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Insula volumes in psychosis probands

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INSULA VOLUMES IN PSYCHOSIS PROBANDS

by

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DEDICATION

I would like to dedicate this work to my mentors, Dr. Keshavan and Dr. Elisabetta Del Re, my family, and my friends (especially Victor, Tammy, Eric, and Lana), all of whom have helped me in immeasurable ways throughout this process.

INSULA VOLUMES IN PSYCHOSIS PROBANDS

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ABSTRACT

Insula is postulated to be a critical cortical region with extensive cortico-limbic connections and is hypothesized to play a role in pain/auditory/facial affect processing and interoception. Morphological abnormalities in this region may contribute to schizophrenia (SZ), schizoaffective disorder (SAD), and psychotic Bipolar disorder (BDP) symptomatology. Previous studies of insula have led to somewhat inconsistent results. Few studies have separately examined the left and right insula's anterior and posterior components, which have distinct functional roles. This study will examine the morphological and cognitive changes which occur in psychosis within the left and right insula, bilateral insula, and anterior and posterior insula. Although exact localization of these deficits is inconsistent, we postulate that control groups will have greater volume, thickness, and local Gyrification Index (LGI) across all measures compared to psychosis groups, with greater reductions confined to the anterior insula since it is hypothesized to play a role in higher-order processing. Due to the hypothesized decrease in LGI in psychosis groups, we postulate to see the most significant correlations in LGI, supporting the view that decreases in gyrification correlate to decreases in cognitive abilities (Gautam et al., 2015; Park et al., 2021). T1-MPRAGE scans were obtained using 3T MRI scans. Insula measurements were extracted using FreeSurfer (FS) 7.1 in healthy controls (NC=935) and psychosis probands (SZ=481, SAD=383, BDP=381). FS measures were correlated with cognition (verbal memory (VM), verbal fluency (VF), digit sequencing

(DS), and symbol coding (SC)), symptomatology in SZ/SAD/BPD. P values < 0.05 adjusted for False Discovery Rate (FDR) were reported. Our observations suggest structural alterations in the insula, predominantly in volume, thickness, and LGI, across affective and non-affective psychotic disorders. Though we observed relations between the insula and cognitive measures, we did not see correlations with symptomatology. Future studies will examine further the relation between insular structure and socio-emotional and self-processing believed to be related to the anterior insula.

PREFACE

The basis for this research stems from the simple, yet unimaginable complex concept of exploring the unknown within ourselves. The brain is an organ we take for granted sometimes yet there is so much left to discover. As someone who loves puzzles, I find no greater pleasure and no more rewarding a task than being able to work on the puzzle of the brain.

I could not have done this without the support of Dr. Keshavan, Dr. Elisabetta Del Re, Victor, Tammy, Eric, and Lana who have guided me and aided me along the way. I have grown quite fond of this puzzle solving team I have become part of and am excited to see what the future holds.

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
ANOVA	Analysis of Variance
BACS	Brief Assessment of Cognition in Schizophrenia
BDP	Bipolar Disorder
BSNIP	Bipolar-Schizophrenia Network on Intermediate Phenotypes
CAS	Clinical Anxiety Scale
dAI	Dorsal anterior insula
DLPFC	Dorsolateral prefrontal cortex
DS	Digital Sequencing
eTIV	Estimated total intracranial volume
FDR	False Discovery Rate
fMRI	Functional Magnetic resonance imaging
FNC	Functional Connectivity
FS	Freesurfer
GAF	Global Assessment of Functioning
IRB	Institutional Review Board
LGI	Local Gyrification Index
MADRS	Montgomery-Asberg Depression Rating Scale
MRI	Magnetic resonance imaging
NC	Normal/Healthy Controls
PANSS	Positive and Negative Symptoms Scale

PARDIP	Psychosis and Affective Research Domains and Intermediate Phenotypes
PET	Positron emission tomography
PI	Posterior insula
POC	Piriform olfactory cortex
ROI	Region of interest
SAD	Schizoaffective Disorder
SES	Socio-Economic Status
SC	Symbol Coding
SCID	Structured Clinical Interview for DSM-IV
SMA	Supplementary motor area
SZ	Schizophrenia
vAI	Ventral anterior insula
VF	Verbal Fluency
VM	Verbal Memory
VTA	Ventral tegmental area
YMS	Young Mania Scale

INTRODUCTION

Background

Traditionally, the insula (**latin for island)**, or "Island of Reil," has been one of the least understood regions of the brain (Uddin et al., 2017). Located deep within the Sylvian Fissure, topographically covered by the fronto-orbital, fronto-parietal, and temporal lobe, this small and highly complex area that encompases 1% to 4% of the total cortical surface area. This region, nonetheless is of great clinical and research significance in its anatomical and functional implication in both disease and non-disease states (Isnard et al., 2004; Semendeferi & Damasio, 2000; Shelley & Trimble, 2004; Uddin et al., 2017). The insula is described as a pivotal corticolimbic structure covering the claustrum and the basal ganglia and is considered to be an integration cortex that plays a role in several functions including, sensorimotor integration, processing of visceral sensations, audition, language, olfaction, addiction, craving, motivation, and emotions such as anxiety, empathy, disgust, happiness, and pain, (Augustine, 1996; Ghaziri et al., 2018; Immordino-Yang & Singh, 2013; Sanjuan et al., 2007; Shelley & Trimble, 2004). Due to the complexity of the insula, previous studies have explored not only intrainsular connections but also the structural connectivity of the insular cortex, finding numerous connections with neighboring limbic and forebrain structures (Augustine, 1996; Ghaziri et al., 2018). In the context of insula function and connectivity, little is known about morphological changes that might occur in the insula, in people affected by neuropsychiatric disorders such as schizophrenia (SZ), schizoaffective disorder (SAD), and bipolar disorder (BDP). Although a growing area of both clinical

and research interest, there are no clear and concise answers to these questions, as published data is not consistent enough to provide a clear picture of insular abnormalities in mental disorders, especially psychosis. Few investigations have looked at the insular cortical regions as a whole as well as at the anterior and posterior components - all of which yield different and sometimes conflicting results of how insula morphological abnormalities correlate to the symptomatology of these disorders. This study aims to utilize a large sample size of psychosis patients to answer such questions by analyzing the insula in a broad sense of left and right insula and analyzing the insula bilaterally and the anterior and posterior components of the region. Given the current fragmented knowledge of the insula and its components, the present study was undertaken to utilize a large sample size of SZ, SAD, and BDP to replicate, test, and build on current findings in the field, finding a synthesis of fragmented data.

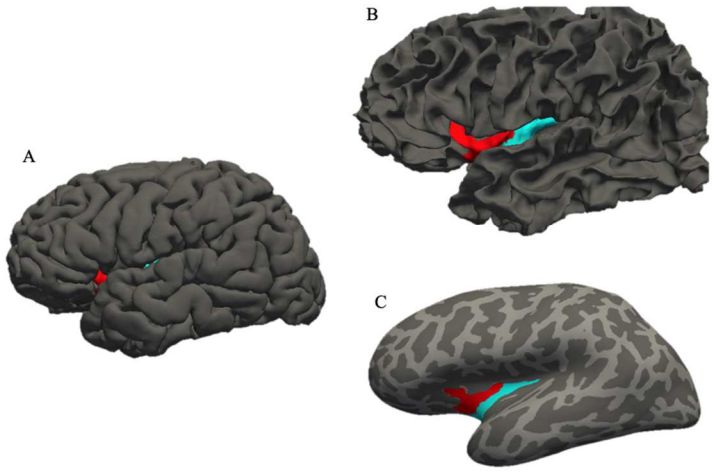

Figure 1: **Brain images generated using Freeview. Anterior insula marked as red. Posterior insula marked as blue.** (A) Healthy control brain with insula hidden in the Sylvian Fissure and covered by the fronto-orbital, fronto-parietal, and temporal lobe. (B) White matter brain with the insula and subregions. (C) Inflated brain with the insula and subregions visible.

Structure and Connectivity

Defined as Brodmann areas 13-16, the central sulcus divides the insula into the anterior region, composed of 3 to 4 short gyri, and a posterior region, composed of 2 long gyri (Brodmann, 1909; Flynn, 1999; Shelley & Trimble, 2004). An "observer-independent" activation-liklihood-estimation meta-analysis done on roughly 1,800 brains, performed by Kurth and colleagues (2010), further added to the speculation of the existence of four functionally distinct regions in the human insula: 1) a socio-emotional region in the anterior-ventral insula; 2) a central-olfactogustatory region 3) a cognitive anterior-dorsal region; and 4) a sensorimotor region located in the mid-posterior insula. (Kurth et al., 2010; Uddin et al., 2017). Additionally, a conjugation analysis across observed domains revealed that all tested functions overlapped in the anterior insula, which might indicate the anterior insula as a center for integration. Although these subdivisions most likely represent a generalization, this broad categorization may aid in the further understanding of intrainsular and insular connectivity with other brain regions.

Insula Organization and Architecture (cytoarchitecture, chemoarchitecture)

Though current knowledge of the microanatomical organization of the insula is fragmented, the insula can be further divided via its cytoarchitecture (the arrangement of cells in the tissues of the brain) and chemoarchitecture (distribution of neurotransmitters in the tissues of the brain). Early work on the insula also divides it into a dys-granular anterior region, that is a region containing few granule cells which are intrinsic excitatory neurons, and a granular posterior region, that is a region which has two layers of granular cells (Brodmann, 1909; Economo & Koskinas, 1925; Morel et al., 2013). Studies on the

monkey's insula, done by Mesulam and Mufson (1982), on which early human insula organization was based on, and on insula pathology in Alzheimer disease done by Bonthius and collogues (2005), proposed a similar cytoarchitectonic organization but with the addition of a third, granular region which was arranged around the piriform olfactory cortex (Poc) (Bonthius et al., 2005; Mesulam & Mufson, 1982; Morel et al., 2013). Further studies on the human insula done by Kurth and colleagues (2010), focused primarily on the posterior insula and described three distinct regions, two granular and one dys-granular (Kurth et al., 2010). Although out of scope for this investigation, it is essential to note that similar studies focusing on the anterior insula, also referred to as the fronto-insular cortex, found the presence of large spindle-shaped bipolar neurons in layer 5 in humans and great apes (Allman et al., 2010; Butti & Hof, 2010; Economo & Koskinas, 1925). These neurons are thought to play a role in social cognitive abilities, intuition, self-awareness, and emotional regulation and are affected in neuropsychiatric disorders with deficits in emotional functions (Allman et al., 2005; Butti et al., 2013; Cauda et al., 2014; E. J. Kim et al., 2012; Santos et al., 2011; Seeley, 2010; Stimpson et al., 2011).

Functional Connectivity

Most of the information regarding structural connectivity of the insula is derived from early seminal work done on nonhuman primates such as macaque monkeys (as reviewed in Uddin et al., 2017). These early studies investigated structural connectivity in macaques using invasive direct cortical stimulation techniques (Uddin et al., 2017). Later, investigative techniques evolved to utilize tracer studies that helped identify anterior-

posterior differences in insular sub-region connections, consistent with the wide variety of functions associated with the insula and its sub-regions (Ghaziri et al., 2017; Uddin et al., 2017). Comparative studies have shown that the insula has undergone a steady increase in size and the complexity of its organization throughout both hominid and primate evolution (Bauernfeind et al., 2013; Semendeferi & Damasio, 2000). Furthermore, it has been suggested that this increase in the size of some areas of the insula correlates with specialized functions such as social cognition/awareness and empathy (Allen et al., 2002; Kaas, 2013; Semendeferi & Damasio, 2000). In light of these latter structural connectivity studies, the structural connectivity of the human insula is much less familiar. A handful of studies reveal many cortical connections between the anterior insular cortex and the orbitofrontal cortex, the thalamus, the amygdala, the temporal pole, and the inferior and superior temporal gyri (Ghaziri et al., 2017; Uddin et al., 2017). The middle insular cortex was found to have connections with the precentral, postcentral, and supramarginal gyri, superior and inferior frontal gyri, the inferior and superior temporal gyri, and the parietal and orbitofrontal cortices (Ghaziri et al., 2017; Uddin et al., 2017). The posterior insular cortex was found to have connections with the precentral and postcentral gyri, the superior and inferior frontal gyri, the inferior and superior temporal gyri, the putamen, and the parietal cortex (Cerliani et al., 2012; Cloutman et al., 2012; Ghaziri et al., 2017, 2018; Jakab et al., 2012). The overall trend was that more anterior insular regions had a more significant number of connections to frontal cortical regions, while more posterior insular regions had a more significant number of connections to the parietal and cingulate cortices (Uddin et al., 2017).

Functional connectivity (FNC) studies, a method of temporal correlation between brain regions using blood-oxygen-level signals, are of growing clinical and research interest (Friston et al., 1994; Uddin et al., 2017). Functional studies in humans give evidence for three distinct sub-regions within the insula, a dorsal anterior (dAI), a ventral anterior insula (vAI), and a mid-posterior insula (PI), which is in line with earlier work (Cauda et al., 2011; Chang et al., 2013; Ghaziri et al., 2018; Nomi et al., 2016; Schmidt, 2018; Taylor et al., 2009; Uddin et al., 2017). The dAI is connected to frontal, dorsal ACC, dorsolateral prefrontal cortex (DLPFC), and parietal areas involved in control processes and tasks of higher cognition (Chang et al., 2013; Deen et al., 2011; Uddin et al., 2014). The vAI is connected to the limbic areas associated with emotions, such as the amygdala, ventral tegmental area (VTA), the posterolateral orbitofrontal cortex, the superior temporal sulcus, and is associated with autonomic function and chemosensation (Chang et al., 2013). The PI is most significantly connected to the anterior cingulate cortex (ACC), supplementary motor area (SMA), and regions associated with sensorimotor processing and language (Chang et al., 2013; Deen et al., 2011; Uddin et al., 2014).

Function

As mentioned previously, the insula is thought to be a pivotal corticolimbic structure that plays a role in various functions including, sensorimotor integration, processing of visceral sensations, interoception, pain, audition, language, olfaction, social cognition, addiction, craving, motivation, and emotions such as anxiety, empathy, disgust, and happiness (Augustine, 1996; Ghaziri et al., 2018; Immordino-Yang & Singh,

2013; Sanjuan et al., 2007; Shelley & Trimble, 2004). Although an oversimplification and a broad categorization, it is vital to understand the general and multifaceted role of the insula before breaking it down and exploring its anterior and posterior sub-regions.

Autonomic-visceral functions and interoceptive processing

With the advent of newer neuroimaging techniques such as tract-tracing studies and electro-cortical stimulation, the insula has been postulated to play a viscero- and somatosensory cortex role, receiving visceral afferent projections from all over the body (Stephani et al., 2011; Uddin et al., 2017). Direct stimulation of the human insula, specifically the anterior insula, elicits visceral or unpleasant feelings ranging from nausea and discomfort to motor responses which include vomiting (Farmer et al., 2018; Uddin et al., 2017). These autonomic-visceral functions of the insula are further supported by fMRI and human stimulation data, some of which implicate the ventral part of the anterior insula as a crucial region for these processes (Immordino-Yang & Singh, 2013; Karnath et al., 2005; Khalsa et al., 2009; Rolls, 2016). These reports conflict with other results, which, although utilizing a very small sample size of people, posit that visceral/somatosensory symptoms are restricted to the posterior insula while the anterior does not produce any clinical responses (Stephani et al., 2011). In regards to the insular sub-regions specifically, Craig proposed a posterior-to-anterior progression of visceral information in the insula, where more primitive signals are first represented posteriorly, then abstracted, and then finally refined and integrated into perceptual maps, in the anterior insula, depicting the state of the organism (Craig, 2002, 2009; Namkung et al., 2017; Uddin et al., 2017)

Beyond somatosensory and visceral processing, the visceral afferent projections mentioned above play a broad role and are responsible for conveying the body's interoceptive information, i.e., the sense of the physiological condition of the body (Tayah et al., 2013; Tran The et al., 2021; Uddin et al., 2017). This concept is further supported by studies that report that activation of the anterior insular cortex is associated with increased interoceptive attention and that lesions in this area lead to decreased interoceptive discrimination accuracy and sensitivity(Craig, 2009; Xingchao Wang et al., 2019). Moreover, fMRI studies from Critchley and colleagues, Kong and colleagues, Lovero and colleagues, and Singer and colleagues demonstrate the insula's response to the perception of physiological states such as heart palpitations and skin conductance, thermal pain, light touch, and pain induced electrically, respectively (Critchley et al., 2002, 2004; Kong et al., 2006; Lovero et al., 2009; Singer et al., 2004; Tran The et al., 2021; Wylie & Tregellas, 2010). The conclusion was that the insula is activated in processing each of these alterations to bodily physiological states. This evidence supports the concept of the insula as an interoceptive processor.

Nociceptive and thermal functions

In general, the insula seems to have high involvement as both a thermosensory cortex and a somatosensory cortex, especially regarding pain (Baier et al., 2014; Craig et al., 2000; Farmer et al., 2018; LaBar, 2010; Papoiu, 2016; Uddin et al., 2017). Regarding thermosensory functions of the insula, Craig and colleagues, by employing PET imaging of cerebral blood flow in a sample of health subjects to examine changes in brain activity relating to the intensity of graded cooling stimuli, found that intensity of graded cooling

correlated to activity in the middle/posterior insula and not to activity of parietal somatosensory regions, indicating that the insula acts both as a nociceptive and a thermo-sensory cortex (Craig et al., 2000; Uddin et al., 2017). A study done by Brooks and colleagues echoed these results using fMRI indicating activation of the posterior insula after heat stimulation of the skin (Brooks et al., 2002). Further studies have shown that the posterior insula receives sensory input from the secondary somatosensorial cortices, which are integrated within the anterior insula to produce a subjective evaluation of the emotional elements of pain (Coghill, 2009; Craig, 2009; Garcia-Larrea et al., 2010; Haukvik et al., 2013; Ong et al., 2019; Segerdahl et al., 2015; Tran The et al., 2021). These pain evaluations are accomplished by anterior insular cortical connections with the limbic system and the prefrontal cortex (Augustine, 1996; Haukvik et al., 2013; Tran The et al., 2021). Essentially, these two sub-regions work in a complementary fashion, with the posterior insula processing the experience of pain while the anterior insula evaluates the intensity of the pain. In this way, these two regions become activated when a subject feels the subjective pain sensation (Kong et al., 2006; Tran The et al., 2021).

Language, audition, gustatory, and olfaction functions

The insula's language, audition, and gustatory functions are related to the extensive connectivity of the insula. Lesion studies have shown a relationship between insular lesions and aphasia, suggesting that the left anterior insula is part of the language system (Penfield & Faulk, 1955). This is in contract with other studies which show that aphasia might be due to a secondary disruption of association fibers surrounding the insula (Naqvi & Bechara, 1955; Shuren, 1993). With the advent of newer analytical techniques, recent studies find that the left anterior insula is prominently involved with the motor production of speech (Ackermann & Riecker, 2004; Naqvi & Bechara, 2009).

Auditory information, in line with Craig's view of posterior-to-anterior progression in stimuli processing, arrives at the posterior insula directly from primary auditory cortices, where it is passed onto the anterior insula for higher-order processing (Flynn et al., 1999; Craig, 2009; Mesulam & Mufson, 1982; Naqvi & Bechara, 2009; Wylie & Tregellas, 2010). Supporting the insula's involvement in audition, studies of patients with strokes affecting the insula showed that patients suffered from a range of symptoms, including auditory verbal agnosia (i.e., decreased sensitivity/perception to sound) and hyperacusis (i.e., increased sensitivity to sound) following the event (Bamiou et al., 2006; Boucher et al., 2015; Karimi et al., 2020; Spreen et al., 1965). Distortions and hallucinations have also been reported following intracerebral electrode stimulation of the posterior insula (Nguyen et al., 2009; Uddin et al., 2017).

Although chiefly studied in primates and rodents, the anterior insula's role in gustation relates to its connections to the primary taste cortex (Kadohisa et al., 2005;

Plata-Salaman et al., 1992, 1993, 1995; Plata-Salamán et al., 1996; Pritchard et al., 1986; Rolls, 2016; Verhagen et al., 2004). In light of these studies, human lesion studies have been conflicted as some studies show that lesions in the posterior insula seem to affect taste recognition, while others postulate that the primary gustatory area in humans is in the anterior insula (Cereda et al., 2002; Naqvi & Bechara, 2009; Pritchard et al., 1999; Uddin et al., 2017). Such conflicting results show that these same regions are also involved in attention (to taste), oral somatosensory functions, and other higher-order processes related to gustatory functions (Seubert et al., 2013; Uddin et al., 2017). Lastly, similar to audition, electrical stimulation of the mid-insular cortex or short insular gyri may cause gustatory hallucinations, presenting as a strange and unpleasant taste (Uddin et al., 2017).

There is not much known about the insula's involvement in olfaction. Although neuroimaging studies consistently show insular activation, specifically the left posterior insula following a stroke, by olfactory stimulation and other neighboring regions, little is known about the insula's direct involvement in processing olfactory stimuli (Papathanasiou et al., 2006; Uddin et al., 2017; Zu Eulenburg et al., 2012).

Empathy and emotions

Empathy refers to the ability to share and perceive others' affective states, implying an affective, sensorimotor, and cognitive component (Fan et al., 2011; Gu et al., 2012; Mutschler et al., 2013; Singer et al., 2009). The affective component especially may implicate interception and interoceptive awareness in order to understand the emotional states of others. (Ernst et al., 2013; Fukushima et al., 2011; Heydrich et al.,

2020; Mutschler et al., 2013). Just as the anterior insula was posited to play a crucial role in interoception, numerous studies have also suggested the anterior insula's role in empathy and the understanding of emotional states (Craig, 2009; Critchley et al., 2004; Fan et al., 2011; Gu et al., 2012; Mutschler et al., 2013; Paulus & Stein, 2006; Xingchao Wang et al., 2019; Ying et al., 2018). One meta-analysis in particular done by Fan et al. demonstrated that the right anterior insula was more frequently involved in the affective-perception form of empathy while the left insula was active in affective-perception and cognitive-evaluative forms (Fan et al., 2011). Additionally, a meta-analysis done by Mutschler et al. further expanded on these insights and found not only that the gray matter density of the left dorsal anterior insula correlated with empathy but also that the location of this region is such that it overlaps and is situated between functional systems that are involved with cognition, motor tasks, pain, and emotion (Mutschler et al., 2013). The anterior insula's implication in empathy is further supported by lesion studies that reveal that focal anterior insular lesions result in decreased empathetic pain processing (Gu et al., 2012).

Regarding emotions, Damasio speculated that the right insula and somatosensory cortices are responsible for the subjective feeling of emotion due to their role in mapping bodily states during the expression of emotion (AR Damasio, 1999; Naqvi & Bechara, 2009). Although yielding incongruent results in terms of location, further studies build on this idea, focus on the specific emotions of desire, love, and disgust, specifically that of physical disgust (Cacioppo et al., 2012; Antonio Damasio, 2006; Uddin et al., 2017; Ying et al., 2018). A study done by Cacioppo et al. investigated the relationship between

sexual desire and love and found that the left posterior insula was activated by feelings such as sexual desire, while the anterior insula was activated by love (Cacioppo et al., 2012; Ying et al., 2018). This posterior-to-anterior pattern from desire to love follows Craig's proposed progression as the primary feeling of desire leads to the more abstract and complex representation that characterizes this desire, love (Cacioppo et al., 2012; Craig, 2009). Regarding the feeling of disgust, using intraoperative stimulation in conscious and alert patients undergoing neurosurgery, Damasio demonstrated how stimulation of the left insula altered the patient's ability to recognize facial expressions of various emotions, with the only significant outcome being that to the emotion of disgust (Antonio Damasio, 2006; Uddin et al., 2014). When considering all of these studies, the left insula seems to be strongly implicated in its role in empathy, interoceptive awareness, and affective and cognitive evaluations.

Moral judgement, decision making, urge processing

Interestingly enough, some of the studies which looked into disgust also investigated the role of the insula in moral judgment and moral disgust relative to pure disgust (Moll et al., 2005; Ying et al., 2018). The anterior insula was activated in various moral tasks, including processing easy moral dilemmas and challenging moral dilemmas, especially in the scenarios involving or affecting humanized victims. (Borg et al., 2008; Cooper et al., 2010; Greene et al., 2004; Kédia et al., 2008; Majdandžić et al., 2012; Ying et al., 2018). Contrary to these findings, some studies speculate that the insula is only involved in moral judgements and sensitive to norm violations in the scope of deontological judgement and is activated in care and justice cognition and the perception

of inequity (Cáceda et al., 2011; Fumagalli & Priori, 2012; Hsu et al., 2008; Huebner et al., 2009). Although the concept of morality and moral judgement is not defined by a single structure or region but by several circuits that make up a vastly complex process, the insula seems to be implicated as part of this process (Pascual et al., 2013).

Given the insula's numerous connections and its role in emotions, interoception, and judgment, it is likely to play a role in decision making. Unlike the previously defined roles, the insula's role in decision making is much less mapped out; however, studies still point to the activation of the insula in studies investigating anticipation of gain and loss and urge processing (Garavan, 2010; Knutson & Greer, 2008). Droutman and colleagues explored this topic by examining the four phases of decision making (focusing attention, evaluation, action, and outcome processing) in the scope of the insular and its subregions (Droutman et al., 2015). They determined that there is no single subregion responsible for a single phase, and instead explored the role each component plays (Droutman et al., 2015). Their investigation found that the dorsal anterior insula seems to be specialized for executive functioning and cognition and plays a role in each decision-making phase (Chang et al., 2013; Dosenbach et al., 2006; Droutman et al., 2015; Ploran et al., 2007; Tops & Boksem, 2011). Furthermore, this same region seems to form a salience network with the ACC, which helps identify the most homeostatically relevant stimuli and recruitment of the executive network (Dosenbach et al., 2006; Droutman et al., 2015; Menon & Uddin, 2010). Moreover, the dorsal anterior insula also plays a role during the evaluation phase in tracking arousal, risk, and urge processing (Droutman et al., 2015; Myrick et al., 2004; Paulus & Stein, 2006; Smith et al., 2009; Wu et al., 2012). During

the last phase, the action and outcome processing phase, the dorsal anterior insula is involved in choice as well as for deciding whether to act or not and processing error and harm prevention (Droutman et al., 2015; Harsay et al., 2012; Xue et al., 2010). On the other hand, the ventral dorsal insula is responsible for urge generation and monitoring of risk prediction error during the evaluation phase (Droutman et al., 2015; Engelmann et al., 2012; Myrick et al., 2004). Lastly, the posterior insula was found to be only involved in the evaluation phase, where it is involved in signaling homeostatic imbalances and urge generation -which is consistent with its role in sensorimotor processing (Droutman et al., 2015; Egan et al., 2003).

Interestingly enough, the ventral and posterior insula was also shown to play a crucial role in addiction, specifically both for cigarettes and the posterior for alcohol and cocaine (Engelmann et al., 2012; Garavan, 2010; Myrick et al., 2004; Tapert et al., 2004). A proposed mechanism behind this activation is when the drug stimulus is presented, its somatic marker is expressed by the dorsal anterior insula, which is represented in the ventral anterior insula (Droutman et al., 2015; Naqvi et al., 2014). This then initiates the physical sensation of craving processed by the posterior insula, which implies that the posterior insula is necessary for registering the reinforcement value of drugs (Droutman et al., 2015; Naqvi et al., 2014).

Insula and Psychosis

Involvement of the insula and its subregions is common in studies focusing on psychosis spectrum disorders (SZ, SAD) and BDP, a mood disorder, yet its exact contribution to disease pathology remains a mystery. Although morphological

irregularities in this region may contribute to psychosis symptomatology, previous studies of the insula are relatively few and inconsistent as few previous studies have examined the insula and its subregions separately (Crespo-Facorro et al., 2000; Makris et al., 2006; McDonald et al., 2005; Shepherd et al., 2012; Takahashi et al., 2009). Being a region with extensive connections to cortical and limbic regions, many of the deficits seen in psychosis implicate these regions and thus may implicate the insula as a crucial structure for the observed pathology (Wylie & Tregellas, 2010).

Schizophrenia – Structural changes

Morphological reductions in cortical thickness, gray matter volume, and abnormalities in gyrification have been observed within the insula in schizophrenia. The most consistent finding has been gray matter volume reductions, although the location of these deficits has been inconsistent, with studies finding deficits in the anterior and posterior insula, right posterior, left insula, and bilaterally (Arasappa et al., 2012; Ellison-Wright et al., 2008; Fornito et al., 2009; Honea et al., 2005; Kasai et al., 2003; J. J. Kim et al., 2003; Makris et al., 2006; McDonald et al., 2005; Saze et al., 2007; Sheffield et al., 2021). Additionally, not all studies have found deficits in gray matter, bilateral or otherwise (Crespo-Facorro et al., 2000; Honea et al., 2005). While a meta-analysis done by Honea et al., 2005 observed deficits localized on the right, left, and bilaterally, other meta-analyses found more consistent bilateral deficits (Ellison-Wright et al., 2008; Fornito et al., 2009; Glahn et al., 2008). Lastly, although showing incongruent results, studies suggest that these insular gray matter volume deficits have a neurodevelopmental origin, as these deficits could have appeared at a relatively early age in schizophrenia

high risk youth (Brent et al., 2013; Tran The et al., 2021). Moreover, neurodevelopmental vulnerability brought on by volume deficits may present as a risk for psychosis spectrum disorders and is associated with symptomatology. (Sheffield et al., 2021)

Similar to the deficits in gray matter volume, although cortical thickness deficits and changes in gyrification may be present, these findings remain inconsistent, especially in studies about cortical thickness (Kuperberg et al., 2003; Matsuda & Ohi, 2018; Nesvåg et al., 2008; Palaniyappan & Liddle, 2012; Pham et al., 2021; Roiz-Santiáñez et al., 2010; Yan et al., 2019). One study conducted at the University of Iowa exploring the insular cortex morphology in schizophrenia observed that a reduction in both volume and the cortical surface of the left insula which was amplified by the severity of symptoms: the more severe the symptomatology, the more severe the deficits (Jang et al., 2006). These findings are not consistent however, as expressed by the previously mentioned studies.

Gyrification refers to the folds of the cerebral cortex, which has been hypothesized to play a role in cognitive functionality (Gautam et al., 2015; Park et al., 2021). Studies by Damme and colleagues observe gyrification to be stable over one year in youths at high clinical risk for psychosis (Damme et al., 2019; Sheffield et al., 2021). These findings suggest that abnormalities or deficits in gyrification reflect early developmental changes closely linked with neural connectivity patterns and may even contribute to early symptomatology in populations that may develop schizophrenia (Damme et al., 2019; Sheffield et al., 2018, 2021; Van Essen, 1997). Studies done by Pham and colleagues and Drobinin and colleagues found similar decreases in LGI in patients with first-episode schizophrenia and youths with psychotic symptoms, reflecting

early neurodevelopmental changes in morphology (Drobinin et al., 2020; Pham et al., 2021).

Schizophrenia – Symptomatology and pathology

Regarding symptomatology, some studies, such as Crespo-Facorro et al., Duggal et al., and Pressler et al., have found that both positive and negative symptoms were associated with deficits in gray matter volume while other studies have not (Crespo-Facorro et al., 2000, 2010; Duggal et al., 2005; Kasai et al., 2003; Pressler et al., 2005; Sheffield et al., 2021; Takahashi et al., 2005). Moreover, Shapleske and colleagues observed that bilateral deficits in gray matter volume were associated with hallucinations in schizophrenia (Shapleske et al., 2002). Additionally, these alterations may be present in never treated first episode schizophrenia patients suggesting that they may be present early in the illness (Jayakumar et al., 2005) and there may be a significant gender effect, being more prominent in females (Duggal et al., 2005). Giakoumatos and colleagues discovered that insular volume reductions may also be related to suicidal behavior (Giakoumatos et al., 2013). Again, it is essential to note that although these results may be inconsistent, they may help correlate changes in insular morphology to symptomatology and pathology of schizophrenia.

The pathological function of the insula in schizophrenia encompasses different affect and pain processes and disfunction in interoception or the perception of the self. As mentioned before, the insula plays a role in distinguishing facial expressions, especially that of disgust. Paralleling the symptoms of patients with insular lesions who experience difficulty recognizing facial expressions, so do patients with schizophrenia (Wylie &

Tregellas, 2010). Although responses to specific expressions may vary, the most profound difficulties lie in recognizing negative emotions such as disgust, sadness, fear, and anger are found to be most common (Bediou, Franck, et al., 2005; Bediou, Krolak-Salmon, et al., 2005; Leppänen et al., 2008; Schneider et al., 2006; Van't Wout et al., 2007). Furthermore, facial recognition test scores correlate with negative symptom severity, implying generalized cognitive deficits for recognition and processing facial information in schizophrenic patients (Gur et al., 2006; Martin et al., 2005; Sachs et al., 2004; Turetsky et al., 2007). Studies have also shown a decreased response in regions responsible for processing facial affect, including the medial prefrontal cortex, amygdala, and the anterior cingulate gyrus, all of which have extensive connections to the insula (Arce et al., 2008; Baas et al., 2008; Mesulam & Mufson, 1982; Morris et al., 1998; M. L. Phillips et al., 1997; Mary L. Phillips et al., 1999; Sprengelmeyer et al., 1998; Williams et al., 2007). Overall, it is the anterior insula that is implicated due to its role in evaluating emotions, predominantly negative emotions, and both patients with schizophrenia and patients with insular lesions present with difficulties evaluating emotional expressions (Carr et al., 2003; Schneider et al., 2006; Wylie & Tregellas, 2010).

Other disturbed processing types in schizophrenia are auditory affect processing, specifically that of evaluating emotional vocal expressions, pain processing, and the processing of emotional words (Sanjuan et al., 2007; Wylie & Tregellas, 2010). Prosody is the emotional aspect of speech, encompassing variations in rhythm, intonation, and stress, and deficits in prosody expression and perception are observed in schizophrenia (Edwards et al., 2002; Hoekert et al., 2007; Leitman et al., 2005; Pinheiro et al., 2013;

Ross et al., 2001; Wylie & Tregellas, 2010). Paralleling the findings of facial affect processing, these deficits in prosody perception were most profound in the discrimination of negative emotions (Bozikas et al., 2006; Edwards et al., 2001; Hoekert et al., 2007; Pijnenborg et al., 2007; Pinheiro et al., 2013). Both functional and lesions studies implicate the anterior insula in prosody processing, which resembles symptoms found in schizophrenia (Calder et al., 2000; Cancelliere & Kertesz, 1990; Shuren, 1993). Additionally, Sanjuan et al. discovered that the activity of the insula is enhanced in patients with schizophrenia when hearing emotional words compared to controls which further demonstrates the insula's role in emotional response and the impact that psychosis has on this region (Sanjuan et al., 2007). Regarding pain, pain insensitivity has been observed in patients with schizophrenia; however, despite any findings, no imaging studies have investigated the role of the insula in pain processing in schizophrenia (Wylie & Tregellas, 2010).

Insula pathology in schizophrenia is associated with poor perception of self and an overall difficulty attributing self-generated sensory stimuli (Wylie & Tregellas, 2010). While some studies implicate these symptoms to disturbances in the anterior insula, other studies point to the ventral premotor cortex and posterior insula as the regions that underlie deficits in self-other relationships and self-experience (Tran The et al., 2021; Wylie & Tregellas, 2010). To support the latter hypothesis, lesions studies in the posterior insula lead to a condition called somatoparaphrenia, which involves a disruption in a person's sense of self, as it relates to their body, where ownership of a limb is attributed to a different person (Wylie & Tregellas, 2010). Studies such as this suggest

that damage to the insula leads to disruptions of self, which mirrors schizophrenia symptomatology. Other body delusions in patients with schizophrenia show a decreased accuracy in recognizing their faces from faces of strangers, decreased perception of their bodies, and being independently alive or belonging to another person (Harrington et al., 1989; Irani et al., 2006; Kircher et al., 2007; Orbach et al., n.d.; Wylie & Tregellas, 2010).

Moreover, when experiencing hallucinations, patients with schizophrenia make more external attribution errors (Costafreda et al., 2008; Johns et al., 2001) which further implicate the insula as a crucial region in interoception that, when disrupted, leads to the misperception of the self, and in the case of hallucinations, being a distinct entity from the surrounding world (Wylie & Tregellas, 2010). This could be attributed to the insula and its vast processing connections that lead to confusion between internal and external sensory sources when disrupted. A similar idea proposed by Churchland posits that hallucinations result from of a blurring of boundaries between the self and the non-self (Churchland, 2002). Overall, given these findings, it is possible to hypothesize that the self and non-self attribution and disruption in interoception is related to a threshold phenomenon: that the insula, likely the anterior insula, which is the region posited to play a role in interoceptive processing, is too weak to identify sensory information as internal or external correctly (Shergill et al., 2000; Sommer et al., 2008; Wylie & Tregellas, 2010).

Schizoaffective Disorder – Structural changes

There have only been two voxel-based morphometry studies of schizoaffective disorder, both of which come from the same group. Ivleva and colleagues observed reductions in gray matter volume in the brain, not reductions specific to the insula, which were less extensive than those observed in schizophrenia (Amann et al., 2016; Ivleva et al., 2010, 2013). A systematic review of case-control studies done by Birur et al. found similar results, explaining that the lack of studies on schizoaffective disorder is due to it being most commonly grouped under schizophrenia and not being a distinct diagnostic category (Birur et al., 2017; Keshavan et al., 2011; Lake & Hurwitz, 2007).

Schizoaffective Disorder – Symptomatology and pathology

The lack of insight and research around schizoaffective disorder makes it one of the most misdiagnosed psychiatric disorders in clinical settings (Abrams & Arciniegas, 2021). The challenge in diagnosing this disorder is that the symptomatology shares criteria with other more prominent psychiatric disorders (Abrams & Arciniegas, 2021). Moreover, the two types of schizoaffective disorder, bipolar type and depressive type include symptoms of schizophrenia which further complicates and blurs its distinction as a unique classification (Keshavan et al., 2011).

Psychotic Bipolar Disorder – Structural changes

Observations in gray matter volume and gyrification of bipolar disorder differed from schizoaffective disorder and schizophrenia in that a reduction in these measures was rarely observed or observed only on frontotemporal cortical regions in bipolar disorder

(Amann et al., 2016; Birur et al., 2017; Ivleva et al., 2010; Sheffield et al., 2021). Although confirmed by a few studies, the result of observing no gray matter volume reduction in bipolar disorder is inconsistent. One meta-analysis done by Fusar-Poli et al. on gray matter volume loss in young subjects observed that subjects at enhanced clinical risk for psychosis showed reduced gray matter volume in the anterior insula (Fusar-Poli et al., 2011). However, a separate analysis by Yu et al. and Wang et al. found the most prominent decreases in gray matter volume in the right insula, right thalamus, and bilateral medial orbital frontal cortex, and only small regional clusters showing reduced volume in the left insula (Xiuli Wang et al., 2019; Yu et al., 2019). Wang further expanded on these findings and hypothesized that the group's findings suggest that abnormalities in the right insula could be structural pathological markers correlating to mood states (Xiuli Wang et al., 2019). Further supporting these volumetric findings, a voxel-wise meta-analysis done by Bora et al. found the most consistent reduction to gray matter volume in the right anterior insula, this following Craig's proposed anterior-posterior gradient (Bora et al., 2010; Craig, 2009). Other structural changes observed were decreases in cortical thickness, with a study done by Abe et al. confirming these findings (Abé et al., 2016).

Psychotic Bipolar Disorder – Symptomatology and pathology

The insula's involvement in various pathways causes any abnormalities in this region to have significant broad effects. The insula is one of the two major hubs of the salience network and is tasked with detecting changes in the external and internal environment and creating appropriate emotional responses to these changes (Maletic &

Raison, 2014). As such, disruption to the insula may explain the inability to modulate emotional response to changes in the environment, as seen in bipolar disorder (Maletic & Raison, 2014). Being a crucial limbic structure, elevated mood states seen in bipolar disorder may result in compromised regulation in regions such as the insula, manifesting as irritability, impulsivity, and emotional reactivity (Maletic & Raison, 2014). Moreover, regarding elevated insular activity, several studies have observed more significant responses to negative facial expressions limbic structures, such as the insula, which has been established as having a role in emotional processing (Hulvershorn et al., 2012; Ketter et al., 2001; Townsend & Altshuler, 2012). Overall, the involvement of the insula in bipolar disorder requires further attention. Unique insight on insular activation and morphological changes in psychosis spectrum disorders and mood disorders, such as bipolar disorder, may help differentiate between the different diagnostic groups.

With previous research showing a wide array of results across a variety of measures, this study will examine the morphological and cognitive changes which occur in SZ, SAD, and BDP within the left and right insula, bilateral insula, and anterior and posterior insula. Although exact localization of these deficits is inconsistent, we postulate that control groups will have greater volume, thickness, and LGI across all measures compared to proband groups, with greater reductions confined to the anterior insula since it is hypothesized to play a role in higher order processing. Due to the hypothesized decrease in LGI in proband groups, we postulate to see the most significant correlations in LGI with BACS cognition tests, supporting the view that decreases in gyrification correlate to decreases in cognitive abilities (Gautam et al., 2015; Park et al., 2021).

METHODS

Participants

This study utilized participants from the BSNIP1 (Bipolar-Schizophrenia Network on Intermediate Phenotypes), BSNIP2, and PARDIP (Psychosis and Affective Research Domains and Intermediate Phenotypes) studies. These studies were conducted through the collaboration of seven sites which include the: Beth Israel Deaconess Medical Center (Boston, MA); Olin Neuropsychiatry Research Center (Hartford, CT); University of Maryland (Baltimore, MD); University of Chicago (Chicago, IL); Wayne State University (Detroit, MI); University of Georgia (Athens, GA); and the University of Texas Southwestern Medical Center (Dallas, TX). All participants provided informed written consent and Institutional Review Board (IRB) approval was obtained from each site for the BSNIP1, BSNIP2, and PARDIP studies.

All participants were evaluated using a comprehensive battery including magnetic resonance imaging (MRI), electrophysiology, saccade, neuropsychological evaluations, clinical measures and, the Structured Clinical Interview for DSM-IV (SCID). The Hollingshead Four-Factor Index was used to measure socioeconomic status (SES). Handedness, illness duration, and the number of weeks since the first psychotic break, were also obtained.

Patients' inclusion criteria included were: Meeting the Axis I diagnoses for SZ, SAD, or BPD with psychotic features. None of the patients included in this study had any familial ties with other patients within the study. Further recruitment inclusion and

exclusion criteria are described in detail in a paper by Tamminga et al (Tamminga et al., 2013).

Cognitive and Clinical Measures

Prior to any tests utilizing the left and right insula volumes and their corresponding anterior and posterior regions, volumes were winsorized using R Studio to remove outliers and subjects without measures for these regions.

Trained and reliable raters performed all clinical assessments, and diagnoses were confirmed in consensus meetings led by senior clinicians. The Positive and Negative Symptoms Scale (PANSS) measured positive and negative symptoms and their severity via seven measures each (Kay et al., 1987). The Global Assessment of Functioning (GAF) scale was used to assess the impact of symptoms on day-to-day life (Hall, 1995). The Young Mania Scale (YMS) was used to measure mania severity (Young et al., 1978). Lastly, the Montgomery-Asberg Depression Rating Scale (MADRS) measured depression severity (Montgomery & Asberg, 1979). PANSS General Scale was used to measure patient psychopathology via 16 measures (Leucht et al., 2005). PANSS Total Scores were used to sum up the scores of the PANSS Scale and the PANSS General Scale, with the minimum score being 30 and the maximum being 210. Clinical Anxiety Scale (CAS) scores were used to measure participant anxiety levels (Snaith et al., 1982). Penn Emotion Recognition Task was used to determine facial emotion recognition (Kohler et al., 2003). Cognition (verbal memory (VM), verbal fluency (VF), digit sequencing (DS), and symbol coding (SC) was measured using Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). The VM task included list

learning, which involved patients being presented with a list of 15 words and asked to recall as many as possible. This procedure was repeated five times with two alternate forms. The VF task included category instances which involved a timed task where patients had to name as many words as possible within a presented category and a controlled oral word association test, which was another timed task involving patients having to generate as many words as possible that begin with a given letter. The DS task involved patients being given a cluster of numbers of increasing length, after which they were to order the numbers from lowest to highest. The SC task involved patients wrote numerals 1-9 as matches to symbols presented on a response sheet. Patients with psychosis were seen to score lower across all tasks.

Assessments were performed on the general probands group as well as the specific clinical diagnostic groups of SZ, SAD, and BDP. All clinical assessments were run on the left and right insula volumes and their anterior and posterior components. Area, thickness, and local gyrification index (LGI) measurements were also analyzed for the insular anterior and posterior components.

Image Processing

T1-MPRAGE scans were obtained using 3T MRI scans at each site. Automated brain segmentation was performed using FreeSurfer (FS) 7.1, and the Destrieux atlas was used to parcellate the anterior and posterior regions of both the left and right insula. For the bilateral measurements, volume measures were summed, while for thickness, the measures were averaged for the left and right anterior and posterior measures.

The final sample included a total of 2,180 participants, healthy controls (NC=935) and psychosis probands (SZ=481, SAD=383, BDP=381).

Statistical Analysis

All statistical analyses were performed using R 3.3. Independent chi-square tests or one-way analysis of variance (ANOVA) were performed to compare clinical and demographic data between groups. ANOVA was also used to test the moderating effects of sex, race, age, site, handedness, pt Hollingshead score, estimated total intracranial volume (eTIV), and of medications, specifically lithium and chlorpromazine. Most of the significant predictors were used for covarying all insular measures. Predictors such as pt hollscore, handedness, and medication, although significant, were omitted due to the lack of a complete set of responses for all the participants. Age, sex, race, T1 site, and eTIV had the most significant impact on insular measures and were used as covariates for the volumetric, thickness, and LGI measures. The clinical measure GAF did not covary for eTIV. The significance level was set to $p<0.05$. All P values < 0.05 adjusted using the Benjamini-Hochberg False Discovery Rate (FDR) were reported (Benjamini & Hochberg, 1995). Spearman correlations were performed in separate proband groups between clinical and insular measurements. The effect size was calculated using Cohen's d (denoted by "d"). BACS scores and insular measurements were z-transformed and winsorized to ± four standard deviation, with outliers being removed.

RESULTS

Demographics

Clinical and demographic information is summarized in Table 1. There was a significant difference between diagnostic groups for age (p=.009), sex (p=<.001), race (p=<.001), site (p=<.001), pt hollscore (p=<.001), med daily cpz (p=.003) and eTIV (p=.029). Race, site and pt hollscore were significant between all groups, but not for age, sex, med daily cpz, and eTIV

Table 1: Demographics

		NC (n=759)	SZ (n=481)	SAD (n=383)	BDP (n=381)	p value	Significant group comp.
6	Age (mean, SD)	36.116 (12.228)	36.551 (12.252)	38.543 (11.869)	36.118 (11.986)	0.009	SAD-NC**, SAD-SZ*, BDP-SAD**
3	Sex (M/F)	323/436	307/174	177/206	141/240	<0.001	SZ-NC***, SAD-SZ***, BDP-SZ***, BDP-SAD*
2	Race (CA/AA/OTH)	420/233/106	186/238/57	175/151/57	269/80/32	<0.001	SZ-NC***, SAD-NC**, BDP-NC***, SAD-SZ*, BDP-SZ***, BDP-SAD***
4	T1_site Baltimore Boston 2 Boston 4 Boston 5 Chicago 1 Chicago 2 Dallas 1 Dallas 2 Detroit Georgia 1 Hartford 2 Hartford 3 Hartford 4	55 51 23 18 69 98 91 54 41 99 57 10 93	66 7 9 36 41 59 22 48 39 40 37 0 77	25 4 14 14 24 60 39 39 7 40 29 0 88	29 24 2 8 56 70 50 14 33 18 27 17 33	<0.001	SZ-NC***, SAD-NC***, BDP-NC***, SAD-SZ***, BDP-SZ***, BDP-SAD***
5	handedness (R/L/B)	451/288/12	255/208/13	236/134/12	211/162/7	0.058	SZ-NC*, SAD-SZ*
10	pt_hollscore (mean, SD)	34.552 (13.436)	50.333 (14.677)	46.63 (14.223)	41.161 (14.486)	<0.001	SZ-NC***, SAD-NC***, BDP-NC***, SAD-SZ***, BDP-SZ***, BDP-SAD***
8	MED_DAILYCPZ (mean, SD)	NA (NA)	600.054 (736.253)	559.227 (886.719)	379.77 (464.505)	0.003	BDP-SZ***, BDP-SAD*
9	MED_LITHIUM_totaldosesum (mean, SD)	NA (NA)	844.643 (453.86)	966.279 (583.275)	1000.269 (594.455)	0.45	
7	EstimatedTotalIntraCranialVol (mean, SD)	1450459.651 (187424.134)	1458982.022 (201498.91)	1421256.756 (194530.43)	1439837.079 (199633.156)	0.029	SAD-NC*, SAD-SZ**

Group Comparisons

Right versus Left

Volume. Proband versus NC comparisons showed that the left and right insula volume were both equally and significant lower in probands compared to NCs (d=-0.26). Similarly, each of the diagnostic group had significantly lower volume than NC. SZ-NC showed a slightly more significant reduction in the left insula (d=-0.23) than the right (d=-0.2). SAD-NC showed a considerably greater reduction in the right insula (d=-0.34) than the left (d=-0.29). BDP-NC yielded equal reductions in the left and right insula (d=-0.23). There were no findings between proband groups.

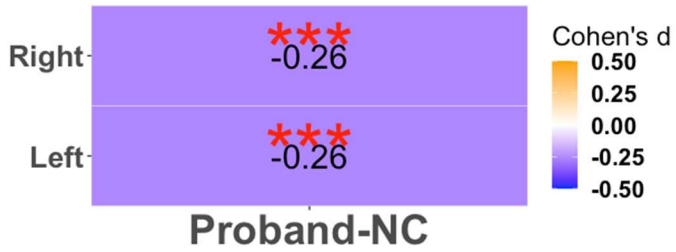

Figure 2: Probands vs Controls: Volume

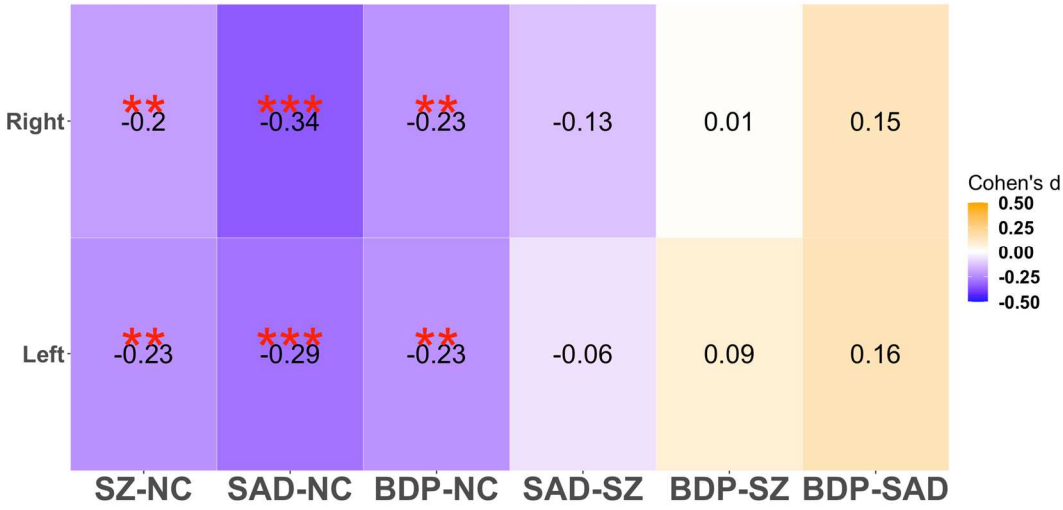

Figure 3: Insula Volumes across diagnostic groups

Cortical Thickness (CT). Proband versus NC comparisons showed the CT of the left and right insula was significantly reduced in probands compared to NCs (left: d=-0.28; right: d=-0.3). Diagnostic group versus NC comparisons yielded a more significant reduction in right CT in SZ and SAD versus NC groups (d=-0.36 and d=-0.3, respectively) but not the BDP-NC group. Between-group findings indicated significance differences between BDP-SZ and BDP-SAD groups with a larger right insular CT in BDP for both groups (d=.27 and d=.28, respectively).

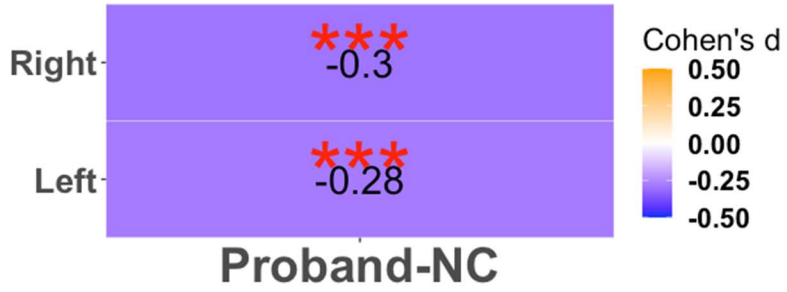

Figure 4: Probands versus Controls: Thickness

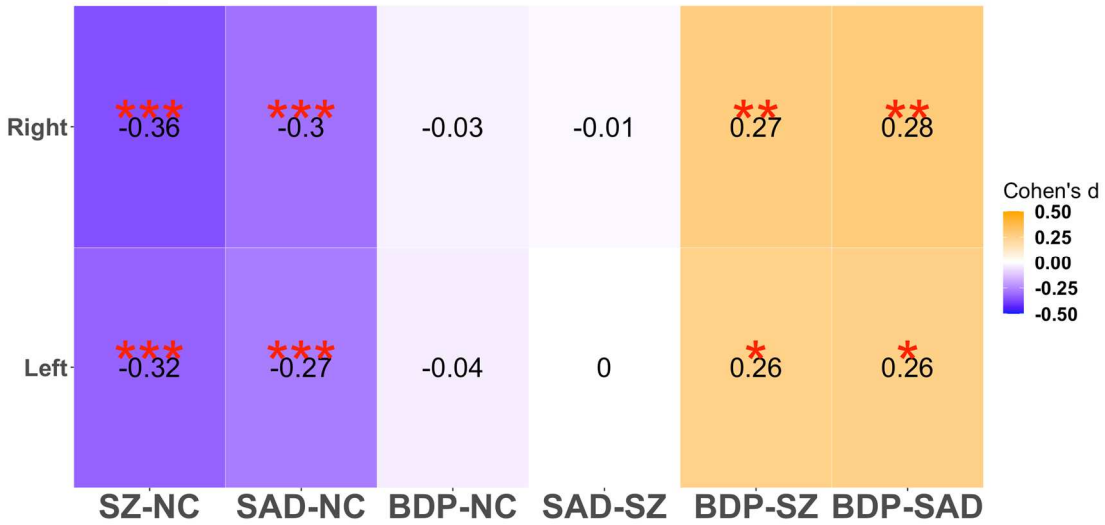

Figure 5: Insula Thickness across diagnostic groups

Local Gyrification Index (LGI). Proband versus NC comparisons showed that the LGI of the left and right insula was greater in the NCs (left: d=-0.18; right: d=-0.25). Diagnostic group versus NC comparison yielded significant reductions in LGI compared to NCs in only in the SAD-NC group comparison for the right insula (d=-0.21).

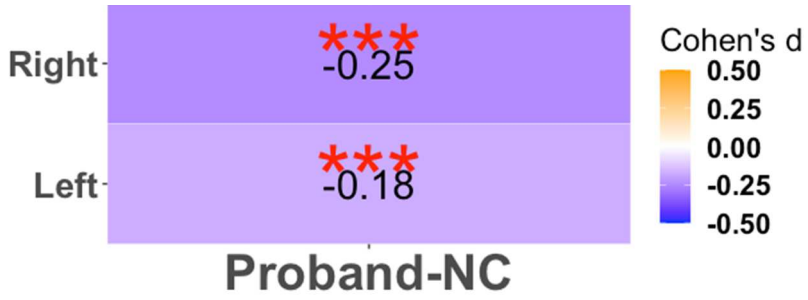

Figure 6: Probands versus Controls: LGI

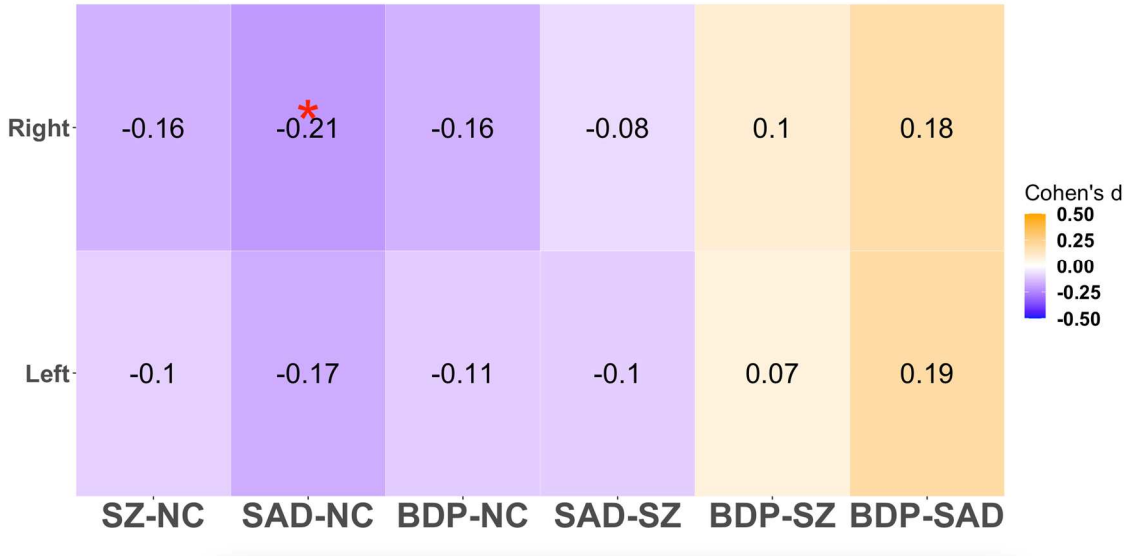

Figure 7: Insula LGI across diagnostic groups

Bilateral

Volume. Diagnostic group versus NC comparisons, showed that bilateral anterior insula volume was greater in the NCs (d=-0.22 for SZ; d=-0.31 for SAD; d=-0.18 for BDP). The SZ-NC group, also had larger bilateral posterior volume (d=-0.17). No between group comparisons were found.

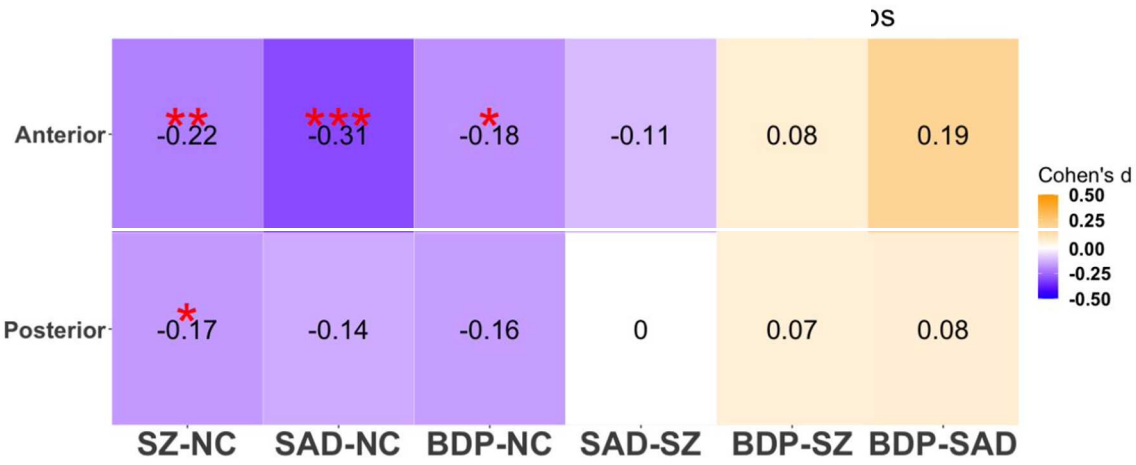

Figure 8: Bilateral Insula Volume across diagnostic groups

CT. SZ and SAD versus NC comparisons yielded greater bilateral anterior insula compared to NCs (d=-0.22 and d=-0.21, respectively). BDP yielded reduced CT than

NCs (d=-0.19). Moreover, BDP was found to have greater bilateral anterior CT than SAD (d=0.22).

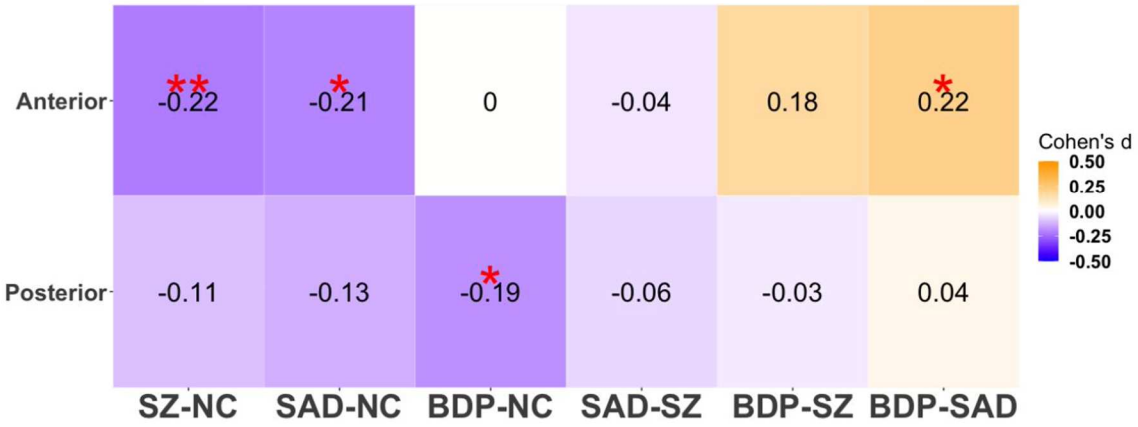

Figure 9: Bilateral Insula Thickness across diagnostic groups

LGI. SAD versus NC comparisons showed bilateral anterior insula was greater in the NCs (d=-0.21).

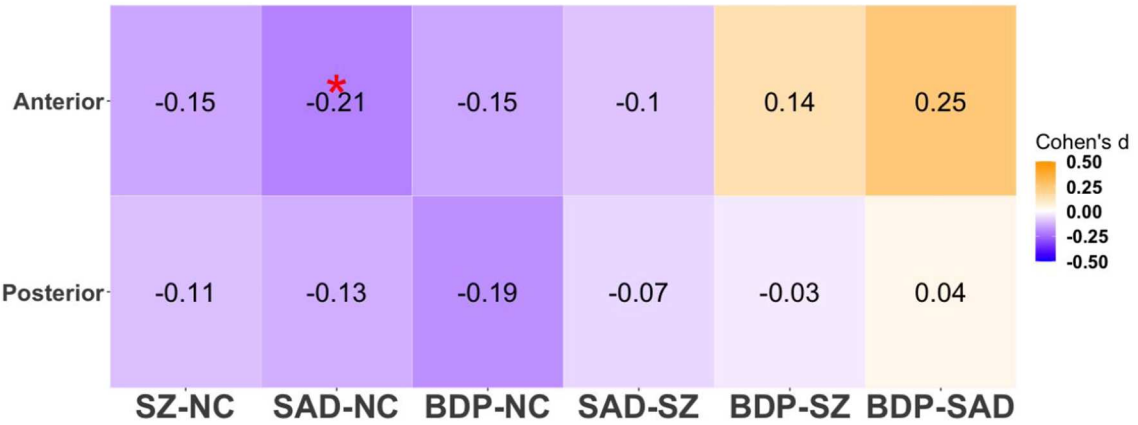

Figure 10: Bilateral Insula LGI across diagnostic groups

Anterior versus Posterior

Volume. Proband versus NC tests show greater volume reduction in left (d=-0.24) and right (d=-0.22) anterior than posterior insula (d=-0.16 for both). Diagnostic group versus NC comparisons showed that the right anterior insula volume was lower in SZ (d=-0.2) and SAD (d=-0.28) groups compared to NCs. The left anterior insula volume was also lower in SZ Z (d=-0.19), SAD (d=-0.28), and BDP (d=-0.19) compared to NCs. The right posterior insula volume was smaller in BDP (d=-0.19) compared to NC (d=-

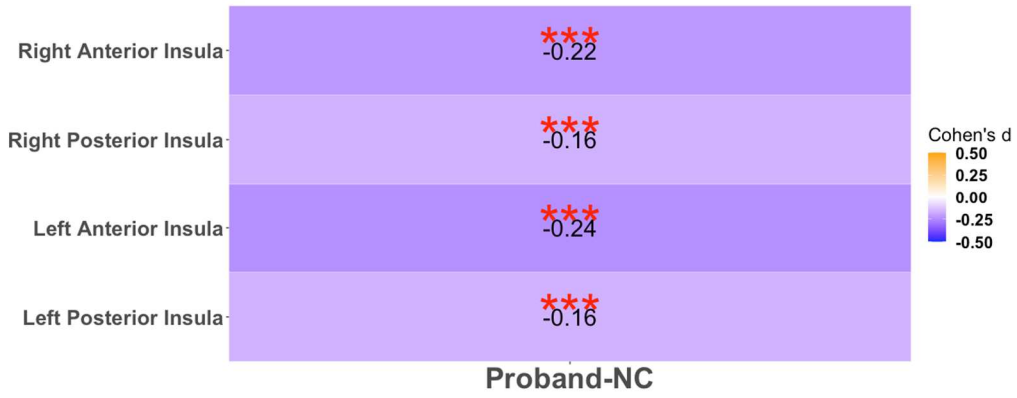

Figure 11: Probands vs Controls: Anterior/Posterior Volume

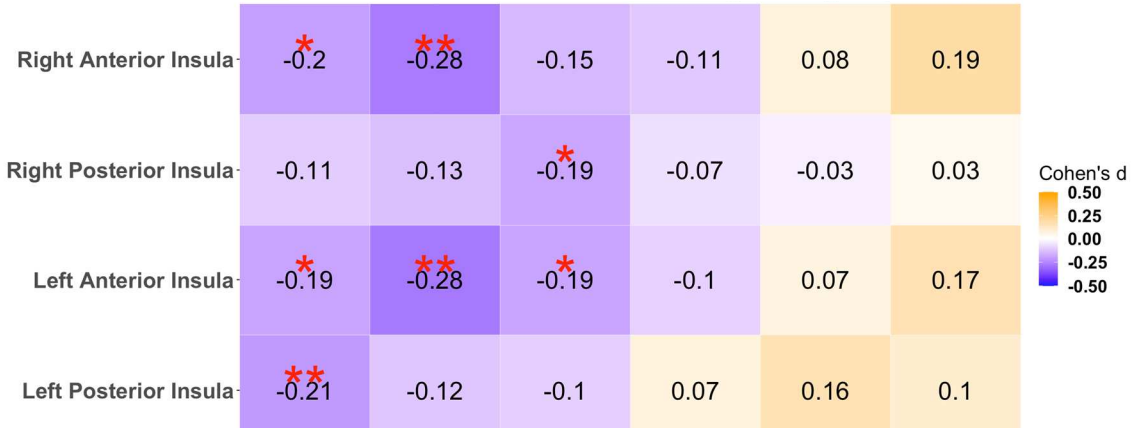

Figure 12: Anterior/Posterior Insula Volume across diagnostic group

.19); while the left posterior was smaller in SZ (d=-0.21) compared to NCs. No between-group differences were found.

CT. Proband versus NC tests show significant thickness reduction in left anterior (d=-0.22) and posterior (d=-0.18) insula more than the right anterior (d=-0.14) and posterior (d=-0.16) insula in probands compared to NCs. Diagnostic group versus NC comparisons showed that left anterior (d=-0.24) and left posterior (d=-0.23) insula thickness was greater in NCs than in SZ. SZ-NC group also showed greater NC thickness in the right posterior insula (d=-0.2). SAD-NC group showed greater NC thickness in the

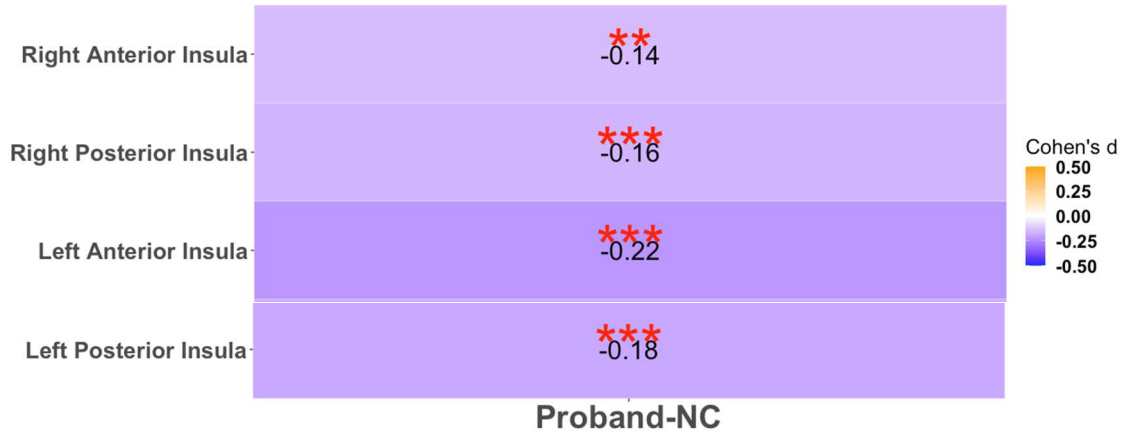

Figure 13: Probands versus Controls: Anterior/Posterior Thickness

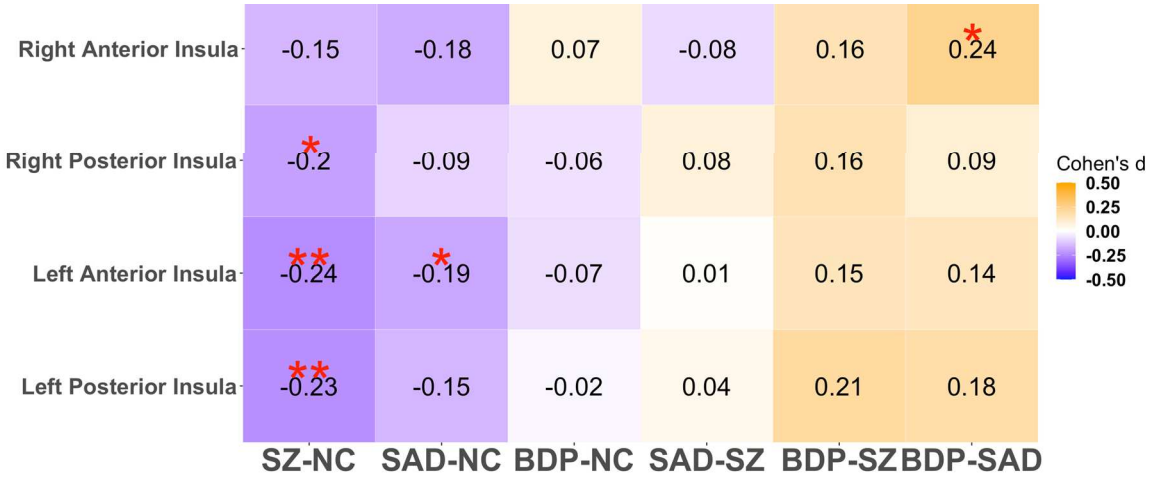

Figure 14: Anterior/Posterior Thickness across diagnostic group

left anterior insula (d=-0.19). Between-group differences were found in the BDP-SAD comparison, with BDP yielding a greater thickness in the right anterior insula than SAD (d=0.24).

LGI. Proband versus NC tests show that NCs had greater LGI in the right posterior (d=-0.24) and left anterior (d=-0.21) than their corresponding left posterior (d=-0.17) and right anterior (d=-0.2) measurements. Diagnostic group versus NC comparisons showed that right anterior (d=-0.2) LGI was greater in NCs in SZ. Right posterior insula yielded greater LGI in NCs in SZ (d=-0.18), SAD (d=-0.21), and BDP (d=-0.26) groups. Left anterior insula yielded greater LGI in NCs in SAD (d=-0.19), and greater left posterior LGI in BDP (d=-0.18). No between-group differences were found.

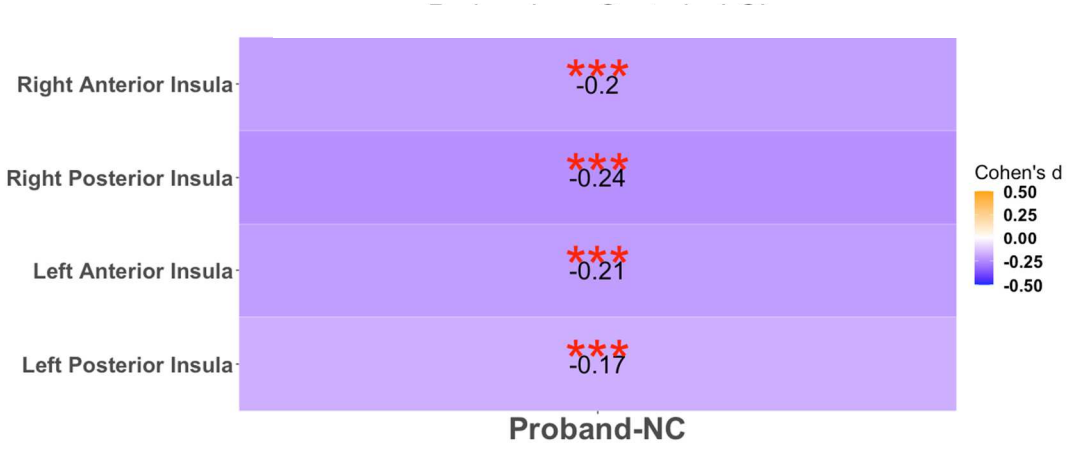

Figure 15: Probands versus Controls: LGI

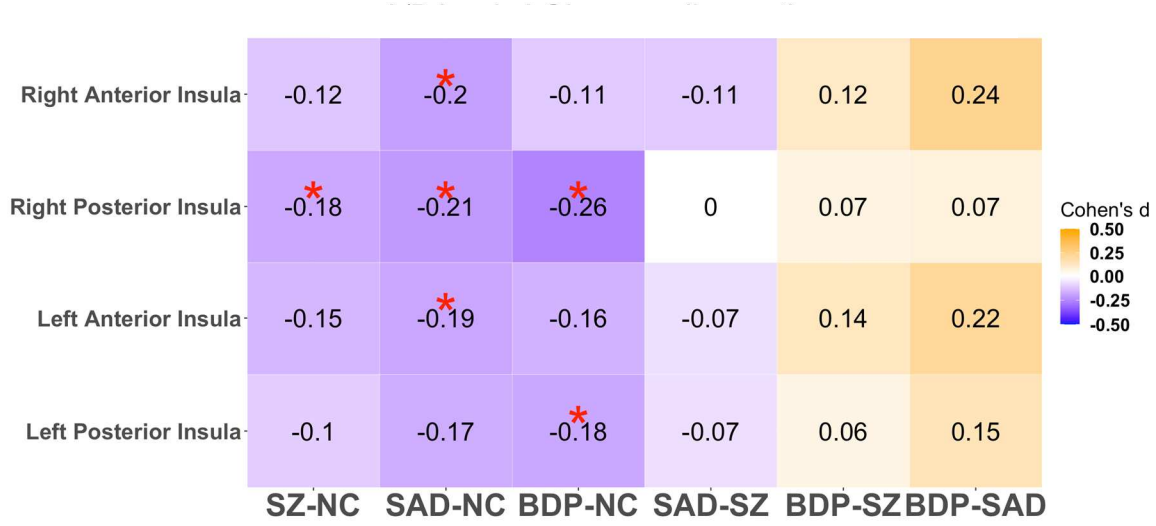

Figure 16: Anterior/Posterior Insula LGI across diagnostic group

Correlations with symptoms and cognition

No significant correlations were seen between insula and clinical measures/symptomatology, however, correlations between cognition and insula were found.

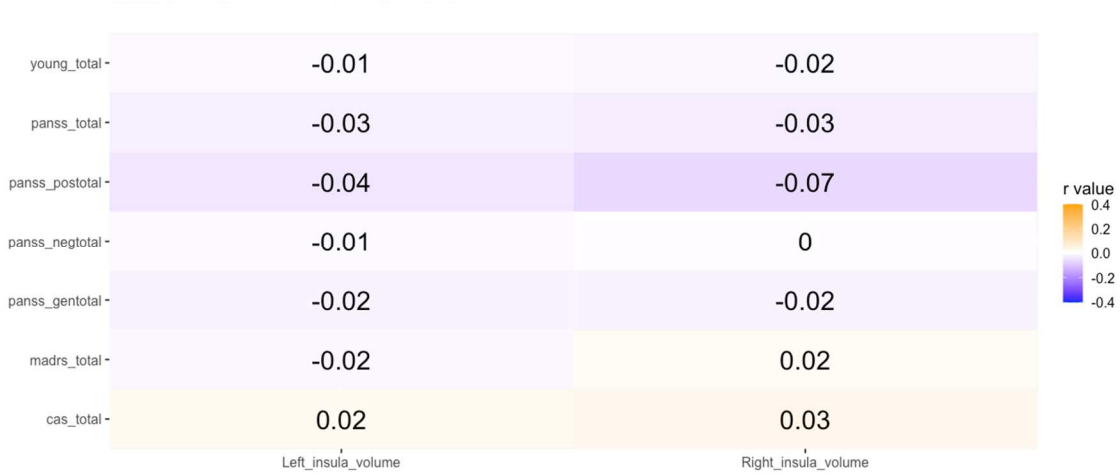

Figure 17: SZ Volume Symptomatology Correlations

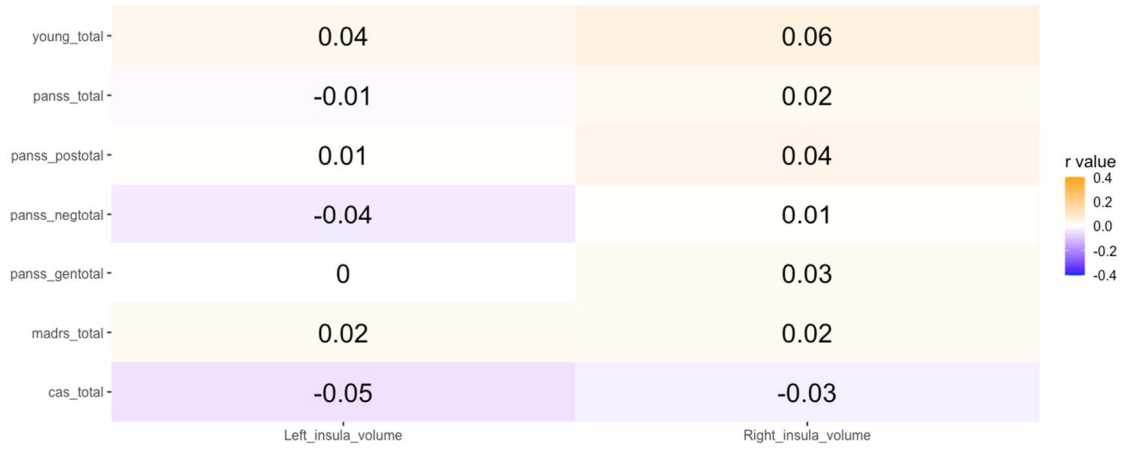

Figure 18: SAD Volume Symptomatology Correlations

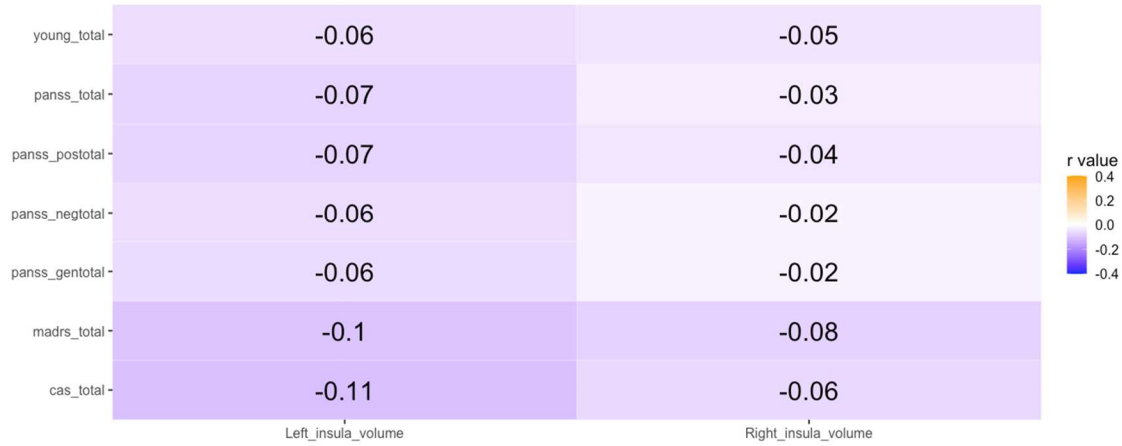

Figure 19: BDP Volume Symptomatology Correlations

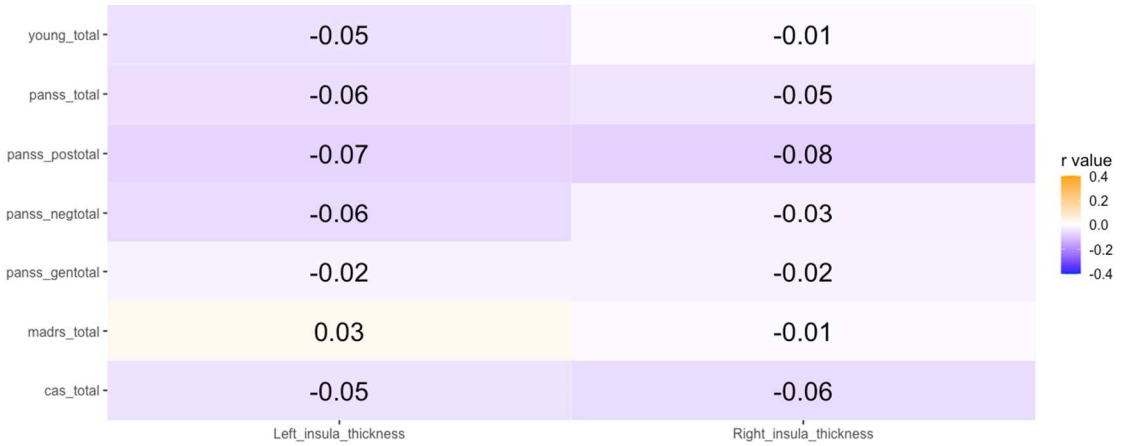

Figure 20: SZ Thickness Symptomatology Correlations

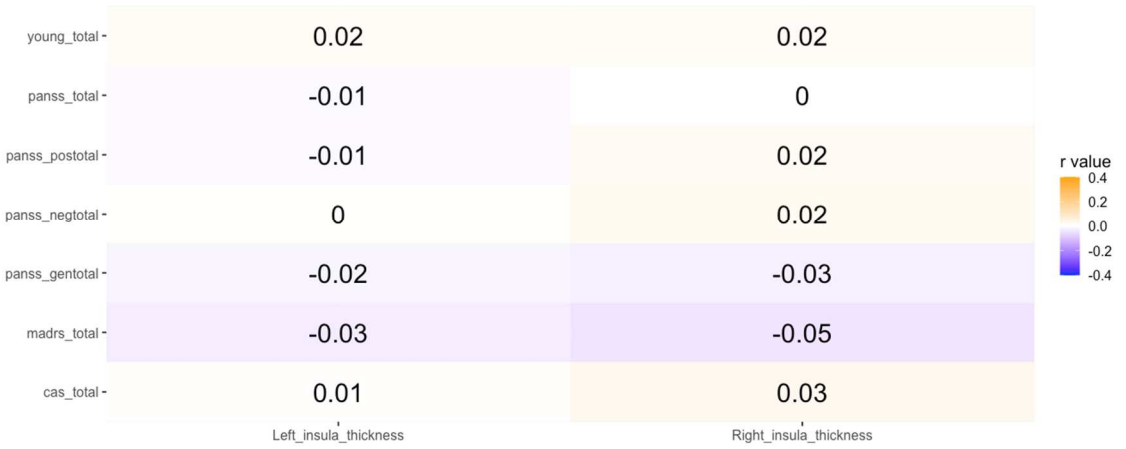

Figure 21: SAD Thickness Symptomatology Correlations

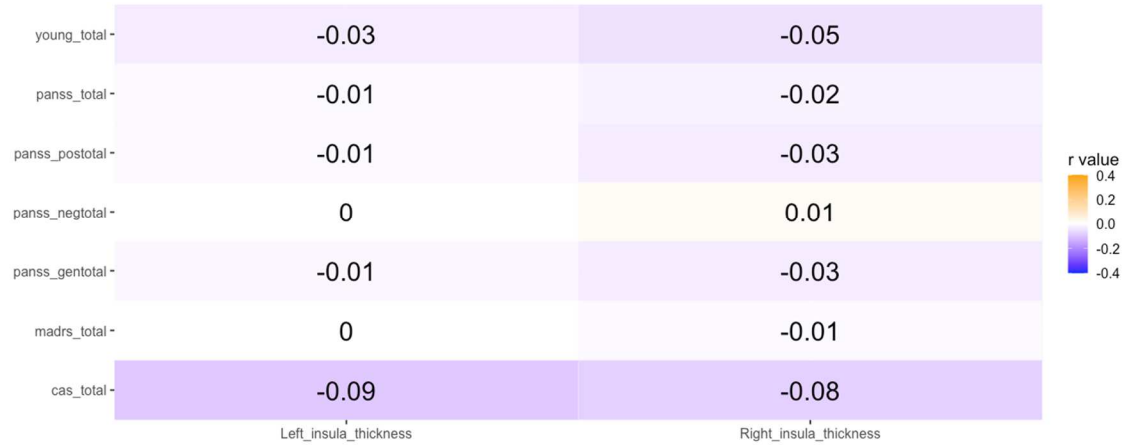

Figure 22: BDP Thickness Symptomatology Correlations

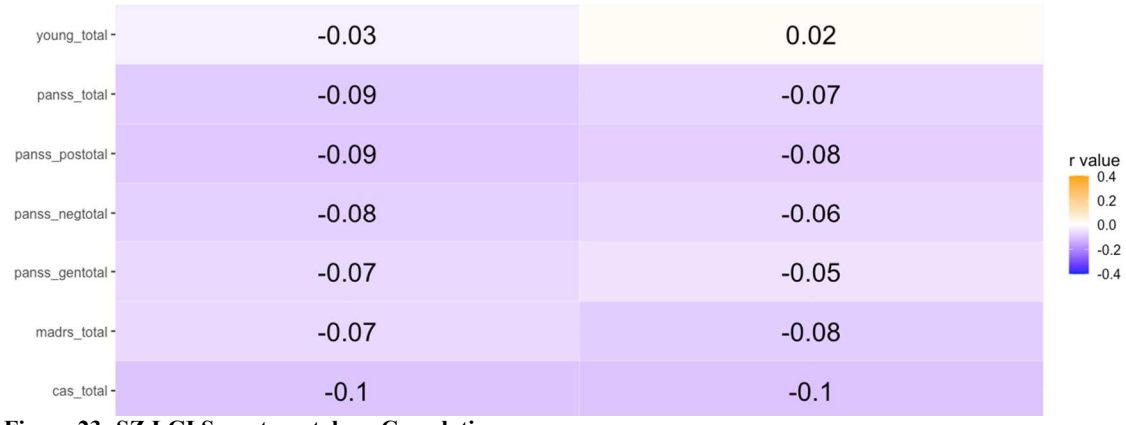

Figure 23: SZ LGI Symptomatology Correlations

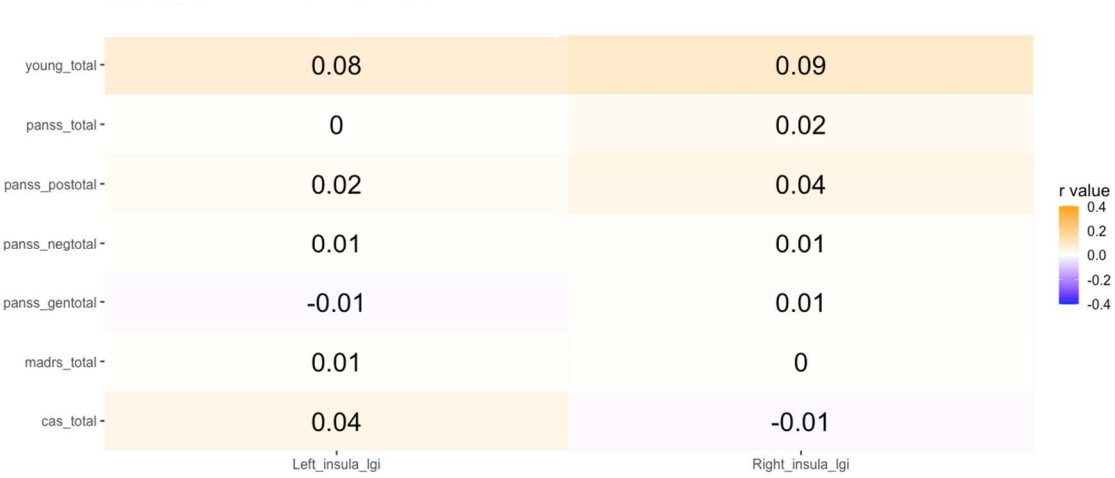

Figure 24: SAD LGI Symptomatology Correlations

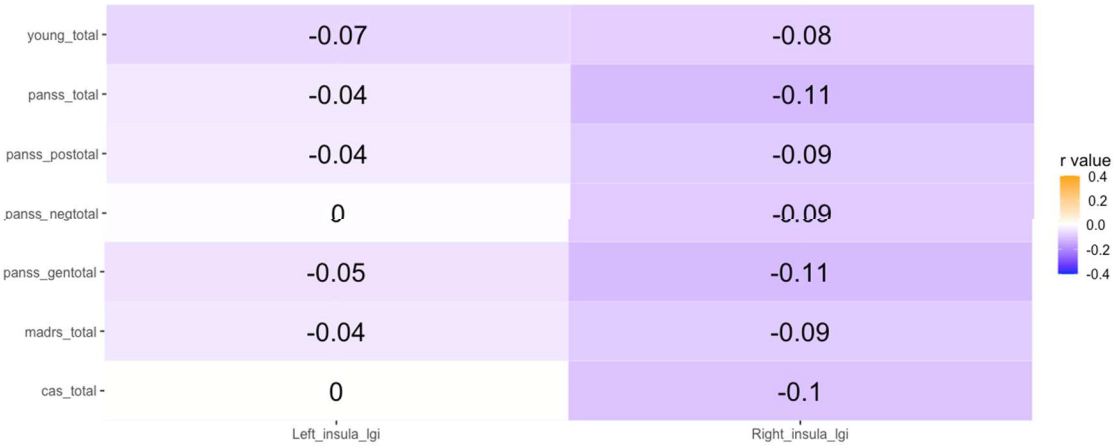

Figure 25: BDP LGI Symptomatology Correlations

Right versus Left

No correlations were found between left and right insula volume in SZ and BDP and cognition. SAD, however was discovered to yield an equal and positive relationship in both left and right insula volume (r=0.15) for Digital Sequencing (DS).

Insular cortical thickness yielded a positive relationship only in the left insula in the SZ diagnostic group for Verbal Memory (VM).

LGI yielded positive relationships in SZ, SAD, and BDP. In the SZ group, positive correlations were found between the left LGI and VF (r=0.11) and DS (r=0.16) and between the right LGI and VM (r=0.11), VF (r=0.12) and DS (r=0.13). In the SAD group, correlations were found between both left and right insula with VM (r=0.13; r=0.12), Verbal Fluency (VF) (r=0.15; r=0.13), and DS (r=0.16; r=0.12), respectively. In the BDP group, positive correlations were found between the left LGI and VM (r=0.13)

Figure 26: SZ Insula Volume/Thickness/LGI versus BACS

and between the right LGI and VM (r=0.14), VF (r=0.14), SC (r=0.12), and DS (r=0.13) for the right LGI.

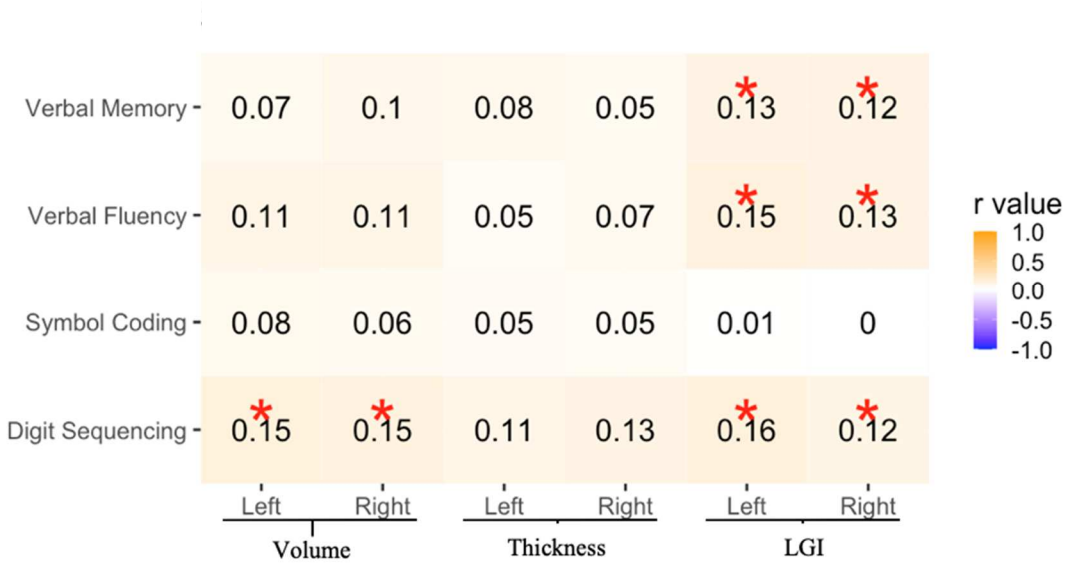

Figure 27: SAD Insula Volume/Thickness/LGI versus BACS

Figure 28: BDP Insula Volume/Thickness/LGI versus BACS

Bilateral

Positive relationships were found between the anterior insula volume in SZ and VM (r=0.13), VF (r=0.11), and DS (r=0.14), and in BDP in VM (r=0.14). The posterior volume yielded significant relationships with VM (r=0.13) and DS (r=0.15) in the SZ group, VF (r=0.12) and DS (r=0.18) in the SAD group, and in VM (r=0.13) in the BDP group.

Significant relationships in cortical thickness were only found between the posterior insula and DS (r=0.19) in the SZ group and DS (r=0.19) in the SAD group.

Significant relationships between the anterior insula LGI were found in the SZ group with DS (r=0.15), the SAD group with VM (r=0.16), VF (r=0.15), and DS (r=0.17), and the BDP group with VM (r=0.17), VF (r=0.13), and DS (r=0.16). For the posterior insula, positive relationships were found with VM (r=0.12) and DS (r=0.19) in the SZ group, VF (r=0.12) and DS (r=0.19) in the SAD group, and VM (r=0.12) in the BDP group.

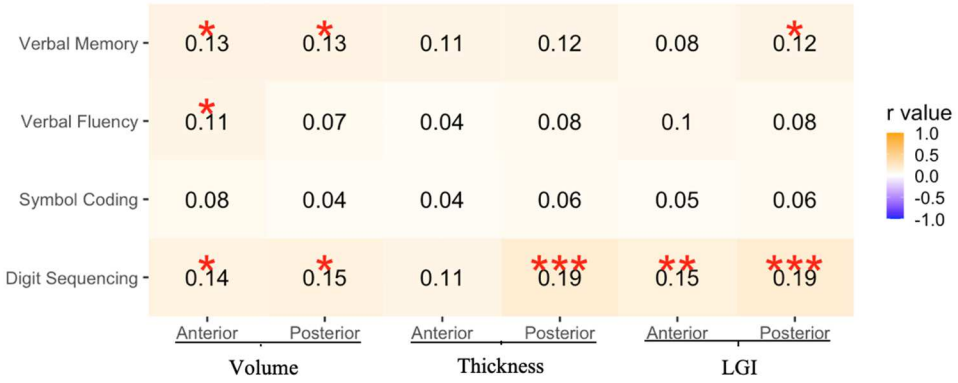

Figure 29: SZ Bilateral Anterior/Posterior Volume/Thickness/LGI versus BACS

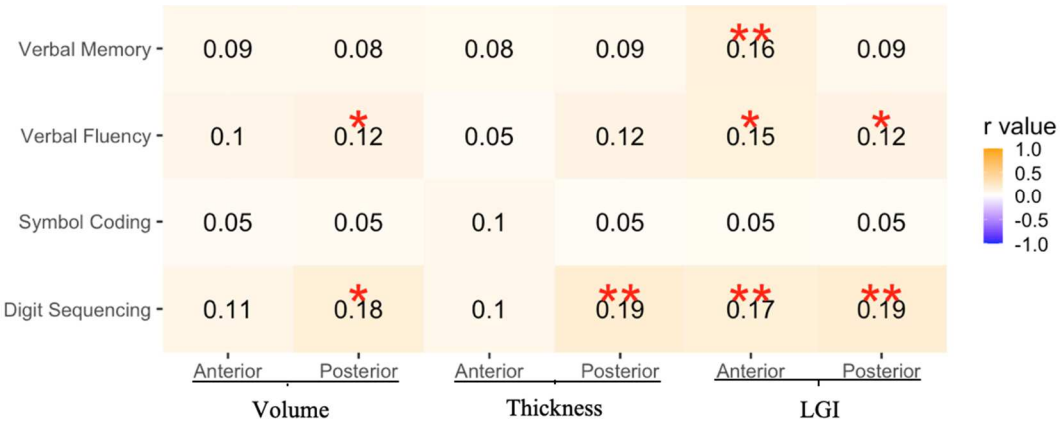

Figure 30: SAD Bilateral Anterior/Posterior Volume/Thickness/LGI versus BACS

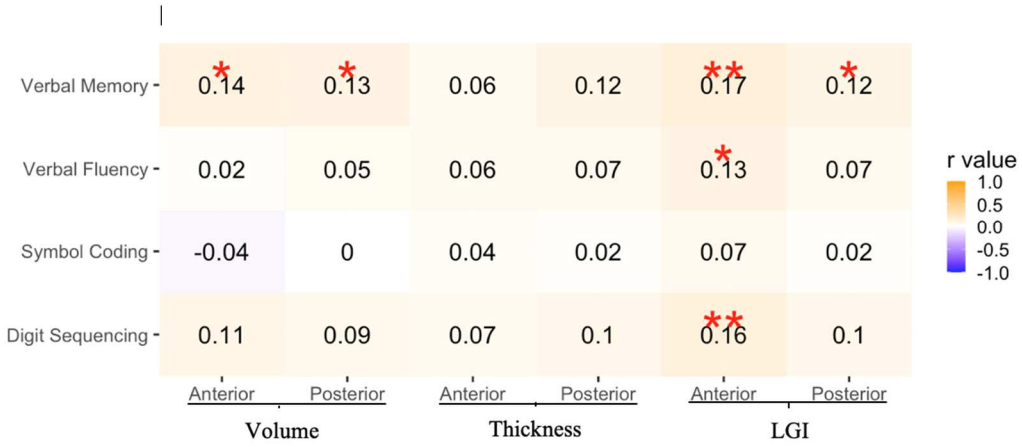

Figure 31: BDP Bilateral Anterior/Posterior Volume/Thickness/LGI versus BACS

Anterior versus Posterior

Positive relationships in volume were found for the SZ group between the left anterior insula and VM (r=0.14) and the right posterior insula and DS (r=.16) and for the SAD group between the right posterior insula and DS (r=.16).

Significant relationships in cortical thickness were only found in the SZ group between the right anterior (r=.14) and right posterior insula (r=.19) with VM and between the left posterior (r=.14), right anterior (r=.15), and right posterior (r=.13) with DS

Significant relationships in anterior insula LGI were found in the SZ group between the left anterior insula in DS (r=.11) and with VM (r=.14), VF (r=.17), SC (r=.16), and DS (r=.23) in the left posterior insula. The right anterior insula showed a positive correlation with DS (r=.17) and the right posterior insula with VM (r=.12), VF (r=.13), SC (r=.12), and DS (r=.21). Positive relationships were found in the SAD group between the left anterior insula and VM (r=.17, VF (r=.13) and DS (r=.15) and between the left posterior insula and VM (r=.17) and DS (r=.14). The right anterior was found to have a positive relationship with VM (r=.11), VF (r=.15), and DS (r=.16). A similar trend was found in the right posterior insula as well (VF (r=.13), VM (r=.14), DS (r=.19). The left anterior insula in the BDP group was found to have a positive relationship with VM (r=.14), VF (r=.12), and DS (r=.16). The left posterior, right anterior, and right posterior insula were all found to have positive relationships with VM (r=.16, r=.16, r=.13, respectively) and DS (r=.14, r=.11, r=.13, respectively).

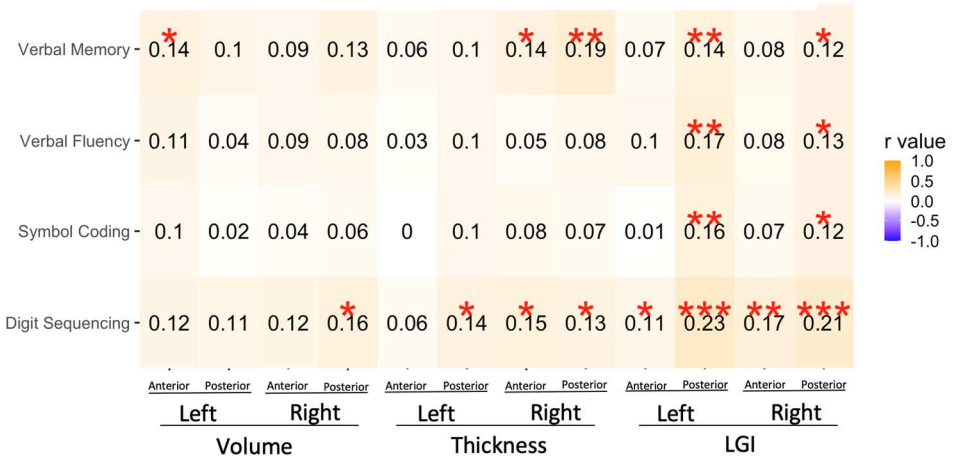

Figure 32: SZ Anterior/Posterior Volume/Thickness/LGI versus BACS

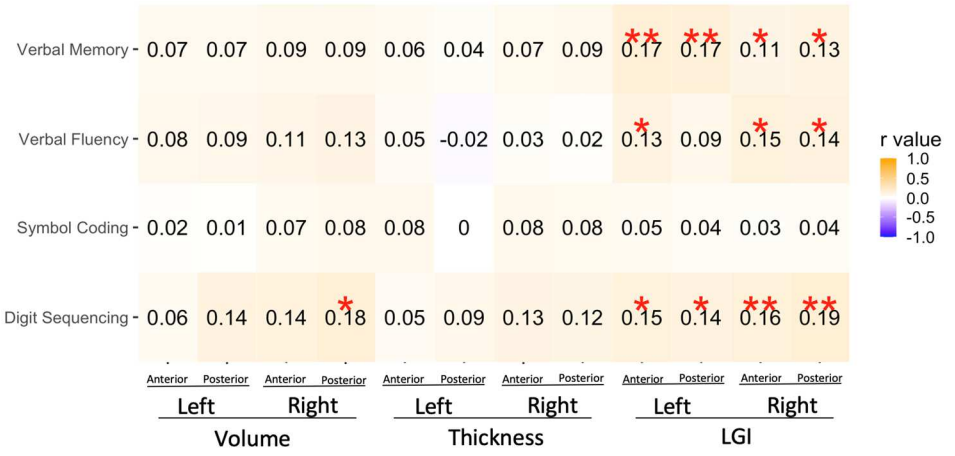

Figure 33: SAD Anterior/Posterior Volume/Thickness/LGI versus BACS

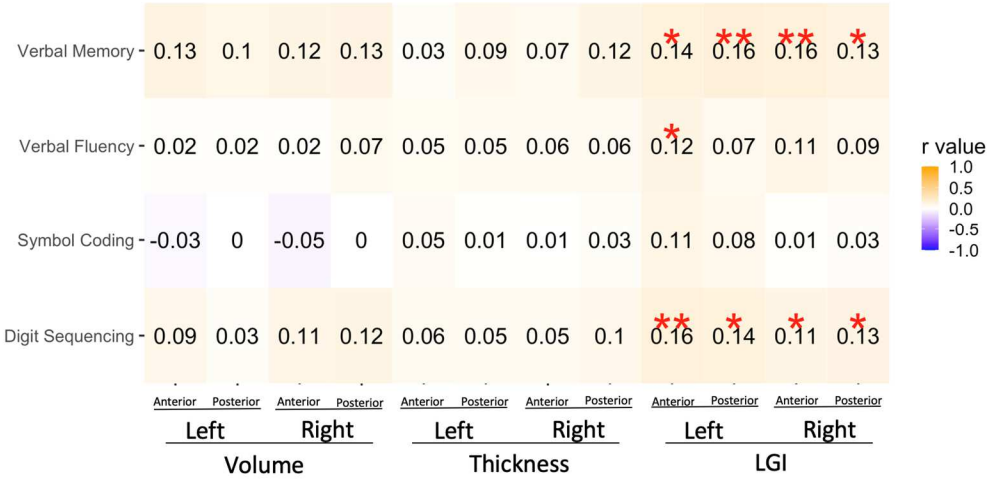

Figure 34: BDP Anterior/Posterior Volume/Thickness/LGI versus BACS

DISCUSSION

To the best of my knowledge, this is the first study to investigate the insula's role in SZ, SAD, and BDP in 3 perspectives: left versus right insula, bilaterally, and anterior versus posterior insula. Compared to controls, the individuals with SZ showed a volumetric reduction in both the left and right insula, with a greater reduction in the left, which is a finding consistent with Saze et al, 2007, Makris et al., 2006, and Arasappa et al., 2012. Furthermore, compared to controls, in individuals with SZ, both the bilateral anterior and posterior insula showed a volumetric reduction, with a greater reduction in the anterior insula. This is a finding which has been reported across multiple studies, as noted in Wylie & Tregellas, 2010, however, the exact localization of this reduction has been inconsistent. Via this large sample size, we were able to conclude that the bilateral

anterior insula that has the larger volumetric decrease. Compared to controls, individuals with SZ, were shown to have a greater volume reduction in the left and right anterior and left posterior insula, with the greatest reduction seen in the left posterior insula. This is a finding that is contrary to the left posterior insula observation by Saze et al., 2007. This is furthermore contrary to studies that have found no gray matter reductions or bilateral reductions as noted in Wylie & Tregellas, 2010.

Compared to controls, individuals with SZ showed a decreased thickness in both the left and right insula, with a greater decrease in the right insula which is consistent with findings from Nesvåg et al., 2008 but contrary to findings from Kuperberg et al., 2003. Furthermore, SZ bilateral findings were only found in the anterior insula while total anterior and posterior insula reductions were only found in the right and left posterior insula and in the left anterior insula, with the greatest reduction being in the left anterior insula. These findings are novel considering the inconsistency and lack of insight into changes to insular thickness in psychosis.

Changes to LGI in SZ is another topic that seems to have a lack of consistency in the literature. Although left and right and bilateral measurements yielded no significant differences, the anterior and posterior measurements for individuals with SZ yielded significant decreases in LGI in the right posterior insula.

Compared to individuals with SZ, patients with SAD yielded more severe reductions in volume in the left and right insula with the greatest reduction found in the right insula. This trend continues bilaterally with the bilateral anterior insula in SAD-NC having a greater reduction in volume compared to SZ-NC. With this said, however, the

bilateral posterior insula in individuals with SAD did not show any significant volumetric reductions. Similarly, anterior and posterior measurements yielded greater reductions in the left and right anterior insula in the SAD-NC group than that of the SZ-NC group.

Compared to controls, individuals with SAD showed reductions to thickness in both the left and right insula with the greatest reductions found in the right insula, mirroring the trend found when comparing controls to individuals with SZ. Similarly, bilateral thickness measurements showed that the bilateral anterior insula also had a greater decrease in thickness with no significance observed in the bilateral posterior insula. Unlike the SZ-NC group, however, anterior and posterior measurements yielded significant reductions to thickness only in the left anterior insula.

Overall, there seems to be a distinct lack of research done on the insula in SAD. The reason for such a lack of studies done on SAD is due to SAD not being seen as a distinct diagnostic category, as explained by Birur et al., 2017. However, our results show that SAD not only has distinct volumetric reductions from that of SZ but these reductions for certain morphometric variables.

Observations in BDP are similarly inconsistent to those reported for of SAD because of the lack of research into the insula in BDP. Amenn et al., 2016, Birur et al., 2017, Ivleva et al., 2010, and Sheffield et al., 2021 observed no findings for BDP in volume and LGI however we observed significant BDP-NC volume reductions in the left and right insula, the bilateral anterior insula, and the right posterior and left anterior insula. Furthermore, although no BDP-NC reductions in thickness were found in the left

and right insula, the BDP group was the only group to produce between-group findings, where in BDP-SZ and BDP-SAD group's comparisons. BDP showed greater thickness compared to SZ and SAD. Bilaterally we observed a greater decrease in thickness in the posterior insula BDP-NC groups' as well as a greater thickness in the anterior insula BDP-SAD group's comparisons. In the anterior and posterior measurements, the only significant observation was for the right anterior insula in the BDP-SAD group. Regarding LGI, significance was only observed in the anterior and posterior measurements in BDP-NC in the right posterior insula and left posterior insula, with the greater decrease in LGI found in the right posterior insula.

Regarding cognition, although we observed significant relationships between the insula and cognitive measures, we did not see correlations with symptomatology, which is contrary to findings noted in Wylie & Tregellas, 2010, as well as other studies, which correlated deficiencies in volume, thickness, and/or LGI to more severe. The lack of findings could be due to that functional activity correlates more to symptoms rather than volume, thickness and LGI. Additionally, the lack of findings could be explained by the data collection itself and the way that the symptoms were collected does not capture the underlying mechanism of those symptoms, meaning that this could be due to issues with the PANSS tests themselves.

For all three groups, SZ, SAD, and BDP, LGI measurements for the left and right insula seemed to have the highest correlations with VM, VF, and DS BACS measures. For the SZ group, left insula thickness showed significant correlations in VM. LGI, however, showed significant correlations between the left LGI and VF and DS and

between the right LGI and VM, VF and DS. The SAD group showed correlations between the left and right volume and DS and between both the left and right LGI and VM, VF, and DS. BDP, on the other hand, only yielded positive correlations between the left LGI and VM and between the right LGI and all BACS measures. This finding could indicate that reductions in LGI are correlated to higher severity of cognitive defects.

Bilaterally, BACS measure correlated to a much more scattered localization, with the strongest correlations for SZ observed between the posterior thickness and DS, and between the anterior and posterior LGI and DS. Likewise, the strongest correlations in SAD were observed between posterior thickness and DS, anterior LGI and VM and DS, and between the posterior LGI and DS. Smaller, but still significant correlations were also seen between the anterior LGI and VM and VF. BDP yielded a similar trend, with the strongest correlations seen between the anterior LGI and VM and DS and smaller, but still significant correlations seen between the anterior LGI and VM and VF as well. Again, our results show that anterior and posterior LGI and posterior thickness have the strongest correlations to cognitive measures, specifically that of DS and VM.

Anterior and posterior measurements follow this same observed trend. The SZ group yielded the strongest correlations between the right posterior thickness and VM and between the left posterior LGI and all BACS measures. Additionally, the right anterior LGI yielded positive correlations with DS and the right posterior LGI yielding smaller, but significant, correlations with all BACS measures. The SAD group had the strongest correlations between the left anterior and posterior LGI and VM with smaller but significant correlations with DS as well. The right anterior and posterior LGI were

significantly correlated with DS, with smaller significant correlations seen with VM and VF. Lastly, BDP had the most significant correlations between the left anterior LGI and DS, left posterior LGI and VM and right anterior and VM as well. Smaller significant correlations were seen with VM and DS for all LGI measures.

In general, these BACS correlations seem to define LGI as a key correlate to cognition which supports the view that greater gyrification is related to greater cognitive function (Gautam et al., 2015; Park et al., 2021). Although precise localization is hard to define, with each perspective (right versus left, bilateral, and anterior versus posterior) showing slightly different results, each perspective pointed towards LGI as the primary indicator of cognition. Additionally, the small effect sizes could be explained by the large sample size, as a larger sample size usually yields a smaller r value. Additionally, the small effect sizes could be due to that we are missing a covariate or some sort that we have not considered in our testing. Lastly, the smaller effect sizes could be due to the imperfections of the tests themselves as there is a small time difference between patient MRI collection and the administration of the BACS tests. Although the collection is attempted to be done close together, variables such as patient health and technological issues might increasing the spacing between these two events, which may have an effect on the subsequent effect size.

The goal of this study was to utilize a large sample size of SZ, SAD, and BDP to examine the insula not only on a macro scale (left versus right and bilaterally) but also on a more micro scale (individual anterior and posterior components). In doing so, the study seeks to build upon current knowledge and explain and rectify current contradictions in

data by providing observations from such a large dataset. Future studies will examine further not only the relation between insular structure and socio-emotional and self-processing variables believed to be related to the anterior insula but also examine the structural connectivity of the insula to surrounding regions to determine how these connections are affected in psychosis.

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