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Insula Functional Connectivity in Schizophrenia

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Abstract

The insula is structurally abnormal in schizophrenia, demonstrating reductions in volume, cortical thickness, and altered gyrification during prodromal, early and chronic stages of the illness. Despite compelling structural alterations, less is known about its functional connectivity, limited by studies considering the insula as a whole or only within the context of resting-state networks. There is evidence, however, from healthy subjects that the insula is comprised of sub-regions with distinct functional profiles, with dorsal anterior insula (dAI) involved in cognitive processing, ventral anterior insula (vAI) involved in affective processing, and posterior insula (PI) involved in somatosensory processing. The current study builds on this prior work and characterizes insula resting-state functional connectivity sub-region profiles in a large cohort of schizophrenia (N=191) and healthy (N=196) participants and hypothesizes specific associations between insula sub-region connectivity abnormalities and clinical characteristics related to their functional profiles. Functional dysconnectivity of the insula in schizophrenia is broadly characterized by reduced connectivity within insula sub-networks and greater connectivity with regions not normally connected with that sub-region, reflected in significantly greater similarity of dAI and PI connectivity profiles and significantly lower similarity of dAI and vAI connectivity profiles ($p<.05$). In schizophrenia, reduced connectivity of dAI correlates with cognitive function ($r=.18$, $p=.014$), whereas stronger connectivity between vAI and superior temporal sulcus correlates with negative symptoms ($r=.27$, $p<.001$). These findings reveal altered insula connectivity in all three

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Contributors

Julia Sheffield led the development of the research questions, performed data analysis and wrote the initial draft. Neil Woodward contributed to the development of research questions, provided consultation throughout the project, and edited the initial draft. Neil Woodward and Baxter Rogers led the development of methods and statistical design. Baxter Rogers performed data processing and wrote sections of the Methods section. Jennifer Blackford and Stephan Heckers contributed to development of research questions and provided editorial comments. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflicts of interest

sub-regions and converges with recent evidence of reduced differentiation of insula connectivity in schizophrenia, implicating functional dysconnectivity of the insula in cognitive and clinical symptoms.

Keywords

Insula; schizophrenia; resting-state functional connectivity; cognition; positive symptoms; negative symptoms

1. Introduction

Abnormal structure of the insula is one of the most robust anatomical findings in schizophrenia. Meta-analyses have concluded that grey matter volume is reduced in bilateral insula and that smaller insula volume, while present in other mental illnesses, is most pronounced in psychotic disorders (Goodkind et al., 2015; Shepherd et al., 2012). Insula volume alterations are seen across the disease course (Ellison-Wright et al., 2008), demonstrating reductions in first-episode patients within the first few years of illness (Lee et al., 2016) with even more robust, progressive reductions during the chronic state (Chan et al., 2011). Neurobiological alterations of the insula may even represent a useful early marker of schizophrenia-risk, as smaller initial bilateral insula volume is seen in ultra-high risk patients who transition to psychosis, as compared to ultra-high risk patients who do not transition (Takahashi et al., 2009). Furthermore, structural abnormalities of the insula are associated with psychotic experiences (Krishnadas et al., 2014; Palaniyappan et al., 2011) and smaller insula volume at first episode predicts clinical course of positive and disorganized symptoms (M. Li et al., 2019). Combined, these findings implicate insula cortex integrity in the pathophysiology of schizophrenia.

Considerably less is known about functional abnormalities of the insula in schizophrenia. This critical knowledge gap is likely due to the fact that the insula is involved in a diverse range of functions (Wylie and Tregellas, 2010), including cognition (e.g. cognitive control, error processing), social and emotion processing (e.g. disgust), interoception, and pain (Craig, 2009; Namkung et al., 2017; Uddin, 2015). The functional diversity of the insula is reflected in its heterogeneous structure and connectivity. At the level of cytoarchitecture, there are at least three sub-divisions of the insula, including a dysgranular dorsal anterior region (dAI), an agranular ventral anterior region (vAI), and a granular posterior region (PI) (Mesulam and Mufson, 1982). Identification and specificity of these sub-regions in humans has been confirmed through convergent analysis of task-based activations and connectivity assessed with functional neuroimaging (Deen et al., 2011; Nelson et al., 2010). Meta-analysis of functional co-activation during performance of various tasks has revealed preferential involvement of the dAI in cognition, the vAI in affective processing, and the PI in somatosensory processes (Uddin et al., 2013). The different functional roles of insula sub-regions are recapitulated by their dissociable functional connectivity profiles (i.e. the regions with which they are reliably most strongly inter-connected). The dAI is functionally connected to regions associated with higher-level cognition, including the dorsal anterior cingulate cortex (dACC), prefrontal cortex, frontal eye fields and intraparietal sulcus (Deen

et al., 2011). Consistent with its role in emotion, the vAI exhibits robust functional connectivity with other emotion-related brain areas, including the pregenual anterior cingulate, inferior frontal gyrus, portions of the superior temporal sulcus (Deen et al., 2011), and the amygdala (Mutschler et al., 2009). Similarly, the PI, which is involved in sensorimotor processing, is connected to primary and secondary somatosensory and motor cortices (Deen et al., 2011). The insula is also highly interconnected with itself, underscoring its role in integrating cognitive, emotion, and sensorimotor information (Deen et al., 2011; Uddin et al., 2013).

Studying the functional connectivity of insula sub-regions in schizophrenia may expand our understanding of the pathophysiology of the disorder and inform the neural substrate of clinical phenotypes (Wylie and Tregellas, 2010). However, the majority of studies looking at the insula in schizophrenia investigated either connectivity of the whole insula (Pang et al., 2017) or within the context of broader cortical resting-state networks that include the insula, such as the salience, cingulo-opercular, and somatosensory networks (Huang et al., 2019; Sheffield et al., 2015). Directed connectivity of the anterior insula (a hub of the salience network) to nodes within the default mode network (DMN) and central executive network is reduced in schizophrenia (Moran et al., 2013; Palaniyappan et al., 2013). Studies investigating connectivity of the insula with the whole brain have observed a range of findings in relatively small samples of schizophrenia participants (N<50) including: reduced connectivity of the whole insula with the ACC, caudate, and Heschl's gyrus (Pang et al., 2017), increased connectivity between right PI and thalamus (Chen et al., 2016), and reduced connectivity of the vAI with regions of the DMN (Moran et al., 2013). Recent analysis also revealed reduced differentiation of insula connectivity sub-networks for anterior and posterior regions (Tian et al., 2019). Together, these studies indicate insula functional connectivity alterations in schizophrenia that have yet to be fully characterized in a large sample of patients.

The current study leverages a large resting-state fMRI dataset to characterize functional connectivity of insula sub-regions in schizophrenia and test specific *a-priori* hypotheses about the associations between dysconnectivity of specific insula sub-regions and clinical phenotypes. Given the dAI's well-defined role in higher-order cognition (Dosenbach et al., 2006; Moran et al., 2013), we hypothesized that dAI connectivity would be reduced in schizophrenia and associated with impaired general cognitive ability. The vAI is implicated in emotion processing (Simmons et al., 2013), a core feature of social cognition believed to underlie negative symptoms (Kohler et al., 2000; Martin et al., 2005). Therefore, we hypothesized that reduced vAI connectivity with affective regions would contribute to negative symptom severity. Finally, the PI plays a critical role in interoception, perception, and sensorimotor integration (Craig, 2009; Cauda et al., 2012), aspects of the human experience that are altered in psychosis. Greater interoceptive awareness in schizophrenia has been associated with more severe psychosis (Ardizzi et al., 2016) and a region in the insula that was activated during a symptom-capture study of auditory hallucinations was hyper-connected to the cerebellum and angular gyrus when compared to controls (Mallikarjun et al., 2018). We therefore hypothesized that stronger connectivity of the PI would be associated with more severe positive symptoms.

2. Materials and methods

2.1 Participants

210 healthy individuals and 234 people with a schizophrenia spectrum disorder (i.e. schizophrenia, schizophreniform disorder, or schizoaffective disorder- hereafter referred to as “schizophrenia”) participated in one of three MRI studies (CT00762866; 1R01MH070560; 1R01MH102266) conducted in the Department of Psychiatry and Behavioral Sciences at Vanderbilt University Medical Center (VUMC) (include/exclusion criteria described in Supplement). Schizophrenia participants were recruited from the Psychotic Disorders Program at VUMC. Healthy controls were recruited from Nashville and the surrounding area via advertisements and word-of-mouth. The study was approved by the Vanderbilt Institutional Review Board and written informed consent was obtained before participation. The Structured Clinical Interview for DSM-IV (SCID-IV) was administered to all study participants to confirm diagnoses in people with schizophrenia and rule out psychopathology in healthy individuals (First et al., 1995). From our initial cohort of 444 individuals, 14 healthy and 43 schizophrenia participants were excluded for data quality reasons (described in Supplement). Thus, the final sample included 196 healthy and 191 schizophrenia participants (Table 1).

2.2 Clinical Data and Cognitive Data

Positive and negative symptoms of psychosis were quantified with the Positive and Negative Syndrome Scale (PANSS (Kay et al., 1987)). One subject was missing a positive scale score, so the average PANSS positive score across all schizophrenia participants was used for that subject. All individuals were administered the Screen for Cognitive Impairment in Psychiatry (SCIP), a brief (10-15 minute) measure of immediate and delayed verbal memory, verbal fluency, working memory and processing speed (for description of SCIP see (Menkes et al., 2018)). Scores from each sub-test were z-scored based on published norms (Purdon, 2005) and summed as a measure of cognitive ability.

2.3 Neuroimaging Data Acquisition and Preprocessing

Neuroimaging data were collected on one of two identical 3T Philips Intera Achieva scanners located at Vanderbilt University Institute of Imaging Sciences. Details of scanning parameters and pre-processing steps are included in the Supplement. Briefly, a seven or ten-minute echo-planar imaging (EPI) resting-state fMRI scan and T1-weighted anatomical (1mm isotropic resolution) were collected for each participant. Preprocessing of fMRI data, performed in SPM12, included correction for head motion using rigid body motion correction, spatial co-registration to T1-weighted anatomical images, and spatial normalization to MNI-space using the parameters obtained from the grey matter segmentation normalization.

2.4 Functional Connectivity of Insula Sub-Regions

A-priori masks for left and right insula sub-regions (dorsal anterior insula (dAI), ventral anterior insula (vAI), and posterior insula (PI)), derived by Deen and colleagues ((Deen et al., 2011) https://bendeen.com/data/) were used as seeds in separate seed-to-voxel functional

connectivity analyses in MNI-space. Mean gray matter signal, six head motion parameters and their first temporal derivatives, and six principal components from an eroded white matter/CSF mask obtained from the individual T1 segmentations were removed in voxelwise regression (Behzadi et al., 2007). The fMRI time-series data was simultaneously band-pass filtered (0.01-0.10 Hz). Time series were averaged from voxels within each insula ROI and correlated with every voxel to generate a whole-brain connectivity map for each insula sub-region. Correlations were converted to Fisher Z-scores. The resultant sub-region connectivity maps were averaged across hemisphere to generate average connectivity maps for right/left sub-regions (results for left/right insula sub-regions presented in Table S1) and were smoothed using 4mm FWHM Gaussian kernel.

2.5 Statistical Analyses

Voxel-wise analyses of neuroimaging data were done in SPM12. To compare connectivity between groups, insula sub-region connectivity maps were entered into separate independent-sample t-tests, controlling for head motion, gender and the research study for which the data was collected (given the three studies noted above). Independent samples t-tests were thresholded at cluster-level $p_{FWE}<.05$ for voxel-wise cluster-defining threshold p=.001 (uncorrected). To help determine whether medication dose was driving group difference results, connectivity from clusters showing a significant group difference were correlated with chlorpromazine-equivalent (CPZ) values.

In addition to comparing connectivity between groups, we examined how similar/dissimilar insula sub-region connectivity profiles were to one another and compared this across groups using eta-squared (Cohen et al., 2008). Eta-squared is a coefficient calculated on a point-by-point basis that is equal to the fraction of the variance in one signal accounted for by the variance in a second signal. The more similar two signals, the higher the eta-squared coefficient (range: 0-1, with 1 representing identical signals). Eta-squared can be used to determine the degree of similarity between connectivity maps and is used here to provide additional insight into whether differentiation of sub-region functional profiles was reduced in schizophrenia. Eta-squared for dAI-PI, dAI-vAI, and PI-vAI within-group estimated the proportion of variance in one map (e.g. dAI) accounted for by variance in another map (e.g. PI). Unlike the correlation coefficient, eta-squared is sensitive to differences in center and scale.

Two strategies were used to test a-prior brain-behavior relationships. First, to maximize statistical power and limit the number of correlations performed, functional connectivity was extracted from the clusters demonstrating group differences using the volume of interest (VOI) tool in SPM, resulting in an average connectivity measure of each insula seed for each individual, at each contrast (e.g. healthy > schizophrenia). These values served as dependent variables in the correlation analyses, that were Bonferroni-corrected for three tests (.05/3 = significance threshold of p<.0167). We complemented this approach with whole-brain voxel-wise correlation analyses with the hypothesized clinical variable entered as a predictor of functional connectivity including study and head motion (median voxel-displacement log10) as covariates. Whole-brain correlation analyses were cluster-level corrected at p_{FWE} <.05 for voxel-wise cluster-defining threshold of p=.001 (uncorrected).

3. Results

3.1 Functional Connectivity of Insula Sub-regions

Insula sub-regions demonstrated relatively distinct patterns of connectivity that were qualitatively similar in healthy controls and schizophrenia, and highly consistent with prior studies of insula connectivity (e.g. (Deen et al., 2011); Fig.1). Briefly, dAI was connected with fronto-parietal regions, dACC, and temporal sulcus. Connectivity with vAI was seen in ventral ACC, inferior parietal lobe, and inferior temporal sulcus. The PI was largely connected with primary sensory and motor cortices, as well as the anterior cingulate. All insula sub-regions were negatively connected with the regions in the DMN (i.e. precuneus, posterior cingulate cortex (PCC), medial prefrontal cortex, and posterior cerebellum).

3.2 Insula Connectivity Abnormalities in Schizophrenia

Group differences in insula connectivity are shown in Fig. 2 and summarized in Table 2 (and Table S1 for results by hemisphere). Group differences were highly consistent across both right and left insula and were largely unrelated to CPZ-equivalent doses (Table S2)

3.2.1 Dorsal Anterior Insula (dAI).—Schizophrenia was characterized by a combination of increased and decreased dAI connectivity. Specifically, dAI positive connectivity with bilateral sublenticular substantia innominata (part of the extended amygdala), dACC, and the orbital frontal cortex (OFC) was reduced in schizophrenia. In contrast, the dAI demonstrated relatively stronger positive connectivity with sensorimotor and attention regions (left parietal cortex, primary visual cortex, right somatosensory cortex, and the cerebellum) as compared to healthy participants, who exhibited negative connectivity with most of these regions. Additionally, dAI was negatively connected with a region in the cerebellum associated with the ventral attention network in healthy participants (Buckner et al., 2011) but exhibited minimal connectivity (close to zero) in the schizophrenia group.

3.2.2 Ventral Anterior Insula (vAI).—Reduced positive connectivity between the vAI and dACC was seen in schizophrenia. Furthermore, vAI was more weakly negatively connected with regions comprising the DMN, namely the precuneus and cerebellum.

3.2.3 Posterior Insula (PI).—Individuals with schizophrenia demonstrated widespread dysconnectivity within the PI. Patients showed reduced positive connectivity between PI and the somatosensory cortex and hippocampus, relative to healthy participants. The PI was negatively connected with the superior temporal gyrus and PCC in both groups, but the strength of that negative connectivity was stronger in the schizophrenia participants.

In schizophrenia, the PI was more strongly positively connected to the superior parietal cortex, frontal eye fields, and right parietal cortex – regions that exhibited minimal connectivity in healthy participants (i.e. connectivity close to zero). There were also several regions with strong negative connectivity in the healthy participants that showed weaker negative connectivity in schizophrenia. These regions included the prefrontal cortex,

precuneus, regions of the cerebellum associated with the ventral attention network, and a ventral portion of the PCC.

3.2.4 Similarity Analysis.—PI-dAI connectivity profiles were significantly more similar in schizophrenia than healthy participants (eta-squared 0.023 higher, 95% CI(0.008, 0.04)) whereas dAI-vAI connectivity profiles were significantly less similar (eta-squared 0.043 lower, 95% CI(−0.079, −0.005)) (full results presented in Table S3). The similarity between vAI-PI maps did not differ between groups (eta-squared 0.021 lower in schizophrenia, 95% CI(−0.061, 0.031)). These findings further demonstrate a greater similarity in functional profiles between the PI and dAI and less similar functional profiles between the dAI and vAI in schizophrenia than is typical.

3.3 Associations Between Insula Connectivity and Clinical Variables

3.3.1 Region of Interest Correlation Analysis.—Consistent with our hypothesis, reduced dAI connectivity in schizophrenia correlated with worse cognitive function (r=.18, p=.014), surviving multiple comparisons correction (Fig. 3a). Neither positive nor negative symptoms correlated with average dAI connectivity (positive: r=−.002, p=.978; negative: r=.01, p=.949), suggesting a specific relationship between dAI connectivity and cognition. Our hypotheses that reduced vAI connectivity would correlate with negative symptoms (r= −.01, p=.944) and increased PI connectivity would correlate with positive symptoms (r= −.05, p=.538) were not supported.

3.3.2 Whole Brain Correlation Analysis.—In an effort to further explore brain-behavior relationships between insula sub-regions and clinical characteristics of schizophrenia, whole brain voxel-wise correlations were performed for sub-region correlations and specific a-priori symptoms. At cluster-level p_{FWE}<.05 threshold, connectivity between vAI-posterior superior temporal sulcus (STS) was positively correlated with negative symptom severity (r=.27, p<.001) (Fig. 3b). Relationships between dAI and cognition and between PI and positive symptoms were not significant at this threshold.

4. Discussion

In contrast to well-documented structural abnormalities of the insula, comparatively little is known about functional connectivity disturbances of the insula in schizophrenia. This is especially true for insula sub-regions, including dAI, vAI, and PI divisions, which demonstrate distinct connectivity profiles in keeping with their divergent functional roles. To address this knowledge gap, we analyzed functional connectivity of insula sub-regions in a relatively large cohort of people with schizophrenia and healthy individuals. We found widespread insula dysconnectivity in schizophrenia characterized by both increased and decreased connectivity of all three insula sub-regions. Further comparison revealed greater similarity between dAI and PI functional profiles in schizophrenia than healthy participants, as well as less similarity between dAI and vAI. Reduced dAI connectivity correlated with cognitive impairment and stronger vAI-STS connectivity correlated with negative symptoms. Our findings add to prior literature (Tian et al., 2019) suggesting a less

differentiated insula connectome in schizophrenia that is associated with clinical phenotypes.

Only one prior study of insula connectivity in schizophrenia has examined insula sub-regions, yielding some convergent findings (Chen et al., 2016). In a smaller, older sample of patients, Chen and colleagues (Chen et al., 2016) also observed dAI dysconnectivity with OFC, the basal ganglia, and dACC. However, they observed no differences in vAI connectivity and their main finding of increased PI-thalamus connectivity was not replicated here. Recent analysis of anterior/posterior insula connectivity also found reduced anterior insula connectivity with OFC, ACC, and basal ganglia, and reduced PI connectivity with superior temporal gyrus and PCC (Tian et al., 2019). Our results build on these findings and, in a large, relatively young sample, characterize insula functional connectivity in schizophrenia in the following ways: 1) all three sub-regions are hypo-connected with areas typically connected in healthy participants. This follows the structural literature identifying widespread structural abnormalities of the insula in schizophrenia (e.g. reduced volume and thickness), suggesting that the entire insula is impacted (Shepherd et al., 2012); 2) dAI and vAI are *less* strongly connected with DMN, salience, and central executive regions while PI is *more* strongly negatively connected with the PCC, a hub of the DMN. As a hub of the salience network, the anterior insula plays an integral role in switching attention between internal and external stimuli (Menon, 2011). This momentary state of stimulus evaluation, termed proximal salience, relies on the connectivity between the insula, DMN, and central executive network (Palaniyappan and Liddle, 2012). Alterations in the connectivity between these networks is hypothesized as a core feature of schizophrenia (Palaniyappan et al., 2013). Recently dynamic functional connectivity analysis revealed reduced cross-network interactions and more variable salience network connectivity in schizophrenia, correlating with positive symptoms (Supekar et al., 2019). Our findings of reduced resting anterior insula connectivity with DMN and central executive regions provides further evidence of a dysregulated saliency system schizophrenia. Stronger connectivity between PI and DMN warrants further research into the possible role of the PI in the proximal salience model; 3) dAI is hyperconnected with somatosensory/parietal regions and PI is hyperconnected with cognitive regions, indicating inappropriate connectivity of dAI with regions typically connected to PI, and vice versa. Similarity analysis showed that the connectivity profiles of these two sub-regions were significantly more similar in schizophrenia than healthy participants, suggesting less clearly differentiated functional profiles. Recently, Tian and colleagues (Tian et al., 2019) reported reduced differentiation of anterior/posterior insula connectivity in schizophrenia based on reduced modularity (Q) of insula clusters and a more diverse connectivity profile along the rostrocaudal axis. Our findings further suggest that dAI and PI sub-networks, which typically support different aspects of information processing (i.e. cognitive and somatosensory), are less specifically connected in schizophrenia, leading to a more disorganized insula connectome.

Motivated by growing awareness of insula sub-region functions, we tested several a-priori brain-behavior hypotheses. Our hypotheses were guided by evidence that dAI, vAI, and PI are preferentially involved in cognition, emotion processing, and somatosensory functions, respectively. In line with our first hypothesis, overall reduced dAI connectivity was associated with greater cognitive impairment, consistent with prior findings implicating dAI

in cognitive ability (Moran et al., 2013; Sheffield et al., 2015). Our second hypothesis, that reduced vAI connectivity would be associated with more severe negative symptoms, was not supported. However, whole-brain voxel-wise analysis within the schizophrenia group identified *stronger* connectivity between vAI-STS related to worse negative symptoms. The posterior STS is considered a core area involved in social cognition (Deen et al., 2015) that exhibits hyperactivity during processing of neutral faces in schizophrenia (Mier et al., 2017). The vAI also plays a major role in social cognition through emotional understanding (Gallese et al., 2004). While the insula and STS are both implicated in models of social cognitive deficits in schizophrenia (Billeke and Aboitiz, 2013) these are some of the first findings to demonstrate that their connectivity is associated with negative symptom severity in schizophrenia. Our third hypothesis of increased PI connectivity correlating with severity of positive symptoms was also not supported, in either the ROI or whole-brain analysis. More direct analysis of PI functioning in schizophrenia, such as was seen in symptom-capture studies (Mallikarjun et al., 2018), may be more sensitive to relationships between PI integrity and psychosis than resting-state data. Finally, all brain-behavior relationships were hypothesized based on canonical (i.e. “healthy”) sub-region functional profiles. We found reduced specificity of these functional profiles in schizophrenia. Therefore, while speculative, less differentiated functional profiles may have made it more difficult to detect the expected brain-behavior associations for all three insula sub-regions.

The general finding of reduced functional differentiation of the insula suggests a more disorganized insula connectome in schizophrenia, thereby implicating developmental processes in these abnormal connectivity profiles. The insula is the earliest cortical region to develop and differentiate (Chi et al., 1977) with the anterior-posterior gradient as one of the first identifiable factors of embryonic development (Fjell et al., 2018). Longitudinal imaging of infants has revealed anterior/posterior functional sub-divisions, and connectivity with frontal and somatosensory regions, respectively, within the first two years of life (Alcauter et al., 2015). Insula connectivity continues to be refined throughout childhood and adolescence (Uddin et al., 2011) and reduced centrality of the anterior insula is associated with childhood maltreatment (Teicher et al., 2014), indicating its connectivity may be particularly vulnerable to developmental insult. In our data, the anterior sub-regions were inappropriately connected with more posterior brain areas while the PI was inappropriately connected with more anterior brain areas, reflected in greater similarity of functional profiles. The vAI and dAI were also less similar in schizophrenia, suggesting that connectivity from anterior insula was being “pulled away” to posterior insula. Schizophrenia has been associated with both pre- and perinatal risk factors such as viral infections and stress of the mother during pregnancy (King et al., 2010), and childhood maltreatment (DeRosse et al., 2014), providing many opportunities for insula specificity to go awry. Abnormal connectivity of all three insula sub-regions converges with the notion that altered insula structure and function may be shaped throughout development in ways that confer risk for schizophrenia and, although speculative, suggests that the specific connections associated with insula sub-regions may develop in a more disorganized fashion, contributing to the pathophysiology of schizophrenia.

Regarding limitations, nearly all schizophrenia participants were taking anti-psychotic medications. The vast majority of clusters demonstrating group differences in connectivity

were unrelated to medication dosage suggesting that the widespread alterations in connectivity observed in our data are unlikely to be driven by medication use. Additionally, it is important to note that the presented results underwent removal of the average signal from all grey matter regions (a method akin to global signal regression). Global signal regression has been shown to improve the reliability of functional connectivity data (Parkes et al., 2018) and strengthen associations with behavior (J. Li et al., 2019). However, in simulated data, global signal regression can introduce “artifactual” anti-correlations and can differentially impact groups with different noise characteristics (Murphy and Fox, 2017). Although we are careful not to over-interpret anti- or negative correlations in our results, instead working to couch them in terms of patterns of group difference and consistency with previous findings, global signal regression should be considered when interpreting our results.

In conclusion, there is significant and widespread dysconnectivity of insula sub-regions in schizophrenia. This dysconnectivity is characterized by reduced positive connectivity with regions typically connected in the healthy brain, altered connectivity with DMN regions, and inappropriate connectivity of dAI with parietal/somatosensory regions and PI with higher-order cognitive regions, revealing a disorganized connectome. Weaker connectivity of dAI was associated with worse cognition, while vAI-STS connectivity related to negative symptoms. It is clear from these results that the well-characterized structural abnormalities of the insula in schizophrenia have consequences for functional connectivity compelling future research into structure and function of insula sub-regions throughout development and illness course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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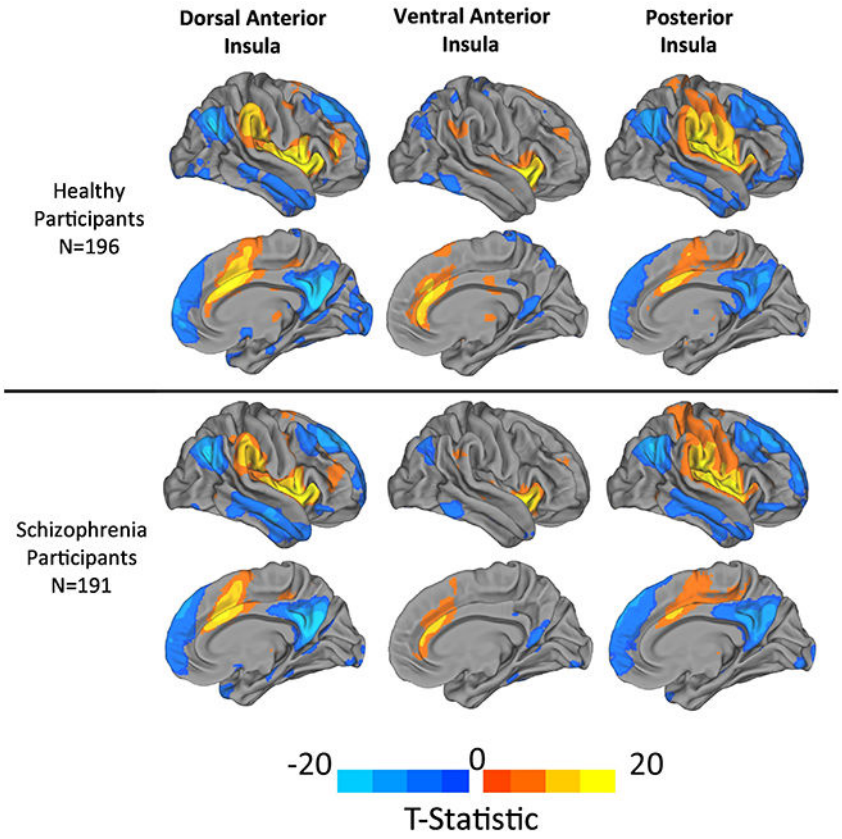

Fig. 1:

Within-group functional connectivity of insula sub-regions projected onto inflated right-hemisphere surfaces to illustrate functional profiles of each sub-region. Results thresholded at whole-brain (FWE) cluster-level corrected p=.05 using a voxel-wise p=.001 (uncorrected) cluster-defining threshold.

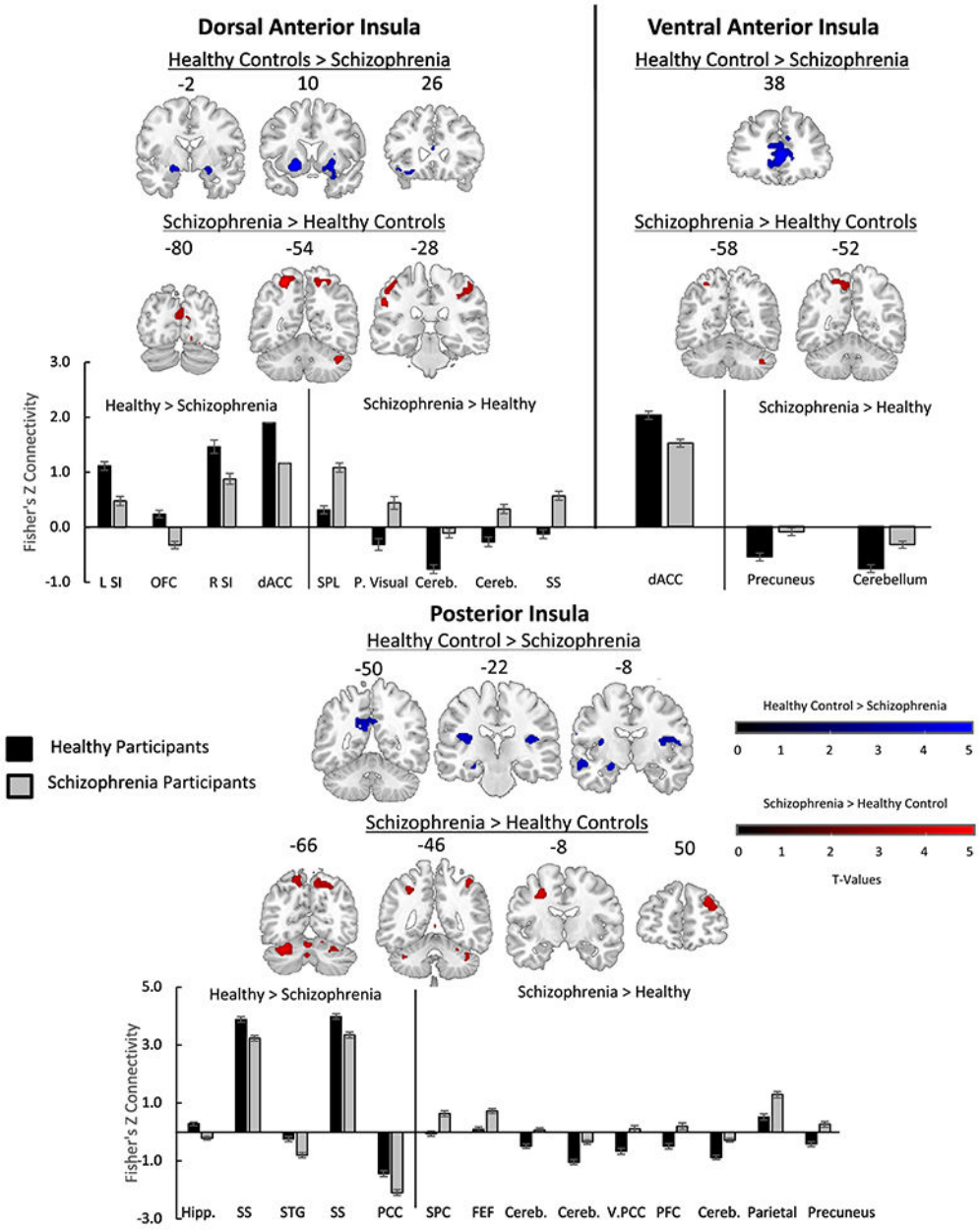

Fig. 2:

Clusters demonstrating significant group differences for each insula sub-region. Group difference maps were thresholded at cluster-level p_{FWE} <.05 for voxel-wise cluster-defining threshold p=.001 (uncorrected), controlling for head motion, study protocol and gender. Numbers of coronal sections designate MNI-Y position of slice. Bar plots illustrate average functional connectivity within each significant cluster. *L SI = Left Substantia Innominata; OFC = Orbitofrontal Cortex; R SI = Right Substantia Innominata; SPL = Superior Parietal Lobe; P. Visual = Primary Visual Cortex; SS = Somatosensory Cortex; dACC = Dorsal Anterior Cingulate Cortex; Hipp. = Hippocampus; STG = Superior Temporal Gyrus; PI = Posterior Insula; PCC = Posterior Cingulate Cortex; SPC = Superior Parietal Cortex; FEF =*

Frontal Eye Field; Cereb. = Cerebellum; V. PCC = Ventral Posterior Cingulate Cortex; PFC = Prefrontal Cortex.

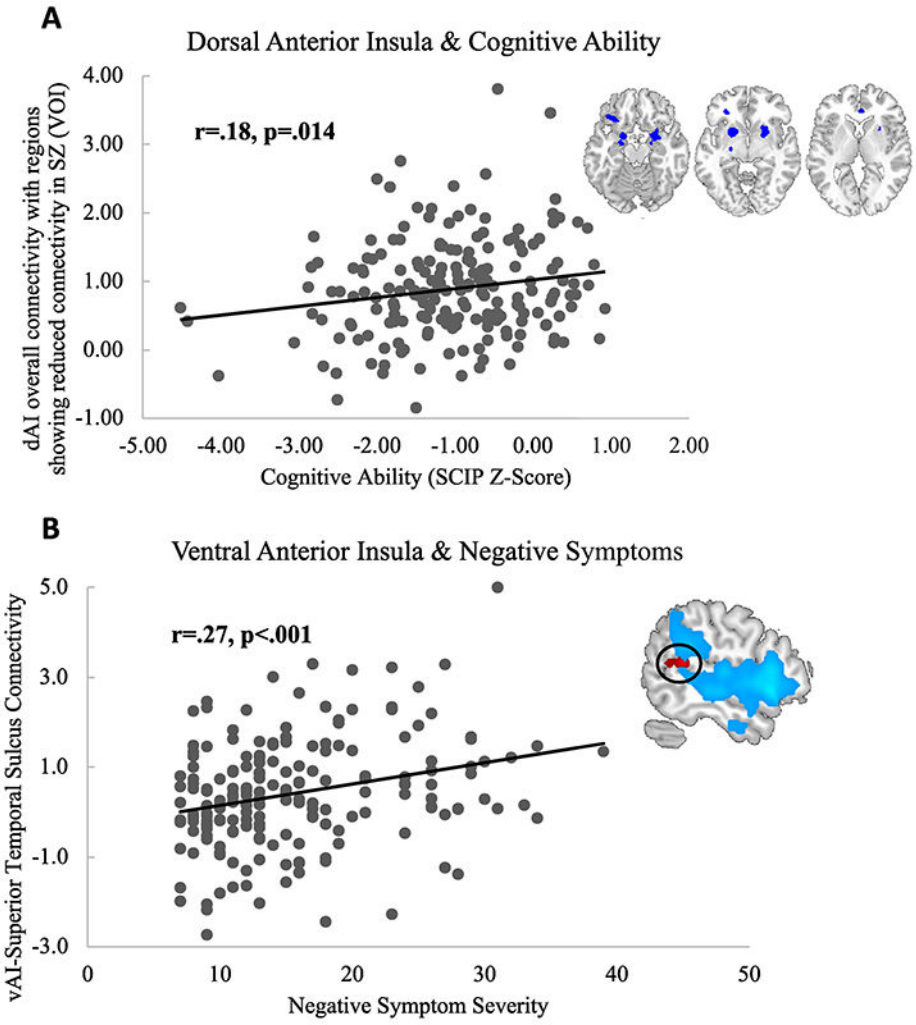

Fig. 3:

A) Average connectivity extracted from the regions that demonstrated reduced connectivity with the dAI in schizophrenia (shown in blue) was associated with better overall cognitive ability (total SCIP z-score) (VOI = volume-of-interest analysis in SPM). B) Whole-brain voxel-wise analysis revealed a positive association between vAI connectivity with right posterior superior temporal gyrus (shown in red) and negative symptoms. Connectivity of vAI with the whole brain in the healthy group is overlaid in blue, demonstrating no significant connectivity between vAI and STS in healthy participants, suggesting that vAI-STS are abnormally connected in schizophrenia, contributing to negative symptom severity.

Table 1.

Demographics Table: CPZ=chlorpromazine; F=female; IQ= intelligence quotient; M=male; PANSS= positive and negative syndrome scale; SCIP= screen for cognitive impairment in psychiatry.

	HEALTHY PARTICIPANTS N=196	SCHIZOPHRENIA PARTICIPANTS N=191	STATISTIC
AGE	28.83 (10.33)	27.90 (10.22)	t(385)=.89, p=.373
GENDER (M/F)*	120/76	136/55	X^2=4.30, p=.038
RACE (CAUCASIAN/AFRICAN AMERICAN/OTHER)	139/46/11	131/54/6	X^2=7.40, p=.116
PERSONAL EDUCATION*	15.23 (2.12)	13.37 (2.20)	t(365)=8.25, p<.001
PARENTAL EDUCATION	14.42 (2.35)	14.74 (2.75)	t(342)=−1.19, p=.235
PREMORBID IQ*	111.25 (11.05)	101.24 (15.20)	t(373)=7.31, p<.001
SCIP TOTAL-Z*	0.12 (0.63)	−1.05 (.99)	t(385)=13.92, p<.001
MOTION	−1.38 (.14)	−1.40 (.17)	t(385)=.92, p=.357
MEDIAN VOXEL DISPLACEMENT (LOG10)			
PANSS POSITIVE	--	17.46 (7.89)	--
PANSS NEGATIVE	--	15.68 (6.99)	--
PANSS GENERAL	--	31.33 (8.29)	--
DURATION OF ILLNESS (MONTHS)		85.53 (115.65)	
CPZ-EQUIVALENT	--	420.33 (242.39)	--

Table 2:

Connectivity differences between healthy and schizophrenia participants for insula sub-regions

Seed Region of Interest, Contrast, and Brain Regions	Montreal Neurological Coordinates (x,y,z)	Brodmann Area	Peak t-value	p[a]	Cluster Size (Voxels)
Dorsal Anterior Insula					
Healthy Controls > Schizophrenia					
Left Substantia Innominata	−20, 8, −10	49	5.76	<.001	487
Right Substantia Innominata	22, 2, −12	49	5.13	<.001	441
Right Dorsal Anterior Cingulate Cortex (dACC)	2, 38, 6	24/32	4.70	0.029	135
Left Orbitofrontal Cortex (OFC)	−30, 36, −8	47	4.26	0.004	207
Schizophrenia > Healthy Controls					
Left Superior Parietal Lobe	−24 −54 60	7	5.35	<.001	1117
Right Somatosensory Cortex	42, −32, 58	1	4.36	<.001	985
Cerebellum (Ventral Attention Network)[b]	40, −52, −32	N/A	4.79	0.039	126
Cerebellum (Ventral Attention Network)[b]	26, −70, −20	N/A	4.23	<.001	290
Primary Visual Cortex	22, −68, 10	17	3.98	0.001	261
Ventral Anterior Insula					
Healthy Controls > Schizophrenia					
Right Dorsal Anterior Cingulate Cortex (dACC)	2, 38, 6	24/32	5.74	<.001	591
Schizophrenia > Healthy Controls					
Cerebellum (Default Mode Network)[b]	40, −60, −38	N/A	4.37	0.038	124
Precuneus	−8, −54, 52	7	3.81	0.041	122
Posterior Insula					
Healthy Controls > Schizophrenia					
Left Hippocampus	−24, −10, −12	54	4.54	0.025	129
Superior Temporal Gyrus (STG)	−56, −6, −10	22	4.22	0.022	143
Right Somatosensory Cortex	38, −12, 20	1	4.50	<.001	385
Left Somatosensory Cortex	−42, −20, 20	1	4.40	<.001	280
Right Posterior Cingulate Cortex (PCC)	8, −44, 30	23	3.97	<.001	335
Schizophrenia > Healthy Controls					
Prefrontal Cortex/Response Inhibition	28, 48, 26	9	4.47	0.013	159
Left Frontal Eye Fields (FEF)	−28, −6, 46	6	4.65	0.020	146
Right Cerebellum (Ventral Attention)[b]	40, −54, −32	N/A	5.80	<.001	466
Left Cerebellum (Ventral Attention)[b]	−32, −56, −28	N/A	5.87	<.001	564
Left Cerebellum (Ventral Attention)[b]	−2, −66, −20	N/A	4.25	0.003	207
Precuneus	8, −68, 52	7	4.20	0.001	276
Ventral Posterior Cingulate Cortex (PCC)	0, −38, −2	N/A	4.67	0.042	122
Right Parietal	42 −44 56	7	4.79	0.013	161
Left Superior Parietal Cortex	−16 −64 60	7	4.23	<.001	282

[a]Values represent cluster-level family-wise error corrected p-value

[b] Cerebellum coordinates were compared to cerebellar parcellations provided in Buckner et al., (2011), *Journal of neurophysiology*. Network names in parentheses indicate the network that that region of the cerebellum is primarily functionally connected with, based on the Buckner parcellation. Group differences control for head motion, gender, and study protocol.