MAPPING GENETIC RISK FOR SCHIZOPHRENIA ONTO THE TRIPLE NETWORK ACROSS ADOLESCENT DEVELOPMENT: A LONGITUDINAL STUDY

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Mapping Genetic Risk for Schizophrenia onto the Triple Network Across Adolescent Development: A Longitudinal Study
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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

MAPPING GENETIC RISK FOR SCHIZOPHRENIA ONTO THE TRIPLE NETWORK ACROSS ADOLESCENT DEVELOPMENT: A LONGITUDINAL STUDY

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The Triple Network Model, which includes the Default Mode Network (DMN), Frontoparietal Network (FPN), and Salience Network (SN), is a core model for schizophrenia and explains all the positive, negative, and cognitive symptoms. Many studies demonstrated the importance of the Triple Network Model in schizophrenia; however, no longitudinal study has yet examined the between-network connectivity among the three Triple Network systems in healthy adolescents. To address this gap, we conducted a one-year investigation of between-network functional connectivity during typical development and assessed how genetic liability to schizophrenia moderates these changes. In this thesis, 89 pairs of twins and siblings were recruited and underwent resting-state fMRI at baseline and one-year follow-up, with ROI-to-ROI functional connectivity values computed separately for each session. Participants also completed the CAPE-42 to assess subclinical psychotic symptoms and provided blood or saliva samples for genotyping to derive schizophrenia polygenic risk scores (PRS-SCZ). Using linear mixed-effects models, we evaluated (1) whether significant longitudinal connectivity changes occurred, (2) whether PRS-SCZ moderated these longitudinal changes, and (3) whether connectivity changes were associated with subclinical psychotic symptom scores (total, positive, negative, and depressive). We found no significant time effect from baseline to follow-up; however, PRS-SCZ significantly moderated connectivity trajectories, with higher PRS-SCZ associated with greater increases in FPN–SN, DMN–SN, and DMN–FPN connectivity. Specifically, PRS-related enhancements were observed in the connections between left lateral prefrontal cortex (LPFC)–left supramarginal gyrus (SMG), left posterior parietal cortex (PPC)–right rostral prefrontal cortex (RPFC), right

PPC–right SMG, left anterior insula (AI)–left lateral parietal cortex (LP), left PPC–left posterior cingultae cortex (PCC), and right PPC–right PCC. None of these PRS-modulated connectivity changes, however, were significantly associated with changes in subclinical symptom scores. The PRS-SCZ–related connectivity increases paralleled patterns observed in patients and other high-risk groups, suggesting that these alterations may reflect early neurodevelopmental mechanisms underlying schizophrenia pathology before the emergence of clinical symptoms. These findings highlight the potential of Triple Network Model functional connectivity as an early biomarker of schizophrenia risk and underscore the need for extended longitudinal follow-up to capture non-linear developmental trajectories.

Keywords: Triple Network Model, Resting-state fMRI, ROI-to-ROI Functional Connectivity, Longitudinal Study, Schizophrenia Polygenic Risk Score, Subclinical Psychotic Symptoms.

ÖZET

ŞİZOFRENİ GENETİK RİSKİNİN ADOLESAN GELİŞİMİ BOYUNCA ÜÇLÜ AĞ MODELİNE HARİTALANMASI: BOYLAMSAL BİR ÇALIŞMA

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Varsayılan Mod Ağ (DMN), Frontoparietal Ağ (FPN) ve Salience Ağ'dan oluşan Üçlü Ağ Modeli şizofreninin pozitif negatif ve kognitif semptomlarını açıklayan çekirdek bir ağdır. Çok sayıda çalışma, Üçlü Ağ Modeli'nin şizofrenideki önemini ortaya koymuştur; ancak sağlıklı adolesanlarda bu üç ağ arasındaki ağlar arası bağlantıyı boylamsal olarak inceleyen bir çalışma henüz yapılmamıştır. Bu boşluğu doldurmak amacıyla, normal gelişim sırasında ağlar arası fonksiyonel bağlantı değişimlerini bir yıllık sürede araştırtık ve şizofreniye genetik yatkınlığın (PRS-SCZ) bu değişimleri nasıl etkilediğini inceledik. Tez kapsamında, 89 ikiz ve kardeş çifti en az bir yıl arayla çalışmaya dahil edildi. Her iki zaman noktasında da dinlenim durumu fMRI çekimleri yapıldı ve ROI-ROI yöntemiyle fonksiyonel bağlantı değerleri her oturum için ayrı ayrı hesaplandı. Ayrıca, subklinik psikotik semptomların ölçülmesi amacıyla CAPE-42 anketini her iki deney oturumunda da tamamladı. Buna ek olarak, katılımcıların şizofreni poligenik risk skorları (PRS-SCZ) kişilerden toplanan kan veya tükürük örnekleri sayesinde hesaplandı. Lineer karma modeller kullanılarak (1) anlamlı bir boylamsal bağlantı değişikliği olup olmadığı, (2) PRS-SCZ'nin bu değişimleri nasıl etkilediği ve (3) bağlantı değişikliklerinin subklinik psikotik semptom skorları (toplam, pozitif, negatif, depresif) ile ilişkisi değerlendirildi. Sonuç olarak, başlangıç ve bir yıllık takip arasında anlamlı bir zaman etkisi bulunmadı; ancak PRS-SCZ, FPN–SN, DMN–SN ve DMN–FPN bağlantılarındaki değişim yollarını anlamlı biçimde değiştirdi; yüksek PRS-SCZ, bu ağlardaki daha büyük artışlarla ilişkilendirildi. Özellikle, yüksek PRS-SCZ'li bireylerde sol lateral prefrontal korteks (LPFC)–sol supramarjinal girus (SMG), sol posterior parietal korteks (PPC)–sağ rostral prefrontal korteks (RPFC), sağ PPC–sağ SMG, sol anterior insula (AI)-sol

lateral parietal korteks (LP) , sol PPC–sol posterior singulat korteks (PCC) ve sağ PPC–sağ PCC bağlantılarında artış gözlendi. Fakat fonksiyonel bağlantı değişiklikleri PRS-SCZ tarafından modüle edilen bağlantılar ile subklinik psikotik semptom skorlarının değişimleri arasında anlamlı bir ilişki bulunmadı. Dolayısıyla, PRS-SCZ'ye bağlı bu bağlantı artışları, hasta ve yüksek riskli gruplarda gözlenen örüntülerle paralellik taşıyarak semptomlar ortaya çıkmadan önce şizofreni patolojisinin erken nörogelişimsel mekanizmalarına işaret ediyor olabilir. Bu bulgular, üçlü ağ modelinin ağları arasındaki fonksiyonel bağlantıların şizofreni riskine yönelik erken bir biyobelirteç potansiyeline sahip olduğunu vurgularken, doğrusal olmayan gelişimsel izlerin ortaya konması için daha uzun süreli boylamsal çalışmaların gerekliliğini ortaya koymaktadır.

Anahtar sözcükler: Üçlü Ağ Modeli, Dinlenim Durumu fMRI, ROI-ROI Fonksiyonel Bağlantı, Boylamsal Çalışma, Şizofreni Poligenik Risk Skoru, Subklinik Psikotik Semptomlarm.

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For this thesis, I analyzed data from 164 participants. MRI data of the 36 participants and genetic samples of the 130 participants were collected by me. All the genetic, neuroimaging, and statistical analyses conducted in this thesis are performed by me. The remaining data were gathered by graduate students supervised by Professor Toulopoulou, including Timucin Baş, Rabia Şen, Kübra Çelikbaş, Tuba Şahin İlikoğlu, Seda Arslan, Didenur Şahin Çevik, İlayda Aydoğan, Su Karakelle, Eda Gül Karaca, and Hande Ezgi Atmaca Turan.

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Chapter 1

Introduction

1.1 Brief Overview of Schizophrenia

Schizophrenia is a term first used by Eugen Bleuler in 1908 for the disease formerly known as dementia praecox [2]. According to Eugen Bleuler, the psychic functioning of patients with dementia praecox split, thus he suggested the word schizophrenia to explain this fact, which is rooted in two Greek words, schizoid (splitting) and *phren* (mind) [2, 3]. Nowadays, it is known that schizophrenia is a severe neuropsychiatric disorder that affects both cognition and behavior [4]. This debilitating mental illness manifests various symptoms; however, it is possible to classify these symptoms into three classes as positive symptoms, negative symptoms, and cognitive symptoms. While the symptoms with extra perception or thoughts, such as hallucinations or delusions, are known as the positive symptoms, the symptoms with a lack of normal thoughts or behaviors, like diminished emotional expression or avolition, are known as the negative symptoms. In addition to these, abnormalities in executive functions, attention and memory deficits, and verbal fluency disorders are known as cognitive symptoms[3, 5]. Among these symptoms, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) considers five of them for diagnostic criteria, which are delusions,

hallucinations, disorganized speech, also known as core positive symptoms, disorganized or catatonic behaviors, and negative symptoms [3]. People who have at least two symptoms out of these five, one of which is a core positive symptom, are diagnosed with schizophrenia, and this diagnosis is generally made in late adolescence and early adulthood[5],[6].

These symptoms can also be observed in the form of subclinical psychotic symptoms. However, subclinical psychotic symptoms differ from the clinical symptoms by frequency, severity, and conviction [7]. For that reason, it does not imply that people with subclinical symptoms are always schizophrenic; instead, it could be people on the psychosis spectrum, people with psychosis proneness, or healthy people. Subclinical psychosis symptoms in healthy individuals can be related to different perception and thinking styles, mood disorders. For instance, low optimism, identification with the items, substance use, and physiological state may reflect these symptoms. Also, the age of the individuals is known as a factor that affects the subclinical psychotic symptoms. Therefore, these symptoms are considered both normal and an also an early predictor of the disease. Due to that, subclinical psychotic symptoms are assessed in the studies in several ways, and one of the most common instruments for that is the Assessment of Psychic Experiences (CAPE-42) [7, 8, 9].

Age of onset for schizophrenia differs between sexes: males are typically diagnosed in their mid-20s, while females are usually diagnosed in their late 20s. Apart from that, although it accounts for a small portion of cases, late-onset schizophrenia can be seen after the age of 40 and is more frequent in women as a result of decreasing estrogen within menopause[6],[10].

The lifetime prevalence of schizophrenia is 4.0 per 1000 people [11], while this statistic is estimated as 8.9 per 1000 in the Turkish population [12]. Prevalence between sexes varies in different populations and samples. In the Turkish population, it was found that males are at a higher risk group for psychosis compared to females; on the other hand, no sex difference was found in a worldwide study[6, 12]. The average life span of individuals with schizophrenia is 15 years shorter than that of healthy individuals, owing to increasing suicide tendencies

as well as the more frequently seen infectious, cardio-respiratory, and metabolic diseases[4].

Studies showed that schizophrenia is a complex disease that is caused by both genetic and environmental risk factors. Twin studies examined the genetic component of schizophrenia and showed that the overall heritability estimate is 80%[12], and the remaining 20% is not heritable and stems from environmental risk factors, gene and environment interactions, and de novo mutations[13]. The presence of individuals with schizophrenia with no family history or first-degree relatives with schizophrenia proves that a single gene with a large effect is not valid for schizophrenia, as in Mendelian diseases. Within the developing genome-wide association studies (GWAS), it has been identified that there are 108 genetic loci that are associated with schizophrenia[14] and the genetic liability to schizophrenia is based on numerous common alleles (MAF $>$ 1%) with small effect sizes, as well as the rare copy number and coding variants[13]. Single-nucleotide polymorphisms (SNPs) account for 25 % of the heritability of schizophrenia, and only 2-3 % of the liability to schizophrenia can be explained by the genome-wide significant SNPs[13],[15]. Studies that focus on the non-heritable environmental risk factors revealed that obstetric complications such as stress and malnutrition during pregnancy, prolonged labor, and neonatal hypoxia are some of the environmental hazards that predispose to schizophrenia,[16]. Moreover, urban birth and rearing, drug usage such as cannabis, immigration, and other social adversities are reported as the other environmental factors that significantly contribute to the emergence of the disease[16].

1.2 Brain Development and Schizophrenia

Brain development is a complex and dynamic process that starts in the third gestational week and continues until the mid-to-late 20s [17],[18]. The process begins with neurulation in the womb, followed by neurogenesis, migration, differentiation, synaptogenesis, synapse pruning, and myelination in an overlapping manner [19]. The majority of brain development is completed in the prenatal period and

early childhood years. Basic brain structures, sensation, and perception systems are fully established in these years, and the rate of developmental changes is highest in these stages. In childhood, the brain continues to develop gradually, and when the adolescent years (10-19) arrive, another peak is observed in the rate of developmental changes in the brain. The changes that occur during adolescence improve previously developed sensory and perception systems with the help of experiences, in addition to other systems such as the limbic system and frontal lobe, particularly the prefrontal cortex, which regulates emotions and higher-level cognitive functions like decision-making and memory[17],[19],[20],[21]. The aforementioned improvements in the neurocircuits are possible through synaptic plasticity, which is a process that enables a person to learn and adapt to new skills. Although this process positively contributes to brain maturation, it might also raise the vulnerability of individuals [17]

Previous studies have demonstrated that the sole factor influencing brain development is not genetic; rather, environmental factors have a significant impact on brain development. Drug abuse, cocaine, nicotine, alcohol consumption, eating and sleeping habits, sex hormones raised within puberty, psychosocial factors such as physical and economic status, and stress are the factors that negatively affect brain maturation by weakening the plasticity, increasing pruning, and altering the rewiring process both in the childhood and adolescent years[17],[19] Thus, it was explicitly stated that both genetic and environmental factors should be optimal, and the required input should be ensured for normal and healthy brain development[18].

The neurodevelopmental hypothesis of schizophrenia is a concept that suggests that when the brain does not develop properly, together with the accumulating effect of the various risk factors, the likelihood of an individual having schizophrenia substantially rises [18],[22]. Since the first proposal of the modern neurodevelopmental hypothesis of schizophrenia (NDH) by Weinberger in 1987, [23] multiple studies have been conducted to understand which factors cause abnormal brain development to elevate schizophrenia risk, and various evidence on different domains that support the neurodevelopmental hypothesis[18],[22]. In a broad sense, genetic alterations combined with prenatal and perinatal complications lead to

vulnerabilities in the neural system, and when social and environmental factors are added, the emergence of schizophrenia becomes inevitable. Although some risks originate early in life and the onset typically occurs in adulthood, schizophrenia may manifest earlier through motor abnormalities, delayed language development, and prodromal symptoms. Studies examining these causal factors have identified several influential risk factors for schizophrenia, including being born during winter months or in urban settings, prenatal exposure to infections such as influenza or rubella, famine during pregnancy, rhesus incompatibility, and other birth complications. Furthermore, linkage and allelic association studies have reported mutations in genes involved in brain development, such as neuregulin 1 and dysbindin, as genetic contributors increasing the risk for schizophrenia[16],[22].

1.3 Brief Overview of Polygenic Risk Score for Schizophrenia

The polygenic theory of schizophrenia was first proposed in 1967 by Gootsman and Shields based on the results obtained from a twin study[24]. Although there is evidence for the polygenic nature of schizophrenia, the genetic architecture of it, just like the other complex disorders, could not be fully explained in the pre-genomics area [25]. In the last 25 years, within the completion of the Human Genome Project, genome-wide association studies (GWAS) showed sharp growth, and this eased the research on the complex genetic traits and disorders by identifying the trait-associated genetic variants[25],[26] and helped to understand the etiology of the diseases[27]. Nowadays, psychiatric disorders and some other diseases that do not follow the Mendelian patterns and depend on the combined contribution of multiple genes are known as complex disorders and diseases, and it is known that they are actually polygenic [27],[28].

To elucidate more on these traits and diseases, researchers developed several statistical techniques. In 2011, GCTA (Genome-wide Complex Trait Analysis) that uses mixed models and GREML (genomic-relatedness-based restricted

maximum-likelihood) approach was developed and enabled to estimate the phenotypic variance explained by all SNPs[29]. Currently, this method can be used for heritability, genetic correlation, and phenotype prediction. Another approach is LD Score Regression, which relies on regression analysis of LD scores of the variants against the GWAS test statistics and reveals whether test statistics are inflated due to the bias stemming from population structure or real polygenicity; hence, the accurate heritability of the variants can be estimated in a bias-free manner [27],[30]. While both GCTA and LD score regression can predict the heritability of complex traits and disorders efficiently, they lack the ability to make a prediction on the individual level, in contrast to another commonly used method, polygenic risk score calculation [31]

Polygenic risk score (PRS), also known as polygenic score (PGS) calculation, can be defined as a method that quantifies an individual's genetic predisposition to a trait or a disorder based on the genetic profile[26]. In broad terms, the general framework for calculating these scores, typically derived from the weighted sum of SNPs associated with schizophrenia in GWA studies, whose minor allele frequency (MAF) is between 1% to 5%, was first conceptualized by Wray et al. [32, 25],[33]. *Equation (1.1)* formulates the calculation of the weighted PRS.

$$\mathrm{PRS}_j \;=\; \sum_{i=1}^{N} \beta_i \,\mathrm{dosage}_{ij} \tag{1.1}$$

Here, N represents the number of SNPs in the score, i denotes the index of the SNP, β is the effect size of the variant, and $dosage_{ij}$ refers to the number of copies of the SNP i in the genotype of individual *j[33],[34]*

Over the years, different methods have been developed to calculate PRS in an optimal way. One of the well-known methods among them is the classical clumping-and-thresholding (C+T) approach, in which SNPs with high linkage disequilibrium (LD) are first detected, and independent SNPs are obtained by removing the less significantly associated variants; therefore, an LD-independent SNP set is formed [25]. Next, p-value thresholding is applied according to the

strength of association of those clumped SNPs with the trait. As a result, PRS can be calculated as the sum of these clumped and thresholded SNPs, and the risk of over-fitting is reduced [31]. As the C+T approach treats variants rather strictly and excludes some SNPs in regions of high LD, another method called lassosum was introduced in 2017. Lassosum is based on LASSO-penalised regression. The LD correlation matrix—computed from a reference panel such as the 1000 Genomes Project—first undergoes ridge-like shrinkage; hence, the mismatch between the GWAS summary statistics and the LD matrix is reduced, and the matrix becomes positive definite. In the next step, elastic-net regularisation, which combines both LASSO (least absolute shrinkage and selection operator) and ridge penalties, is applied, imposing a penalty on the SNP effect sizes. Soft-thresholding is then performed to update the effect sizes via a fast coordinate-descent algorithm. Lastly, a pseudo-validation step is used to select the optimal LD-shrinkage parameter s and the LASSO tuning parameter λ , and with these updated effect sizes, the PRS can be calculated, producing a more predictive score that is less affected by LD bias and information loss [35].

The first large-scale empirical application of PRS in the literature was performed by Purcell et al. in one of the earliest studies to reveal the polygenic basis of schizophrenia, which was the GWA study conducted by the International Schizophrenia Consortium (ISC) in 2009. Within the scope of this study, they calculated polygenic scores by using common variants to provide evidence for the theory of polygenic inheritance of schizophrenia and demonstrated that common SNPs account for one-third of the overall variation in liability, and polygenic scores explain 3% of the variance. Hence, the cumulative contribution of common variants with small effect sizes was ascertained, as well as the predictive power of the PRS[36]. Additionally, within the scope of this study, researchers investigated common genetic variants behind schizophrenia, identified novel SNPs in *MHC,* and confirmed the schizophrenia-associated SNPs in *MYO18B* and *ZNF804A* ,[36, 37]. In 2011, another GWAS study conducted by the Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium identified five more new schizophrenia risk loci, and a strongly associated SNP near *MIR137* that is

involved in adult neurogenesis was defined. Moreover, three loci known to be associated with bipolar disorder were found to overlap with schizophrenia-*CACNA1C, ANK3,* and *ITIH3-ITIH4.* With the expansion of GWAS data, the PRS calculation by Purcell et al. (2009) was repeated, increasing the previously observed explained variance from 3% to 6% [38]. In 2013, Ripke et al. conducted another GWA study, and they identified 13 new risk loci for schizophrenia that are mainly relevant to neuronal calcium signaling. Besides, in this study, PRS profiling was performed in order to predict the status of case-control, and the results attested that PRS significantly predicts the phenotype of the samples, however, it was reported that the utilization of the PRS for diagnostic purposes is not feasible, as indicated by Nagelkerke's R^2 value of 3% and the Area Under the Curve (AUC) value of 0.65 under the Receiver Operating Characteristic (ROC) curve [39]. In 2014, the Schizophrenia Working Group of the Psychiatric Genomics Consortium conducted a GWA study and reported 108 new schizophrenia-associated gene loci. This paper led to a steep increase in the understanding of schizophrenia biology, hence the power of the polygenic risk score profiling. When the PRS analysis was repeated by using the same target samples that were used in earlier studies, the rate of explained variance in the liability scale increased to 7%, while Nagelkerke's R2 increased to 18.4% from 3%, with similar AUC values to those of the previous studies.[14],[36]. Furthermore, the complementary contribution of rare and common variances to schizophrenia was suggested in light of the findings[14]. To date, the largest and most updated GWAS data for schizophrenia was studied by the Schizophrenia Working Group of the Psychiatric Genomics Consortium and published in 2022. In this study, researchers reported that variance explained by the PRS in the liability scale accounts for 24% when calculated using all common SNPs. However, despite this finding, the AUC value under the ROC indicates that it is not feasible to use PRS values in clinical settings for diagnosing individuals based on this data[15].

On the other hand, in the literature, it was seen that PRS could be utilized for patient stratification, population-based screening, and prevention methods, investigating responses to drugs and treatment, and genetically informed experimental perturbation[18],[26], [40]. Especially, the usage of PRS to investigate

the gene-by-gene and gene-by-environment interactions is quite common in the literature[31].

1.4 Brief Overview of Resting-State fMRI Analysis

Resting-state fMRI is a neuroimaging technique first described by Biswal et al. in 1995, where they demonstrated that low-frequency fluctuations (< 0.1 Hz) between functionally correlated brain regions observed in the resting condition are temporally correlated [41]. Biswal and colleagues concluded that this correlation is due to neural firing and is a manifestation of functional connectivity, not noise[24][42].

Nowadays, resting-state fMRI is a commonly used method characterized by its ability to provide high spatial and temporal resolution images, enabling the exploration of intrinsic brain activity when a person is awake but not performing any task[24]. Typically, performing a task causes neural firing, leading to increased activation in the brain and a subsequent flow of oxygenated blood to the activated regions. Since oxygenated hemoglobin (Hgb) and deoxygenated hemoglobin (Hgb) differ in their magnetic properties, the MRI machine can detect and measure this difference as a BOLD (Blood-oxygen-level-dependent) signal [43]. Although no task is introduced to participants during resting-state fMRI, spontaneous BOLD signals are still observed and measured by resting-state fMRI. Analyzing these spontaneous BOLD signals allows researchers to investigate functional connectivity, which is a ubiquitous concept described as the measure of similarity in BOLD signals between two different brain regions [41], [42]. Correlation analysis is the most straightforward way of calculating connectivity; while the usage of Pearson's correlation coefficient allows the investigation of functional connectivity (FC) [38], the usage of semi-partial or multivariate correlation allows the investigation of effective or direct connectivity that apprise of causality of the signals in different brain areas [44].

Functional Connectivity (FC) calculation can be performed in diverse ways, such as seed-based analysis, independent component analysis, graph theory, or the ROI-to-ROI (Region of interest) method [45]. ROI-based connectivity is calculated between each predefined ROI pair, therefore creating a symmetrical RRC (ROI-to-ROI correlation matrix) where connectivity values are represented as Fisher-transformed correlation coefficients between two ROI BOLD time series. The correlation coefficient calculation is seen in *Equation 1.2.*

$$r(i,j) = \frac{\int R_i(t)\, R_j(t)\, dt}{\sqrt{\left(\int R_i^2(t)\, dt\right)\left(\int R_j^2(t)\, dt\right)}}\,,$$
$$Z(i,j) = \tanh^{-1}\big(r(i,j)\big) \tag{1.2}$$

where r denotes a correlation coefficient matrix, R represents the BOLD time-series within each ROI, and Z is the RRC matrix composed of Fisher-transformed correlation coefficients [46].

Studies on resting-state fMRI showed that some brain areas are spatially correlated, and the task-based fMRI studies showed that the observed activation patterns are alike in some brain regions. Therefore, the regions are named as "resting-state networks (RSN)" [42]. After the study of Biswal et al.[47] various studies to discover the resting-state networks (RSN) [48], [49], [50] and parcellation studies to assign brain regions to RSNs and understand the organization of the RSNs in a better way were conducted [51], [52]. Nevertheless, the classification of the RSNs slightly differs from each other. Yeo et al. [51] defined 7 canonical major RSNs that frequently appear in the literature, which are Default-Mode Network (DMN), Salience Network (SN) or Ventral-Attention Network (VAN), Fronto-Parietal Network (FPN), Somatomotor Network (SMN), Dorsal Attention Network (DAN), Visual Network (VN), and Limbic Network. In addition to these networks, it is possible to see some other RSNs in the literature named as Language Network, Auditory Network, Cingulo-Opercular Network, or Cingulo-Parietal Network, which differ according to parcellation, algorithms used to define boundaries between the regions [53], [54], [55]

The activation patterns in the resting-state networks may change according to the physiological and mental status of the subject, for example, tiredness, excitement level, or sleep state [56]. Additionally, head motions, vasomotion, blood pressure, and arterial CO^2 concentrations are known as the confounders that affect the low-frequency oscillations in rs-fMRI [57]. In spite of these disadvantages of resting-state fMRI, it has advantages that surpass the disadvantages; for instance, since there is no task in the resting-state fMRI, investigating very young, very old people, and individuals with psychiatric disorders like schizophrenia becomes easier with this technique. Due to the fact that plenty of studies have been conducted on psychiatric disorders, especially schizophrenia [58].

1.5 Default Mode Network

The Default Mode Network (DMN) is one of the first and most well-known resting state networks [42, 59]. Since the discovery of the DMN at the end of the twentieth century, numerous studies have been conducted, and consistent evidence has shown that DMN is activated during the resting condition and when the brain is not engaged in a task [48], [60], due to this reason, later on, this network is also known as the task-negative network [49], [61]. The brain regions that are covered by DMN may differ in different resources based on the atlas and the parcellation that is used. However, it is possible to classify them into four ROIs that are Right and Left Lateral Parietal Cortex (LP), Medial Prefrontal Cortex (MPFC), and Posterior Cingulate Cortex (PCC) [44].

Studies showed that DMN has important roles in higher cognitive processes and becomes active during mind-wandering, autobiographical memory retrieval, emotional processing, social cognition, decision-making, prospective thinking, introspection, and self-referential processing [62, 63, 64]. Various hypotheses have been proposed to explain why the brain exhibits such cognitively demanding activities at rest and the purpose of activation in the DMN; however, two of these hypotheses are more prominent than the others. These are the sentinel and internal mental hypotheses. While the sentinel hypothesis supports that the brain

examines its surroundings to respond to potential upcoming stimuli in an optimal way to mediate adaptation and survival, the internal mental hypothesis supports that these processes increase our self-awareness and allow us to evaluate and explore our past experiences, feelings, or actions [59].

The Default Mode Network is a very interactive hub that collaboratively functions with other networks. [65]. Given the involvement of DMN in cognition, its dynamic activation, and working mechanisms by coupling with other networks, DMN is a significant and central network. Therefore, impairments in these interactions lead to neuropsychiatric disorders, such as schizophrenia [59], [66].

Accumulating evidence has demonstrated that within-DMN connectivity and every ROI significantly contributes to the pathology of schizophrenia and supports the previously proposed dysconnectivity hypothesis of the disorder [67, 68, 69, 70, 71, 72, 73]. Accordingly, it was found that the hyperconnectivity within the DMN FC could be the source of impaired network coordination in patients and in their unaffected siblings. Specifically, the MPFC may be causing abnormal functional organization in schizophrenia [68], disrupting working-memory performance in the patients and their unaffected siblings [70], affecting coordination and information processing in paranoid schizophrenics [69], and resulting in abnormal cognitive ability and symptoms both in patients and unaffected siblings [71, 72].

1.6 Frontoparietal Network

Frontoparietal Network (FPN), also called Central Executive Network (CEN), is an attentional control brain network [74]. Anatomically, FPN primarily includes the lateral prefrontal cortex (LPFC) and the posterior prefrontal cortex (PPC) [75]. Researchers proved that FPN plays essential roles in the goal-directed and externally oriented tasks; therefore, it is classified as a task-positive network [74]. In addition to that, FPN is involved in many high-order neurocognitive functions such as decision-making, working memory, verbal fluency [76], and object-based, feature-based, space-based, and category-based information selection [77],

its maintenance and manipulation in the long-term memory [76].

Various studies examined the FPN profiles of people with schizophrenia at different stages and who had undergone different treatments, and provided evidence for the abnormality in this network. A study that compared schizophrenia patients and healthy individuals showed that within FPN connectivity is significantly lower in the patients than the healthy controls [78]. Similarly, another study conducted by Tu et al. examined both within and between FPN FC and revealed that within FPN is prominently disconnected in schizophrenia patients [79]. Additionally, the aberrant FC within FPN and its relation to clinical symptoms, particularly disorganization symptoms in schizophrenia patients, were confirmed [80, 81, 82]. Hence, it was suggested that dysconnectivity in the FPN can decipher the neural mechanism and cognitive deficits in schizophrenia [79].

1.7 Salience Network

Salience Network (SN) is another large-scale functional, resting-state network that was first defined by Seeley et al in 2007. The brain regions covered by the SN are not as clear as the other RSNs; however, the anterior insular cortex (AIC), the anterior cingulate cortex (ACC) are known as the key seeds of the SN [83] in addition to rostral prefrontal cortex (RPFC), the supramarginal gyrus (SMG), the striatum, the thalamus and amygdala [84, 83]. Therefore, SN contributes to emotion regulation and can be called as "affective network", as well [83].

One of the two core functions of the SN is salience processing. As part of this role, it identifies and prioritizes the most salient stimuli among the other external and internal ones. This prioritization is heavily affected by the novelty, expectancy, and learned value and consequences of the stimuli [1]. The information coming from the different resources, such as introception, homeostasis, conflict monitoring, and autonomic signals, can be combined. Respectively, changes in attention, action, prediction, and learning might occur, and the brain is directed to give the best-suited response to salience [85, 1]. Secondly, SN serves

a function in inter-network communication between DMN and FPN. Given that DMN controls the internally-oriented cognitive processes, whereas FPN controls externally-directed attention and behaviour, SN acts as a switching hub and modulates and configures the network activity in a context-dependent manner [85, 1].

Due to vital functions of the SN and its coordinating power on the cognitive processes, the SN has been extensively investigated, and its contribution to the pathological conditions has been explored. In 2005, Kapur et al. suggested the aberrant salience hypothesis of schizophrenia, which explains that the dysregulated dopaminergic system releases dopamine unnecessarily, and normal stimuli are perceived as salient. As a result of that brain tries to interpret these misperceived salient stimuli through prediction processing; however, it ends up with erroneous evaluation, and eventually, hallucinations and delusions occur in schizophrenia patients [86]. Whereupon, researchers examined the relationship between SN and the positive symptoms and proved that differentially performing SN and aberrant salience are associated with the positive symptoms and their severity [87, 88] While some studies reported hypoconnectivity within SN [89, 90], some other studies reported increased connectivity within the ventral SN were reported in patients with schizophrenia. While the researchers suggested that decreased connectivity can be associated with hallucinations, increased connectivity might be associated with delusions [84]. In addition to that, another study showed that FC in the SN is significantly reduced in the schizophrenia group compared to healthy controls, and this decrease is most prominent between the insula and ACC. Moreover, both positive and negative symptoms were found to be significantly correlated with the FC change in the SN.[91]. Furthermore, many studies proved that schizophrenia patients and those with clinically high-risk for psychosis demonstrate reduced inter-network SN connectivity as a disease-related abnormal pattern [92, 91].

1.8 Triple Network Model

The Triple Network Model for psychopathology was first suggested by Menon in 2011. Until the triple network model emerged, countless studies were conducted, and multiple resting-state networks (RSNs) were examined to understand the neural mechanisms underlying psychopathologies. Therefore, it was already known that some networks are closely associated with some psychiatric disorders and are called neurocognitive networks[1]. Menon&Udin (2009) first suggested that SN, especially the AI and ACC nodes, enables dynamic switching between FPN and DMN, so it has an important role in cognitive control [93]. Soon after that, they suggested that among these RSNs, DMN, FPN, and SN have a tight relationship with each other and form a triple network explaining the common motifs of psychopathologies in the large-scale brain networks by synthesizing the information arising from the multiple networks. This study also emphasizes that this network, in which the SN is at the center and directs behavior by dynamically switching between internal attention and external attention according to the salient stimulus it defines, may also be important for schizophrenia, as it manages cognitive and affective functions [94].

1.8.1 Triple Network Model in Schizophrenia

The Triple Network Model has been comprehensively investigated for schizophrenia, and the abnormality in the Triple Network has been attempted to be identified through multiple studies. Nowadays, our existing knowledge states that in healthy individuals, SN identifies the salient stimuli and disengages with the DMN and engages with the FPN for a proper response to those stimuli. Nevertheless, the Triple Network in schizophrenia patients, as visualized in the *Figure* 1.1, does not work accordingly. They can perceive a normal stimulus as salient due to unnecessary dopamine release in their brains. In addition to that, as a consequence of dysfunction in the SN, the disengagement from the DMN and engagement with the FPN cannot be established as it is supposed to happen. Hence, abnormalities occur in the Triple Network because of the disrupted balance of the

dynamic switching controlled by SN [93, 94, 95, 1, 96].

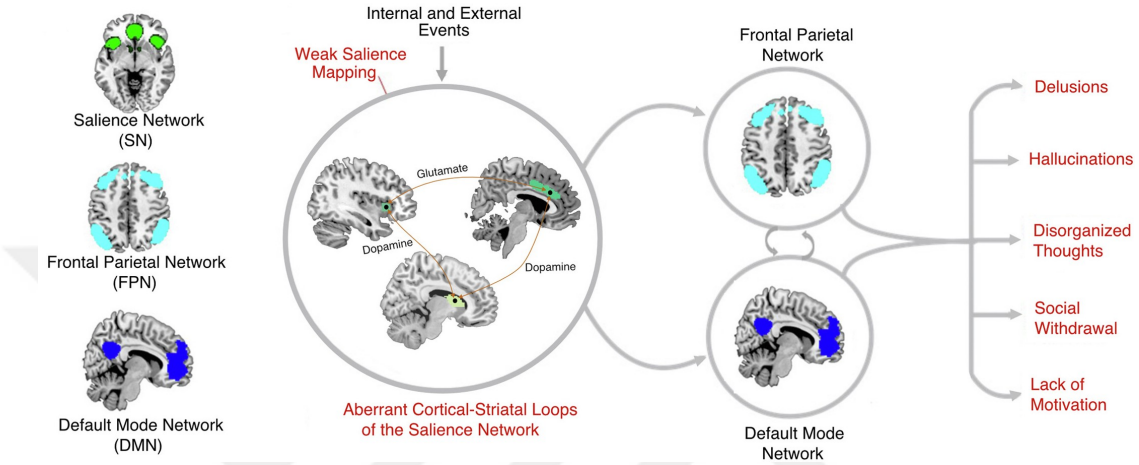

Figure 1.1: Overview of the Triple Network Model, its components, and how it works in people with schizophrenia. Adapted from [1].

In the literature, much evidence was provided that manifests these abnormalities in the Triple Network in schizophrenia patients. The studies focused on DMN-FPN connections showed that the schizophrenia patients show an increasing connectivity compared to healthy controls [97, 98, 81, 79]. Similarly, aligning results were reported by the other studies that confirm the increasing connectivity between the DMN and FPN [99, 78]. In consideration that DMN and FPN are anticorrelated, the hyperconnectivity in the patient groups is explained by the reduced segregation between the networks [78]. In addition to that, the studies positively correlated these increased connectivities with the positive clinical symptoms [99] and with the severity of the negative symptoms [100].

Additionally, investigations examining the connectivity between SN and FPN in schizophrenia patients revealed that SN-FPN FC is significantly higher in the patients than in healthy controls. Similarly, this neural motif and aberration in the AI are associated with the negative symptoms [100]. In line with that, effective connectivity studies also reported that bilateral connectivity between SN-FPN is increasing compared to healthy controls [101]. Moreover, it was stated that in

the patient group, right AI sends elevated control signals to both executive network and task-negative networks; therefore, increased connectivity and negative symptoms are being observed [98].

Furthermore, alterations in SN–DMN connectivity have also been examined, and it was reported that people with schizophrenia exhibit higher FC between dorsal MPFC and bilateral insular cortex than healthy controls [102]. Matching results were obtained from different studies, and hyperconnectivity between SN-DMN in schizophrenia patients was confirmed [103]. A study conducted with hallucinating schizophrenia patients and non-hallucinating patients showed that this increased SN-DMN pattern is more prominent in hallucinating people than non-hallucinating people, and emphasized the contribution of neural networks to clinical symptoms [102]. Besides, a positive relationship between the increased SN-DMN connectivity and both positive and negative clinical symptoms has been found by a study conducted in 2019 by Hare et al, and revealed that this connection aberration contributes to the entire clinical symptoms [104].

In many studies conducted with schizophrenia patients, it was mentioned that being on medication is an essential factor that might substantially affect the results, especially the clinical and behavioural test measurements; therefore, cross-sectional designs in such cases may miss the real results, and longitudinal studies are needed for that [79, 105].

1.8.2 Relationship between Triple Network and PRS-SCZ

A growing body of evidence from various studies has explored the disease-related neural patterns that are observed in schizophrenia patients in the people at clinically high risk (CHR) group or in the unaffected relatives (UR) of the patients. In the light of these studies, aberrant functional connectivity resembling schizophrenia in the AI and other SN regions [106], between SN-DMN and SN-CEN [107, 108], in LPFC and MPFC [109] in both UR and CHR groups was found. Hence, it was suggested that these neural networks can be biomarkers of the disease and used to understand the pathology [107].

Following this, researchers also investigated these potential biomarkers in people with high genetic load for schizophrenia. While some studies used the presence of some polymorphisms [110], in the past couple of years, others have utilized the polygenic risk scores [111]. The studies showed that the PRS-SCZ was found to significantly differentiate between healthy people and patients with different types, as well as a significant correlation between PRS-SCZ and the FC between the DMN-SN dysconnectivity and executive functioning in patients [112]. On the other hand, a study used a microdeletion as a way to assess the genetic load for schizophrenia reported that it was able to detect only the dysconnectivity within the DMN but not the other inter-network connections between DMN-CEN or DMN-SN [110] despite the comprehensive PRS studies [113]. Additionally, polygenic inefficiency in the DLPFC is significantly predicted by the increasing polygenic risk score [114]. System-level studies that explored the relationship between the PRS-SCZ and the functional connectivity across the large-scale networks found that there is a significant association between them [89, 115], especially on the VN, DMN, and FPN. Besides, the FCs that are significantly predicted by the PRS-SCZ were decreased in the schizophrenia patients and correlated with cognitive ability [89]. Apart from that, task-based studies that utilized PRS-SCZ showed consistent results. Overall, through these studies, it was clearly explained that PRS-SCZ can predict the disease features even in healthy individuals; therefore, it can be used in patient stratification, specialized treatment, and to have deeper insight into the pathology of the disease [111].

1.8.3 Stability of the Triple Network Connectivity

It is well known that the brain connectome is dynamic and alters over time due to brain development and aging [116, 117]. While the brain develops, the connections strengthen during adolescence and remain stabilized during adulthood. With advancing age, it starts to lose its stability and decrease in the strength of the connections, and less segregation between the networks is observed. [117].

Many studies were conducted with young and old subjects to show the age-related effects on the connectome, and they proved that within DMN, FPN, and SN, connectivity manifests age-related decreases in the rs-fMRI FC [118, 119, 120]. Another study that focused on the SN reported decreasing SN-CEN connectivity and SN-DMN anticorrelation in the older individuals [121]. Besides, the disruption due to the aging was examined and found that while the CEN/FPN is the most affected network, it is followed by DAN, SN, and DMN [122]. Overall, observed decrements within-network were associated with the cognitive decline in older people. Additionally, between-network FC was found to tend to increase, and this change is explained by decreasing segregation between the networks [123].

To understand the developmental trajectories of the functional connectivity and when exactly the connections start to decrease, the studies with the younger groups were carried out. In a study conducted by Chai et al. with healthy individuals aged between 8 and 24, the DMN was examined, and it was seen that children aged between 8 and 12 showed a positive connectivity between DMN and FPN, but in 13-17 they became anticorrelated [124]. Another study elaborately investigated the maturation of the brain networks in 4 different age groups: 10-12, 13-15, 16-20, and 20-26. It was seen that while within network connectivity remains stable, between network connectivity increases from 13-15 to 16-19 [125]. On the other hand, the studies explained that each network manifests a different developmental trajectory. For instance, while SN develops early and reaches its plateau phase earlier, FPN/CEN development takes longer and matures in the early twenties. Therefore, while SN-DMN connections are mostly established in early adulthood, the SN-FPN connection might show an increase due to the ongoing maturation of the FPN [126]. Consistently, a study with healthy individuals aged 6 to 17 reported that the out-degree of dynamic functional connectivity (dFC), which represents the number of outgoing connections, from the frontoparietal network (FPN), increases with age [127]. Besides, it was proved that when individuals moved to early adulthood (20-26) from late adolescence (16-19), the stable within-network connectivity starts to lose its strength, and the between-network connectivity continues to increase [125]. In general, the time period from

adolescence to adulthood and changes in the FC were summarized with the refinement period where segregation and integration between the networks are in balance [126].

Few longitudinal studies focused on the FC in the triple network in healthy individuals have been conducted. In a longitudinal study conducted in 2020 by Oschmann et al., functional connectivities within the DMN, FPN, and SN were examined 4 years apart in older adults. It was reported that FC within the DMN did not show any significant difference, while the other two networks depicted a significant decrease [128]. Another longitudinal study that investigated the stability of the brain connectome in middle and older-aged groups found that the DMN is the most stable network among the other RSNs over a 2-3 year time interval [129]. Differing from the previous studies, a study with the same purpose conducted with a subject group aged 10 to 13 years old by Sherman et al. showed that within the DMN and FPN, connectivity is increasing over time, and the network segregation between the DMN and FPN is strengthened, where "within connectivity" refers to connections among the regions of a network and "between connectivity" refers to connections across regions of two different networks. [130]. Thanks to all these studies, the changes in the FC in the triple network were proven in the healthy subjects, and the importance of the longitudinal approach to understand the neurobiology of healthy development was highlighted. The previous studies encouraged the study of between-network FC in a longitudinal approach for a better understanding [128].

1.9 Hypotheses and Goals

The triple network model has consistently been implicated in schizophrenia pathophysiology [1]. According to the neurodevelopmental hypothesis of schizophrenia, disruptions due to genetic or environmental factors during the critical developmental period can alter brain connectivity, consequently increasing schizophrenia risk [18]. Therefore, functional connectivity within and between these networks has become an important focus, especially among clinically high-risk individuals and unaffected relatives of patients, as such changes could serve as early biomarkers of psychosis risk and provide prognostic insights [107, 131]. Given that schizophrenia is commonly diagnosed during early adulthood, a critical phase of brain network refinement, it is vital to characterize how triple network connectivity develops during this crucial developmental period in healthy people and at-risk people [126, 95].

Most prior research investigating functional connectivity changes either compares distinctly younger and older populations or investigates children and adolescents using cross-sectional designs, thereby limiting conclusions regarding developmental trajectories [128]. Few longitudinal studies exist, and those available generally examine early childhood or older adult populations over extended intervals, missing the critical transition from adolescence to adulthood[129, 125, 128]. Furthermore, existing studies typically focus on within-network connectivity changes rather than on inter-network interactions. Moreover, how genetic liability to schizophrenia, measured by polygenic risk scores (PRS-SCZ), affects these developmental trajectories has not been sufficiently investigated.

To bridge this gap, the current study employs a longitudinal design to capture subtle yet potentially significant changes in triple-network connectivity, derived from resting-state functional MRI data using an ROI-to-ROI analysis approach, over a one-year period in adolescents and young adults (ages 14–23 at baseline and 14-24 at follow-up). Additionally, we examine how genetic susceptibility to schizophrenia modulates these connectivity trajectories and explore correlations

between PRS-modulated connectivity changes and subclinical psychosis symptoms measured by the Community Assessment of Psychic Experiences (CAPE-42).

In line with these aims, our first hypothesis is that over the one-year follow-up period, compared to baseline, developmental patterns will be characterized by increased DMN-SN and SN-FPN connectivity, which reflects continued maturation and enhanced network integration, and decreased DMN-FPN connectivity, which indicates stronger functional segregation through more anticorrelated networks. Our second hypothesis is that PRS-SCZ will significantly modulate the developmental trajectories of triple-network connectivity. Specifically, individuals with higher PRS-SCZ will show increasing functional connectivity from baseline to follow-up between DMN-FPN, SN-DMN, and SN-FPN, consistent with patterns observed in schizophrenia, clinical high risk (CHR), and unaffected relatives (UR), suggesting a shift toward patient-like profiles with increasing age. Finally, our third hypothesis is that connectivity changes modulated by PRS-SCZ will positively correlate with subclinical psychotic experiences (CAPE-42 scores), indicating that these connectivity alterations have clinical relevance even at subclinical levels.

Chapter 2

Methods

2.1 Participants

In this study, 125 twin and sibling pairs, aged 14 to 23 years, with sibling pairs having a maximum age difference of 24 months, were recruited through flyer distribution at universities and high schools, and social media advertisements. Individuals with a history of neurological disorder and a low IQ level (IQ < 70) were excluded from the study. Prior to the collection of data, all participants provided written informed consent, and those under 18 years old provided their legal guardian's signature in accordance with the Bilkent University Human Research Ethics Committee. Following a minimum interval of one year, the participants aged between 14 to 24 years were contacted and invited to take part in the second wave of the study. Out of the 125 participants, 100 pairs (89 twin pairs and 11 sibling pairs) agreed to join the second wave. Genetic samples and data on demographics were collected at baseline, while resting state functional MRI (rs-fMRI) and cognitive data were assessed both at baseline and at the follow-up session. During the analysis, 11 twin pairs were excluded due to missing MRI data, which was a result of technical issues with the MRI machine, low-quality scans, or the presence of unremovable piercings or other metal accessories on the day of the scan. The remaining 89 pairs, consisting of 78 twin pairs and 11 sibling

pairs, were included in the resting-state functional MRI (rs-fMRI) connectivity analysis.

2.2 Assessment of Subclinical Psychotic Symptoms

The Community Assessment of Psychic Experiences (CAPE-42) [132] is a self-report questionnaire that measures the lifetime frequency and distress associated with psychotic experiences across three domains: positive, negative, and depressive. The tool consists of 42 items, of which 20 assess positive symptoms, 14 assess negative symptoms, and 8 assess depressive symptoms. Each item is rated on a 4-point scale: "*never*," "*sometimes*," "*often*," and "*nearly always*" for frequency, and "*not distressed*," "*a bit distressed*," "*quite distressed*," and "*very distressed*" for distress. Total scores, therefore, range from 42 to 168. In this study, a modified Turkish version of the CAPE-42 was used, and the frequency scores of the CAPE-Positive, CAPE-Negative, and CAPE-Depressive scales and total score were employed to assess participants' psychotic experiences.

2.3 Calculation of Polygenic Risk Score

Biological specimen collection was obtained from either whole blood or saliva. Saliva samples were collected via the commercial kit Oragene (DNA Genotek OG-500; Ottawa, Ontario, Canada) in the National Magnetic Resonance Research Center (UMRAM), Bilkent University, and whole blood samples were collected into purple top blood tubes with EDTA at Bilkent University Health Center. In the following, genomic DNA was extracted from all samples and genotyped using either the Illumina Infinium Psych Array (n=82) or the Illumina Global

Screening Array with the Psych Booster addendum (n=82). In this way, approximately 680,000 markers that are associated with clinical research and psychiatric diseases were screened for all samples. The raw genotype data that were genotyped with different arrays underwent quality control, separately using *PLINK2* (version 2.0;www.cog-genomics.org/plink/2.0/) [133]. SNPs with a minor allele frequency (MAF) $< 1\%$, missing call rates $< 99\%$, a Hardy-Weinberg equilibrium (HWE) p value $< 10^{-4}$, and individuals with missing call rates $< 98\%$ were excluded from the data. Additionally, the genetic sex of the participants was checked to see whether genetic sex and reported sex match. Prior to imputation, reference allele matches of target data with the GRCh37 assembly (Genome Reference Consortium Human Build 37) were checked and fixed using *BCFTools* (http://github.com/samtools/bcftools) [134] The pipeline utilizes EAGLE2 (v2.0.5) for pre-phasing and PBWT (positional Burrows-Wheeler transform) for imputation, was run on the Sanger Imputation Server with the settings of Haplotype Reference Consortium release 1.1 for reference panel [135], separately for each array. The imputed genotype data of each array were merged, and INFO score < 0.8 and MAF $< 1\%$ were applied to the data.

Polygenic risk scores (PRS) for schizophrenia were calculated by the GenoPred pipeline (https://opain.github.io/GenoPred)[136] with the use of summary statistics obtained from wave 3 core meta-analysis GWAS of schizophrenia in the Psychiatric Genomics Consortium [11] by running on TUBITAK ULAKBIM, High Performance and Grid Computing Center (TRUBA resources) (https://portal.truba.gov.tr/). Within the pipeline, 1000 Genomes Phase 3 (1KG) and Human Genome Diversity Project (HGDP) samples, which are limited to the HapMap-3 variants, were used as a reference panel in order to perform a reference-standardized genetic scoring for standardized and comparable results. Then, principal component analysis on the reference data was performed using the thresholds MAF > 0.05, missingness < 0.02, and HWE p-value $>$ 1e-6, -indep-pairwise 1000 5 0.2. Subsequently, the first 6 principal components (PCs) of the reference data were projected to the target data. Additionally, summary statistics data underwent quality control in which variants were aligned with the reference panel, and then INFO < 0.9 and MAF < 0.01 filtering were applied in

addition to the removal of duplicate variants and outlier samples. Then, GWAS effect sizes were adjusted for each population. Similarly, target data was passed from a quality control, in which variants were aligned to reference data, and common variants with the reference data were obtained. Ancestry inference on the target data was conducted, and all samples were assigned to the European population. Thereafter, PRS calculation was performed via the lassosum method [35], and the results attained from the pseudo-validated model were used. Lastly, genetic zygosity was identified, and PCA on the target data was applied; the first 10 PCs were generated after the exclusion of variants in linkage disequilibrium through– indep-pairwise 1500 150 0.2 filtering to use them as covariates in the statistical analyses.

2.4 Calculation of Resting-State Functional Connectivity Values

2.4.1 Image Acquisition

MR images were collected in the National Magnetic Resonance Research Center (UMRAM), Bilkent University, on a 3 Tesla MRI scanner (Magnetom Trio, Siemens AG, Erlangen, Germany) with a 32-channel array head coil.

Resting-state fMRI images were acquired with an echo-planar imaging (EPI) sequence; repetition time, 2000ms; echo time, 35ms; flip angle, 75°; matrix, 64 x 64; resolution, 1x1x1 mm; number of slices, 150; acquisition duration, 5 min 04s. T1-weighted structural images were acquired with a magnetization-prepared rapid gradient-echo pulse (MP-RAGE) sequence; repetition time, 2600ms; echo time, 3.02ms; flip angle, 8°; matrix, 224 x 224; resolution, 3x3x3 mm; number of slices, 150; acquisition duration, 5 min 04s.

2.4.2 Data Analysis

Analysis of both functional and anatomical data was done by the CONN Toolbox release 22a [137] and SPM release 12.7771 (http://fil.ion.ucl.ac.uk/spm) running in MATLAB R2022b (The MathWorks, Inc., Natick, Massachusetts, USA).

Preprocessing of MRI images was performed by a flexible preprocessing pipeline implemented in CONN Toolbox, including motion correction through realignment, slice time correction (STC), outlier detection, functional and structural segmentation, normalization to MNI space, and spatial smoothing. Functional data realignment was performed according to the SPM realignment and unwarping procedure [138]. According to this procedure, functional scans were co-registered to reference images by rigid body transformation and b-spline interpolation. Sinc interpolation was used to fix the temporal misalignments between different slices. Scans with global signal change above the 3 standard deviations and framewise displacement greater than 0.05 mm were detected by the Artifact Detection Tool (ART) and excluded. Smoothing the functional data was done by spatial convolution with a Gaussian kernel of 8 mm full-width half-maximum (FWHM).

Preprocessing was followed by denoising that was performed by the default denoising pipeline of CONN toolbox, which includes regression of confounding effects by using Component-based noise correction method characterized by white matter time-series (10 CompCor noise components), CSF time-series (10 CompCor noise components), motion parameters, their first order derivatives (12 factors) and session and task effects, their first order derivatives (4 factors) and linear trends (2 factors) within each functional run.

Functional connectivity (FC) patterns were estimated by the ROI-to-ROI connectivity (RRC) method, and between-network FCs were examined for the Default Mode Network, Frontoparietal Network, and Salience Network. In the first level analysis, Fisher-transformed bivariate correlation was used for computing RRC matrices. As a result, an RRC matrix that represents the FC between each pair of ROIs was generated for all the subjects. In the second-level analysis,

to generalize connectivity patterns, enable group inference, and enhance statistical power, first-level connectivity measures were used as dependent variables. A General Linear Model (GLM) was performed for each individual connectivity, computing a generalized functional connectivity (FC) pattern across individuals and sessions at rest. Results were thresholded by $p < 0.05$ for voxel-level threshold, and p-FDR < 0.05 for cluster-size threshold. Lastly, FC values for both time points were extracted from the CONN Toolbox and utilized in the statistical analysis.

2.5 Statistical Analysis

All analyses were carried out in RStudio (version 4.4.0). Descriptive statistics for age, sex, and zygosity were calculated using the *psych* package. Prior to analysis, all functional connectivity (FC) and polygenic risk score (PRS) values were standardized, and an outlier check was performed. Δ CAPE z-scores were computed by subtracting the follow-up scores from the baseline scores for the total, positive, negative, and depressive symptom scales, separately.

Linear mixed-effects models (LMM) were fitted in R using the *lme4* and *lmerTest* packages to examine longitudinal connectivity changes. First, for each ROI-to-ROI connection between the DMN–SN, DMN–FPN, and SN–FPN, we fitted separate LMMs to assess whether functional connectivity changed over time. Second, we tested whether those longitudinal changes were moderated by polygenic risk for schizophrenia (PRS-SCZ) by including a PRS-SCZ $\times$ Time term. Third, another set of LMM was run for connections with a significant PRS-SCZ effect to examine whether the PRS-modulated connectivity changes predicted concurrent changes in subclinical psychotic symptom scores (positive, negative, depressive, and total). All models included age, sex, and zygosity as fixed covariates, and where PRS-SCZ was a predictor, we also added the first ten principal components of the PRS. A random intercept for family ID accounted for relatedness among twins and siblings. Model assumptions were checked, and p-values were adjusted for multiple comparisons using the Benjamini–Hochberg method.

Chapter 3

Results

3.1 Sample Characteristics

A sample of 164 individuals was included in this study, each assessed at two time points: baseline and follow-up. The mean age of the participants at baseline was 19.35 ± 2.61 years, and 20.63 ± 2.61 years at follow-up. Of the participants, 63.4% were female (n = 104) and 36.6% were male (n = 60). Zygosity classification, based on genotype data, revealed that the sample included 37.8% monozygotic twins (n = 62) and 50% dizygotic twins (n = 82), in addition to 12.2% sibling participants (n = 20). The demographic characteristics of the participants are presented in *Table* 3.1

Table 3.1: Demographic characteristics of participants at baseline and follow-up.

Statistic	Baseline	Follow-up
Mean Age (SD)	19.35 (2.61)	20.63 (2.61)
Sex n(%)		
Female	104 (63.4%)	104 (63.4%)
Male	60 (36.6%)	60 (36.6%)
Zygosity n(%)		
MZ	62 (37.8%)	62 (37.8%)
DZ	82 (50%)	82 (50%)
Sibling	20 (12.2%)	20 (12.2%)
CAPE-42 Scores		
CAPE Total (SD)	76.69 (16.00)	70.39 (11.69)
CAPE-Positive (SD)	30.99 (6.16)	29.13 (6.21)
CAPE-Negative (SD)	29.39 (7.97)	26.87 (4.97)
CAPE-Depressive (SD)	13.06 (5.41)	14.67 (3.89)

3.2 Functional Connectivity Results

3.2.1 Stability of the Triple Network Connections

The stability of the triple network was investigated by using linear-effect mixed models (LMM) to observe whether there is any significant 1-year longitudinal change as a result of ongoing brain development across adolescence. Age, sex, and zygosity were used as fixed effects, and family ID (FID), which uniquely represents a pair of twins or siblings, was used as a random effect to control the family-relatedness. Results showed that none of the connections between DMN-SN, FPN-SN, and DMN-FPN underwent any significant change between the baseline and 1-year follow-up, and stayed stable ($p > 0.05$).

3.2.2 Association Between PRS-SCZ and Connectivity Differences Over Time

Next, to understand how genetic risk for schizophrenia influences longitudinal changes in the triple network connectivity over one year during adolescence, we ran LMM models separately for each connectivity. Similarly, age, sex, zygosity, and the first ten principal components of the polygenic risk scores were included as fixed effects, while FID was used as a random effect to control the family-relatedness and genetic risk varying across families.

Inter-network connections between DMN-FPN, DMN-SN, and FPN-SN were explored, and among these 28 connections, only 5 of them were found to be significant according to their uncorrected p-values, as can be seen in the *Figure* 3.1.

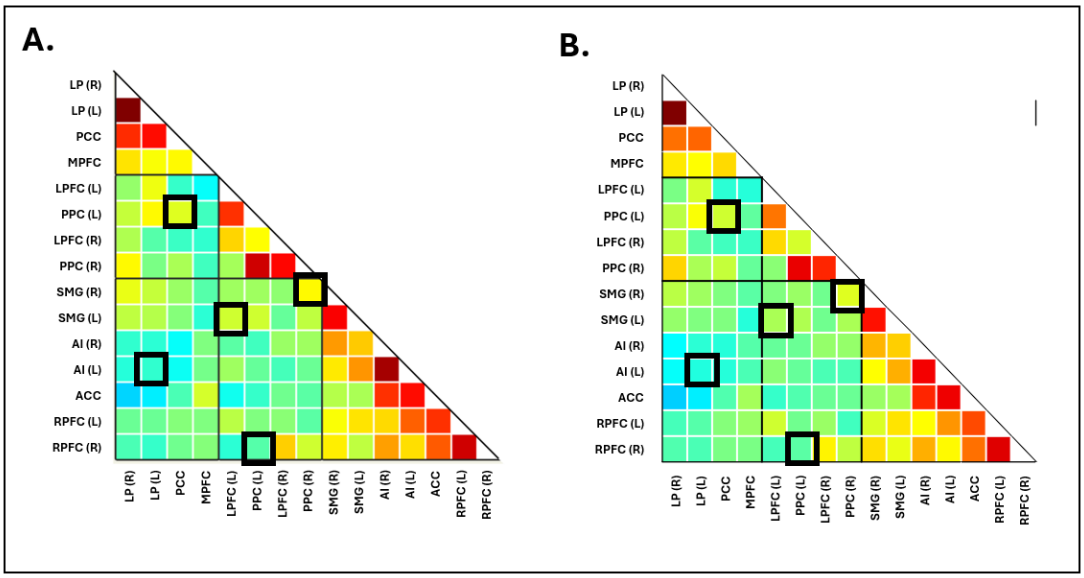

Figure 3.1: *ROI-to-ROI correlation matrix of the triple network.* ***A.*** *Matrix at baseline.* ***B.*** *Matrix at one-year follow-up. Black boxes mark those connections whose change over time is significant at the uncorrected PRS-SCZ threshold.* ***Note:*** *ACC: Anterior Cingulate Cortex, AI: Anterior Insula, L: Left, LP: Lateral Parietal, LPFC: Lateral Prefrontal Cortex, mPFC: Medial Prefrontal Cortex, PCC: Posterior Cingulate Cortex, PPC: Posterior Parietal Cortex, R: Right, SMG: Supramarginal Gyrus*

As a result, as PRS-SCZ increased, longitudinal connectivity in the FPN–SN network showed significant gains from baseline to follow-up for three connections: between the left LPFC and the left SMG (β = 0.22, SE = 0.11, 95% CI [0.01, 0.44] p-uncorrected = 0.04), left PPC and right RPFC (β = 0.26, SE = 0.12, 95% CI [0.03, 0.5] p-uncorrected = 0.03), and right PPC and right SMG (β = 0.25, SE = 0.11, 95% CI [0.03, 0.48] p-uncorrected = 0.03). Additionally, longitudinal FC change between right PPC and ACC (β = 0.23, SE = 0.12, 95% CI [-0.0,0.47], p-uncorrected = 0.05), and right PPC and right RPFC (β = 0.21, SE = 0.11, 95% CI [-0.01, 0.42], p-uncorrected = 0.06) were modulated by PRS-SCZ at the trend-level.

Similarly, between the DMN-FPN connections, the one between left PPC and PCC also exhibited a significant longitudinal increase with higher PRS-SCZ (β = 0.26, SE = 0.12, 95% CI [0.03, 0.5] p-uncorrected = 0.03).

Lastly, among the DMN-SN connections, only the connection between left AI and left LP showed a significant increase from baseline to follow-up as PRS-SCZ rose (β = 0.28, SE = 0.13, 95% CI [0.03, 0.53] p-uncorrected = 0.03).

Moreover, the explained variance of the models was checked, and it was seen that while the marginal R^2 explained 5% to 10%, the conditional R^2 explained up to 30% in all of the models. Furthermore, Benjamini-Hochberg correction was applied to every connection; however, the corrected p-values could not reach the statistical significance level (p-corrected $>$ 0.05). Detailed statistical results of each connection are presented in *Table* 3.2.

Finally, the connections whose longitudinal changes were predicted by PRS-SCZ were examined using linear mixed-effects models, and explored whether changes in CAPE-42 scores (total, negative, positive, depressive) corresponded to these neural shifts at the clinical level. It was seen that there is no significant association between changes in clinical symptoms and changes in functional connectivity.

Table 3.2: LMM results for the PRS-SCZ × Time effect

Connection	Estimate	SE	95% CI	p-raw	p-adj
FPN–SN connections					
LPFC (L) and ACC	-0.11	0.12	[-0.35, 0.13]	0.38	0.9
LPFC (L) and RPFC (L)	0.03	0.11	[-0.19, 0.25]	0.76	0.92
LPFC (L) and RPFC (R)	-0.02	0.12	[-0.25, 0.21]	0.84	0.92
LPFC (L) and SMG (L)	0.22	0.11	[0.01, 0.44]	**0.04***	0.2
LPFC (R) and ACC	0.04	0.12	[-0.2, 0.29]	0.72	0.92
LPFC (R) and AInsula (L)	0.11	0.12	[-0.12, 0.35]	0.35	0.9
LPFC (R) and RPFC (R)	0.03	0.12	[-0.2, 0.26]	0.8	0.92
PPC (L) and ACC	-0.09	0.13	[-0.34, 0.16]	0.48	0.92
PPC (L) and RPFC (R)	0.26	0.12	[0.03, 0.5]	**0.03***	0.2
PPC (L) and SMG (L)	-0.04	0.11	[-0.26, 0.18]	0.71	0.92
PPC (R) and ACC	0.23	0.12	[-0.0, 0.47]	0.05·	0.2
PPC (R) and RPFC (R)	0.21	0.11	[-0.01, 0.42]	0.06·	0.2
PPC (R) and SMG (L)	-0.02	0.12	[-0.25, 0.21]	0.85	0.92
PPC (R) and SMG (R)	0.25	0.11	[0.03, 0.48]	**0.03***	0.2
DMN-SN connections					
ACC and LP (L)	0.15	0.13	[-0.1, 0.4]	0.25	0.64
ACC and PCC	0.09	0.12	[-0.15, 0.33]	0.46	0.64
AInsula (L) and LP (L)	0.28	0.13	[0.03, 0.53]	**0.03***	0.26
AInsula (L) and PCC	0.11	0.12	[-0.13, 0.35]	0.37	0.64
AInsula (R) and LP (L)	0.19	0.12	[-0.05, 0.44]	0.12	0.48
AInsula (R) and PCC	0.04	0.12	[-0.2, 0.29]	0.72	0.84
RPFC (R) and LP (L)	0.11	0.12	[-0.13, 0.35]	0.39	0.64
DMN-FPN connections					
LPFC (L) and LP (L)	0.08	0.12	[-0.16, 0.31]	0.52	0.83
LPFC (L) and PCC	0.04	0.13	[-0.21, 0.29]	0.75	0.89
LPFC (R) and PCC	0.18	0.12	[-0.06, 0.42]	0.14	0.75
PPC (L) and LP (L)	0.07	0.12	[-0.18, 0.31]	0.59	0.86
PPC (L) and PCC	0.26	0.12	[0.03, 0.5]	**0.03***	0.46
PPC (R) and LP (L)	0.08	0.13	[-0.17, 0.33]	0.52	0.83
PPC (R) and PCC	0.12	0.13	[-0.13, 0.37]	0.33	0.83

Note. ACC: Anterior Cingulate Cortex, AInsula: Anterior Insula, LP: Lateral Parietal Cortex, LPFC: Lateral Prefrontal Cortex, PCC: Posterior Cingulate Cortex, PPC: Posterior Parietal Cortex, RPFC: Rostral Prefrontal Cortex, SMG: Supramarginal Gyrus, L: Left, R: Right.

Chapter 4

Discussion and Conclusion

This thesis aims to explore one-year longitudinal changes in functional connectivity within the Triple Network in healthy adolescents and to characterize how genetic liability to schizophrenia modulates these developmental trajectories across one year, as well as how those connectivity changes are associated with subclinical psychosis symptoms. To address these aims, we acquired resting-state fMRI at two time points with a one-year interval and calculated functional connectivity (FC) values using the ROI-to-ROI method. Additionally, PRS-SCZ values were computed as a measure of genetic liability to schizophrenia, and subclinical psychotic symptoms of the subjects were assessed.

The main outcomes of our investigation are as follows: (1) over the one-year period, there were no significant FC differences between DMN–SN, DMN–FPN, and SN–FPN; (2) however, PRS-SCZ moderated these trajectories and individuals with higher PRS-SCZ are associated with higher longitudinal FC changes between left LPFC–left SMG, left PPC–right RPFC, right PPC–right SMG, left AI–left LP, and left PPC–PCC; and (3) these PRS-SCZ–modulated neural changes were not significantly associated with any subclinical symptom dimensions (CAPE-Total, positive, negative, or depressive).

Our first finding is that functional connectivity between DMN–SN, DMN–FPN, and SN–FPN did not significantly differ from baseline (mean age = 19.3) to follow-up (mean age = 20.6) across a minimum one-year interval in healthy adolescents. Reversely, one study conducted by Marek et al., using rs-fMRI, showed that between-network connections increase from late adolescence (16-19) to early adulthood (20-26) in the

DMN-SN, DMN-FPN, but not in the FPN-SN [125]. On the other hand, a recent study carried out on healthy subjects aged between 8 to 21 revealed that FPN-DMN functional connectivity shows a linear relationship and decreases with age, indicating increased anticorrelation [139]. In light of these findings, we expected to observe increasing DMN-SN, SN-FPN, and decreasing DMN-FPN functional connectivity in our study; however, we could not observe any significant difference. In the literature, most of the longitudinal studies do not include both adolescents and young adults; however, one study that analyzed the structural wiring and functional interactions in people aged between 14-25 recruited within a year interval found significant changes in the sensory/unimodal and DMN that reflect the brain maturation [140]. Similarly, a study with a 4-year interval showed a significant decrease within the SN, FPN, and DMN in the old adults [128], another study conducted with middle-aged adults explored with a 2-3 year time interval and indicated that there is no change in the FC and RSNs are stable [129]. In short, the studies concluded that a 3-year period or different approaches, such as accelerated longitudinal designs, are required to observe the age-related differences. Since our dataset includes data collected at only two time points and the time interval is very short, we might not be able to detect the differences in our analysis. Besides, the studies conducted to explore the developmental trajectories at the network-level either by different methodologies or averaging; however, as we conducted an ROI-level analysis for a finer examination, this may lead to undetectable results. In addition, our analysis included age, sex, and zygosity as other fixed effects, but we might have controlled for some other factors, such as traumatic life events occurring between the two waves of the study, or disorders that might affect the connectivity patterns in the brain. For instance, it is known that while depression is an important factor that affects the connectome in the DLPFC, [141], and substance usage, such as cannabis use, alter the functional connectivity on the ACC seed of the SN [142]. However, these are overlooked in the current study and may potentially affect the results.

The second finding of this study is that the PRS-SCZ moderates the one-year longitudinal changes at the uncorrected level, and people with high PRS-SCZ show more pronounced increases in connectivity between the DMN-SN, DMN-FPN, and FPN-SN connections. Consistently, a study conducted by Kim et al. in 2023 found that both in the first episode psychosis (FEP) and unrelated relatives (UR) manifest higher FPN-DMN and FPN-SN connectivity than healthy controls [107]. In contrast to these findings, the same researchers observed the opposite functional connectivity pattern

between the DMN-SN, DMN-FPN, and FPN-SN in the FEP patients in their previous study. In this study, the usage of antipsychotic treatment was highlighted, and the potential impact of the drugs on the connectivity was used to explain these unexpected results [131]. Another rs-fMRI study that explored the triple network connections in people at ultra-high risk of psychosis stages (UHR) was conducted and reported that there is temporal dysfunction in the SN, which creates a transition issue between the FPN and DMN. Consequently, UHR people manifest dysfunctional DMN-FPN functional connectivity [143]. In line with these findings, another rs-fMRI study found that FC between DMN-FPN connectivity is increased despite its small sample size [144]. In all of these studies, the significance of the triple network is emphasized, and it was suggested that they have the potential to be endophenotypes when it is considered that people at risk and unaffected relatives demonstrate similar neural phenotypes to those of schizophrenia patients. In order to interrogate these potential endophenotypes more, stratifying people according to genetic risk profiles is a very informative approach. The number of studies that examine the triple network connectome in people with different genetic risk groups is scarce. In the literature, there is only one study that used PRS-SCZ and resting state data in a longitudinal design; however, this is an EEG study. Despite that, similar to our results, this study reported a significant positive association between the higher PRS and increasing neural connectivity both in the schizophrenia patients and in their relatives [145]. When the results of this study are examined in detail, it can be seen that FPN-SN connections provided more significant results, as well as trend-level results. Two of the significant connections originate from the SMG. Although the AI and the ACC are reported as the key regions that are more important in the switching from task-negative to task-positive attentional network, SMG showed a significant association. It is well-established that this region develops later than the other regions in the parietal lobe, and it contributes to processes such as language formation and working memory that are disrupted due to schizophrenia [146]. On the other hand, we observed only one connection between DMN-FPN and DMN-SN. From the existing studies, it is known that DMN is the most stable network [147]; hence, that could be the reason why we could not observe significant results on the DMN-coupled networks. Furthermore, the studies attested that FPN shows a protracted development, and this may lead to a vulnerability to psychopathologies linked to cognitive control deficits, like schizophrenia [148]. Therefore, we can attribute the greater modulation of longitudinal connectivity changes in the FPN-coupled connections by PRS-SCZ to this fact.

Our last finding is that the connections whose FC changes significantly predicted by PRS-SCZ did not show a corresponding change in the subclinical psychotic symptoms (total, negative, positive, depressive). Although in the literature, many studies showed that the connectome and subclinical symptoms are highly correlated, and the aberrations in the connections can predict the clinical symptoms and their severity, even in the unrelated relatives of the schizophrenia patients [111].

In conclusion, in this thesis, we could not find any significant longitudinal difference from baseline to follow-up over one year. On the other hand, we have observed that the PRS-SCZ moderates one-year longitudinal changes in the connectivity values, and people with higher risk scores show a steeper increase in the DMN-FPN, DMN-SN, and SN-FPN. These increments can be explained by the disrupted SN; hence, disrupted disengagement from the DMN and aberrant engagement with the SN [1]. Also, these results, despite the insignificant time effect, indicate that the genetic risk of schizophrenia may significantly alter the developmental trajectories. Moreover, no significant associations were found between the connectivity change and the clinical symptom changes. As people with high genetic risk show neural phenotypes just like the patients, but no clinical symptoms, triple network connectivity can be an important potential biomarker and enable us to take action even prior to the emergence of the symptoms.

Nevertheless, in addition to the aforementioned drawbacks, this thesis has some limitations. First, our sample size is small, and our results could not survive the multiple testing correction. Second, the fact that Turkish people are not genetically completely European and vary to some extent, despite that we used the European summary statistics, may limit the predictive power of the genetic risk scores and may contribute to nonsignificant results. Third, although this study is longitudinal, there were only two time points, and the time interval was only one year, which might not be enough to observe the longitudinal developmental changes. Also, the age range of the group makes it difficult to speculate whether these changes reflect longitudinal changes or normal brain maturation.

Notwithstanding, this thesis has several notable strengths. First, it examines the triple network comprehensively, focusing on between-network functional connectivity rather than the within-network focus of most existing studies. Second, we conducted our analysis at the ROI level instead of the broader network level, allowing for a more detailed characterization of connectivity. Third, our sample spans ages 14–23, covering

both adolescents and young adults, whereas prior work has typically targeted children or older adults. Finally, by using PRS-SCZ and healthy individuals with high genetic risk, instead of unaffected relatives or clinical high-risk groups, this longitudinal rs-fMRI study helps to fill an important gap in the literature.

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