience, and both are associated with activation of the right AI [70]. Right AI activation has also been associated with numerous positive and negative emotions [67].

Facial emotion recognition (FER), particularly recognition of anger and disgust, is closely associated with insular activation [81]. SZ patients have a reduced ability to process affective expressions in others [82]. A recent neuroimaging meta-analysis by Jani and Kasparek demonstrated FER impairments in SZ patients are associated with reduced activation of the right insula [83].

A complex social process such as empathy requires the recognition and internal representation of the emotional and cognitive states of others, demanding a requisite level of theory of mind (ToM). Impairments in ToM are common in SZ and correlate with emotional processing deficits, including deficits in FER and empathetic processing [84–87]. These deficits are intricately related to insular function. Focal lesions to the AI have been shown to result in impaired processing of other's pain [88]. Similarly, SZ patients demonstrate abnormal activation of the AI and dACC when asked to imagine others in pain [62]. However, compared to healthy controls, no abnormal insular activity is observed in SZ patients when observing others experience pain [62].

27.3.3 Auditory Processing

In SZ, auditory processing deficits manifest as a reduced ability to interpret and generate emotional auditory cues, and in the generation of auditory hallucinations.

In speech, nonlinguistic information transfer is facilitated by a variety of acoustic features, including duration, pitch, and intensity [89]. These nonlexical cues of speech are collectively referred to as prosody. The interpretation of emotional prosody, referred to as auditory emotion recognition (AER, or emotional prosody comprehension), allows listeners to infer significant swathes of emotional information from the speaker and adjust their behavior accordingly. The insula plays an important role in AER. The

AI is associated with the higher-level processing of vocal affect [90] and insular activation is associated with emotional versus neutral prosody [91].

AER impairments are associated with social deficits and broader psychosocial outcomes [92] and are common in SZ [93–95]. Patients exhibit lessened sensitivity to the discrimination of acoustic intensity [96] and demonstrate a tendency to overestimate the emotional intensity of weak auditory emotional prosody [97]. Larger deficits appears in the discrimination of pitch-based features of speech [95, 97, 98], and deficits in tonal discrimination have been correlated with the negative symptoms of SZ [93].

However, exactly when and where these deficits occur is unclear. Such impairments may arise from deficits in low-level acoustic processing that compromise future information processing. Alternatively, these deficits may instead be the product of impaired assignment of meaning to emotional prosody during higher-level cognitive processing [92]. A mismatch negativity (MMN) is an event-related brain potential (ERP) component that reflects pre-attentive auditory deviance detection and has been used to elucidate the neural mechanisms underlying frequency modulation (FM) tone processing [99]. Kantrowitz et al. demonstrated impaired MMN generation in SZ patient's responses to FM tones that correlated with AER deficits [95]. Localizing the auditory cortex and AI as primary MMN sources, resting-state MRI (rsMRI) revealed a significant reduction in the functional connectivity (FC) of the AI and bilateral auditory cortex in SZ patients that correlated with AER deficits. When entered into a simultaneous regression, both the variables of "MMN" and "functional connectivity" contributed significantly to AER deficits. Of relevance, only the right AI exhibited significant deficits in connectivity to the bilateral auditory cortex, suggesting the right AI holds an important role in SZ.

Auditory hallucinations represent another central feature of SZ, potentially resulting from the misattribution of stimulus origin [1]. A voxel-based meta-analysis of SZ patients identified activation in the left insula and right superior temporal gyrus to be associated with auditory hallucinations [100].

27.4 Salience Network

Rather than mapping complex cognitive functions onto localized brain regions, a network perspective understands cognition as being supported by a series of large-scale distributed networks [101]. Using functional connectivity analyses, numerous intrinsic connectivity networks (ICNs) have been described. Such analyses have provided a new window into the neurobiological underpinnings of SZ.

The default mode network (DMN), central executive network (CEN), and salience network (SN) represent three core neurocognitive networks [102]. The DMN includes the posterior cingulate cortex (PCC), medial temporal lobes (MTL), bilateral inferior parietal cortex, and ventromedial prefrontal cortex (VMPFC) and plays a role in internally-focused and self-referential processes [103–105]. The CEN includes the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) and is involved in goal-directed and externally-oriented tasks [106].

The salience network (SN), with key nodes at the AI, dACC, frontal operculum, and anterior prefrontal cortex (PFC), is responsible for the detection and allocation of attention to salient internal and external stimuli [107–109]. Salience refers to the effectiveness of a stimulus to stand out from its neighbors and is determined by myriad features including, visual, motivational, or emotional associations [110].

The SN exerts a causal influence over CEN and DMN activity [111]. It is believed the SN serves to regulate switches between the two networks [111]; however, others understand the insula to have a broader role in coordinating the dynamic activation and repression of functional regions of the brain as required by attentional priorities [112]. Determining the SN has a regulatory role over the CEN and DMN, Sridharan et al. performed a granger causality analysis (GCA) and identified the right AI as underlying

the SN's control over the CEN and DMN [111]. GCA further revealed the right AI as a key outflow hub [111]. This view of the right AI as a key information outflow hub has been supported by additional studies [106, 113].

By Menon and Uddin's view, the right AI dynamically engages and suppresses various neural processes across a variety of domains, according to present attentional priorities. From this, Menon and Uddin propose the AI facilitates task-related information processing through its dynamic control over regions of the brain involved in attentional, working memory, and higher-order cognitive processes [112]. In this view, the SN serves as a hub of integration for bottom-up attentional priorities and top-down sensory control and biasing.

The SN, CEN, and DMN exhibit altered intra- and inter-functional connectivity (FC) in SZ [113, 119–123]. Interestingly, machine learning algorithms can identify SZ patients based on examination of SN resting-state functional connectivity (rsFC) with a 71.4% accuracy [124]. As with structural deficits, abnormal SN connectivity is present prior to disease onset in high-risk populations [82]. Given evidence of the insula's role in the detection and analysis of internal and external stimuli, and its regulation of self-referential and goal-directed processing through the CEN and DMN, dysregulation of the insula can reasonably explain several symptom dimensions in SZ [107, 114].

The aberrant salience hypothesis posits that symptoms in SZ arise from the inappropriate assignment of salience and motivational significance to otherwise irrelevant stimuli [114]. Such aberrant assignment leads to prolonged attention to select sensory inputs, creating a violation between incoming sensory information and top-down priors (expectation). Mismatches between expectation and internal/external stimuli (top-down priors and bottom-up sensory inputs) trigger a prediction error [108]. Under a hierarchical Bayesian framework, prediction errors are passed through higher levels in the hierarchy, probed by updated priors at each level, with the aim of reducing the error sufficiently enough to arrive at an appropriate inference. Importantly, a Bayesian framework assumes higher levels of the hierarchy are ever-updating lower levels to improve performance. Fletcher and Firth propose that SZ patients suffer deficits in the integration of new information [115]. Coupled with the dysregulation of both top-down priors and bottom-up sensory attentional priorities, dysfunctional prediction errors are created and propagated through higher levels of analysis. As a dysfunctional prediction error is processed (driven by a dysfunction in the ability to update inferences and beliefs about the world), the persistent uncertainty of the error demands excessive attention, gaining inappropriately significant influence over inference processes, in theory resulting in the inability to separate experience and belief that characterizes positive symptoms in SZ [115].

As a hub for the integration of internal/external information and top-down behavioral priorities, and a hub for the mediation of dynamic network interactions, the insula is uniquely positioned to sit at the center of this framework. Insular activation is associated with prediction error coding [69, 116], and patients with insular lesions have an impaired ability to update prediction frameworks [117]. Furthermore, psychosis patients demonstrate an absence of insular activation during reward prediction error [118]. It should also be noted that the role of the AI in anticipatory affective stimuli processing, which may in turn modulate the sensitivity of the PI's subsequent sensory component analysis, is of interest within a Bayesian framework [74, 108].

Important to remember, within a network perspective, the consequences of a focal neural insult may yield downstream consequences far exceeding the primary deficit. Abnormalities in the SN illustrate this concept. The normal modulatory influence of the SN over the CEN and DMN is altered in SZ [106, 121]. Disruption of the SN's intra-FC is associated with increased inter-FC between the CEN and DMN and predicts positive symptom severity [106]. In keeping with previous findings, abnormal connectivity within the right AI is specifically associated with increased inter-FC between the CEN and DMN and pre-

dicts hallucination severity [106, 113]. Abnormalities in the FC of the SN and DMN have been associated with persistent auditory hallucinations in SZ patients [125] and further study has demonstrated that SZ patients have reduced activation of the right auditory cortex, PFC, and SN [126]. The reduced activation of these regions was associated with impaired deactivation of the visual system and dorsal attention network. Driven by alterations in the FC of the right AI, impaired SN functioning and the resultant discoordination of broad associated networks may underlie ensuing neurological deficits.

SZ patients in remission demonstrate an interesting asymmetry from those in acute psychosis. Manoliu and colleagues revealed that remission patients exhibit decreased intra-FC between the CEN and DMN, associated with an increased SN and CEN inter-FC [113]. In these patients, abnormal activity within the left AI was correlated with the aberrant FC of the SN and CEN and predicted negative symptom severity. Manoliu and colleagues suggest these findings accord with the idea of an asymmetric representation of body-related interoceptive information in the AI [113]. The left and right AI hold greater association with parasympathetic and sympathetic systems, respectively [67]. The left AI is involved in the processing of positive and pleasant emotion, while the right AI is involved in processing of more taxing, biologically arousing stimuli [64]. Manoliu and colleagues propose the association of the left AI with negative symptomology may arise from impaired responses to pleasant stimuli [113].

Evidence for network dysregulation involving the AI in emotional cognition arrives from Ruiz et al. who utilized real-time fMRI to facilitate self-regulation of the bilateral AI in SZ patients [127]. Following a 2-week training interval, imaging revealed significantly greater FC of the bilateral AI that correlated with improved FER. In a similar study, patients demonstrated volitional upregulation of the left AI. This AI upregulation was associated with higher baseline connectivity between the DLPFC and dorsomedial PFC (DMPFC), as well as improved empathetic pain processing [128].

Conclusion

The insula is a target of significant structural and functional alteration over the course of schizophrenia. As a key node in the salience network, the insula serves to dynamically shift between functional brain states, activating and suppressing regional activity per contextually-relevant requirements. Alterations in insular morphometry and functional connectivity correlate with numerous functional deficits in schizophrenia patients, suggesting insular impairments may underlie these deficits. Future research will continue to parse apart the many neural underpinnings of schizophrenia in order to further elucidate the nature of these interactions.

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