Schizophrenia Research: Cognition 32 (2023) 100277

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

journal homepage: www.elsevier.com/locate/scog

Review Article

The role of the insula in cognitive impairment of schizophrenia☆

Susanna Gebhardt [a,b,*], Henry A. Nasrallah [b]

[a] University of Cincinnati College of Medicine, Cincinnati, OH
[b] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, United States of America

ARTICLE INFO

Keywords:
Schizophrenia
Insula
Cognitive impairment
Neural circuits

ABSTRACT

Cognitive impairment is one of the core clinical symptom domains of schizophrenia. Research shows that cognitive deficits in this neuropsychiatric syndrome is associated with neurodevelopmental pathology affecting multiple brain regions such as the dorsolateral prefrontal cortex, the hippocampus and the parietal lobe. The insula is a relatively small structure that is highly connected with several brain regions as well as multiple brain networks. A large number of studies have reported the involvement of the insula in many of the psychotic and nonpsychotic manifestations of schizophrenia. Here we review the role of the insula as a hub across key neurocircuits which have been implicated in the various cognitive pathologies in schizophrenia. Structural and functional abnormalities in the right and left insulae may serve as a biomarker for susceptibility to schizophrenia.

1. Introduction

Over the past two decades, the insula has emerged as a key neuroanatomical structure whose dysfunction contributes to various symptom domains of the Schizophrenia syndrome (SZ). While other neocortical and cortical brain structures have been implicated in the psychopathology of SZ, dysfunction in the insula is particularly salient, in its extensive interconnectivity to other brain regions and circuits, and its central role in information processing across the neocortex and the limbic system. The insula's role in cognition, both neurocognition and social cognition, has become increasingly appreciated,[1] and the role of the insula in key neuropsychobiological domains is essential to understanding the etiopathogenesis of cognitive deficits in SZ.

The insula is centrally located, bounded by the frontal, temporal, and occipital lobes/opercula, and claustrum. Despite its diminutive size, making up less than "2% of total cortical surface area", it participates in "an astonishingly large number" of significant neural processes (Nieuwenhuys, 2012; Wynford-Thomas and Powell, 2017; Boucher et al., 2015; Shura et al., 2014). The insula should not be conceptualized as a structurally or functionally homogenous entity. An anterior-posterior subdivision has been identified as early as in utero (Alcauter et al., 2015). The anterior and posterior zones have short and long gyri, respectively (Wynford-Thomas and Powell, 2017; Benarroch, 2019; Cloutman et al., 2012). Insular regions are marked by distinct cytoarchitecture (Benarroch, 2019; Cloutman et al., 2012; Nieuwenhuys, 2012; Sheffield et al., 2021), meaning that each section has separate layers, with the anterior (allocortex) lacking a granular layer, the posterior (isocortex) having six layers, with an intermediate "transition zone" or dysgranular region (Kasai et al., 2003; Shura et al., 2014; Benarroch, 2019). The anterior insula (AI) contains von Economo neurons (VENS) (bipolar projection neurons) that permits the AI and anterior cingulate cortex (ACC) to act in concert (Nimchinsky et al., 1999; Alcauter et al., 2015).

1.1. Normal function of the insula

In the healthy brain, the insula processes and integrates sensory information, which it distributes to other areas (Li et al., 2019). A meta-analysis by Kurth et al., 2010 divided the insula into four structural/functional domains, based on 1768 functional neuroimaging studies. Kurth et al. describes the four areas as follows:

(1) the anterior-dorsal, the "dorsal part of the anterior and middle short gyrus". This is activated by cognitive tasks. Cognitive tasks include "attention, language, speech, memory, working

☆ This research was supported by the Medical Student Scholars Program (MSSP) at the University of Cincinnati College of Medicine.It was presented as a poster at the 2022 meeting of the Society of Biological Psychiatry.

* Corresponding author.
E-mail address: gebharsj@mail.uc.edu (S. Gebhardt).

[1] For example, see Gasquoine, 2014.

https://doi.org/10.1016/j.scog.2022.100277
Received 17 June 2022; Received in revised form 21 December 2022; Accepted 31 December 2022

memory". This region also aggregates processes from eleven of the thirteen categories associated with different areas of the insula.

(2) the anterior-ventral. This is activated by social-emotional tasks, meaning emotion and empathy, as well as Theory of Mind.
(3) the central, specifically on the "right middle insular gyrus", activated by olfaction and gustation.
(4) the mid-posterior, spanning from the "posterior insula to posterior short insular gyrus", activated by sensorimotor tasks, or "interoception, somatosensation, pain, motion". (See also Wynford-Thomas and Powell, 2017; Craig, 2009.[2])

The insula has the overarching function of receiving non-self interoceptive stimuli—such as thirst, itch, heartbeat, stomach distention (Craig, 2009)—and integrating this input with information from cortical and subcortical regions (Namkung et al., 2017). This leads to the ability to conceptualize the "self" (Singer et al., 2009) and to differentiate the self from non-self, or internal from external.

1.2. The insula is a hub across key neurocircuits

The insula's central anatomical location underscores its role as a central hub in several brain networks; specifically, it is involved in "information processing across various processing pathways" and networks (Liu et al., 2018). The Salience Network (SN), consisting of the bilateral anterior insula (AI), anterior cingulate cortex (ACC), and ventrolateral prefrontal cortex (fronto-insular cortex), mediates the switch between the central-executive network (CEN) and default-mode network (DMN) (Sridharan et al., 2008; Menon and Uddin, 2010). The right insula is involved in the ventral frontoparietal attention network governing "bottom-up control of attention" (Uddin, 2015). The AI is also involved in the cingulo-opercular network (CON), a network responsible for alertness (Coste and Kleinschmidt, 2016), which is involved in cognitive control (Zanto and Gazzaley, 2013).[3]

1.3. Insula pathology is associated with cognitive deficits

Given the insula's extensive connections to other brain regions, it follows that insular abnormalities have far-reaching effects, both neurobiologically and phenomenologically. In SZ, insula pathology contributes to core symptoms of the disorder, being implicated in delusions, hallucinations, neurocognition, social cognition, and sensorimotor deficits. This selective review will focus on 11 studies related to major neurocognitive and social cognitive functions.

Cognition in SZ has been shown to be impaired across seven separate domains; these are 1) speed of processing, 2) attention/vigilance, 3) working memory, 4) verbal learning, 5) visual learning, 6) reasoning and problem solving, and 7) social cognition. This framework is based on the National Institute of Mental Health Initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative that evaluated and selected the tests best suited to evaluating cognitive function in SZ. These seven domains encapsulate both neurocognition and social cognition, both of which are impaired to varying degrees in SZ (Vingerhoets et al., 2013).

Cognitive functions are disrupted in people with abnormal structures of their insulae. Vingerhoets et al.'s review article describes the insula's "bidirectional connections with most of the brain". Because of the insula's role in sensory and cognitive function, its impairment "has been linked with cognitive impairment across all neuropsychological domains", including verbal and working memory.

Social cognition, also commonly found to be impaired in SZ, can be broadly defined as "how people think about themselves and others in the social world". Penn et al. (2008) identify three domains of social cognition in SZ, as 1) emotional perception, 2) Theory of Mind, and 3) attributional style. In 2014, Pinkham et al. enumerated four domains of social cognition based on the Social Cognition Psychometric Evaluation (SCOPE) study. These were "emotion processing, social perception, theory of mind/mental state attribution, and attributional style/bias"; the authors also added the domains of "social metacognition and social reciprocity". The SCOPE study was a step toward establishing a more concrete means with which to measure social deficits occurring in SZ patients. The capacity to function socially was measured by how a patient could read facial and vocal expression (emotional processing), an ability to read social cues and social context (social perception), to understand the mind of others (theory of mind), to understand/interpret social events (attributional style/bias), to be aware of one's thoughts (social metacognition), and the capacity to share and exist mutually with others (social reciprocity). (See Pinkham et al., 2014: Table 1.) More recently, three of these domains—attributional bias, emotion processing, and theory of mind—have been proposed as domains to assess in order to rapidly identify social deficits, in the brief battery-SCOPE (Halverson, 2022). Overall, these domains assess the degree to which a SZ patient might be able to read and understand another person and their tendency to ascribe paranoid versus pronoid intentions to others.

2. Methods

In this selective review, we focused on controlled studies of structural and functional abnormalities of the insula in SZ, and their clinical correlates. The search excluded uncontrolled studies because studies using a control group had more of a chance of reducing confounders and were therefore considered more reliable.

2.1. Search criteria

The article selection was based on a systematic search that used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) method (Fig. 1). The search syntax was applied to Pubmed and was as follows: "(schizophrenia) AND (insula*) AND (clinical correla*)". Articles were screened according to date, language, and article type. They were written in English, with publication date spanning the last decade (2011−2021). When article types were limited to "Clinical Trial", "Controlled Clinical Trial", and "Randomized Controlled Trial", only seven articles fit the search criteria. As a result, the article type was expanded to include articles with Research Support from the American Recovery and Reinvestment Act, N.I.H. (both extramural and intramural), Non-U.S. Gov't, U.S. Gov't (Non-P.H.S.), U.S. Gov't (P.H.S.), and U.S. Gov't. The search was conducted in July 2021.

2.2. Inclusion and exclusion criteria

This search through Pubmed yielded 70 articles. The exclusion criteria were as follows, leaving 49 studies that met our inclusion criteria:

- Meta-analyses were excluded (1).
- 13 reports that did not use patients diagnosed with SZ were excluded (2 focused on Functional Neurological Disorder; 1 on anorexia; 4 on Major Depressive Disorder/depression; 1 on Autism; 1 used patients diagnosed with schizotypal personality traits). 1 paper dealt with nicotine addiction; 1 with ketamine. 1 focused on empathy; 1 focused on the amygdala.
- 6 other publications were excluded for not having a control group.

[2] See also Nieuwenhuys, 2012, who provides an extensive summary of insular functions drawn from insular studies up to 2012; and Benarroch, 2019, who reviews clinical correlations of insular dysfunction.

[3] Specifically, the CON participates in top-down control on a "longer time scale than the FPN [fronto-parietal network]" (Tu et al., 2012).

Table 1
Overview of findings related to the insula and cognition.

Author	Sample size	Imaging	Main findings involving Insula (with p value)
Kumari et al.	Patients = 56 (1+ positive symptom) HC = 28 ("treatment as usual")	fMRI	—decreased activation of INS after CBT to seeing angry and fearful expressions ($p < .005$)
He et al.	Patients = 115 (FES) HC = 113	fMRI	—functional connectivity b/w left INS and posterior cingulate cortex positively correlated with "factors positive" ($p = .025$); excited/activation ($p = .022$); RVP sustained attention ($p = .02$)
Lindner et al.	Patients = 36 HC = 40	fMRI	—reduced INS activation to microexpression (left: $p = .002$; right = 0.011) —SZ same response as HC in macroexp —reduced INS activation with microexpression positively correlated with social loneliness ($p = .002$) in SZ v. HC —INS response to micro- and macro expressions of disgust negatively correlated with agreeableness (masked disgust v. neutral; $p < .00001$) (unmasked disgust v. neutral; $p = .003$)
van der Meer et al.	Patients = 20 non-affected siblings = 20 HC = 20	fMRI	—hypoactivation in INS (and other areas) in SZ v. HC when reappraising negative pictures ($p < .001$)
Liao et al.	Patients = 93 HC = 99	MRI (VBM)	—GMV decrease in bilateral IC ($p < .05$) —GMV in left IC positively correlated with processing speed ($p < .05$)
Emami et al.	Patients = 66 HC = 33	MRI	—low IS had thinner right INS v. HC ($p < .05$) —low IS had thinner right INS cortex than patients with high IS ($p < .05$)
Massey et al.	Patients = 41 HC = 46	MRI	—patients had cortical thinning in INS (and other areas) ($p < .05$) and impaired cognitive empathy ($p < .01$)
Liu et al.	Patients = 48 FEP (adolescent-onset) HC = 31	rs fMRI	—decreased interhemispheric coordination within STG/INS correlated with processing speed deficit (STG/INS versus TMT-A [$p = .002$] and versus BASC-SC [$p = .043$]) —AOS had lower VMHC values in INS (and other areas) ($p < .000$)
Tian et al.	Patients = 49 HC = 52	fMRI cluster analysis	—right and left AI smaller in SZ ($p < .001$); PI larger ($p < .001$) —differentiation reduced in right ($p = .0038$) and left (0.002) INS —in SZ, AI less connected to bilateral ACC, SMA, paracingulate cortex, SFG ($p = .0118$) and frontal/central operculum ($p = .0035$) —PI less connected to bilateral STG, planum temporale, Heschl's gyrus, MTG, parietal/central operculum ($p = .0091$); also other regions ($p = .0018$) —no significance in laterality —lower INS connectivity to ACC/SMA and STG means poorer cognitive performance, longer illness duration, more severe psychosis ($p = .03$)
Fan et al.	Patients = 19 HC = 17	fMRI during WM task (VBM)	decreased functional activation in INS
Sheffield et al.	Patients = 191 HC = 196		—in SZ, subregions are less connected to each other and more connected to other regions —reduced dorsal AI connectivity correlated with worse cognitive function ($p = .014$)

Key: ACC = anterior cingulate cortex; AI = anterior insula; AOS = adolescent-onset SZ; BASC-SC=Brief Assessment of Cognition in Schizophrenia-Symbol Coding; FESZ/FEP = first episode psychosis; fMRI = functional MRI; GMV = gray matter volume; HC = healthy control; IC = insular cortex; INS = insula; IS = insight into symptoms; MTG = middle temporal gyrus; PI = posterior insula; RVP = rapid visual information processing; SFG = superior frontal gyrus; SMA = supplementary motor area; STG = superior temporal gyrus; SZ = schizophrenia; TMT-A = Trail-Making Task A; VBM = voxel-based morphometry; VMHC = voxel-mirrored homotopic connectivity; WM = working memory.

4. 2 reports were excluded because they discussed the insula's physiological role in taste and touch, not psychiatric symptoms.

3. Results

Some of these studies exclusively examined the insula, whereas others found changes in other anatomical regions in addition to the insula. We further selected studies that focused on cognitive deficits occurring in patients with insular pathology, which yielded 11 studies. Key findings from these studies related to the insula are shown in Table 1 and described below.

Liu et al. (2018)'s study examined the functional connectivity between hemispheres in adolescent-onset SZ patients using voxel-mirrored homotopic connectivity (VMHC). They found lower connectivity/VMHC values in areas including the superior temporal gyrus and insula. The study measured cognition in SZ using the Trail-Making Test: Part A (a measure of processing speed) and the Brief Assessment of Cognition in Schizophrenia: Symbol Coding (among other tests). They correlated poor TMTA performance with decreased STG/insular VMHC.

Liao et al. (2015) examined gray matter volume (GMV) in paralimbic structures of the brain; they found a decrease in GMV in both the right and left insular cortex. Processing speed (cognition) was assessed using the Digit Symbol Substitution Test. The GMV in the left insular cortex was positively correlated with processing speed, meaning that more volume loss correlated with cognitive deficits.

Fan et al. (2019) assessed brain performance in SZ patients during a working memory task of varying difficulty. There were four different levels of difficulty defined by having to memorize four, five, six, or seven digits, respectively. The task included three phases: encoding, maintenance, and retrieval. They identified decreased activation of the insula during the working memory task (specifically maintenance phase) in patients compared to healthy controls, corresponding to a decrease in GMV in patients. There was a statistically significant difference between the two groups during the maintenance phase when the task load was 4, 5, and 6.

Massey et al. (2017) substantiated previous studies that identified the anterior insula as an "empathy-related neural region", a site responsible for social cognitive, specifically empathy. In patients with SZ, they found statistically significant cortical thinning in the insula and also less empathy. In the control group, higher performance on the cognitive empathy task (the Emotional Perspective-Taking task)

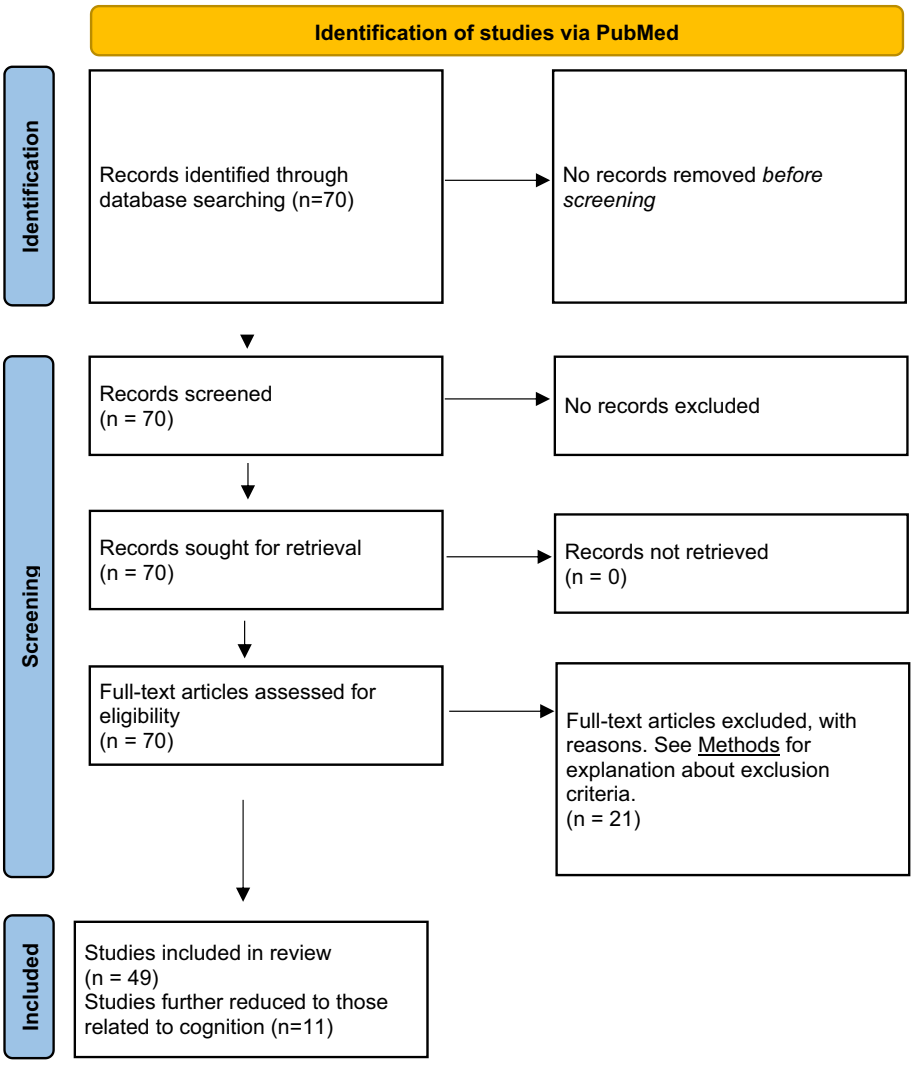

Fig. 1. PRISMA flow diagram
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: https://doi.org/10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

correlated to a thicker bilateral insula; there was not a statistically significant correlation in the SZ group.

Emami et al. (2016) found thinning in the right insular cortex in patients with SZ with poor insight, as compared to healthy controls and patients with SZ and good insight. Insight was measured using the Scale to Assess Insight-Expanded. Insight specifically refers to insight into symptoms, not insight into illness or need for treatment. Anosognosia was therefore associated with right insula abnormalities. Those with poor insight also had more positive symptoms (hallucinations, delusions).

Tian et al. (2019) explored the differences in functional connectivity in SZ patients, namely whether the insula's connections differed from control groups' insulae. They found that a reduced functional connectivity between the posterior insula and the language/auditory cortex was associated with cognitive impairment and poor social functioning (as well as longer duration of illness and negative symptoms).

Sheffield et al. (2020) examined how subregions of the insula were connected, and how aberrant connection might result in specific symptoms of SZ. Cognition was assessed using Screen for Cognitive Impairment in Psychiatry (SCIP), with functional connectivity measured by fMRI. The SZs' posterior insular were more connected to some brain regions (for example, the frontal eye fields) and less connected to others (prefrontal cortex). The reduced connectivity of the dAI was correlated to worse cognitive function (as measured by SCIP score).

He et al. (2013) examined the left insula and its role in the DMN, finding increased connectivity. The DMN is activated at rest and turns off during cognitive tasks; it is "implicated in endogenously generated thought, self-referential activities, monitoring and inner speech (REF)". In SZ, the DMN is "on" more, contributing to more attention to self and introspection. There is concomitant antagonism between the DMN and the task positive network, with the DMN being more deactivated than normal when doing a task. A deficit in rapid visual information processing, measuring sustained attention, correlated with the DMN functional connectivity between the left insula and the posterior cingulate cortex.

Lindner et al. (2014)'s study looked at the insula's activation during social tasks, specifically how well social cognition functioned when viewing macro and micro-expressions of disgust. In the past, studies had found that SZ felt more disgust and were more socially rejected (i.e., they experienced disgust from others). The subjects were assessed using a "passive viewing paradigm" and the facial stimuli was form the Karolinska Directed Emotional Faces catalogue. The lower a SZ patient scored on the agreeableness test (from the 5-factor personality questionnaire NEO-FFI), the more bilateral insula activation there was to covert disgust. Agreeableness was also negatively correlated with bilateral insular activation when looking at overt disgust versus neutral expressions. Overall, this suggested worse social cognition.

Van der Meer et al. (2014) measured activation during an emotional regulation task to test whether a SZ brain would be more or less activated than a sibling or healthy control when observing a picture

generating negative affect (with pictures from the International Affective Picture System). The result revealed hypo-activation in the insula (among other areas) when reappraising the negative picture as compared to healthy controls, with siblings also having hypo-activation.

Kumari et al. (2011) were investigating cognitive behavioral therapy as a treatment for SZ patients, and measured responses to different facial affects. CBT was able to decrease the insula's response to seeing angry and fearful expressions.

4. Discussion

These studies implicate abnormalities in insular structure and function within the cognitive domain of SZ, highlighting the insula's contribution to cognitive deficits, and insular pathology as a potentially useful biomarker and a critical component to the assessment and clinical care of SZ.

Fan et al. (2019)'s finding of GMV reduction in the insula confirmed a frequently cited fMRI finding in SZ patients in many studies. Studies that found morphological changes such as reduced GMV and cortical thinning in the insula were consistent with studies outside of this literature review. (See, for example, Shepherd et al., 2012's meta-analysis that found a "medium-sized reduction of insula volume" bilaterally in chronic and first episode psychotic [FEP] patients compared to controls [$n = 945$; $p = .00001$]). More relevant to this review is their findings related to working memory deficits in SZ—specifically, a diminished capacity to adapt to the task as it become more difficult.

Liu et al. (2018)'s findings confirmed previous studies that identified the importance of interhemispheric connections for cognitive function. This highlights the disruptive role of interhemispheric dysconnectivity in the pathology of SZ. This finding lends credence to the disconnection theory of SZ, where "dysfunctional integration is expressed […] as abnormal *functional connectivity*" that leads to clinical symptoms (Friston and Frith, 1995). Liu et al.'s findings are also clinically significant, given that they analyzed an adolescent-onset cohort, suggesting that lower connectivity could be connected to early-onset SZ. Similarly, Massey et al. (2017) propose that empathetic deficits were not only a function of GMV and density loss, but rather deficits that involved white matter and connectivity. Therefore, instead of viewing empathetic deficits as isolated cortical deficits, they encourage viewing it within the context of a disrupted network.

Tian and Sheffield's studies showed how disruptions to the insula represented disruptions in functional connectivity, and how reduced connectivity related to deficits in cognitive function. He et al. also examined the insula's role in networks—the DMN, a network related to cognitive tasks—and found a correlation between the insula and attentional deficits. These findings highlight, with increased specificity, the role of the insula within brain networks and the impaired functioning that occurs as a result of disrupted networks.

Insular pathology gives rise to deficits that have prognostic and treatment-related importance. Because insight contributes to seeking care and adhering to treatment, Emami et al. (2016) notes the importance of being aware of insight deficits. In addition to emphasizing the insula's involvement in SZ pathology, Liao et al. (2015) confirm that processing speed is "one of the most impaired domains in schizophrenia […] and perhaps a potential endophenotype". Clinical insight, an ability to accurately assess the presence and extent of one's own symptomatology, is important for treatment goals and impairment might lead to more severe symptomatology. Medalia and Thysen (2010) further delineate the importance of understanding both clinical symptoms and neurocognitive symptoms, meaning "attention, memory and executive functioning". The study found that fewer patients had insight into neurocognitive deficits compared to clinical symptoms. More recently, Mervis et al. (2022) have described the insight paradox, which also implicates good insight as "a barrier to health" insofar as a patient may self-isolate or feel shame about their disorder. Bowie et al. (2007) assessed "everyday real-world functioning" in SZ patients by comparing self-reported appraisals of functioning with more objective case manager reports. in addition to being able to accurately assess (versus over- or under-estimate) their quality of life, social skills, clinical symptoms, neuropsychiatric performance. Accurate self-assessment was associated with the best social skills; inaccurate assessment included under-estimators, with better cognition and with depression, and over-estimators, with deficits in cognition and function (Bowie et al., 2007). A daily ecological study of 102 people with SZ (compared to bipolar patients) divided up these patients into "never sad" and "sometimes sad" based on self-report. The "never sad" group over-endorsed their abilities across several domains, including work skills, and interpersonal and cognitive functioning. The never sad group differed from the sometimes sad group, revealing a reduced ability to self-appraise within SZ itself (Jones et al., 2021). Overall, the symptomatic manifestations of insular dysfunction provide valuable insight into SZ's variable manifestations.

Lindner et al. (2014), van der Meer et al. (2014), and Kumari et al. (2011) all examined impaired social cognition in SZ patients, with their work supporting previous studies' findings of impairment in ability to read and assess emotions in the self and other, and deviations from "normal" responses to emotions. Van der Meer and Kumari both identified insular hypoactivation during social appraisal tasks. These findings provide insight into the ways in which SZ patients assess their social environment—particularly assessing faces of others. Of particular interest is van der Meer et al.'s finding that the unaffected sibling had hypoactivation in their insula as well. These studies build upon previous research that examined the involvement of the insula in reading and appraising emotion, such as in facial expressions and reactions, and relative deficits in SZ patients in completing specific social appraisal tasks. Wylie and Tregellas (2010) reviewed the insular pathology in SZ for the preceding 15 years and summarized facial affect studies in which the insula was involved. The insula showed an increased response when viewing disgusted, angry, and fearful faces (see Table 1 in their review for a list of these studies), responding "abnormally", sometimes with hypoactivation and sometimes with hyperactivation. Further studies might be done examining the relationship between disrupted cognition and positive and negative symptoms.

This literature review has several limitations. It represents subjective assessments. The studies varied in terms of patient populations and sample sizes, but we tried to use controlled studies in order to include credible findings. Because SZ is a heterogenous syndrome, different studies had variability in patient composition and inconsistencies in findings. This review was selective, not systematic, and intended to provide an overview of studies conducted over a decade period, with additional exclusionary criteria outlined in the Methods section, assessing the insula's multi-faceted role in SZ. Furthermore, our search criteria was limited and yielded a small sample of studies overall, that was further pared down to 11 studies that we considered to be related to neurocognition and social cognition in the insula.

5. Conclusions

The heterogenous functions of the insula and the far-reaching effects of its dysfunction and its role in the clinical phenotype of SZ is being increasingly investigated and appreciated. This review set out to briefly evaluate the findings of controlled studies conducted over a decade-long period in order to identify areas in which further research is warranted.

Overall abnormalities of the insula structures and functions, postulated to be of neurodevelopmental etiology, appear to have a key role in generating clinically significant symptoms of SZ, including several cognitive functions. Recognizing the insula's role in these symptoms could lead to targeted interventions and perhaps using insular hypoplasia as an early biomarker for susceptibility to SZ.

Declaration of competing interest

The authors, S.G. and H.N., have no competing interests to declare.

References

Alcauter, S., Lin, W., Keith Smith, J., Gilmore, J.H., Gao, W., 2015. Consistent anterior–posterior segregation of the insula during the first 2 years of life. Cereb. Cortex 25, 1176–1187.

Benarroch, E.E., 2019. Insular cortex: functional complexity and clinical correlations. Neurology 93, 932–938.

Boucher, O., Rouleau, I., Lassonde, M., Lepore, F., Bouthillier, A., Nguyen, D.K., 2015. Social information processing following resection of the insular cortex. Neuropsychologia 71, 1–10.

Bowie, C.R., Twamley, E.W., Anderson, H., Halpern, B., Patterson, T.L., Harvey, P.D., 2007. Self-assessment of functional status in schizophrenia. J. Psychiatr. Res. 41, 1012–1018.

Cloutman, L.L., Binney, R.J., Drakesmith, M., Parker, G.J., Ralph, M.A.L., 2012. The variation of function across the human insula mirrors its patterns of structural connectivity: evidence from in vivo probabilistic tractography. NeuroImage 59, 3514–3521.

Coste, C.P., Kleinschmidt, A., 2016. Cingulo-opercular network activity maintains alertness. NeuroImage 128, 264–272.

Craig, A.D., 2009. How do you feel–now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10, 58–70.

Emami, S., Guimond, S., Chakravarty, M.M., Lepage, M., 2016. Cortical thickness and low insight into symptoms in enduring schizophrenia. Schizophr. Res. 170, 66–72.

Fan, F.M., Xiang, H., Wen, Y., Zhao, Y.L., Zhu, X.L., Wang, Y.H., et al., 2019. Brain abnormalities in different phases of working memory in schizophrenia: an integrative multi-modal MRI study. J. Nerv. Ment. Dis. 207, 760–767.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome. Clin. Neurosci. 3 (2), 89–97.

Gasquoine, P.G., 2014. Contributions of the insula to cognition and emotion. Neuropsychol. Rev. 24, 77–87.

Halverson, T.F., 2022. Brief battery of the social cognition psychometric evaluation study (BB-SCOPE): development and validation in schizophrenia spectrum disorders. J. Psychiatr. Res. 150, 307–316.

He, Z., Deng, W., Li, M., Chen, Z., Jiang, L., Wang, Q., et al., 2013. Aberrant intrinsic brain activity and cognitive deficit in first-episode treatment-naive patients with schizophrenia. Psychol. Med. 43, 769–780.

Jones, S.E., Moore, R.C., Depp, C.A., Ackerman, R.A., Pinkham, A.E., Harvey, P.D., 2021. Daily ecological momentary assessments of happy and sad moods in people with schizophrenia and bipolar disorders: what do participants who are never sad think about their activities and abilities? Schizophr. Res. Cogn. 26, 100202.

Kasai, K., Shenton, M.E., Salisbury, D.F., Onitsuka, T., Toner, S.K., Yurgelun-Todd, D., et al., 2003. Differences and similarities in insular and temporal pole MRI gray matter volume abnormalities in first-episode schizophrenia and affective psychosis. Arch. Gen. Psychiatry 60, 1069–1077.

Kumari, V., Fannon, D., Peters, E.R., Ffytche, D.H., Sumich, A.L., Premkumar, P., et al., 2011. Neural changes following cognitive behaviour therapy for psychosis: a longitudinal study. Brain 134, 2396–2407.

Kurth, F., Zilles, K., Fox, P.T., Laird, A.R., Eickhoff, S.B., 2010. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct. Funct. 214, 519–534.

Li, X.B., Wang, L.B., Xiong, Y.B., Bo, Q.J., He, F., Li, F., et al., 2019. Altered resting-state functional connectivity of the insula in individuals with clinical high-risk and patients with first-episode schizophrenia. Psychiatry Res. 282, 112608.

Liao, J., Yan, H., Liu, Q., Yan, J., Zhang, L., Jiang, S., et al., 2015. Reduced paralimbic system gray matter volume in schizophrenia: correlations with clinical variables, symptomatology and cognitive function. J. Psychiatr. Res. 65, 80–86.

Lindner, C., Dannlowski, U., Walhöfer, K., Rödiger, M., Maisch, B., Bauer, J., et al., 2014. Social alienation in schizophrenia patients: association with insula responsiveness to facial expressions of disgust. PLoS One 9, e85014.

Liu, Y., Guo, W., Zhang, Y., Lv, L., Hu, F., Wu, R., et al., 2018. Decreased resting-state interhemispheric functional connectivity correlated with neurocognitive deficits in drug-naive first-episode adolescent-onset schizophrenia. Int. J. Neuropsychopharmacol. 21, 33–41.

Massey, S.H., Stern, D., Alden, E.C., Petersen, J.E., Cobia, D.J., Wang, L., et al., 2017. Cortical thickness of neural substrates supporting cognitive empathy in individuals with schizophrenia. Schizophr. Res. 179, 119–124.

Medalia, A., Thysen, J., 2010. A comparison of insight into clinical symptoms versus insight into neuro-cognitive symptoms in schizophrenia. Schizophr. Res. 118 (1-3), 134–139.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667.

Mervis, J.E., Vohs, J.L., Lysaker, P.H., 2022. An update on clinical insight, cognitive insight, and introspective accuracy in schizophrenia-spectrum disorders: symptoms, cognition, and treatment. Expert. Rev. Neurother. 22 (3), 245–255.

Namkung, H., Kim, S.H., Sawa, A., 2017. The insula: an underestimated brain area in clinical neuroscience, psychiatry, and neurology. Trends Neurosci. 40, 200–207.

Nieuwenhuys, R., 2012. The insular cortex: a review. Prog. Brain Res. 195, 123–163.

Nimchinsky, E.A., Gilissen, E., Allman, J.M., Perl, D.P., Erwin, J.M., Hof, P.R., 1999. A neuronal morphologic type unique to humans and great apes. Proc. Natl. Acad. Sci. 96, 5268–5273.

Penn, D.L., Sanna, L.J., Roberts, D.L., 2008. Social cognition in schizophrenia: an overview. Schizophr. Bull. 34, 408–411.

Pinkham, A.E., Penn, D.L., Green, M.F., Buck, B., Healey, K., Harvey, P.D., 2014. The social cognition psychometric evaluation study: results of the expert survey and RAND panel. Schizophr. Bull. 40 (4), 813–823.

Sheffield, J.M., Rogers, B.P., Blackford, J.U., Heckers, S., Woodward, N.D., 2020. Insula functional connectivity in schizophrenia. Schizophr. Res. 220, 69–77.

Sheffield, J.M., Huang, A.S., Rogers, B.P., Blackford, J.U., Heckers, S., Woodward, N.D., 2021. Insula sub-regions across the psychosis spectrum: morphology and clinical correlates. Transl. Psychiatry 11, 1–13.

Shepherd, A.M., Matheson, S.L., Laurens, K.R., Carr, V.J., Green, M.J., 2012. Systematic meta-analysis of insula volume in schizophrenia. Biol. Psychiatry 72, 775–784.

Shura, R.D., Hurley, R.A., Taber, K.H., 2014. Insular cortex: structural and functional neuroanatomy. J. Neuropsychiatry Clin. Neurosci. 26, iv–282.

Singer, T., Critchley, H.D., Preuschoff, K., 2009. A common role of insula in feelings, empathy and uncertainty. Trends Cogn. Sci. 13, 334–340.

Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc. Natl. Acad. Sci. 105, 12569–12574.

Tian, Y., Zalesky, A., Bousman, C., Everall, I., Pantelis, C., 2019. Insula functional connectivity in schizophrenia: subregions, gradients, and symptoms. Biol. Psychiatry 4, 399–408.

Tu, P.C., Hsieh, J.C., Li, C.T., Bai, Y.M., Su, T.P., 2012. Cortico-striatal disconnection within the cingulo-opercular network in schizophrenia revealed by intrinsic functional connectivity analysis: a resting fMRI study. NeuroImage 59, 238–247.

Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. Nat. Rev. Neurosci. 16, 55–61.

van der Meer, L., Swart, M., van der Velde, J., Pijnenborg, G., Wiersma, D., Bruggeman, R., 2014. Neural correlates of emotion regulation in patients with schizophrenia and non-affected siblings. PloS one 9, e99667.

Vingerhoets, W.A., Bloeman, O.J., Bakker, G., van Amelsvoort, T.A., 2013. Pharmacological interventions for the MATRICS cognitive domains in schizophrenia: what's the evidence? Front Psychiatry 4, 157.

Wylie, K.P., Tregellas, J.R., 2010. The role of the insula in schizophrenia. Schizophrenia Research 123, 93–104.

Wynford-Thomas, R., Powell, R., 2017. In: Navigating the Island of Reil: How to Understand the Insular Cortex, pp. 122–126.

Zanto, T.P., Gazzaley, A., 2013. Fronto-parietal network: flexible hub of cognitive control. Trends Cogn. Sci. 17, 602–603.