EFFECTS OF GENETIC LIABILITY TO PSYCHOSIS PRONENESS AND PSYCHOSIS PRONENESS ON FUNCTIONAL CONNECTIVITY OF THE SALIENCE NETWORK

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Effects of Genetic Liability to Psychosis Proneness and Psychosis Proneness on Functional Connectivity of the Salience Network
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We certify that we have read this thesis and that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

EFFECTS OF GENETIC LIABILITY TO PSYCHOSIS PRONENESS AND PSYCHOSIS PRONENESS ON FUNCTIONAL CONNECTIVITY OF THE SALIENCE NETWORK

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The effect of psychosis proneness, a psychometrically defined index of subclinical psychosis, has limited research on its effect on brain connectivity in healthy populations. In addition, functional connectivity research in psychosis proneness mainly focuses on brain networks such as the default-mode network (DMN) and the central executive network (CEN) but not on the salience network (SN). On a similar note, research on genetic susceptibility to psychosis in healthy populations and the combinatory analysis between brain connectivity and genetic liability have not been explored thoroughly. This thesis assessed the relationship between psychosis proneness and genetic liability to psychosis to functional connectivity of the salience network. Seventy-two pairs of twins, siblings, and triplets were included in the analysis for genetic liability and functional connectivity. Participants' psychosis proneness was assessed via the Community Assessment of Psychic Experience (CAPE-42) questionnaire, and genetic liability scores (PRS-SCZ) were calculated through PLINK and PRSIce-2 software. Global patterns of connectivity, seed-based connectivity, and network topology of the salience network were examined. The findings have revealed that the connectivity levels within the salience network differed in individuals with high psychosis proneness compared to individuals with low psychosis proneness. Further analysis has shown that PRS-SCZ did not show a significant difference between high and low psychosis proneness groups. The results show that connectivity levels in the salience network differ in individuals with psychometrically defined psychosis proneness. These results were not explained by differences in genetic loading among the participants

Keywords: psychosis proneness, genetic liability to psychosis, resting state functional connectivity, network connectivity.

ÖZET

PSİKOZA OLAN GENETİK YATKINLIĞIN VE PSİKOZA EĞİLİMİN DİKKAT ÇEKERLİK AĞINDAKİ FONKSİYONEL BAĞLANTISALLIK ÜZERİNE ETKİLERİ

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Aralık 2022

Literatürde sağlıklı popülasyonda görülen psikoz riskinin, beyin bağlantıları üzerindeki etkisine ilişkin sınırlı sayıda araştırma yapılmıştır. Ek olarak, psikoz riski ve beyin ağları ile yapılmış olan araştırmalar dikkat çekerlik ağından (SN) ziyade, varsayılan durum ağı (DMN) ve merkezi yürütücü ağına (CEN) odaklanmıştır. Benzer olarak, sağlıklı popülasyonlarda psikoza olan genetik yatkınlık ve bu yatkınlığın beyin ağları üzerindeki etkisini birleştiren çalışmalar yeterince kapsamlı değildir. Bu tez, dikkat çekerlik ağının işlevsel bağlantısı ile psikoza yatkınlık ve psikoza olan genetik yatkınlık arasındaki ilişkiyi değerlendirmiştir. Çalışmaya ergenlik ve genç yetişkinlik dönemlerinde olan yetmiş iki çift ikiz, kardeş ve üçüz katılmıştır. Psikometrik olarak tanımlanmış bir subklinik psikoz indeksi olan psikoz eğiliminin etkisi, Toplumda Psişik Yaşantıları Değerlendirme Ölçeği (CAPE-42) ile değerlendirilmiştir. Psikoza olan genetik yatkınlık (PRS-SCZ) ise PLINK ve PRSIce-2 yazılımları aracılığıyla hesaplanmıştır. Bu tezde dikkat çekerlik ağının küresel bağlantı modelleri, çekirdek tabanlı bağlantı modelleri ve ağ topolojisi incelenmiştir. Bulgular, dikkat çekerlik ağı içindeki bağlantı düzeylerinin, psikoza yatkınlığı yüksek olan bireylerde, psikoz eğilimi düşük olan bireylere göre farklılık gösterdiğini ortaya koymuştur. Daha ileri analizler ise, PRS-SCZ'nin yüksek ve düşük psikoza yatkınlık grupları arasında anlamlı bir fark bulunmadığını göstermiştir. Sonuçlar, dikkat çekerlik ağındaki bağlantı düzeylerinin, psikometrik olarak tanımlanmış psikoza yatkın olan bireylerde farklılık olduğunu göstermektedir. Bu sonuçlar, katılımcılar arasındaki genetik ağırlıktaki farklılıklarla açıklanamamıştır.

Anahtar sözcükler: psikoz eğilimi, psikoz ilişkili genetik yatkınlık, dinlenim durumu fonksiyonel bağlantı modelleri, ağ topoloji analizi.

Acknowledgement

This thesis study uses Prof. Dr. Timothea Toulopoulou's research protocol and her experimental design that studies the various mechanisms, including but not limited to genetic, cognitive and neurobiological, shown to affect an individual's susceptibility to psychosis proneness. This research protocol was set up before my graduate studies, and many other graduate students in Prof. Dr. Toulopoulou's Lab have worked on and continue working toward recruitment, data collection, and analysis.

I have used a part of these data to work on genetic liability to psychosis and resting-state brain connectivity in adolescents. I recruited five twin pairs and collected DNA samples from 63 participants during my master's degree. I calculated the polygenic risk score for psychosis for 168 people. Additionally, I got permission from the Ministry of Education to hang and distribute posters in high schools and visited 15 high schools to distribute posters. MRI analysis and its subsequent statistical analysis were performed by myself.

Dedication

First, I would like to show my appreciation to my advisor, **Prof. Dr. Timothea Toulopoulou**, for including me in her research group and allowing me to work with her. She was conducive to my academic growth with her suggestions and feedback.

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Chapter 1

Introduction

1.1 Brief Overview of Psychosis Risk

Psychosis, a term generated from the Greek word '*psyche*' signifying the soul, body, and mind, was first used in 1845 as an umbrella term for any mental disorder that disrupted a person's ability to carry out imperative daily activities for proper functioning [1]. Today, psychosis, in general, is defined by the distorted relation between one's self and reality in various ways, i.e., perception, emotions, and cognition [2]. It is believed that around 3% of the world population is afflicted with psychotic disorder, with its prevalence being in adolescents and young adults [3]. The presence of psychosis classified according to hallucinations, delusions, and disordered thoughts, is an essential component of psychotic disorders [4]. Symptoms of psychosis can be grouped under two main categories: positive and negative. Positive symptoms of psychosis include hallucinations, detection of non-present stimuli, delusions, and resolute incorrect or extreme beliefs, whereas negative symptoms of psychosis include lack of motivation, asociality, and anhedonia [5, 6].

The onset of psychosis can be summarized in 3 general phases. Premorbidity can be understood as the degree of functionality observed before the onset of disorders [7]. Thus, in the premorbid phase of psychosis, poorer functioning or early-stage dysfunction can be related to earlier disease onset and increased severity of psychotic symptoms [8]. The prodromal phase of psychosis is usually characterized by the gradual rise in psychotic symptoms that are lower in intensity for a diagnosis but effective enough to start causing changes in a person's perception of reality [9]. Usually, negative symptoms are more dominant during the prodromal phase of psychosis than positive symptoms [10]. If the symptoms persist and increase to exceed the diagnostic threshold, a person will enter the acute phase of psychosis, where the symptom severity is expected to disrupt daily functioning, and positive symptoms are expected to have a consistent presence [11].

The increase in symptom severity required for a diagnosis of psychosis further supports the idea that symptom distribution in a population depends on the quantitative aspect of the symptoms rather than their presence [12]. The necessity for a quantitative increase of psychotic indications supports the continuum model for psychosis: it is believed that proneness to psychosis follows a half-normal distribution in a population where the disease symptoms and vigor increase toward the tail [13]. Before showing symptoms of clinical value, a person goes through normative experience, non-clinical psychosis, and attenuated psychosis [14]. Psychosis proneness thus covers healthy individuals with heightened vulnerability to experience psychotic symptoms due to their environmental and genetic backgrounds [15]. Approximately 6% of the population reports a psychotic experience in their lifetime [16]. Of these psychotic experiences, 75 to 90% are found to be temporary [15]. The persistence of psychotic experiences can then lead to the establishment of psychotic symptoms followed by a diagnosis of a psychotic disorder which compromises 3% mentioned previously.

Various factors, both environmental and genetic, can make a person more vulnerable to such experiences [17]. The combination of vulnerability to and the persistence of psychotic experiences can lead to the passing of clinical significance. In a healthy individual, psychosis risk can increase in the presence of obstetric complications, infections, and stress during early development; injuries

(especially the ones related to the head) and trauma in childhood; ethnicity, urbanization, adverse social environment, and drug use such as cannabis [18, 19, 20]. Family history covers a significant portion of genetic risk factors that contribute to psychosis proneness, where psychotic disorders are centralized in families indicating a hereditary quality of specific genetic characteristics in both affected and healthy family members [21]. Research has shown that, in families with at least one affected individual, relatives scored higher in assessments aimed to show the forementioned vulnerability to psychosis [22]. Schizophrenia, for example, has an approximate heritability of 65 to 80%, further highlighting genetics' importance in psychosis [23]. Hence, it was seen that a genetic liability is required for someone to be more vulnerable to developing psychosis.

1.2 Brief Overview of Polygenic Risk

The principles of inheritance, suggested by Gregor Mendel in 1866 following his work with pea plants, have been accepted as the foundation of modern genetics [24]. Modern genetics classifies hereditary diseases into two main categories according to their pattern of transfer to the next generation: Mendelian or Polygenic. Disorders that are seen due to the inheritance of a single gene, such as the mutated HBB gene in sickle-cell anemia, are classified under Mendelian diseases as a similar pattern of transfer was observed in the characteristics of pea plants by Mendel [24, 25]. However, not every disorder is inherited by the transfer of a single gene. Polygenic disorders cover the conditions where a combination of various genes is required for a disease to manifest itself in an individual [26]. The contribution of each gene in a polygenic disease varies, with some having little effect and others being essential for the disease phenomena [27]. Schizophrenia and bipolar disorder are classified under polygenic diseases as their expression depends on the presence of multiple genetic traits [28].

Identifying the genetic framework of any disease was a time-consuming and expensive endeavor as sequencing one's genome was an arduous process with Sanger sequencing, which was developed in the latter half of the 1970s [29]. Next-generation sequencing (NGS), developed around 2004, made sequencing one's genome more efficient with quicker results and lower cost, has been a turning point in understanding the genetic makeup of various disorders, both Mendelian and polygenic [30]. Mendelian disorders, while easier to detect patterns, are less common than their polygenic counterparts, which are more common with a more severe social and economic burden on the ones diagnosed with one [26]. Following these newer sequencing techniques, research on polygenic diseases gained traction as DNA sequencing analysis became more attainable. In the last decade, genome-wide association studies (GWAS) were developed to study and identify the variants involved in the development of various disorders [27]. Whole genome sequencing of participants and their consequent analysis led to the recognition of traits present in the ones diagnosed with the disorder of interest compared to those who did not [31]. GWAS studies aim to understand better how genes alter the onset of disease, disease course, and treatment effectiveness [26]. GWAS is also actively used to understand various psychiatric disorders, particularly psychotic disorders, where the impact on one's daily functioning is significant. Collaborative research in understanding the genetic mechanisms of psychiatric disorders such as schizophrenia and bipolar disorders started in 2008 when ZNF804A polymorphism was associated with these disorders [32]. Following this research, more GWAS studies regarding the topic have followed with Stefansson and colleagues as well as the International Schizophrenia Consortium in 2009 as they added the major histocompatibility complex (MHC), transcription factor 4 (TCF), and neurogranin (NRGN) to be associated with schizophrenia and bipolar disorder [33, 34]. Following the formation of the Psychiatric Genome-Wide Association Study Consortium (PGC), papers were published in 2014 and 2022 respectively where 108 followed by 287 distinct locations were identified associated with schizophrenia and related disorders where genes involved mainly in glutamatergic neurotransmission and dopamine transmission such as dopamine receptor D2 (DRD2), Glutamate Metabotropic Receptor 1 (GRM2), glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A) and SP4 transcription factor [35, 36].

Even though associations between psychotic disorders and genes are found, it was also observed that a particular gene by itself is not enough to explain the polygenic liability [37]. Due to this observation, the additive effect of genes regarding the polygenic liability of disorders started being studied. Polygenic risk score (PRS) is one of the most preferred methods in assessing an individual's polygenic burden of diseases, as it is calculated as the weighted sum of the gene versions or polymorphisms associated with the disorder of interest [38]. PRS scores do not consider gene-gene and gene-environment interactions but give the general genetic liability of a person to a specific disease [38]. Similarly, the polygenic risk for schizophrenia is calculated to assess one's genetic liability to psychosis and psychotic disorders. Finally, GWAS research has shown that schizophrenia PRS (PRS-SCZ) accounted for approximately 18% of the variance between healthy and affected individuals for psychosis and 7% of the variance for schizophrenia [39, 40].

1.3 The Relationship Between Psychosis Risk and Polygenic Risk Score

PRS-SCZ has been essential in observing the symptom severity concerning the genetic liability of a person. It was seen that individuals diagnosed with a form of psychotic disorder had higher PRS-SCZ scores compared to their healthy counterparts [41]. Inheritance of the disorder was also observed when the first-degree relatives of patients were compared with healthy controls. It was seen that the PRS-SCZ scores of the first-degree relatives of patients were significantly higher than healthy controls but were also lower than the patients' scores [22]. In addition to score comparisons within families, the relationship between symptom severity and PRS-SCZ was studied. In addition, increased PRS-SCZ scores have been linked with individuals' decreased cognitive ability, heightened anxiety and negative symptoms [42]. Associations between IQ and PRS-SCZ were also made, where lowered IQ and reduced performance in working memory tasks were also shown in people with higher PRS-SCZ scores [43].

PRS-SCZ turned out to be higher in diagnosed patients with more severe symptoms than in patients with more moderate symptoms [39]. Symptom severity, however, depends on more than the genetic liability, and further research was done to see the other components determining the severity of symptoms [38]. The relation between the PRS-SCZ and environmental risk factors contributing to psychotic experiences was investigated with the degree of psychosis proneness increasing along with the genetic liability for psychotic disorders, further justifying the necessity for gene-environment interactions for the onset of psychosis [44]. Higher scores for PRS-SCZ correspond to an increased genetic risk of psychosis, but without the environmental stress, such as infection or trauma, a person's genetic vulnerability does not correspond to a high-risk status for psychosis [40]. Correspondingly, environmental stress without the increased genetic liability will not put a person at risk for psychosis; however, it can increase the frequency of psychotic experiences [19]. This increase in psychotic-like experiences in terms of frequency depends on the severity of the previously mentioned traumas, urbanicity, infections, migration, and drug usage. Measurement of psychotic experiences can be done in various ways where the frequency and severity of these occurrences are the most critical in its computation [45]. In addition, increased psychotic experiences and a higher score of PRS-SCZ put a person at risk for psychosis.

1.4 Brief Overview of Resting-State fMRI

The human brain is one of the most complex entities in the human body, with its many neuronal connections responsible for many cognitive processes. Although understanding the brain has been a topic of interest in the scientific community for a long time, the process is thought to be highly invasive and likely fatal throughout history [46]. The invention of noninvasive imaging methods has been a turning point in understanding how the brain works, as a plethora of research has been and continues to be conducted in understanding both normal and abnormal brain functioning[47]. Studies involving mental disorders have also increased in frequency to understand the affected cognitive processes to understand disease symptomology and to provide reliable disease markers [48]. Magnetic resonance

imaging or MRI is one of these noninvasive imaging techniques that can take anatomical images of the human body via a solid magnetic field created by the scanner [47].

Briefly, magnetic fields and radio waves are used to detect the distribution of water molecules in the body [49]. This water dispersion varies from region to region in the body, and stimulation of these water molecules creates the image. Functional MRI (fMRI) has a similar setup to MRI, but instead of being limited to stable anatomic imaging, fMRI aims to assess the brain activity of individuals based on the changes within the blood flow in the brain [50]. In general, blood flow is associated with the activation of neurons as more energy is necessary for the region of the brain that is in use during a task [49]. The change in blood flow or the hemodynamic response in a specific area is assessed by the blood oxygen level-dependent (BOLD) contrast, where an increase in blood flow is affiliated with the activation of a region and its decrease with the deactivation of that region [51]. MRI and fMRI scanning procedures utilize the same scanner where the parameters entered by the researcher determines the type of scan to be completed [50]. The scanner first generates an anatomical image and fits the functional BOLD contrast on top so that activated or deactivated regions can be mapped on top of the structural image [50]. In imaging research, fMRI is used to see which regions are activated when a specific task is being performed by a participant so that cognitive processes required to perform that task can be detected.

Due to the brain's intrinsic activity, the human brain is claimed to be still active and shows regional dynamic changes in the blood flow even at rest [52]. Resting-state fMRI (rsfMRI) is a form of fMRI where interactions between various brain regions can be computed when no task is conducted or at a rest state [53]. The BOLD response can still be detected even at rest, albeit with less intensity than the responses obtained from task studies. When there is no additional task at hand, BOLD responses seen across the brain can provide the researchers with insights into the brain's functional organization [54]. Functional connectivity analysis can shed light on how and when brain regions communicate in healthy people and ones diagnosed with a disorder. A comparison between these two

conditions shows the abnormalities in functional connectivity, which can then be associated with symptoms of the disorders [55]. In addition, mental disorders such as schizophrenia and other psychiatric disorders have been featured in rsfMRI studies so that changes in functional organization can be utilized to generate disease markers and therapeutic advances [52].

1.5 Brief Overview of the Salience Network

A network is defined as a system of related items where these items can be computers, people, or brain regions [56]. Network science is thus the academic field researching how many items, termed as nodes, are included within a network and how these nodes are linked, termed as edges [57]. The human brain is one of the most complex biological networks, where billions of neurons interact with one another through multiple synapses. Brain network studies aspire to understand and identify the organization and connectivity between brain regions so that human behavior and cognition can be understood on a more topographical level [58]. The connectivity of brain regions is studied under two sections depending on the type of connectivity a researcher is interested in. Structural connectivity focuses more on the anatomical connections of the brain where cortical and subcortical regions are linked through the white matter projections [59]. Functional connectivity, on the other hand, aims to understand the patterns of activation in the brain regions during an external stimulus or a task so that statistical relations can be made in a time-dependent manner [58]. Large-scale brain networks, or core brain networks, are interconnected brain regions where structural and functional connectivity can be observed at a macro scale [59]. Today, six core brain networks are identified: Occipital (visual), Pericentral (somatomotor), Dorsal Frontoparietal (attention), Lateral Frontoparietal (control), Mid-cingulo Insular (salience) and Medial Frontoparietal (default-mode) [60].

From these six core networks, the mid-cingulo insular network or salience network has been gathering particular interest from researchers in recent years. Salience is described as the state of being noticeable so that it can captivate one's attention

[61]. When an item or a thought becomes salient, it will have priority to occupy one's thoughts and can become more conspicuous compared to neighboring items or thoughts. The salience network, first defined by Seeley and colleagues in 2007, is essential in sorting the continuous internal and external stimuli encumbering the nervous system so that the most relevant input can be processed [62]. Prioritization of the most pertinent internal and external stimuli is crucial in guiding proper behavior, as both internal thoughts and environmental contexts are necessary for adequate conduct [61]. Although a core brain network on its own, salience network is also imperative in regulating the proper functioning of other networks. Both the default-mode and attentive states of an individual depend on the salience network. For example, the salience network provides the switch between the aforementioned states [63]. Thus, when there is a salient stimuli, the anterior insula and the anterior cingulate cortex, regions of the salience network, send signals that activate the CEN regions which results in the subsequent deactivation of the DMN regions [64].

The key regions that form the salience network are the anterior cingulate cortex (ACC) and the anterior insula (AI), with additional regions such as the thalamus, amygdala, ventral tegmental area, ventral striatum, and temporal pole showing similar patterns of activation in Seeley and colleagues' initial paper [62]. The anterior insula, studied under its three subregions named dorsal-anterior, ventral-anterior and posterior, has been of great interest in salience studies where the dorsal-anterior region of the AI node was found to be the region the most involved within the network as it is the region with high connectivity to the anterior cingulate cortex (ACC) [61]. Structural connectivity between these regions has been shown to differentiate compared to others at a cellular level, as specialized neurons called the von Economo neurons (VENs) were found to populate both AI and ACC [65]. Further research showed that VENs had wider axons indicative of a faster neuronal transmission, and thus, the interaction between AI and ACC tends to be quicker. This accelerated transmission can also be observed in the signals originating from the AI and ACC that advances to other regions, including the thalamus [66]. This rapid transmission within the network is why the salience network was studied religiously and assumed to be the switch between the medial

frontoparietal and dorsal frontoparietal networks. The connection between AI and ACC was paramount in managing novel stimuli and its regulatory effect on interactions between cognition, emotions and actions [67]. Structural connectivity of the regions within the salience network is valuable so that these connections can be mapped in an understandable way. Studies on primates have shown that there are observable direct connections between the critical nodes of AI and ACC with regions such as the supplementary motor area (SMA), dorsolateral prefrontal cortex (dlPFC), bilateral supramarginal gyri (SMG), amygdala and thalamus, leading to the conclusion of ACC being a vital region in the translation of motives into action [61].

In addition to the structural connectivity between the AI and ACC, functional connectivity studies, including these two key nodes with other regions, have been studied thoroughly. Functional connectivity of the salience network does not depend on the direct structural tracks between the regions of interest, like the specialized neuronal pathways seen between the AI and ACC. Instead, activation patterns during a task or rest state have been analyzed to see the regions that activate along with AI and ACC. Thalamus is responsible for cognitive flexibility as it is seen to mediate emotions, arousal, and motivations, which is essential in filtering the most relevant stimuli [68]. On the other hand, the amygdala tends to be activated when faced with emotionally heightened stimuli that are novel to a person. AI is also associated with bottom-up salience processing, where one's emotional awareness and feelings go to the AI from the neural activation within the amygdala [69]. In addition to the thalamus and amygdala, the caudate nucleus was found to have close relations with the AI and the ACC, implying that it is one of the subcortical regions of the salience network [70]. In their 2016 review, Peters and colleagues summarized that the caudate nucleus is active during the various tasks that aim to observe cognitive control. Tasks such as the Stroop task and Go-No-Go task aim to study the response selection and inhibition have shown the importance of the caudate nucleus in switching from more inner-directed states to task-based activities [70].

The salience network has been a significant area of research as the regions involved within the network, especially AI and ACC, are the most activated regions

during imaging studies. These regions overlap with other networks and show co-activation under various tasks [59]. As proper activation of the salience network is such a significant process, its dysfunction tends to result in greater impact on the brain's operations. Salience network dysfunction in illnesses has been documented initially through voxel-based morphometry studies, and impairment of the network has especially been highlighted within mental diseases [65]. Disruption in the salience network has been observed in psychiatric illnesses such as obsessive-compulsive disorder, attention deficit, and hyperactivity disorder, and psychotic conditions such as bipolar disorder and schizophrenia [70]. As there are significant correlations between psychotic disorders and disrupted networks, the salience network is justifiably the highlight of imaging studies in such disorders.

1.6 The Relationship Between Psychosis Risk and Brain Structure

The effect of psychosis on brain structure has been studied and reported thoroughly in recent years as the alterations seen in the brain have been observed to correlate with the symptomology of psychotic disorders [71]. It is believed that the alterations observed within the brain start during the prodromal phase of the disorder as it was seen that minor cognitive deficits start during this prodromal phase of the psychosis onset [72]. Research has shown that teenagers and young adults aged between 14 and 23 are the ones experiencing stronger psychotic-like symptoms [73]. It was also seen that the age of onset for psychotic disorders is on the younger side, with the average age of onset being 18 [74, 75]. These findings were further supported by developmental and imaging research as the brain goes through a pivotal developmental stage where the alterations within the brain are fast and connections involved with higher cognitive functions, such as the prefrontal cortex, are matured [75, 76]. The salience network contains regions that go through this fast and critical developmental stage in adolescence and early adulthood, where a disruption in maturation can have psychiatric outcomes [77, 69, 78].

Today salience network is established to be the switch between the default mode and central executive networks; its structural and functional disruption due to psychosis has gained the attention of researchers in recent years [67]. Structural disruption of the salience network refers to the anatomical changes of regions involved within the network. Voxel-based morphometry studies targeting patients with psychotic disorders have shown deficits in the grey matter of the AI and ACC, critical network regions [61]. Although the highest reduction of gray matter is observed within the bilateral insula, a decrease in the ACC and parahippocampal gyrus gray matter follows the AI in this decline [79]. Volumetric studies have also supported the voxel-based morphometry studies in AI along with its cortical thinning and lowered blood flow has been shown with an absolute decrease in the anterior cingulate cortex in psychotic patients [63]. Size reductions in these two key salience regions have been studied further in psychotic disorders where disruptions in the von Economo neurons, specific to the regions above, were found to be diminished in patients [65].

Additionally, volumetric weakening of dlPFC, ventromedial and frontal temporal cortices and hippocampus in patients have been reported [53, 80, 81]. Adding on to these regions, the caudate nucleus shows volume reductions in antipsychotic-naïve patients and its comparable shrinkage was also observed in the clinically high-risk groups [82]. The severity of the symptoms in psychosis was found to be related to the degree of decline in the critical regions of the brain, especially in the frontal cortices, where speedier degradation corresponded to more severe symptomatology [54, 83].

The anatomical deficits of the salience network result in reduced connectivity between brain regions, causing issues in functional communication in people diagnosed with a psychiatric disease, their relatives, or in people at risk of developing such disorders due to their proneness. Identifying and prioritizing the most salient stimuli requires a competent interaction between various brain regions so that task switching and many other high-order cognitive processes go through without issue [61]. Lessened connectivity of the AI and ACC consequently lowers the activity of the network where previously triggering stimuli will not be able to engage the salience network enough to promote the shift between networks and

fails to deactivate the default mode network (DMN) in psychosis [84]. A particular focus is given to AI in salience research where self-monitoring errors of the network were associated with hallucinations, heightened uncertainty with inappropriate associations, problematic information processing with disorganization, and poor goal-oriented activity with psychomotor deficits [63].

Both anatomical and functional dysfunctions in the salience network are the highest in patients with the most extreme symptoms [65]. The lesser the damage in the network, the less severe the disease symptoms. While the decrease in volume and gray matter is the most significant in patients, similar deficits were seen in the first-degree relatives of affected individuals to a lower degree than the patients but higher than the healthy controls [85]. The frequency and severity of psychotic experiences are negatively correlated with the size of the AI and ACC; thus, individuals in the prodromal phase of psychosis onset were seen to show lessened connectivity between salience hubs compared to the healthy group [86]. Parallel patterns of reduced connectivity and structure were also observed in people with a higher risk for psychosis [48]. Individuals prone to psychosis show similar deficits in salience regions with disruption rates depending on where the person is on the psychosis continuum [85]. The higher the risk for psychosis, the faster the shrinkage rate in the salience network areas, where the proper switch between networks is broken.

1.7 The Relationship Between Polygenic Risk Score and Brain Structure

Associative analysis between the polygenic risk scores for schizophrenia (PRS-SCZ) and the alterations observed in the brain structure has increased in the last few years as more information was revealed regarding the brain networks [87]. PRS-SCZ have been associated stronger with the negative symptoms of psychosis compared to the positive symptoms such as hallucinations [39]. Imaging studies have also shown a decrease in cognitive abilities due to the alterations

observed in the brain structure of people prone to psychosis though the direction is not clear [88]. Both genetic liability and structural disruption in brain networks have been shown to increase in people at a higher risk for psychosis [89]. Higher PRS-SCZ correlates with structural and functional alterations within various brain networks in which the salience network is also included [53, 87, 90]. Cortical thinning has been observed in the frontotemporal cortex along with decreased hippocampal volume especially in the left CA 2/3 region in individuals with higher PRS-SCZ [91]. On a similar note, Alloza and colleagues have found reduced cortical thickness in the AI, disruption in the supramarginal gyri and a significant association with auditory hallucinations observed in healthy individuals with high PRS-SCZ [92]. A decrease in cortical thinning of the ventromedial prefrontal cortex (vmPFC) and a volumetric decrease in the hippocampus was found to be related with PRS-SCZ for people found to be at risk for psychosis [93, 94]. Cao and colleagues (2021) presented abnormalities across the whole brain where lessened connectivity in visual, default mode and frontoparietal networks were associated with higher PRS-SCZ. This study has further shown that the deactivation of the default mode network was prolonged in people with higher PRS-SCZ resulting in the disruption of the proper switching mechanism of the salience network and the processing of stimuli, both internal and external [94]. Additionally, Toulopoulou and colleagues and Cao and colleagues found IQ to be negatively correlated with PRS-SCZ, implying that lowered functional connectivity can be observed through the cognitive abilities of affected individuals [94, 95]. Differentiation between patients and healthy control groups has shown more precise results where cumulative gray matter volume differences were demonstrated in various regions, including the thalamus, ACC, basal ganglia and the frontal lobe, with more significant correlations between the hippocampus [81, 89]. These studies imply that abnormalities observed in the salience network go hand in hand with one's genetic liability to psychosis.

1.8 Hypotheses and Goals

Although there has been a multitude of studies examining the genetic liability concerning psychosis, the same cannot be said about psychosis proneness. Additionally, combinatory research including genetic liability to psychosis proneness and brain alterations due to psychosis proneness, has been limited at best, and no studies are available where the participant cohort consists of related individuals or twins in this case. Furthermore, available combinatory research primarily focuses on differentiation between patients and healthy controls and not on the general population, where the symptoms are more subtle. Similarly, the preferred age group in these studies is between 18-65 and not adolescents, where disruptions in the brain structure are drastic from a neurodevelopmental point of view. The maturation of the brain in relation to higher cognitive abilities is observed in adolescents and in young adults where disruptions in this developmental process increase an individual's vulnerability to psychosis [77]. Most of the research on psychosis proneness has been toward early detection so that preventive measures can be taken in people determined to be at risk [96]. The main priority of this earlier research was to understand the role of the default mode network, where its prolonged activation has been associated with the positive symptoms of psychosis [71]. Although the salience network provides the switch between the default mode network and the central executive network, it has not been prioritized in combinatory research between PRS and brain structure in twin cohorts.

Multiple goals have been proposed to highlight functional connectivity and genetic liability in twin samples. The first goal of this study is to understand the relationship between psychosis proneness and genetic liability to psychosis. The second goal is to report how the connectivity of salience network regions changed with increasing proneness to psychosis. A final and third goal was also set to question how psychosis proneness combined with genetic liability scores (PRS-SCZ) affect the salience network in the resting brain.

The following hypothesis was proposed to reach the goals mentioned above of this study: Adolescents who scored higher in psychosis proneness assessments

have higher genetic liability compared to those who scored lower in psychosis proneness. Consecutively, people with higher proneness to psychosis would show lower connectivity in salience network regions such as the anterior cingulate cortex, anterior insula and supramarginal gyri. Following up on these hypotheses, a final hypothesis was set that claims: high psychosis proneness and PRS-SCZ would show lowered functional connectivity in the salience network regions such as the dorsal anterior cingulate cortex, anterior insula, supramarginal gyri and the thalamus.

Chapter 2

Method

2.1 Participants

As part of a larger project on brain development and psychosis research, twins, triplets, and siblings, who have an age gap of at most 24 months between ages 14-23, were recruited (PI Prof. Dr. Toulopoulou). This project has ethics approval from Bilkent University and Ankara University Medical Faculty. Upon the completion of genotyping of 162 twin and sibling pairs and quality control of their respective rsfMRI data, the sample set was divided into high psychosis proneness and low psychosis proneness groups depending on their psychosis proneness assessments. In the final analysis, 73 people were classified as having high psychosis proneness and 73 as having low psychosis proneness. The age of the samples varied between 14 and 24 ($\bar{x} = 19.97$, $SD = 2.63$), with 78 of them being female (53.4%) and 68 of them being male (46.6%). Before beginning each experiment, participants read and signed a consent form with minors requiring at least one signature from their guardians along with the guardians' presence during the procedure. The study excluded any participant with an IQ score lower than 70 and who had a known neurological or psychiatric diagnosis.

2.2 Assessment of Psychosis Proneness

The Turkish version of Community Assessment of Psychic Experience (CAPE), a self-report questionnaire, was used to evaluate the psychotic-like experiences of the participants. CAPE, is a reliable questionnaire created to understand how psychotic experiences are dispersed in the general population [45, 97]. CAPE covers three subdimensions (positive, negative, and depressive) of such experiences to assess each event comprehensively. It is a 42-item instrument with 20 items related to positive symptoms, 14 items associated with negative symptoms and 8 remaining items for the depressive symptoms. Both for frequency and severity of the experience, a 4-point Likert scale was used for scoring. Frequency of symptoms included 'never' (1), 'sometimes' (2), 'often' (3), and 'nearly always' (4), whereas the severity of the symptoms included 'not distressed' (1), a 'bit distressed' (2), 'quite distressed' (3) and 'very distressed' (4) in their respective scales. A person's scores would then fall anywhere between 42 and 168 [88]. Participants were divided into the high psychosis proneness, and low psychosis proneness groups depending on the median total CAPE score, where those who scored lower than the median CAPE value were categorized as low psychosis proneness group and those who scored higher as high psychosis proneness groups [98, 99].

2.3 Calculation of Polygenic Risk Score

Either saliva or blood samples were collected from each participant for genotyping. Saliva was collected using saliva DNA isolation kits at Bilkent University National Magnetic Resonance Research Center (UMRAM), and blood was collected with the aid of Bilkent University Health Center. Genotyping was performed via Illumina's Infinium Psych Array chip for all samples. PLINK (version 2.0; www.cog-genomics.org/plink/2.0/) was used to complete the quality control steps in the collected target data [100]. Variants that passed the quality control included characteristics such as allele frequencies > 0.01, missing call rates

for SNPs < 0.01, and missing call rates for samples < 0.01. Hardy-Weinberg threshold, determined following the analysis on p-value distribution, was set to be 0.01 and variants lower than this threshold were excluded from the analysis. Pruning was performed on the samples to select the variants that were believed to be uncorrelated, given the parameters [101]. Assigned parameters for pruning were a window size of 1500 alleles, a step of 50 variants to shift within the window, and a pairwise r^2 threshold of 0.2 to remove SNPs believed to be in linkage disequilibrium. Zygosity analysis was performed on the pruned samples to compare the reported zygosity of the twins with their genetic one to perform the following analysis accordingly. Principal component analysis in related samples (PC-AiR) was preferred in the sample cohort so that population stratification could be accounted for, and the first ten principal components (PCs) were added to the polygenic risk score calculation. The most recent meta-analysis of the Schizophrenia GWAS study was selected as the base data to compute the polygenic risk scores of the target data [36]. PRSice-2 was used to calculate PRS at 10 different p-value thresholds (0.00000005, 0.000001, 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.5, 1) and PRS values with p-value threshold of 0.05 were selected [96]. Selected PRS values were then standardized for further analysis.

2.4 Acquisition of rsfMRI

3T Siemens Magnetom Trio scanner with a 32-channel head coil was used to collect the resting-state fMRI data of the participants at Bilkent University National Magnetic Resonance Research Center (UMRAM) in Ankara, Turkey. In order to map the functional connectivity, high-resolution T1 weighted structural images were acquired with ensuing parameters: repetition time (TR) = 2600 ms, echo time (TE) = 3.02 ms, slice thickness = 1 mm. 256 x 256 matrix size was used to generate 176 slices during the 7 minutes 18 seconds of T1 imaging. Resting-state fMRI imaging lasted 5 minutes and 04 seconds and generated 150 slices in a 64 x 64 matrix configuration. Parameters used to acquire rsfMRI data were TR = 2000 ms, TE = 35 ms, and slice thickness = 3 mm. During the acquisition of rsfMRI, participants were told to stay awake and be as relaxed as possible.

2.5 Analysis of resting-state fMRI

2.5.1 Preprocessing of rsfMRI

The raw resting-state fMRI data was converted from Dicom filetype to nifti filetype via DICOM2NII software following the removal of the first 5 slices to account for the stability of the scanner. SPM 12 (Statistical Parametric Mapping version 12; http://www.fil.ion.ucl.ac.uk/spm/) and CONN functional connectivity toolbox version 21a (https://www.nitrc.org/projects/conn) were utilized using MATLAB's 22a version for the preprocessing of the rsfMRI data [102]. CONN's default preprocessing pipeline was used for the preprocessing procedure, which includes the functional realignment of the data, slice-timing correction, outlier identification, direct segmentation, and normalization which uses the Montreal Neurological Institute (MNI) template with a functional smoothing set to Gaussian kernel of 8mm full width at half maximum. No outliers were detected during this procedure; thus, all participants were included in the following steps.

2.5.2 Global Correlation Analysis

Following the completion of the preprocessing steps, global correlation analysis was performed via CONN toolbox in MATLAB to check how the global pattern of connectivity is altered between high psychosis proneness and low psychosis proneness groups. In this analysis, the average correlation coefficients of each voxel are computed with respect to the whole brain. This process is highly automatized and can be implemented easily through the default pipeline offered by the toolbox.

2.5.3 Seed Based Connectivity Analysis

Seed-based connectivity analysis was performed to assess how a specific region of interest's average connectivity correlates with other voxels' BOLD response. Seed-based connectivity comparisons were made to assess how salience regions' connectivity patterns within themselves and regions that are closely related to the SN, are altered depending on psychosis proneness. Both seed-to-voxel and region-to-region connectivity analyses were performed in the CONN toolbox to see the connectivity difference in relation to salience seeds with varying voxels as well as to create a Fisher transformed correlation coefficients between each ROI with each voxel's BOLD response called ROI-to-ROI connectivity correlation matrix.

2.5.4 Functional Connectivity Analysis

Following the generation of region-to-region connectivity matrices for all participants during seed-based connectivity analysis, graph-theory results were extracted from the CONN toolbox in MATLAB. All regions of interest or ROIs were termed nodes within the analysis, and the connections that pass the set supra-threshold values were termed edges. The toolbox automatically creates a graph adjacency matrix that contains all the ROI-to-ROI correlation matrices that were thresholded by the absolute threshold of $z > 0.5$. Following the graph adjacency matrix computation, networks can be created by selecting the regions of interest, such as regions of the salience network.

2.6 Statistical Analysis

2.6.1 Demographic Analysis

Demographic characteristics of the sample cohort were compared between different psychosis proneness groups. R software (version 4.2.1.) was used to perform

Chi-square, independent sample t-test, and Mann-Whitney U depending on the normality of the feature. The genetic overlap between siblings and twins was assessed using the Identity-by-Descent method of PLINK software (version 2.0; www.cog-genomics.org/plink/2.0/).

2.6.2 Group Level Analysis

SPM12 was used along with the CONN Toolbox in MATLAB to compute higher-level analysis and to perform group-level comparisons. In addition, General Linear Model (GLM) was selected following the preprocessing procedure.

Global correlation analysis assesses the global patterns of activation of the whole brain, followed by the computation of independent sample t-tests to compare the aforementioned activation patterns between groups. Age, sex, IQ, years in education, and the ten principal component values obtained from the PCAiR analysis were incorporated into the analysis as covariates to account for their confounding effects. FDR corrected p-value threshold of 0.05 was used to correct for possible false positives and to examine the differences in both Low Psychosis Proneness > High Psychosis Proneness and High Psychosis Proneness > Low Psychosis Proneness directions in terms of average connectivity.

Similarly, seed-based connectivity analysis has been conducted for both seed-to-voxel and region-to-region based connectivity so that the connectivity between the selected salience regions and BOLD response at each voxel along with the generation of correlation coefficients between each region can be generated and visualized. Age, sex, IQ, years in education of the participants in addition to the ten principal components were added as covariates in the GLM model. Following the seed to voxel analysis, independent sample t-tests were performed for the selected salience regions to check how connectivity differed between the voxels of interest due to psychosis proneness. Selected regions include the anterior cingulate cortex (ACC), anterior insula (AI), supramarginal gyri (SMG), rostral prefrontal cortex (rPFC), dorsolateral prefrontal cortex (dlPFC), medial prefrontal cortex (mPFC), orbitofrontal cortex, insular cortex, amygdala, thalamus, hippocampus,

caudate nucleus, and putamen. Analysis was conducted in the direction of Low Psychosis Proneness > High Psychosis Proneness and in High Psychosis Proneness > Low Psychosis Proneness so that regions with altered connectivity due to high psychosis proneness could be identified. Following the group-level analysis, the connectivity values for the regions found to be significant were extracted, and clustering of the twins was done to perform clustered independent sample t-tests using the R software (version 4.2.1.) to further account for the relatedness in the sample set.

2.6.3 Functional Connectivity Analysis

Functional connectivity analysis was performed following the generation of region-to-region connectivity matrices. Average connectivity values of each region were conducted within this region to region or ROI to ROI matrices for all samples. Individual-level connectivity values were used to generate a general network for salience network regions that are independent of the connectivity values of other regions. The generated connectivity matrix was then used to extract Fisher transformed z-values and generate the correlation matrix between regions for all samples. Graph theory results for the matrices of all samples were analyzed by setting up an absolute threshold of $z > 0.5$ to select the areas that showed significant activation. Following the creation of the graph adjacency matrix, graph theory metrics called global efficacy and local efficacy were computed via the CONN toolbox in MATLAB. 2 thresholds were set separately for the analysis of all forms of analysis measures; a strict FDR corrected p-value < 0.05 and a more liberal uncorrected p-value < 0.5.

Chapter 3

Results

3.1 Demographics Analysis

R software (version 4.2.1.) was used to perform the statistical analysis. To understand the differences between groups of interest, descriptive statistics were applied. Mean values and standard deviations were given together with the utilization of various statistical tests and their corresponding significance values (p-values). Shapiro-Wilk test was selected to control the distribution of the data and to see whether the data at hand was continuous or not. Sample sizes and outliers were checked before the selection of statistical tests. If the selected parameter was found to be normally distributed, an independent sample t-test was preferred to compare the groups' features. If the distribution did not meet the criteria from the Shapiro-Wilk test, the parameter of interest was compared between groups via the Mann-Whitney Wilcoxon test. Table 3.1. contains the results of the performed descriptive statistics.

The majority of the characteristics of the data set did not show a normal distribution, thus the dominance of the Mann-Whitney Wilcoxon test in the analysis. There was no statistical difference in age between low psychosis proneness ($M = 19.77$, $SD = 2.77$) and high psychosis proneness ($M = 20.18$, $SD = 2.47$) groups

($W = 2449.5$, $z = 15$, $p = 0.40$). Chi-square analysis showed no statistical difference in terms of sex between groups (χ^2 (1, $N = 146$) = 1.35, $p = 0.25$). There was no significant difference in IQ scores between low psychosis ($M = 103.89$, $SD = 15.85$) and high psychosis groups (M =104.30, $SD = 18.74$) ($W = 2402$, $z = 15$, $p = 0.45$). Years of education did not show any significant difference between high psychosis proneness ($M = 14.24$, $SD = 2.55$) and low psychosis proneness groups ($M = 13.64$, $SD = 2.68$) ($W = 2266$, $z = 15$, $p = 0.24$). PRS-SCZ scores between low psychosis (M = - 0.13, $SD = 1.13$) and high psychosis (M = - 0.02, $SD = 0.9$) groups found to be insignificant when proper tests was applied ($W = 2520$, z = - 5.65, $p = 0.57$).

Total CAPE and its resulting dimension scores found significant differences between groups. Total CAPE scores were significantly higher in high psychosis group ($M = 85.59$, $SD = 11.14$) compared to the low psychosis group ($M = 59.90$, $SD = 8.80$) (t (144) = -15.58, $p < 0.001$). In parallel to total CAPE results, significant differences were detected in positive ($W = 451.5$, $z = 15$, $p < 0.001$), negative ($W = 265.5$, $z = 15$, $p < 0.001$) and depressive ($W = 430.5$, $z = 15$, $p < 0.001$) dimension with higher scores detected in the group with high psychosis proneness. Similar observations were also made between groups in the distress scores of positive ($W = 1130.5$, $z = 13.1$, $p < 0.001$), negative ($W = 1135$, $z = 13$, $p < 0.001$) and depressive ($W = 1049$, $z = 14.1$, $p < 0.001$) dimensions.

The zygosity of the samples was computed using PLINK software's (version 2.0; www.cog-genomics.org/plink/2.0/) Identity-by-Descent method to check the genetic overlap between participants. Table 3.2 shows the zygosity results of the included samples. Additionally, PRS-SCZ calculated at different thresholds were compared between the high psychosis proneness and low psychosis proneness group via Mann Whitney-U or independent sample t-test following the normality control via Shapiro-Wilk test. The results can be found in the Appendix, in addition to the correlation analysis of PRS with each dimension of CAPE.

Table 3.1: Demographic Characteristics of Participants Between Groups

	Low Psychosis Proneness	**High Psychosis Proneness**	**Statistic**	***p*-value**
Age	19.77 (2.77)	20.18 (2.47)		0.40
Sex (n, %)			*X2 (1, N=146)= 1.35*	0.25
Male	38 (55.9 %)	30 (44.1 %)		
Female	35 (44.8 %)	43 (55.1 %)		
IQ	103.89 (15.85)	104.30 (18.74)		0.45
Years in Education	13.64 (2.68)	14.24 (2.55)		0.24
PRS-SCZ	-0.15 (1.11)	0.02 (0.9)		0.57
CAPE-42 questionnaire				
Total CAPE	59.9 (8.8)	85.79 (11.14)	t (144) = -15.58	< 0.001 **
Positive Dimension	25.38 (4.37)	34.44 (5.08)		< 0.001 **
Negative Dimension	22.1 (4.44)	32.73 (6.4)		< 0.001 **
Depressive Dimension	11.11 (2.12)	16.56 (3.77)		< 0.001 **
The positive dimension distress	2.77 (1.67)	4.78 (1.92)		< 0.001 **
The negative dimension distress	3.18 (2.17)	5.56 (2.12)		< 0.001 **
The depressive dimension distress	3.32 (1.88)	5.86 (2.33)		< 0.001 **

Table 3.2: Zygosity Analysis of the Samples

	Monozygotic Twin	**Dizygotic Twin**	**Triplet**	**Sibling**	**Total**
Counts	62	62	6	16	146 samples
Pairs	31	31	2	8	72 pairs

3.2 Global Patterns of Connectivity

The difference in activation in salience network regions between low psychosis proneness and high psychosis proneness groups was analyzed using the general linear model (GLM). Participants' sex, age, IQ, years in education, and the ten

principal components obtained from the PCAiR analysis that accounts for relatedness were added as covariates to the applied model. A whole-brain analysis that compares the connectivity difference between the psychosis proneness group shows lowered connectivity in the right region of the superior frontal gyrus (right SFG) (FDR $p < 0.05$) in the group with higher psychosis proneness compared to the low psychosis proneness group. The connectivity values were then extracted, and members of the same family were clustered to perform clustered independent sample t-test to check whether the low connectivity of right SFG in high psychosis proneness group was present when genetic relatedness was accounted for. The results obtained from the clustered independent t-test analysis indicated that the connectivity of the right SFG in regard to the whole brain was significantly lower in the high psychosis proneness group compared to low psychosis proneness group ($p < 0.05$).

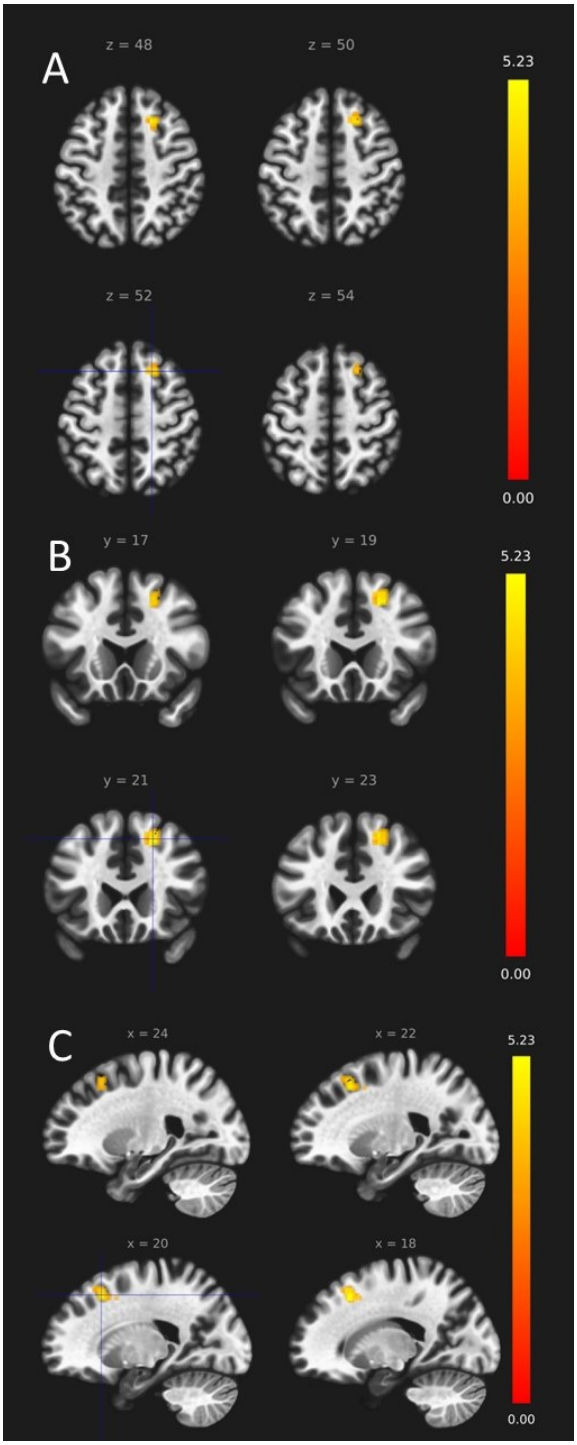

Figure 3.1: Results of whole brain connectivity analysis assessing global patterns of connectivity for the Low Psychosis Proneness > High Psychosis Proneness group (FDR $p < 0.05$). Axial (A), coronal (B) and sagittal (C) planes show the activation of the left Superior Frontal Gyrus on the Montreal Neurological Institute (MNI) template.

3.3 Seed Based Connectivity

Seed-to-voxel analysis of salience network regions produced significant results when an independent sample t-test was applied (FDR $p < 0.05$). The analyses were done in both the Low Psychosis Proneness > High Psychosis Proneness and in the reverse direction of High Psychosis Proneness > Low Psychosis Proneness. Regions showing higher connectivity with the selected seeds in the low psychosis proneness group compared to the high psychosis proneness group can be observed in Table 3.3, and the opposite where regions show higher connectivity in the high psychosis proneness group compared to the low psychosis proneness group can be seen in Table 3.4. As one of the key hubs of the network, anterior cingulate cortex (ACC) was associated with lowered connectivity of the left occipital pole as well as higher connectivity in the right frontal pole for people with lower psychosis proneness. As the second key region, the anterior insula (AI) was associated with higher connectivity with the insular cortex, orbitofrontal cortex and temporal pole; lower connectivity with the posterior cingulate gyrus and precuneus cortex in low psychosis proneness groups. Supramarginal gyri (SMG) were additionally found to produce significantly lowered connectivity with the anterior cingulate gyrus, paracingulate gyrus, posterior cingulate gyrus, frontal pole, while heightened connectivity was observed in the inferior frontal gyrus in low psychosis proneness group compared to high psychosis proneness group. In the high psychosis proneness group, connectivity analysis resulted in higher connectivity between the orbitofrontal cortex and posterior cingulate cortex as well as the thalamus compared to the low psychosis proneness group. Connectivity of regions with the thalamus reached significant levels as lowered connectivity was observed with the cuneal cortex, precuneus cortex and inferior frontal gyrus in the low psychosis proneness group compared to the high psychosis proneness group. The caudate nucleus shows higher connectivity in the low psychosis proneness group with regions such as the precuneus cortex, insular cortex, middle temporal gyrus and supramarginal gyri. Significant associations were finally observed in the amygdala with the higher connectivity observed with the postcentral gyrus, precuneus cortex and superior parietal lobe in the low psychosis proneness group compared to the high psychosis proneness group. Several subregions belonging to

the prefrontal cortex was compared between differing psychosis proneness groups with mPFC reaching significance in its higher connectivity with the orbitofrontal cortex, insular cortex and the temporal pole in the high psychosis group. rPFC has shown significant associations in its higher connectivity of the putamen, caudate nucleus and the accumbens in the low psychosis group. Parahippocampal gyrus was seen to have moderate associations in the activation of the precuneus cortex, posterior cingulate gyrus, thalamus, caudate and the accumbens ($p < 0.05$, uncorrected). Following the extraction of connectivity values in regions found significant in the sample set, members belonging to the same family were clustered together to perform clustered independent t-tests so that genetic relatedness between samples can be accounted for. Following clustered t-tests, only the connections found within the anterior insula has passed the significance threshold ($p < 0.05$).

Table 3.3: Salience network regions with seeds showing higher connectivity in the low psychosis proneness group compared to the high psychosis proneness group (p-FDR < 0.05)

Region of Interest	**Region with Heightened Connectivity**
ACC	Frontal Pole
AI	Insular Cortex
AI	Orbitofrontal Cortex
AI	Temporal Pole
rPFC	Putamen
rPFC	Accumbens
rPFC	Caudate Nucleus
Insular Cortex	Temporal Pole
Insular Cortex	Putamen
SMG	Inferior Frontal Gyrus
Caudate Nucleus	Precuneus Cortex
Caudate Nucleus	Supramarginal Gyri
Caudate Nucleus	Middle Temporal Gyrus
Caudate Nucleus	Insular Cortex
Amygdala	Postcentral Gyrus
Amygdala	Precuneus Cortex
Amygdala	Superior Parietal Lobe
Accumbens	Frontal Pole

Table 3.4: Salience network regions with seeds showing higher connectivity in the high psychosis proneness group compared to the low psychosis proneness group (p-FDR < 0.05)

Region of Interest	**Region with Heightened Connectivity**
mPFC	Orbitofrontal Cortex
mPFC	Insular Cortex
mPFC	Temporal Pole
AI	Posterior Cingulate Cortex
AI	Precuneus Cortex
SMG	Frontal Pole
SMG	Posterior Cingulate Gyrus
SMG	Paracingulate Gyrus
SMG	Anterior Cingulate Gyrus
Insular Cortex	Thalamus
Insular Cortex	Posterior Cingulate Cortex
Thalamus	Cuneal Cortex
Thalamus	Precuneus Cortex
Thalamus	Inferior Frontal Gyrus
Orbitofrontal Cortex	Posterior Cingulate Cortex
Orbitofrontal Cortex	Thalamus

3.4 Functional Network Topology

ROI-to-ROI analysis did not show any significant correlations when the strict FDR corrected p-value of 0.05 was set as the threshold but showed results when a more liberal uncorrected p-value of 0.05 was applied. The connectivity correlation matrix generated from this analysis were then used for the graph theory analysis, following the generation of Fisher transformed z-values for the region-to-region connectivity. Selected regions for the network nodes were: ACC, AI, SMG,

dlPFC, orbitofrontal cortex, superior frontal gyrus, thalamus, caudate, parahippocampal gyrus, hippocampus, and amygdala. When the strict p-value threshold of FDR corrected 0.05 was applied to the analysis measures, none of the metrics, both global and local, returned significant results. When the more liberal p-uncorrected < 0.5 was applied to the analysis, global and local efficacy metrics returned associations between the ACC, AI, SMG, caudate nucleus, orbitofrontal cortex, amygdala, thalamus, and hippocampus.

Chapter 4

Discussion and Conclusion

The main goal of this thesis was to understand whether the genetic liability to psychosis increased the scores in psychosis proneness assessments and whether it caused changes in the brain structures primarily belonging to the salience network. A secondary aim of this thesis was to report how activation of the salience network is altered in people with high psychosis proneness compared to people with low psychosis proneness. Resting-state functional magnetic resonance imaging (rsfMRI) was used to assess the activity of the resting brain in siblings and twins aged between 14 and 23. Confounding factors such as the participant's age, sex, IQ, the ten principal components derived from the PCAiR analysis to account for genetic relatedness and years of education were controlled for in all of the analyses that were performed.

The main findings of this thesis include: (1) there were no significant differences in genetic liability scores for psychosis between high psychosis proneness and low psychosis proneness groups; (2) Superior frontal gyrus showed decreased activation in people prone to psychosis on the whole brain level compared to the individuals with lower psychosis proneness; (3) Seed to voxel analysis showed significant differences between psychosis proneness groups within the regions of the salience network; (4) graph theory analysis created with the salience network regions did not show significant network topologies between psychosis proneness

groups.

This thesis replicated some of the connectivity differences observed due to increased levels of psychosis proneness at the seed to voxel-level and whole brain level. At the whole brain level, the right superior frontal gyrus showed decreased connectivity patterns in the global correlation analysis for high psychosis proneness group. In previous studies, the superior frontal gyrus (SFG), have been found to be connected with the key regions of the SN, DMN and CEN [103]. Hu and colleagues have associated the right SFG connectivity with better response inhibition in Go-No Go tasks, indicating that lowered connectivity of the right SFG may result in lessened control in restraining responses [104]. Connectivity of the right SFG was significantly lower in the high psychosis proneness group, indicating that response inhibition may be lower in individuals with higher psychosis proneness. The relation between decreased response inhibition and increased impulsivity was previously reported by various studies, and the results obtained in this thesis are in support of these previous observations [105, 104].

Seed-based connectivity analysis was divided into seed-to-voxel analysis and region-to-region analysis. In seed-to-voxel analysis, regional connectivity differences of salience network regions between the psychosis proneness groups were compared. In this type of analysis, the connectivity between the selected seed and all the available brain regions was compared between psychosis proneness groups. Following the independent sample t-test comparisons between groups, connectivity values for regions that produced significant results were extracted for clustered independent t-tests to account for the relatedness of the samples. Although, there were significant connectivity differences between psychosis proneness groups in salience network regions and regions closely correlated with the salience network, not all passed the significance levels following the clustered independent sample t-test analyses. Differential connectivity between groups can indicate how the functionality of the salience network may be disrupted while switching between DMN and the CEN and vice versa. As a task-based fMRI scan was taken right before the start of the resting state FMRI, the participants' CEN was expected to be more active with the switch from CEN to DMN expected to occur during the resting state fMRI scan. Compared to the high psychosis proneness group,

the low psychosis group demonstrated a higher connectivity between the ACC and the frontal pole; AI with the insular cortex and the temporal pole; caudate with the insular cortex, SMG and the temporal pole; superior frontal gyrus with SMG when the selected seed's average time-series were associated with the average BOLD timeseries of the regions that were mentioned. Similarly, the average BOLD response was lowered between the ACC and the occipital pole; AI with the posterior cingulate cortex (PCC) and the precuneus cortex; SMG with ACC and PCC; SFG with the frontal pole; amygdala with SMG and finally, thalamus with the cuneal when the selected seed and voxels average BOLD time-series were taken into the analysis. As the regional connectivity of the salience network seeds included regions from both the DMN and the CEN, it can be said that the switch is happening between the network following the completion of the task-based fMRI. As the switch between networks is expected to be faster in individuals with lower psychosis proneness, lowered connectivity to some of the salience regions as well as the DMN were expected as the brain returns to default mode due to the speedy switch that would then result in a lowered BOLD timeseries between the salience seed and the voxel in question.

However, only the regions showing different connectivity patterns with the anterior insula were found significant following the clustered independent sample t-test analysis that accounts for the genetic relatedness of the samples. In addition to being a core region of the salience network, anterior insula is involved in processing various aspects of experience ranging from sensory stimuli to decision-making [106]. In the results obtained from this thesis, it was seen that the high psychosis proneness groups had higher connectivity observed in AI with the PCC and the precuneus cortex, which indicates that in people with high psychosis proneness, the connections between the salience network and the default mode network are stronger. This result is similar to research that studies the switch mechanism in psychosis, where patients diagnosed with a psychotic disorder have stronger connectivity with the DMN and do not easily switch from the DMN to CEN in the case of salient stimuli [61].

Graph theory analysis was performed in this thesis to observe the inherent functional connectivity of the salience network [107]. Although none of the metrics

assessing functional connectivity provided significant associations with any of the selected SN nodes, when more liberal, uncorrected thresholds were applied, some associations were found with the nodes in question. Although no significant network topology was detected even with different analysis metrics, when more liberal thresholds were applied, several SN regions were associated with psychosis proneness in the Low Psychosis Proneness > High Psychosis Proneness direction. When the global efficacy metric was utilized with p-uncorrected < 0.5, positive associations were observed for the low psychosis group and the orbitofrontal cortex, bilateral thalamus, bilateral SMG, and left caudate, while negative associations were made between low psychosis proneness and the right amygdala and right hippocampus. With local efficacy metric and p-uncorrected < 0.5 threshold, positive associations were observed between low psychosis proneness and the right caudate, superior frontal gyrus, right orbitofrontal cortex and the left amygdala and negative associations were made for the left thalamus and left hippocampus. Positive associations indicate that when psychosis proneness is lower, regions that show positive associations are connected with the network using the shortest topological distances. Thus, positive associations in the low psychosis group imply that the switch between the DMN and CEN networks is fast and that when psychosis proneness is low, the person can assess the most salient stimuli appropriately. Finally, as the speed of connectivity decreases with increasing psychosis proneness, the individual is expected to stay longer in the DMN, and the switch to CEN takes longer [67].

This thesis focused on twins and siblings between the ages of 14 and 23, as this age range is crucial in the development of brain networks which is essential for accurate information processing [108]. Developmental research has shown that connectivity within the DMN and CEN increases with age, implying that information processing continues to develop during adolescence and early adulthood [108, 109, 110]. Unlike the more general connectivity increases observed within the DMN and CEN, SN development shows that with increasing age, connectivity of the ACC and AI increases with regions belonging to the frontal cortex, such as the superior frontal cortex and the subcortical regions such as the amygdala [108, 111]. On the other hand, a decrease in connectivity was replicated multiple

times between the core regions (ACC and AI) and mPFC [112]. When correlation analysis of the regions was found significant in the performed global correlation and seed-based connectivity analysis, it was seen that age was positively correlated with the connectivity between the AI and the temporal pole. Furthermore, age was positively correlated with the connectivity between the insular cortex, putamen, temporal pole; between the thalamus, orbitofrontal cortex and inferior frontal gyrus; between the caudate and temporal pole. The results of these correlation analyses replicate some of the findings of developmental research on the SN, and significant results obtained from the correlation analysis between age and SN regions can be found in the appendix [113]. Graph theory analysis was performed for all participants to see how age affected the SN connectivity, stronger connectivity for the frontal cortices and the amygdala was observed at a liberal threshold. When the liberal results obtained from the graph theory analysis of group-level comparison were taken into account, the low psychosis proneness group gave expected salience network connectivity values by itself and when compared with the high psychosis proneness group. SN development was also studied in relation to psychotic disorders where the expected developmental patterns in connectivity were not observed, which further supports the findings of aberrant SN connectivity with both the DMN and the CEN due to psychosis [114].

This thesis included 72 twins/siblings/triplet pairs in the analysis. Participants were divided into low and high-psychosis proneness groups by the median split of their CAPE-42 scores. Thirty of the twins/sibling pairs were discordant in the psychosis proneness groups they were assigned to, and out of the 30 pairs, 16 were monozygotic twins, 10 of them dizygotic twins, and 4 of them were siblings. Within twin, correlation analysis was performed additionally to get an idea of whether a feature is mostly genetic, environmental, or both. Correlation analysis performed for CAPE, although gave significant results, its correlation coefficient for MZ twins ($r(30) = 0.64$, $p < 0.01$) was not twice the correlation coefficient for DZ twins ($r(28)=0.40$, $p < 0.05$) indicating that both additive genetics and a shared environment may play a role in psychosis proneness. Similar results were also observed for the WASI scores, with MZ twins having a correlation

coefficient of $r(30) = 0.70$, $p < 0.01$, and DZ twins having a correlation coefficient of $r(27) = 0.41$, $p < 0.05$. The only connectivity value passing the significance threshold was the connection between the insular cortex and the temporal pole, where the correlation coefficients were equal for both MZ ($r(30) = 0.52$, $p < 0.01$) and DZ twins ($r(26) = 0.56$, $p < 0.01$). As significant differences were not observed between the MZ and DZ twins, the results imply that shared and unique environmental factors might be more important and should be studied in further research with the samples [115].

This study has several drawbacks in its methodology. The first limitation is the number of samples used within the study, which is small. Secondly, this study mainly comprises participants with genetic overlap: siblings and dizygotic twins, who share 50% of their genetic makeup, and monozygotic twins, who share 100% of their genetic makeup. As most studies that prefer to use the PRS-SZ scores require at least 300 or more independent samples to capture the proper distribution of genetic liability in the population, the PRS-SZ scores may not reflect the population's genetic liability to psychosis proneness in a reliable fashion due to the genetic similarities. Another limitation of this thesis was the parameters set in the resting state fMRI where regions known to be involved in the salience network such as the parahippocampal gyrus, hippocampus, amygdala and the cerebellum couldn't be included in the window set in the task for all participants. Even though a portion of the samples contained these regions where their connectivity values could be extracted, not all generated connectivity values for these regions, which may alter the comparison tests performed between psychosis proneness groups. In addition, only salience network regions were selected for connectivity analysis. As the salience network's main function is to switch between DMN and CEN connectivity analysis with salience regions in addition to DMN and CEN regions may provide insights to the switch mechanism of the network [67]. Future studies that replicate the study with an increased number of samples and by selecting regions from DMN and CEN along with the SN may provide a fuller picture of connectivity in psychosis proneness.

In conclusion, increased psychosis proneness shows decreased connectivity within the salience network of the brain in adolescents and in young adults. However,

the effect of genetic liability didn't show any significance in between psychosis proneness groups as well as the functional connectivity analysis. These results indicate that psychosis proneness has a significant impact on the levels of functional connectivity within the salience network of the brain but the difference in seed-based connectivity was not due to the genetic liability of an individual to psychosis.

Appendix A

Appendix

Table A.1. shows the mean (M) and standard deviation (SD) of PRS-SZ for low and high psychosis proneness groups calculated at different p-value thresholds (P_T $< 5\times10^{-08}$, 1×10^{-06}, 1×10^{-04}, 1×10^{-03}, 0.01, 0.05, 0.1, 0.2, 0.5, 1). For all 10 different PRS-SCZ values calculated at different thresholds, independent sample t-test was used with family ID's being the clustering coefficient. No significant results between psychosis proneness groups were found. PRS score with the p threshold of 0.05 was selected to be consistent with the latest PGC results [36].

Table A.1: Statistics of PRS-SCZ scores for low and high psychosis proneness groups calculated at different p-value thresholds

Polygenic Risk Score (PRS)	p-value cut off	Low Psychosis Proneness N = 73		High Psychosis Proneness N = 73	
		Mean	SD	Mean	SD
Level 1	5.0e-8	-0.07	1.13	0.08	0.90
Level 2	1.0e-6	-0.03	1.18	0.04	0.83
Level 3	1.0e-4	-0.02	1.19	-0.05	0.80
Level 4	1.0e-3	-0.08	1.17	-0.01	0.81
Level 5	1.0e-2	-0.09	1.10	-0.01	0.93
Level 6	5.0e-2	-0.15	1.11	0.02	0.92
Level 7	1.0e-1	-0.15	1.10	0.00	0.92
Level 8	2.0e-1	-0.15	1.07	0.00	0.98
Level 9	5.0e-1	-0.16	1.04	0.03	1.00
Level 10	1.0e+0	-0.17	1.06	0.02	0.99

Pearson correlation analysis were performed with all 10 PRS-SCZ values calculated with different p-value thresholds with the dimensions of CAPE questionnaire. The results are presented in Figure A.1 for the analysis between PRS-SCZ ($P_T = 0.05$) with the dimensions of the CAPE. PRS-SCZ and CAPE ($r(144)$=0.05, p=0.56) was not found to be significantly correlated. Correlation analysis between PRS-SCZ and positive ($r(144)$=-0.04, p=0.65), negative ($r(144)$=0.10, p=0.23) and depressive ($r(144)$=0.07, pp=0.42) dimensions of CAPE didn't produce significant results. In addition, PRS-SCZ did not significantly correlate with the positive ($r(144)$=-0.01, p=0.89), negative ($r(144)$=0.07, p=0.07) and depressive ($r(144)$=0.06, p=0.49) dimension distress scores of CAPE. Correlation analysis between CAPE dimensions and remaining PRS-SCZ values did not produce any significant correation results as well.

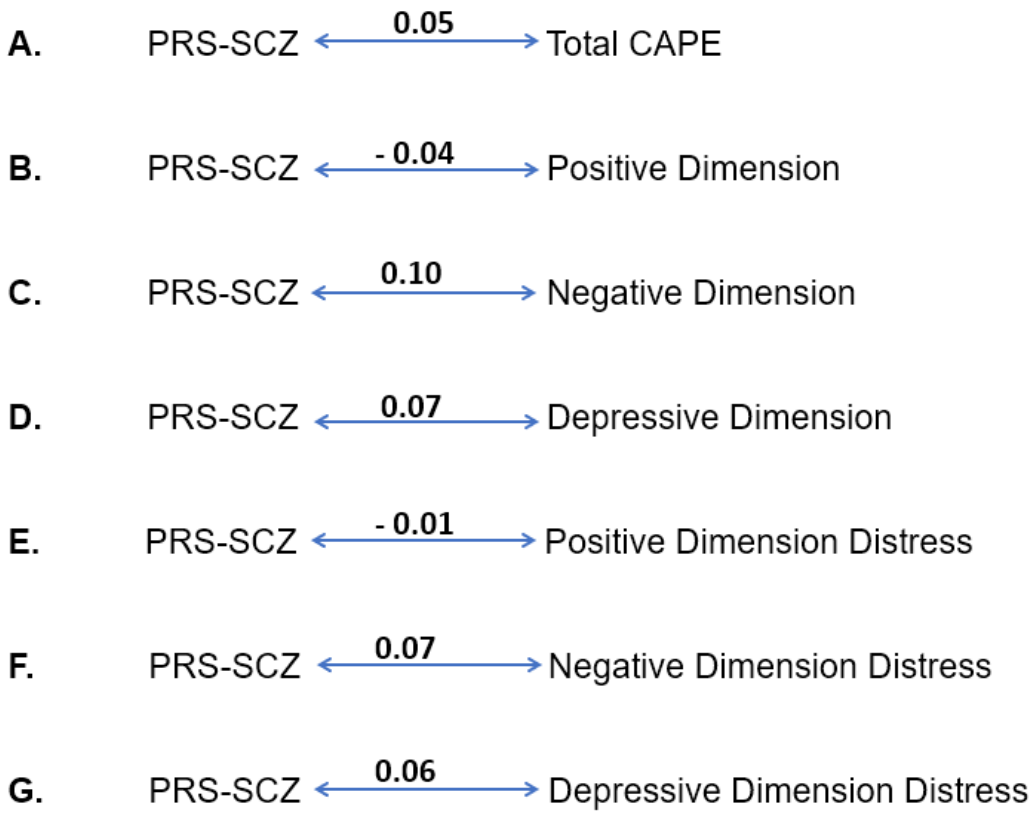

Figure A.1: Correlation between PRS-SCZ (P_T = 0.05) and CAPE dimensions performed via Pearson correlation analysis.

Pearson correlation analyses were performed for age and seed-based connectivity results of SN regions. Correlation analysis was first performed in connections that were found significantly higher in the low psychosis proneness group compared to the low psychosis proneness groups. The connections between AI and temporal pole ($r(139)$=0.25, p<0.01); insular cortex and temporal pole ($r(142)$=0.23, p<0.01); caudate nucleus and temporal pole ($r(142)$=0.21, p<0.05) were found to significantly correlate with age (Figure A.2). Similarly, Pearson correlation analysis was performed in regions with significantly higher connections in the high psychosis proneness group compared to low psychosis proneness groups. The connectivity between thalamus and inferior frontal gyrus pole ($r(141)$=0.17, p<0.05) and the connectivity between the orbitofrontal cortex and thalamus pole ($r(134)$=0.21, p<0.05) was found to significantly correlate with age (Figure A.3).

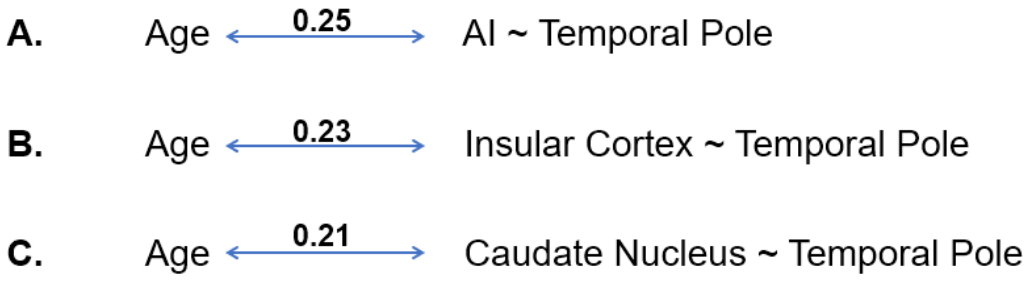

Figure A.2: Correlation analysis between age and connections that were significantly higher in the low psychosis proneness group compared to the high psychosis proneness group.

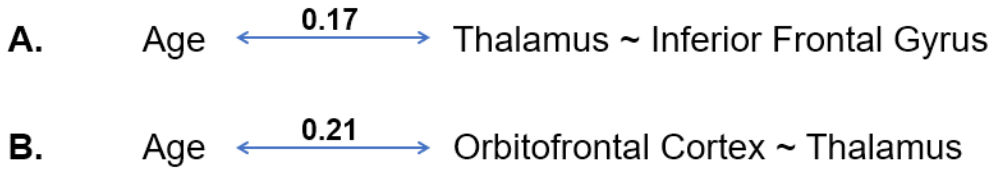

Figure A.3: Correlation analysis between age and connection that were significantly higher in the high psychosis proneness group compared to low psychosis proneness group.

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