GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO PSYCHOTIC-LIKE EXPERIENCES AND WORKING MEMORY CONNECTIVITY IN TURKISH ADOLESCENTS AND YOUNG ADULTS: A TWIN STUDY

A DISSERTATION SUBMITTED TO

THE GRADUATE SCHOOL OF ENGINEERING AND SCIENCE

OF BILKENT UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR

THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

NEUROSCIENCE

By

Didenur Şahin Çevik

December 2024

Signed Declaration

The data presented in this thesis was obtained as part of a comprehensive research program investigating the environmental and genetic risk factors affecting brain development in psychosis. The Principal Investigator for this study is Professor Dr. Timothea Toulopoulou. Although the protocol, functional MRI setup, environmental assessments, and other evaluations were established prior to my joining the study, I played a significant role in executing the study, as well as in the data analysis and interpretation, which is entirely my own work.

For this thesis, I analyzed data from 474 participants. I collected 197 fMRI scans, 54 cognitive tests, and 58 environmental assessments. I was involved in scoring all of these data together with the other members of the lab. The remaining data were gathered by graduate students supervised by Professor Toulopoulou, including Timucin Baş, Rabia Sen, Kübra Çelikbaş, Tuba Şahin İlikoğlu, Seda Arslan, İlayda Aydogan, Su Karakelle, Hande Ezgi Atmaca Turan, and Kader Kubat. Any additional contributions from colleagues, such as diagrams, calibrations, or data analysis codes, are explicitly referenced in the text.

I understand the university's policy on plagiarism and certify that this thesis has been written by me, except for parts of Chapter 3. The work presented in Chapter 3 was previously published in *Psychiatry Research: Neuroimaging* as " The effect of SARS-CoV-2 virus on resting-state functional connectivity during adolescence: Investigating brain correlates of psychotic-like experiences and SARS-CoV-2 related inflammation response". This paper included my supervisor Timothea Toulopoulou and the following collaborators: Helin Yılmaz Kafalı, Hacer Daşgın, Didenur Şahin Çevik, Sara Sinem Sozan, Kader Karlı Oğuz, Müge Mutlu, Aslınur Özkaya Parlakay. I contributed by collecting and scoring the data and preparing the database for the analysis. All authors made significant contributions to the conception, statistical analysis, and writing of that paper.

Didenur Şahin Çevik

Genetic and Environmental Contributions to Psychotic-Like Experiences and Working Memory Connectivity in Turkish Adolescents and Young Adults: A Twin Study

By Didenur Şahin Çevik

December 2024

We certify that we have read this dissertation and that in our opinion it is fully adequate, in scope and in quality, as a dissertation for the degree of Doctor of Philosophy.

Timothea Toulopoulou(Advisor)

Orhan Murat Koçak

Ausaf Ahmed Farooqui

Yasemin Hoşgören Alıcı

Hüseyin Boyacı

Approved for the Graduate School of Engineering and Science:

Orhan Arıkan
Director of the Graduate School

ABSTRACT

GENETIC AND ENVIRONMENTAL CONTRIBUTIONS TO PSYCHOTIC-LIKE EXPERIENCES AND WORKING MEMORY CONNECTIVITY IN TURKISH ADOLESCENTS AND YOUNG ADULTS: A TWIN STUDY

Didenur Şahin Çevik
Ph.D. in Neuroscience
Advisor: Timothea Toulopoulou
December 2024

Psychosis lies on a continuum, with psychotic-like experiences (PLEs) observed in healthy populations to full-blown psychotic disorders such as schizophrenia. PLEs are relatively common during adolescence, with distress associated with these experiences playing an essential role in determining their clinical significance. Adolescence is a critical time period where the brain undergoes substantial functional reorganization and where psychotic disorders first manifest. One promising intermediate phenotype for psychosis is the working memory with both patients, their first-degree relatives showing disruptions in performance and functional connectivity (FC). The overall aim of this thesis was to investigate the relationship between PLEs and FC mechanisms. The first study investigated the relationship between PLEs and task-based FC during a working memory task in adolescents. Moreover, we aimed to decompose the genetic and environmental influences in PLEs and FC measures via twin modeling. Our findings revealed that altered connectivity in the inferior frontal gyrus was associated with increased frequency and distress of PLEs during adolescence. Importantly, distress associated with PLEs showed moderate heritability, while the frequency of PLEs was predominantly shaped by environmental factors. The FC measures were mainly influenced by unique environmental factors, highlighting the critical role of environmental exposures during adolescence. The second study investigated COVID-19 as an environmental risk factor for psychosis and examined the differences in FC between COVID-19 patients and healthy controls. Further, the effect of the frequency of PLEs and the inflammation markers on functional connectivity differences was studied. The results demonstrated that while COVID-19

patients showed hypoconnectivity in the sensorimotor, central executive, and language networks, they showed hyperconnectivity in the visual network compared to healthy controls. Furthermore, including positive PLEs as a covariate revealed that the COVID-19 group exhibited greater functional connectivity within the salience and central executive networks. The findings of this thesis highlight the importance of environmental risk factors that increase psychosis risk by altering the underlying functional brain mechanisms.

Keywords: psychosis, psychotic-like experiences, working memory, environment, genetics, adolescent, fMRI.

ÖZET

TÜRK ERGEN VE GENÇ YETİŞKİNLERDE PSİKOTİK BENZERİ DENEYİMLER VE ÇALIŞMA BELLEĞİ İŞLEVSELLİK BAĞLANTISINA GENETİK VE ÇEVRESEL ETKİLER: BİR İKİZ ÇALIŞMASI

Didenur Şahin Çevik
Nörobilim, Doktora
Tez Danışmanı: Timothea Toulopoulou
Aralık 2024

Psikoz, sağlıklı popülasyonlarda gözlemlenen psikotik benzeri deneyimlerden şizofreni gibi ciddi psikotik bozukluklara kadar uzanan bir kontinyumda yer alır. Psikotik benzeri deneyimler (PBD) ergenlik döneminde yaygın olarak görülmektedir ve bu deneyimlerle ilişkili distres, klinik önemlerinin belirlenmesinde anlamlı bir rol oynar. Ergenlik dönemi, beynin önemli ölçüde işlevsel yeniden yapılanmaya uğradığı ve psikotik bozuklukların ilk kez ortaya çıktığı kritik bir zaman dilimidir. Çalışma belleği psikoz için bir ara fenotip olarak kabul edilmektedir ve hem psikoz hastaları hem de hastaların birinci derece akrabaları çalışma belleğinde değişiklikler göstermektedir. Bu tezin temel amacı, PBD'ler ve beyin işlevsel bağlantı mekanizmaları arasındaki ilişkiyi araştırmaktır. İlk çalışmada, ergenlerde psikotik benzeri deneyimler ve görev tabanlı işlevsel bağlantı arasındaki ilişki araştırılmıştır. Ayrıca, PBD'ler ve fonksiyonel bağlantı ölçümlerindeki genetik ve çevresel etkilerin ikiz modellemesi ile saptanması amaçlanmıştır. Sonuçlar, inferior frontal girusta gözlemlenen değişmiş bağlantısallığın ergenlik döneminde PBD'lerin sıklığı ve distresi ile ilişkili olduğunu göstermiştir. Dahası, PBD'lerle ilişkili distres, orta düzeyde kalıtılabilirlik gösterirken, sıklık esas olarak çevresel faktörlerden etkilenmiştir. Benzer şekilde, çalışma belleğiyle ilgili işlevsel bağlantı ölçümleri ağırlıklı olarak çevresel faktörlerle şekillenmiş ve ergenlik döneminde çevresel etkilerin kritik rolünü vurgulamıştır. İkinci çalışma, COVID-19'u psikoz için bir çevresel risk faktörü olarak araştırmış ve COVID-19 hastaları ile sağlıklı kontroller arasındaki işlevsel bağlantı farklılıklarını incelemiştir. Ayrıca, PBD'lerin sıklığı ve inflamasyon belirteçlerinin fonksiyonel bağlantı üzerindeki etkisi değerlendirilmiştir. Sonuçlar, COVID-19 hastalarının sağlıklı kontrollere kıyasla sensorimotor ağ,

merkezi yürütme ağı ve dil ağında hipokonnektivite, görsel ağda ise hiperkonnektivite gösterdiğini ortaya koymuştur. Ayrıca, pozitif PBD'lerin bir ortak değişken olarak analize dahil edilmesi, COVID-19 grubunun dikkat çekerlik ağı ve merkezi yürütme ağı içinde daha yüksek işlevsel bağlantı sergilediğini göstermiştir. Bu tezin bulguları, altta yatan işlevsel beyin mekanizmalarında değişikliklere yol açarak psikoz riskini artıran çeşitli çevresel risk faktörlerinin önemini vurgulamaktadır.

Anahtar sözcükler: psikoz, psikotik benzeri deneyimler, çalışma belleği, çevre, genetik, ergenlik, fMRI.

Acknowledgement

This thesis is part of a larger research program in the Brain Development and Psychosis lab (P.I: Toulopoulou). The aims and hypotheses of my PhD work are novel, but they are within the existing research framework. Therefore, I would like to first extend my deepest gratitude to my supervisor, Prof. Dr. Timothea Toulopoulou, for her invaluable guidance and support throughout my PhD studies. I am sincerely grateful for the opportunities she provided, which allowed me to grow as an independent researcher. I would also like to express my thanks to my TIK members Prof. Orhan Murat Koçak and Prof. Ausaf A. Farooqui for their insightful feedback and constructive suggestions, which were instrumental in shaping this thesis.

I am deeply grateful to my amazing friends who have been my lifeline throughout this journey. First, to İlayda, Hande and Tuğçe my wonderful former lab mates who have all graduated (and left me behind to fend for myself). Thank you for your guidance, and support, and for all the fun times that made the lab feel like a second home.

To Merve and Afife, thank you for being with me since day one of this process. From celebrating milestones to surviving meltdowns, your unwavering support and friendship carried me through every up and down. I couldn't have asked for better companions on this rollercoaster. I can't imagine having made it without you two by my side.

I would also like to thank my partner in crime, Eda Gül Karaca, who stood by my side during the hardest of times. Your unwavering support and friendship made even the toughest days bearable, and your camaraderie will forever hold a special place in my heart. I always knew I could turn to you for anything, and for that, I am endlessly grateful.

To my best friends, Büşra, Elif, and Emine, thank you for always being there, even when you didn't fully understand what I was doing or why I chose to do it. Thank you for always telling me that I've got this -even at times when I didn't- thank you for your words of encouragement.

To all of you, thank you for being part of this journey. You've added laughter, strength, and so much joy to what could have been a very lonely road. I am lucky

to have you in my corner.

Most importantly, I am forever grateful to my parents Mehmet and Nuray, whose unwavering love and sacrifices have been the backbone of every achievement in my life: thank you for always believing in me, even when I struggled to believe in myself. Mom and Dad, your endless support, encouragement, and faith in my abilities are the reasons I stand here today. To my siblings Gülnihal, İbrahim, and Aybike thank you for always being there as my greatest cheerleaders and occasional reality checks. And to my husband Kerim, my constant source of strength and reassurance: thank you for your patience, and understanding, and for standing by me through every late night, every challenge, and every triumph. You have all been my rock.

Finally, I would like to express my gratitude for the financial support I received from the Scientific and Technological Research Council of Turkey (TUBITAK BIDEB 2211 A Program, 2211 BIDEB National Graduate Scholarship Program).

Second to the right, and straight
on 'til morning.

J.M. Barrie, *Peter Pan*

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Chapter 1

Introduction

1.1 Overview of Psychosis and Psychosis Proneness

1.1.1 Psychosis Definition and Characteristics

The word psychosis originates from the Greek word psyche, meaning the mind or the soul, and -osis, meaning disease [1], and it was first coined by an Austrian physician, Ernst von Feuchtersleben, in 1845. Feuchtersleben described psychosis as a disorder in which patients lose their contact with reality [2]. During the late 19th and early 20th centuries, German psychiatrist Emil Kraepelin played an important role in advancing the understanding of psychosis. His contributions led to significant developments in the conceptualization and classification of psychotic disorders. He proposed a division between the conditions of "dementia praecox" (now known as schizophrenia) and "manic-depressive insanity" (now known as bipolar disorder). By separating these two conditions from each other, he paved the way for further research to better understand and define the dimensions of psychotic disorders [3].

Building on Kraepelin's work, Karl Jaspers introduced the concept of phenomenology, which emphasized that the patient's subjective experiences were central to the understanding of the disorder. Jaspers made a distinction between primary and secondary delusions, with primary delusions being central to psychotic disorders and secondary delusions being seen as a result of other mental disorders [4]. His work laid the foundations for the diagnostic criteria used today to categorize and diagnose psychotic disorders. Later expanding on his work, Kurt Schneider proposed "first rank symptoms in schizophrenia", including symptoms such as auditory hallucinations, delusions, thought insertions, and thought broadcasting, which became the primary symptoms in diagnosing psychotic disorders [5]. This emphasis on phenomenology shifted the understanding of psychosis from purely focusing on a set of fixed observable symptoms to the internal experiences of the patients [6].

The identification of specific diagnostic criteria established the foundation for defining and categorizing psychosis in contemporary psychiatric classification systems [6]. In 1949, the International Classification of Diseases (ICD-6) published by the World Health Organization (WHO) for the first time included a section on psychotic disorders. Over the years, the ICD has undergone significant revisions regarding the categorization of psychotic disorders [7]. The latest edition, ICD-11, published in 2019, emphasizes the importance of the severity and the duration of the symptoms as well as the functionality of the patient. It takes a more dimensional approach to diagnosing psychotic disorders, including various degrees of psychotic severity, from acute episodes to chronic states [8].

Similarly, in 1952, the Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA), introduced a diagnostic manual specifically for psychiatric disorders, including a category for psychotic disorders titled "Disorders of Psychogenic Origin" [7]. Since then, the DSM has undergone five major revisions. The most recent version of the DSM-5 has moved away from a categorical classification of psychotic disorders to an emphasis on dimensional assessments where psychotic disorders are characterized along a spectrum [9] [10].

Today, psychosis is characterized by a core set of symptoms, including delusions, hallucinations, disorganized thinking, and impaired functioning [7]. However, it is important to recognize that psychosis is a phenotypically heterogeneous disorder, meaning that it can manifest differently across different individuals in terms of symptoms and clinical presentations [11]. Traditionally, the symptoms of psychosis have been categorized into two main groups (positive and negative symptoms) and, more recently, into three main categories that also include cognitive symptoms. Positive symptoms represent distortions of reality, with delusions (persistent false beliefs that continue despite contradictory evidence) and hallucinations (perceptual experiences that occur without external stimulus) being the most prominent [12]. Negative symptoms, on the other hand, represent a reduction in normal functioning, including blunted affect (restriction in emotion expression), anhedonia (inability to experience pleasure), and avolition (lack of engagement in goal-directed behaviors) [13] [14]. Finally, cognitive symptoms include deficits in memory, attention, and executive functioning [15] [16] [17].

1.1.2 Incidence and Prevalence of Psychosis

Psychotic disorders typically first clinically manifest during adolescence [18]. The lifetime prevalence of psychotic disorders is estimated to be around 3% [19] [20]. Psychosis is associated with higher levels of suicidality [21] and functional impairment [22], which contributes to the overall disease burden by both affecting the individuals directly as well as placing a significant strain on families, society, and economies. The incidence rate of psychotic disorders was found to be 0.3 per 1.000 person-years and showed a peak during adolescence. Males, migrants, and people of ethnic minorities are at increased risk for developing psychotic disorders [23]. A recent study done in the Turkish population reported the incidence rates of all psychiatric disorders as 0.38 per 1.000 person-years, with the highest incidence rate during adolescence and young adulthood group (15-24 years) [24].

1.1.3 Psychosis Proneness Definition and Significance

Psychosis phenotype lies on a continuum in which psychotic-like experiences (PLEs) seen in psychosis patients can also be seen in non-clinical populations (See Figure 1.1) [25]. Experiencing PLEs in itself is not an indicator of a psychosis diagnosis. A psychotic disorder diagnosis depends on the intensity, duration, and frequency of the symptoms as well as an assessment of functioning [8] [9]. Psychosis proneness refers to the expression of the psychosis phenotype at levels well below its clinical manifestation. It represents having a predisposition to psychotic disorders such as schizophrenia (SCZ). It has been widely established that psychosis proneness and psychotic disorders share common etiological risk factors, cognitive correlates, and neurodevelopmental trajectories [25].

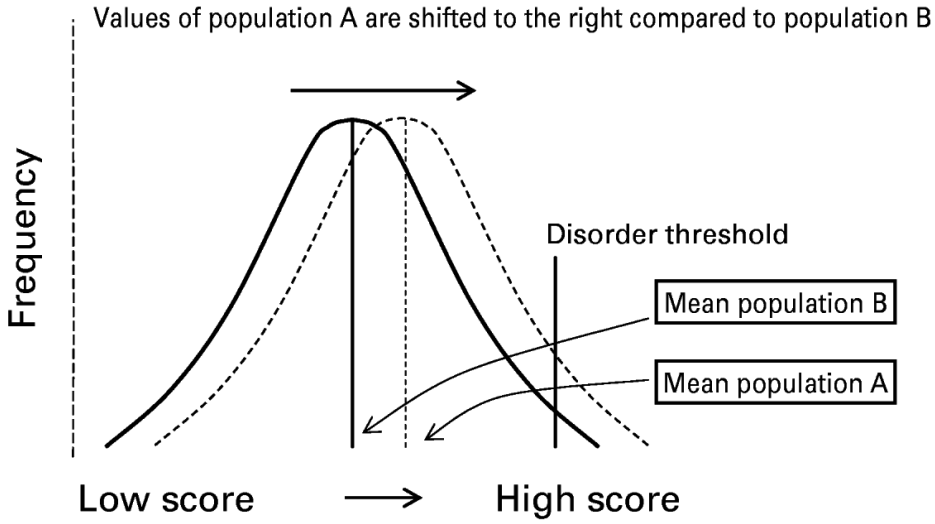

Figure 1.1: The graph displays the continuum of psychosis phenotype. The mean values of population A (psychosis-proneness population) are shifted to the right compared to the mean values of population B (population without psychosis proneness). Reprinted, with permission, from ref. [25]

PLEs are relatively common during adolescence; however, many psychotic symptoms experienced during this time are transient in nature and do not persist [26]. Around 6% of individuals report experiencing a psychosis-like experience,

such as hallucinations or delusions, at least once in their lives [27]. In a recent meta-analysis study, the incidence rate of PLEs was reported as 22.5 per 1.000 person-years, with this rate showing a peak in adolescence at 50 per 1.000 person-years [28]. Most individuals classified as clinically high risk (CHR) for psychosis do not go on to develop psychotic disorders later on in life. Studies show that when clinically high risk individuals are followed up at two years, the rate of developing a psychotic disorder is between approximately 15% [29] [30] and 30% [26] [31].

Even though psychosis proneness is relatively common during adolescence, and individuals do not convert to a full-episode psychotic disorder, they still exhibit impaired functioning and are at increased risk for mental disorders and suicidal ideation [32] [33] [34]. There is cumulating evidence indicating that regardless of the clinical status, psychosis proneness is associated with poor functional outcomes when the PLEs are distressing or when they persist and expose the individuals to the risk state for an extended period of time [35]. Moreover, studies show that almost 30% of individuals with PLEs consult a mental health professional and report reduced functioning [34]. Furthermore, the conversion rate to a psychotic disorder was found to be around 3.5 times higher in individuals who have experienced PLEs when compared to individuals who have not experienced PLEs [36].

Given the functional impairments and increased risk for psychosis, identifying PLEs in healthy populations is important in studying the trajectory of these symptoms. Psychosis proneness is typically assessed using a variety of self-report questionnaires and clinical interviews. One well-established measure to assess PLEs is the "Community Assessment of Psychic Experiences" (CAPE-42) questionnaire. CAPE-42 is a self-report questionnaire that measures the psychotic experiences that an individual goes through in life. This instrument has three subscales, positive, negative, and depressive, which are all assessed for their frequency and distress [37]. The CAPE-42 questionnaire has been found to be especially reliable when studying adolescents and younger populations [33]. Therefore, in this thesis, PLEs were measured with the Turkish version of the CAPE-42 questionnaire [38].

Overall, the findings in the literature show that the presence of PLEs is a risk factor for later development of psychotic disorders. It is now widely understood that psychotic disorders exist on a continuum and that along this continuum, cognitive deficits play a crucial role [15] [25]. Cumulating evidence characterize psychosis as a neurodevelopmental disorder with the presence of cognitive dysfunction as a core feature [39]. Impairments in executive functioning, attention, and working memory are hallmarks of psychosis and are prominent even before illness onset [40]. In fact, abnormalities in brain function and a decline in cognition are observed in individuals who later on develop schizophrenia and in individuals with psychosis proneness [41] [42]. Therefore, understanding cognitive deficits and their neural correlates in psychosis and psychosis proneness is critical. The next chapter will focus on working memory mechanisms and alterations in functional connectivity in individuals along the psychosis continuum.

1.2 Working Memory and Functional Connectivity in Psychosis

1.2.1 Working Memory as an Endophenotype in Psychosis

For many psychotic disorders, such as schizophrenia, genetic factors account for a significant portion of disease risk [22]. However, the manifestation of these disorders at the clinical level is far removed from the direct effects of genes [43]. Instead of genes directly influencing clinical symptoms, it is thought that they act through 'intermediate' levels, such as neural mechanisms, which serve as a bridge between the genotype and the clinical phenotypes [44]. These intermediate markers are known as endophenotypes or intermediate phenotypes. They represent measurable traits and provide insights into the underlying neurobiology of the disorder. Endophenotypes are heritable, cosegregate with the illness, are present in unaffected members of the family higher than the general population,

and are not dependent on the disease state [45].

Psychotic disorders are commonly associated with cognitive deficits in attention, executive functions, and working memory [46]. The presence of cognitive deficits greatly hinders the daily functioning of the patients and does not improve with the use of antipsychotic medications [47]. Cognitive deficits typically onset before the manifestation of the first episode and include reductions in IQ and impairments in multiple domains such as processing speed, memory, reasoning, and attention [46]. In fact, Toulopoulou and colleagues provided evidence that cognitive dysfunction accounted for a quarter of the total variation in schizophrenia liability, suggesting that cognitive impairments play a causal role in the etiology of schizophrenia [48]. Furthermore, the Consortium on Genetics of Schizophrenia (COGS) examined the genetic foundations of neurocognitive biomarkers and has identified working memory, attention, and declarative memory as endophenotypes of schizophrenia [49].

A promising cognitive intermediate phenotype for psychosis is working memory (WM) [50]. Working memory is a key component of higher-order cognitive functions, allowing the temporary storage and manipulation of goal-oriented information [51]. It has a limited capacity and consists of four components. It is made up of the phonological loop, the visuospatial sketchpad, the central executive, and the episodic buffer [52]. The phonological loop is responsible for storing and processing auditory information, the visuospatial sketchpad manages visual and spatial information, the central executive is responsible for attention and the coordination of the other systems, and the episodic buffer combines and integrates the information from different sources (See Figure 1.2) [52] [53].

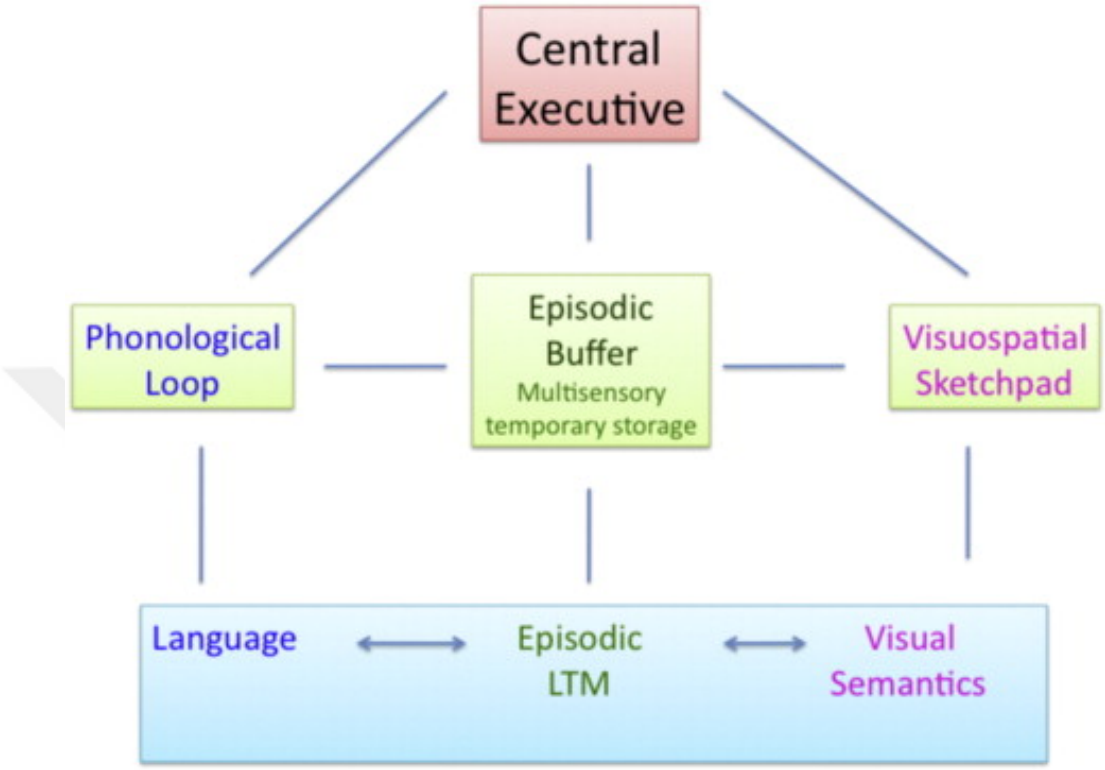

Figure 1.2: The Working Memory Model by Baddeley. Reprinted, with permission, from ref. [53]

Psychosis patients consistently perform worse than their first-degree relatives on working memory tasks [54], and these impairments are associated with poorer functional outcomes and the degree of negative psychotic symptoms [55]. Moreover, first-degree relatives of psychosis patients also exhibit poorer working memory performance compared to healthy populations [56]. In a longitudinal study, researchers investigated the working memory differences in clinically high risk groups, comparing neurocognitive functioning in those who later converted to psychosis vs those who did not. They found that working memory impairments were a significant indicator of conversion to psychosis [57]. While these impairments are more pronounced in patients and their first-degree relatives, they are also observed to a lesser extent in healthy individuals with PLEs [58]. Studies conducted in healthy populations have found reduced working memory capacity [58] and decreased accuracy [59] in individuals with PLEs. This gradual decline

in working memory abilities across different groups (from patients to their first-degree relatives to individuals with PLEs) highlights the role of working memory deficits as an endophenotype in psychosis.

The idea that working memory is an endophenotype for psychosis is further supported by findings from genetic studies that indicate common genetic influences between working memory deficits and psychosis. Psychotic disorders such as schizophrenia are highly polygenic, and therefore, the variance in these disorders cannot be explained by a single gene. One method used to study the genetic liability in these disorders is the polygenic risk score (PRS). PRS is calculated by weighing the contributions of individual risk alleles associated with the disease [60]. In one study, researchers found a relationship between the PRS for schizophrenia and working memory-related activation in the frontal lobe [61]. Additionally, the genetic overlap between PRS for schizophrenia and cognition has been demonstrated by showing that liability to schizophrenia was significantly associated with alleles that were known to be linked to lower cognitive abilities [62]. Building on these findings, Toulopoulou and colleagues have found through casual modeling that cognitive deficits mediated over 33% of the genetic liability to schizophrenia. Moreover, they found that more than one-third of the variation in PRS to schizophrenia was also mediated by cognitive impairments [17]. Similar findings have been observed in twin studies. For instance, bivariate twin models have shown that working memory and liability to schizophrenia share significant genetic correlations, suggesting that common genetic influences contribute to the risk for schizophrenia and working memory impairments [63] [64] [65]. Together, these findings suggest that cognitive deficit, especially working memory, indicates a risk-associated intermediate phenotype for schizophrenia.

1.2.2 Working Memory Related Functional Connectivity Alterations in Psychosis

Working memory impairments during psychosis are also demonstrated through functional Magnetic Resonance Imaging (fMRI) studies, providing valuable insights into the neural dysfunctions associated with the psychosis. fMRI relies on detecting changes in blood flow through the Blood Oxygen Level Dependent (BOLD) signal to identify which brain regions are active during specific tasks [66]. fMRI studies often employ functional connectivity analysis to explore how the activity of different brain areas correlates during specific tasks. This technique captures how distant brain areas interact by synchronizing their BOLD signals, offering insights into the brain networks involved in working memory processes [67]. Although it doesn't provide any information regarding causal relationships between different brain regions, functional connectivity analysis is particularly useful in psychosis research as it helps identify disrupted communication patterns across brain networks crucial for cognitive functions like working memory [66].

According to the results of neuroscience studies, one of the most implicated neuronal regions for working memory processes is the prefrontal cortex (PFC). This view is rooted in decades of studies showing the involvement of PFC in different working memory tasks both in humans and nonhuman primates [68] [69] [70]. It is well known that the prefrontal cortex is involved in various higher-order cognitive functions, such as planning and decision-making, which all require the use of working memory mechanisms [71] [72]. Recent views suggest that the prefrontal cortex is a key region in working memory processes as it plays a top-down control over the rest of the brain areas, thus emphasizing the connectivity between the prefrontal cortex and other brain regions [73]. Notably, the prefrontal cortex has also been shown to be associated with liability to psychosis and disease symptoms [74] [75].

Schizophrenia, which falls under the psychosis spectrum, is generally defined as a dysconnectivity disorder where disruptions in functional integration between

brain regions are predominant [76] [77]. Previous research shows that unaffected first-degree relatives of psychosis patients exhibit abnormal signaling and connectivity patterns in working memory brain mechanisms compared to healthy controls, suggesting working memory to be an intermediate endophenotype for psychosis [50] [78].

Studies report both increased and decreased activation patterns during working memory tasks in schizophrenia patients [79] [80] [81]. These differences are thought to reflect different cognitive demands required by the task. Especially in tasks with higher working memory loads, such as the 2-back task, patients are known to exhibit increased activation in several regions, suggesting that they may require greater resources to compensate for functional impairment [82]. Working memory paradigms vary in their task loads, and as a result of this, different neuronal responses are seen in healthy vs patient groups in different studies. It is thought that as cognitive demands of the task increase, patients display an inverted-U-shaped neuronal response, which is shifted to the left compared to healthy controls (See Figure 1.3) [83]. This model argues that when task difficulty is easy, schizophrenia patients show increased neuronal responses compared to healthy controls, which may indicate compensatory mechanisms. However, when task difficulty increases, they start showing decreases in neuronal responses. This pattern is also reported in the first-degree relatives of patients [78].

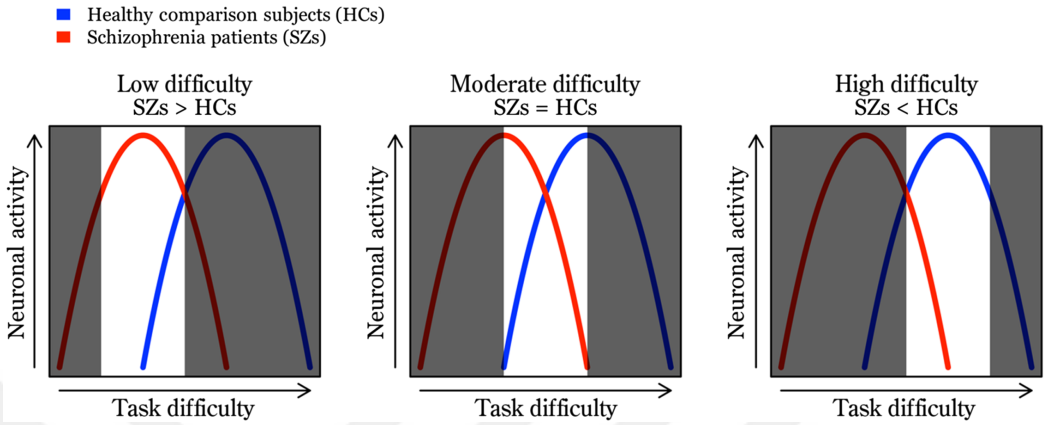

Figure 1.3: Inverted U-shaped model of neuronal function in schizophrenia patients vs. healthy controls. Task difficulty is illustrated with the shift of the white window. Reprinted, with permission, from ref.[83]

Abnormal activation patterns are mainly observed in frontal regions in patients and their unaffected siblings compared to healthy controls [78]. In an fMRI study, the authors found that individuals with a genetically high risk for psychosis had abnormal frontoparietal connectivity during a working memory paradigm when compared to healthy individuals. Moreover, the degree of connectivity was negatively related to the presence of psychiatric symptoms [84]. In a meta-analysis study, the 1st-degree relatives of schizophrenia patients were shown to have increased activity in the left inferior parietal lobule (IPL), thalamus, and frontopolar area and reduced activation in the right middle frontal gyrus (MFG) and the right inferior frontal gyrus (IFG) compared to healthy controls [78]. Authors discuss that decreased activation in middle frontal gyrus and inferior frontal gyrus may reflect impairments in cognitive control whereas the increased activation in frontopolar area and inferior parietal lobule may reflect compensatory mechanisms. In addition to the abnormal activation patterns in psychosis patients and their unaffected relatives, alterations in the activation of prefrontal regions have also been documented in individuals with psychosis proneness. In a population-based study, researchers found hypoactivation in the prefrontal areas, including the dorsolateral prefrontal cortex (dlPFC) and frontal pole, in individuals with PLEs compared to individuals without PLEs [85]. Likewise, another study found that during working memory, children with PLEs showed hypoactivation in the

dlPFC, striatum, and pallidum [86].

Similar to alterations in the activity of the prefrontal regions, functional connectivity impairments have also been reported in patients, unaffected relatives, and individuals with PLEs. In a recent study, researchers investigated the effective parietal-prefrontal connectivity during a working memory manipulation task in schizophrenia patients and healthy controls. They found that deviations in the functional connectivity correlated positively with delusion severity in patients. Moreover, they found that in healthy controls, individuals with higher PRS for schizophrenia had more impairments in parietal-prefrontal connectivity [87]. In another study, researchers investigated the working memory-related connectivity in healthy individuals with varying levels of delusional ideation. They found that individuals with high delusional ideation showed hypoconnectivity within the parietal-prefrontal network [88]. Impaired prefrontal-parietal effective connectivity in patients with schizophrenia has been reported consistently in the literature [89] [90].

To summarize, psychosis is consistently associated with working memory impairments, which are evident in task performance, functional activation, and functional connectivity of different networks. These impairments are also seen to a lesser extent in their 1st-degree relatives and individuals with psychosis proneness, suggesting working memory to be a promising intermediate phenotype for psychosis. Especially alterations of prefrontal regions are implicated in these deficits as the prefrontal cortex plays a key role in regulating working memory processes through its connections with other brain regions.

It is important to note that regions like prefrontal cortex are undergoing accelerated development during adolescence, a time frame in which psychotic disorders onset. The time frame for the maturation of these higher-order brain networks correlates with the onset of schizophrenia; therefore, adolescence and young adulthood indicate a critical period of vulnerability for the illness [91]. Consequently, it is important to better understand the developmental changes that take place during adolescence and how they may create heightened vulnerability to psychosis.

1.3 Adolescent Brain Development and Vulnerability

Adolescence is a period of time in which the brain undergoes rapid developmental changes both in structure and function [92]. It is also a time period where many neurodevelopmental psychotic disorders, such as schizophrenia, first manifest both clinically or sub-clinically. According to a recent study worldwide, many psychiatric illnesses have an onset before the age of 18 (48.4%) and 25 (62.5%) [93]. During this time frame, processes such as synaptic pruning, myelination, and fluctuations in sex hormones take place. Prefrontal regions, which are crucial for the development of working memory mechanisms, become more localized as synaptic pruning and increased myelination occur [94]. The maturation of higher-order brain networks correlates with the onset of psychotic disorders, which indicates a critical window of vulnerability [91]. These rapid neurobiological changes during adolescence can influence the risk of psychosis proneness [95].

Pruning is the process of reducing the number of synaptic connections that are less commonly used while maintaining the more frequently used connections [96]. It is essential for efficient synaptic transmission and enables more refined connections. The etiology of schizophrenia has long been linked to disturbances in the development of pruning processes [97]. During adolescence, pruning processes show a peak for higher-order cortices [98]. Studies indicate that microglia, immune cells of the nervous system, show an increased involvement in the synaptic pruning of the prefrontal cortex during adolescence [99] and thus increase the risk for psychotic disorders [100]. Furthermore, a recent meta-analysis study shows that individuals with psychosis proneness had decreased gray matter volumes in frontal regions when compared to the control group. These findings are consistent with the findings of gray matter volume studies conducted in psychosis patient groups [100]. Moreover, in a longitudinal study, researchers found that gray matter volume was lower in individuals at clinically high risk of psychosis for the prefrontal cortex and continued to decrease as individuals transitioned

to psychosis [101]. Taken together, these findings suggest that as frontal regions underlie executive functions such as working memory and attention, gray matter disruptions in these areas might increase vulnerability to psychosis risk.

While less frequent connections are eliminated, the transmission speed and efficiency of the remaining connections are improved by the myelination processes. Myelin sheath forms around the axons to ensure rapid communication between different regions of the brain while reducing energy costs [102]. In adolescence, white matter tracts such as the superior longitudinal fasciculus and the accumbofrontal tract (the connection between the nucleus accumbens and orbitofrontal cortex) have been shown to have increases in myelination [103] [104]. Cumulating evidence suggests that white matter disruptions are found both in psychosis patients and individuals with psychosis proneness [105] [106]. Especially decreases in fractional anisotropy (FA), which reflects myelination, have been reported extensively in frontal cortices [107] and in the superior longitudinal fasciculus [108] in psychosis patients [105]. Likewise, in a population-based study, disruptions in white matter have been reported in adolescents with PLEs [109]. These results suggest that psychosis proneness is associated with disruptions in white matter integrity, and individuals with psychosis proneness show a divergence from the typical developmental trajectory of the brain, resembling those evident in psychosis patients.

These changes in synaptic pruning and myelination during adolescence contribute to the reorganization and fine-tuning of subcortical and cortical regions. However, brain maturation occurs in waves, which results in different developmental periods of brain circuitries [110]. The imbalance model of adolescent development proposes that adolescence is defined by the mismatch between the maturation times of the subcortical limbic regions and the prefrontal cortex (See Figure 1.4) [111] [112]. As the frontal cortex continues to mature during this time in a linear fashion, the development of executive and higher-order cognitive functions extends well beyond the maturation of subcortical areas [113]. This difference between the maturation timelines of the limbic system and the prefrontal cortex is thought to play a significant role in shaping behavior during adolescence, particularly underlying the increase in risk-taking behaviors, sensation-seeking,

and reward sensitivity [114]. Behaviors such as drug use, delinquency, reckless driving, binge drinking, and unprotected sex show peak during this time [114].

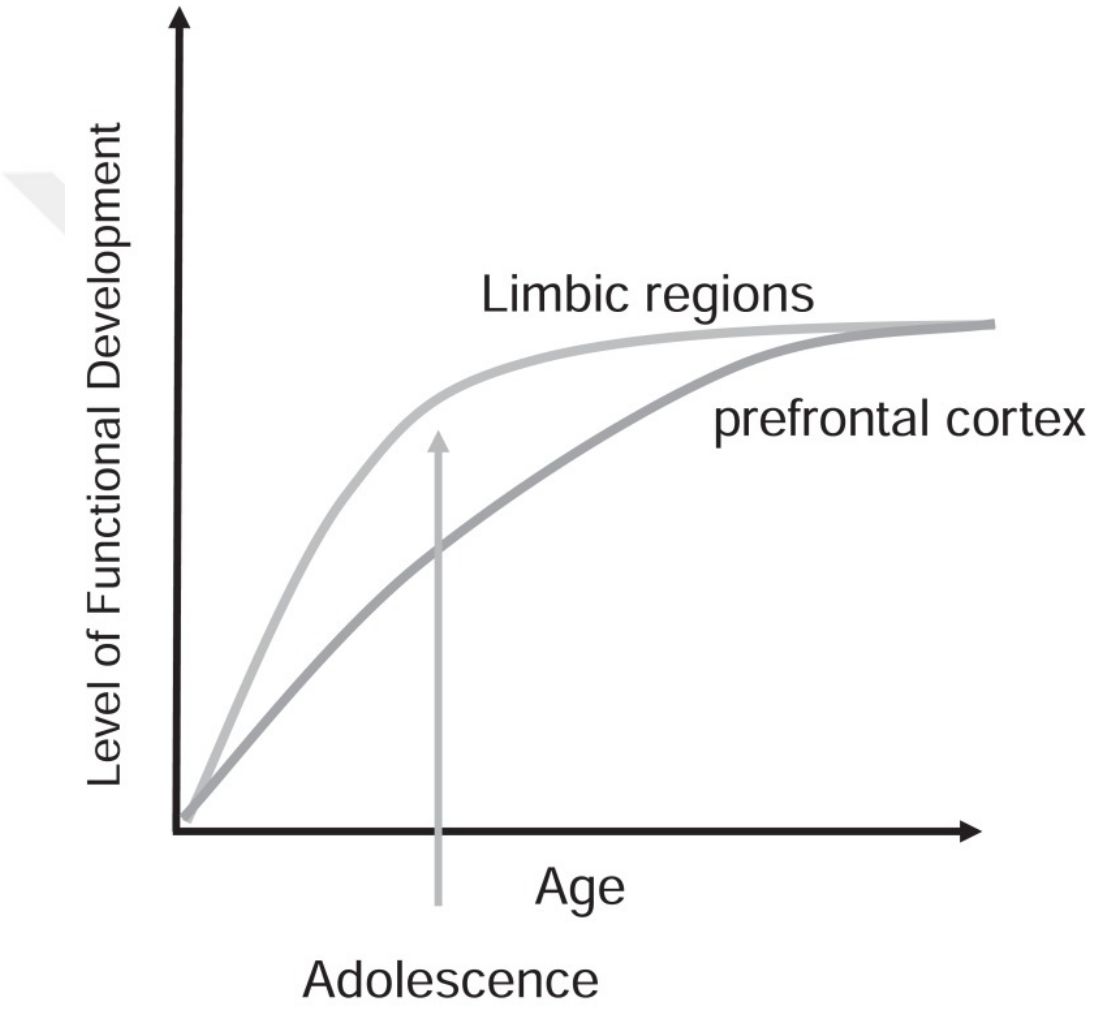

Figure 1.4: The imbalance model between the developmental trajectories of the prefrontal cortex vs limbic regions in adolescence. Reprinted, with permission, from ref. [112]

Research shows that while adolescents can assess risky situations and predict negative outcomes when the situations are emotionally salient, the involvement of the emotionally driven limbic system may override the prefrontal cognitive control

system [111]. For example, compared to adults, adolescents show increased activation in the ventral striatum when making risky decisions, and this activation shows a peak in mid-adolescence [115]. One example of increased emotionally salient environments is the presence of peers. Studies have shown that adolescents were more likely to engage in more risky behaviors, such as gambling and risky driving, when peers were observing them as compared to when they were alone [116] [117]. At the same time, the presence of peers has been found to increase engagement in exploratory behavior and better learning of both positive and negative outcomes [118]. This suggests that when assessing the outcomes of risky situations, acceptance by their peers might be more important than the risky outcome for adolescents. This may be another indication of the imbalance between the limbic and prefrontal systems.

However, the imbalance between the two systems does not necessarily point to maladaptive functioning and is rather the normal trajectory during adolescence. From an evolutionary perspective, adolescence is a period where individuals experience separation from their families, find mates, and establish independence [119]. During this time, sensation-seeking and risk-taking behaviors may serve adaptive purposes. These behaviors can help adolescents assert independence, explore new opportunities, and establish social hierarchies, which are essential for achieving social status, securing resources, and attracting mates as they transition into adulthood [120]. For example, establishing good relationships with peers during adolescence was shown to predict better psychosocial functioning later in life [121]. In accordance with this, an alternative model, the Life-span Wisdom Model, has been proposed in which the role of the environment and the experiences gained during adolescence play a key role [122]. This model argues that increased risk-taking and sensation-seeking are adaptive strategies for adolescents and help them successfully transition into adulthood by facilitating the exploration of new opportunities and learning new skills. In addition to the neurobiological changes that occur during adolescence, which heighten mechanisms like sensation seeking, this model emphasizes the role of experiences and the environment, which in turn shapes cognitive and emotional development (See Figure 1.5) [122].

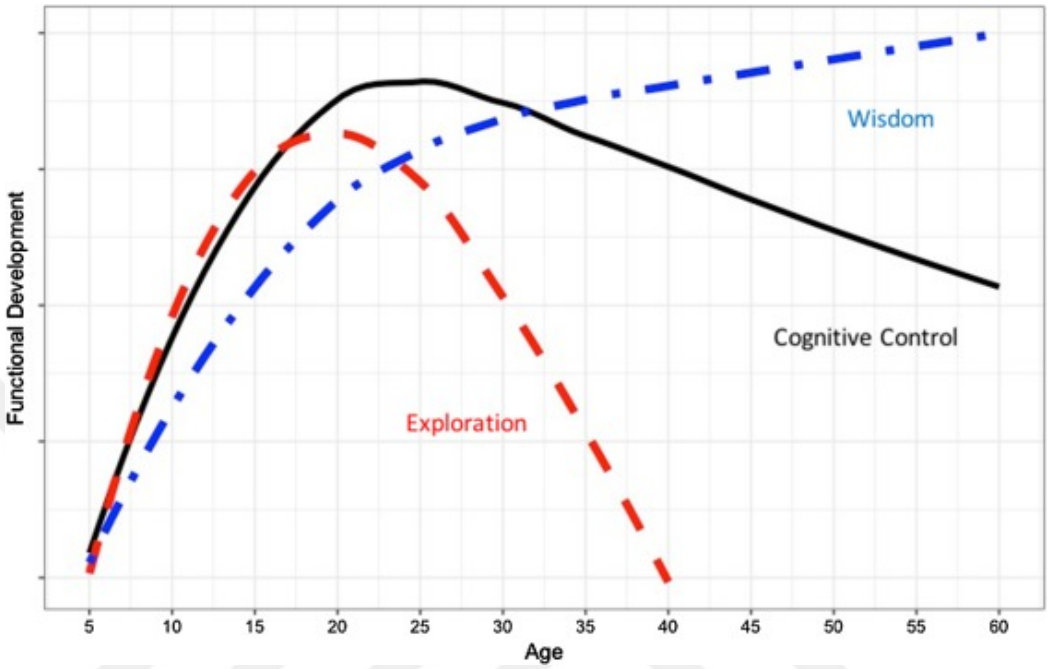

Figure 1.5: The Life-span Wisdom Model illustrating the trajectories of cognitive control, exploration and wisdom throughout life. Reprinted, with permission, from ref.[122]

In summary, adolescence is a time period characterized by an accelerated phase of development and maturation [123]. During this time, cognitive and executive functions such as working memory undergo major functional reorganization [94]. However, this period of heightened neuroplasticity can be seen as a double-edged sword. On the one hand, brain plasticity supports the maturation of executive functions and cognitive abilities and facilitates evolutionary adaptive behaviors, but on the other hand, it leaves neural mechanisms especially vulnerable to exogenous influences [102]. These influences can be beneficial in terms that they can lead to the enhancement of executive functions but also detrimental in the sense that they can lead to psychopathology [102]. When there is a disruption to the normal developmental trajectory, especially in the face of adverse external environments, it may pave the way for long-lasting negative health outcomes and put the individual at risk for developmental disorders such as psychosis. Therefore, it is of utmost importance to understand the effect of environmental risk factors before and during adolescence and how they may increase the risk for

psychosis.

1.4 Genetic and Environmental Risk Factors in Psychosis

1.4.1 Environmental Risk Factors and Psychosis

Psychosis was first described as a neurodevelopmental disorder in 1891 by Thomas Clouston [124]. Over the years, this model was expanded to include environmental risk factors by research showing that different early adversities, such as obstetric complications [125], infections during pregnancy [126], and nutritional deficiencies [127], increased disease liability. Later, in a systematic review, researchers showed that the incidence of schizophrenia was highly heterogeneous and discussed the role of population-level risk factors such as urbanicity, ethnicity, and migration status [128]. Building on this and other studies investigating both individual-level and population-level environmental risk factors expanded the neurodevelopmental model to include environmental risk factors.

The Developmental Risk Factor Model proposes that schizophrenia differs from other neurodevelopmental disorders, such as autism, in that the environmental risk factors interact with the neurodevelopmental risk factors to increase disease risk, especially during critical developmental periods. This model also takes into account that psychosis lies on a continuum, and therefore, it recognizes that psychotic-like experiences share the same environmental and genetic risk factors as psychosis [129].

Another influential model that further expands our understanding of the etiology of psychosis is the diathesis-stress model. This model highlights how genetic vulnerabilities interact with environmental risk factors later in life, particularly during adolescence, to increase disease risks [130]. The hypothalamic-pituitary-adrenal (HPA) axis is responsible for regulating adrenal hormones to maintain

homeostasis in the face of stressors. Dysregulation of the HPA axis has been observed in psychosis and clinically high risk groups and is, therefore, usually implicated in the diathesis-stress model of psychosis. It is proposed that environmental stressors and genetic predispositions interact to alter normal developmental trajectories. These alterations, such as the dysregulation of the HPA axis, lead to maladaptive responses to later stressors in life, which in turn increases the risk of psychotic disorders (See Figure 1.6) [131].

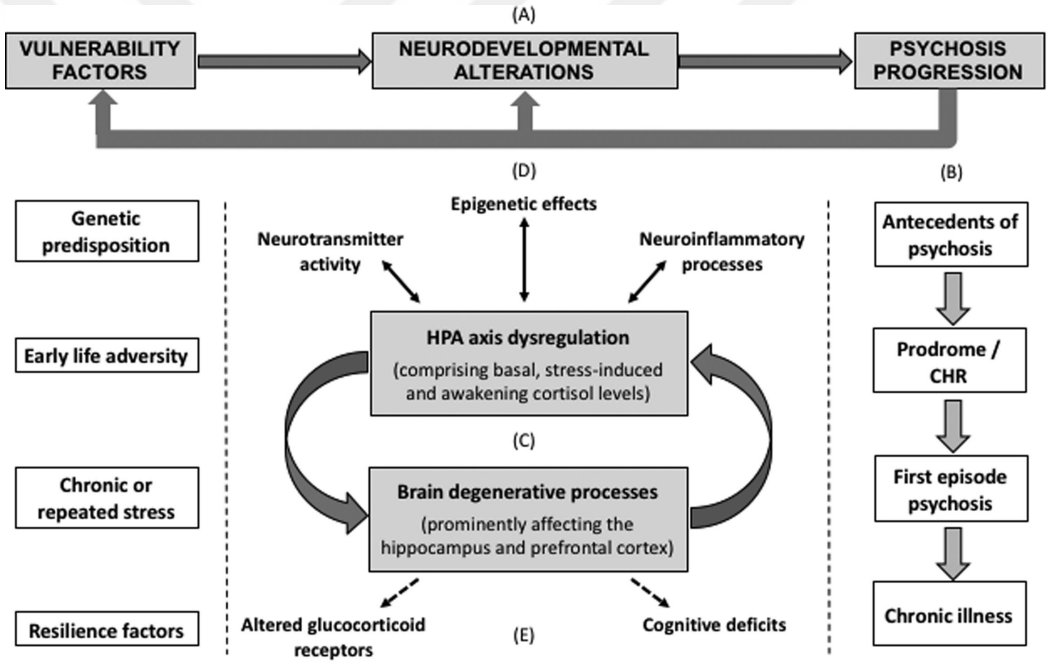

Figure 1.6: The extended diathesis-stress model for psychosis. A: Right-facing arrows show the effect of vulnerability factors on neurodevelopmental alterations, which lead to psychosis progression. The left-facing arrows show the effect of psychosis symptoms to further increase the risk of illness by contributing to alterations and vulnerability. B: Shows the development of psychosis from subclinical symptoms to disease onset. Arrows indicate the causal effect of HPA axis dysregulation and brain degenerative processes. The effect is bidirectional. D: Arrows show the bidirectional relationship of the HPA axis with other processes. E: Dashed arrows indicate the results of alterations in brain mechanisms. Reprinted, with permission, from ref. [131]

Animal studies show that being exposed to enriched environments during adolescence not only can bring about neural changes such as increased spine density but also behavioral changes such as increased memory capacity [132] [133]. Likewise, human studies suggest that protective factors can act as a buffer to stressors [134]. In a study, researchers found that low socioeconomic status was associated with decreased gray matter volume in the hippocampus. However, this effect was not seen in individuals who had high self-esteem levels [135]. On the other hand, being exposed to environmental stressors during this critical period may alter the normal developmental trajectory of the brain by affecting ongoing mechanisms such as neural pruning, myelination, and remodeling of synaptic connections, which in return can increase liability to psychosis [136]. This becomes particularly important, considering that during adolescence, risk-taking behaviors and exposure to stressors such as cannabis use increase.

It is well established that cannabis use can have adverse effects on working memory brain mechanisms [137] [138]. For instance, in a study, researchers showed that even though there were no differences in behavioral measures between cannabis users and controls, the effective connectivity between the right dorsolateral prefrontal cortex and left caudate decreased in cannabis users during a working memory task [139]. It is further known that the risk for the development of psychotic disorders is 2-fold for cannabis users and 6-fold for heavy and chronic cannabis users compared to non-users [140] [141]. Cannabis users also have an earlier onset of psychosis [142] and have more severe and frequent symptoms [143]. A meta-analysis study showed that psychosis patients with a lifetime of cannabis use performed worse on cognitive tasks such as working memory compared to patients without cannabis use [144].

Another well-studied risk factor for psychosis risk is childhood maltreatment (CM). Childhood maltreatment can include different maltreatment types, such as psychological, physical, and sexual abuse, as well as psychological and physical neglect. Psychosis patients retrospectively report higher exposure to childhood maltreatment compared to controls [145] [146]. Exposure to trauma in childhood has also been found to be associated with symptom severity [147] and resistance to treatment [148]. In fact, some studies have shown a causal effect of trauma on

disease onset [145]. Similar findings have been reported in healthy populations with PLEs. Both longitudinal and cross-sectional studies have shown that individuals who were exposed to childhood trauma were more likely to experience PLEs [149] [150]. Childhood maltreatment is also known to affect executive brain function, which in turn may increase vulnerability to psychosis [151]. Impaired functional connectivity has been observed in psychosis patients with a history of childhood maltreatment [152]. Individuals with childhood maltreatment show alterations in the function of critical brain regions such as prefrontal cortex, anterior cingulate cortex (ACC), orbitofrontal cortex, and striatum [153] [154]. For instance, researchers found that children with high risk for psychosis and exposure to childhood maltreatment had lower IQ and poorer cognitive performance compared to high-risk children who were not exposed to childhood maltreatment [155]. Another study found abnormal activation patterns in the parietal regions of schizophrenia and bipolar disorder patients with childhood maltreatment compared to patients without childhood maltreatment during an n-back working memory task [156].

Similar to the results in childhood maltreatment, adversities experienced during adolescence are also known to be risk factors for psychotic disorders [157]. Studies show that different types of victimization experienced in adolescence can be a predictor of psychopathology later in life [158]. Both childhood and adolescence reflect two critical vulnerability windows for psychosis development [91]. Exposure to adversities during these critical periods may alter the functional connectivity of brain networks and lead to the persistence of PLEs, thereby exposing the individual to an extended duration of psychotic-like experiences and increasing the risk of developing psychotic disorders [159].

In addition to individual-level factors, population-level factors such as urbanicity, migration, and exposure to air pollution are known to be valid risk factors for psychosis risk and influence individuals across the psychosis continuum [129]. One of the most consistent findings in schizophrenia is the increased incidence rate for people born in urban environments compared to rural environments [160]. In a Swedish population study including 4.4 million individuals, it was observed that the incidence rate for schizophrenia was higher in urban areas and that living

in densely populated areas increased the risk of the disorder by around 68-77% [161]. Moreover, a dose-response relationship was found between urbanicity and psychosis risk; as the time spent in an urban environment increased, so did the risk for schizophrenia development [162]. Researchers have suggested that some of the underlying factors between urbanicity and schizophrenia may be factors such as pollution, isolation, access to green spaces, and social inequity [163] [164] [165] [166]. Similar results were found for PLEs as well. For example, the current neighborhood stress was found to predict PLEs in adolescents [167]. In an fMRI study, it was demonstrated that urban upbringing was correlated with reduced connectivity in the pregenual anterior cingulate cortex (pACC), and current city living was correlated with increased amygdala activity, indicating an effect of early life exposure on brain mechanisms [168].

Recent studies have shown that even though individual environmental risk factors increase the vulnerability to psychosis, they also act in aggregate and that there is a dose-dependent relationship between environmental risk factors and disease risk. For instance, in a study, researchers found that risk factors such as childhood trauma, cannabis use urbanicity, and hearing impairment additively increased the risk for PLEs [169]. Building on these findings, an aggregate measure, 'The Maudsley Environmental Risk Score' (ERS), was developed by Vassos and colleagues. According to meta-analysis studies, six different environmental risk factors for schizophrenia were identified: high paternal age, urbanicity, cannabis use, obstetric complications, ethnic minority status, and childhood maltreatment. In this method, the weighted score based on their effect sizes was estimated for each individual risk factor, and then risk ratios for each factor were summed up to calculate a total score [170]. In follow-up studies, the ERS was found to successfully distinguish psychosis cases from controls and was also associated with psychosis risk in a dose-dependent fashion [171] [172]. Later, using predictive modeling, another measure, 'The Exposome' which also takes into account the correlations between different risk factors, was developed. This measure included exposure to five different risk factors: hearing impairment, winter birth, cannabis use, childhood maltreatment, and bullying [173]. The Exposome score was able to distinguish between schizophrenia patients, 1st-degree relatives, and healthy

controls [174]. In accordance with the diathesis-stress model of psychosis, these cumulative risk scores propose that different environmental risk scores interact to increase the vulnerability to disease. Therefore, using aggregate environmental risk factors such as the ERS and Exposome may be powerful tools to investigate liability to disease.

While well-established environmental risk factors such as urbanicity, childhood trauma, and cannabis use have been well-documented, the recent COVID-19 pandemic has introduced a new potential risk factor for psychosis risk, which is the coronavirus (severe acute respiratory syndrome-2 (SARS-CoV-2)) [175]. The COVID-19 pandemic has affected millions of people globally and has had major effects on mental health. Although primarily known to be associated with upper respiratory tract infections, varying levels of neurological symptoms were also observed in almost half of the cases. A study showed that among hospitalized patients, around 57.4% experienced a form of neurological symptoms [176]. The relationship between psychosis risk and viral infections is not new and has been well-reported over the years [177]. Previous studies have reported that exposure to neuroinflammation during critical periods may increase the liability to psychosis [178]. Meta-analysis studies suggest that the mental burden of the infection continues for a year after recovery in half of the patients [179]. Other studies have found associations between COVID-19 infections and psychosis symptoms, with some cases attributed to the use of medications, particularly steroids [180] [181]. Case studies show new-onset psychosis in patients diagnosed with COVID-19 accompanied by increased neuroinflammatory markers [182] [183] [184] [185]; however, the causality between the coronavirus and psychosis has not been established and remains a subject of debate [186].

In addition to the possible effects of the coronavirus through neuroinflammation, additional psychosocial factors may add to the stress associated with the pandemic. These include lockdowns, social isolation, less exposure to sunlight, limited physical activity, and anxiety regarding the disease [187] [188]. In an adolescent sample, researchers found that more than half of the participants reported PLEs during lockdown. The frequency of PLEs was higher in individuals who had a history of childhood trauma, had a loved one diagnosed with COVID-19, or

spent more time looking at COVID-19-related media. Moreover, social support was found to be a protective factor for PLEs [189]. Another study investigating the effect of social isolation during COVID-19 found that both cognitive dysfunction and the frequency of PLEs increased in individuals with more limited social interactions [190]. In a longitudinal study, PLEs were measured before and after lockdowns. Researchers found significant increases in PLEs after lockdowns compared to before lockdowns. Moreover, the new onset-PLEs during the lockdown were associated with increased anxiety and depressive symptoms [191]. These studies suggest that COVID-19 related stressors may also increase the risk of PLEs.

Alongside studies showing an association between COVID-19 and PLEs, research has also demonstrated changes in the functional connectivity of brain networks in COVID-19 patients [192] [193]. Alterations in connectivity measures were observed after COVID-19 infections in major networks such as the default mode network (DMN), salience network (SN), and frontoparietal network (FPN) [194]. In a resting-state fMRI (rsfMRI) study, researchers compared dynamic and static functional connectivity and activity in COVID-19 patients and controls. They found decreased dynamic connectivity in the precentral gyrus and decreased static functional connectivity between lingual and occipital areas. Moreover, they were able to distinguish patients from controls using dynamic and static measures of brain activity and connectivity [195]. Another study found increased connectivity in the basal ganglia and the precuneus and reduced connectivity in the language network in COVID-19 patients compared to controls [196]. In line with these findings, researchers found disruptions in the temporal dynamics of the visual and sensorimotor networks in COVID-19 patients after 6 months of recovery. These alterations were also associated with the post-traumatic symptoms related to COVID-19 diagnosis [197].

While the exact mechanisms for the relationship between PLEs and COVID-19-related stressors are unknown, disruptions to functional brain networks might be an underlying factor. Taken together, these studies suggest that similar to other well-established environmental risk factors, the coronavirus is associated

with increased risk for PLEs. However, more research is needed to fully understand the long-term impacts of COVID-19 on brain function and psychosis risk. Overall, the current state of the literature suggests that different environmental risk factors during critical periods of development can disrupt the normal trajectory of brain development and thus increase the risk for psychotic disorders.

1.4.2 Genetic Risk Factors and Psychosis

Psychotic disorders such as schizophrenia are known to be polygenic and highly heritable (65-80%) [198]. Initial family and twin studies reported higher risk in the relatives of probands with psychosis, suggesting an important genetic component to the disorder [199]. Early efforts to understand the genetic underpinnings of psychosis focused on identifying candidate genes. These methods were hypothesis-driven therefore, researchers focused on candidate genes based on their location or involvement in neurotransmitters such as dopamine or glutamate [200]. One of the most well-known candidate genes is the catechol-O-methyltransferase (COMT), which is related to dopaminergic function and is located in the 22q11 chromosome [201]. Some studies showed that its deletion was linked to psychotic disorders such as schizophrenia [202]. The Val158/108Met (Val/Met) polymorphism of COMT was found to also affect prefrontal cortex function and working memory [203]. In a working memory fMRI study, researchers found that during the manipulation task, the changes observed in the dlPFC, parietal, and striatal regions were associated with COMT Val/Met polymorphism. Similar effects were observed for ventrolateral prefrontal cortex (vlPFC) [204]. The results of the study highlight the role of dopaminergic function and the COMT gene in working memory processes, which are known to be implicated in psychosis. However, the findings on the COMT and psychosis relationship have been inconsistent [205].

Studies investigating the effects of candidate genes were statistically underpowered and not cost-effective [206]. With the advancements in technology, these early studies set the stage for statistically powerful research tools like Genome-Wide Association Studies (GWAS) [207]. GWASs are able to discover genetic

variants that are associated with a specific disease, such as psychosis. Instead of focusing on specific genes and locations, they scan the entire genome in individuals to detect single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) that occur more in individuals with the disease compared to healthy controls [208]. SNPs reflect genetic variations at a single nucleotide position, which can influence disease risk by affecting gene expression or function [209]. On the other hand, CNVs reflect variation in the number of copies of DNA fragments among individuals [210]. This approach is especially valuable in studying complex disorders such as schizophrenia, where various genetic variations cumulatively impact liability to disease [211].

GWAS analyses have identified numerous different risk alleles associated with psychotic disorders [212] [213]. Importantly, with the efforts of organizations like the Psychiatric Genomics Consortium (PGC), international collaborations among research groups have enabled large-scale studies and have been critical in the effort to understand the genetic underpinnings of psychotic disorders. One of the first GWAS on schizophrenia [214] included 178 schizophrenia patients, whereas the most recent GWAS by the schizophrenia working group of PCG included 76,755 patients. In this large-scale study, researchers have identified 287 distinct genomic loci associated with schizophrenia [213].

Studies over the years have shown that while in isolation, individual variants do not explain a lot of the variance, but combined, they explain around 24% of the variation in liability to schizophrenia [212] [213]. Through these studies, it has become even more clear that psychotic disorders like schizophrenia are polygenic in nature, and genes individually have small effect sizes and cannot capture the variance in the disorder [215]. The effect of each gene varies in psychotic disorders, with some genes contributing more than others [216]. Therefore, efforts have been focused on studying the additive effects of genes. One way to examine the polygenic burden of disease is through the polygenic risk scores. PRS reflects a weighted sum of the number of risk alleles of each SNP for a specific disease and predicts disease risk [217].

The PRS for schizophrenia (PRS-SCZ) reflects an individual's liability to

schizophrenia, where higher scores indicate more risk [60]. The PRS-SCZ was found to explain around 8.5% of the variance in schizophrenia [213]. Further, results from the ABCD group showed that PRS-SCZ was associated with the distress associated with PLEs but not frequency. Children with higher PRS-SCZ reported experiencing more distressing PLEs compared to children with lower PRS-SCZ [218]. These findings may suggest that distress, as opposed to frequency of PLEs, may be more genetically relevant to schizophrenia risk. Moreover, studies have reported that PRS-SCZ showed associations with lower levels of IQ [219] and impaired cognitive function [220]. In one study, researchers investigated the relationship between working memory-related activation and PRS in schizophrenia patients and controls. Results showed that higher levels of PRS were associated with decreased activation in the superior prefrontal cortex and the right inferior frontal gyrus [61]. Further, another study demonstrated that in healthy individuals, higher PRS was associated with hypoactivity in dlPFC during working memory manipulation [221]. These findings suggest that PRS-SCZ is not only associated with the disease state but is also associated with well-established endophenotypes for schizophrenia, such as working memory. This association emphasizes psychotic disorders as complex disorders where cumulative genetic risk may manifest as cognitive and functional abnormalities.

1.5 Twin Studies as a Methodological Approach

As discussed in detail in previous chapters, psychotic disorders are complex disorders under both genetic and environmental influences. Twin studies provide a unique and powerful approach to studying the extent of these genetic and environmental contributions within a trait [222]. They also offer insights into the heritability of a trait, which is the proportion of variance that is attributable to genetic factors [223]. Moreover, twin designs can also inform us about the covariance between the genetic and environmental influences between two different traits [224].

The classical twin design compares the phenotypic variability within a trait

between monozygotic (MZ) and dizygotic twins (DZ). Univariate twin models, often called the ACE models, decompose the variance in a trait (Vp) into the additive genetic (A), common environment (C), and unique environment (E) components. Additive genetic factors reflect the cumulative effect of individual genes that combine in an additive fashion. The common environment reflects shared environmental influences that are the same for both twins, such as maternal/paternal age at birth or the socioeconomic status of the family. Unique environmental factors, on the other hand, reflect environmental influences that are different between the twins within a pair, such as experiencing trauma or cannabis use. It is important to note that the E component also includes the measurement error. An alternative to the ACE model is the ADE model where the C component is replaced with the variance that is due to dominant genetic factors (D). The ADE model is used instead of the ACE model when there is evidence of dominant genetic effects in a trait. A rule of thumb when choosing the right model is observing the MZ and DZ correlations. Typically, when rDZ is less than half of rMZ, an ADE model is preferred over the ACE model [224].

The classical twin designs rely on the assumption that the MZ twins share 100% of their segregating genes while the DZ twins share around 50%. Thus, the correlation of A is assumed to be 1 for the MZ twins and 0.5 for the DZ twins. Since the C component reflects common environmental influences, its correlation is assumed to be 1 regardless of the zygosity. Lastly, the E component is unique to each twin and is calculated as the total variance in the trait minus the MZ correlation E = Vp – rMZ (See Figure 1.7).

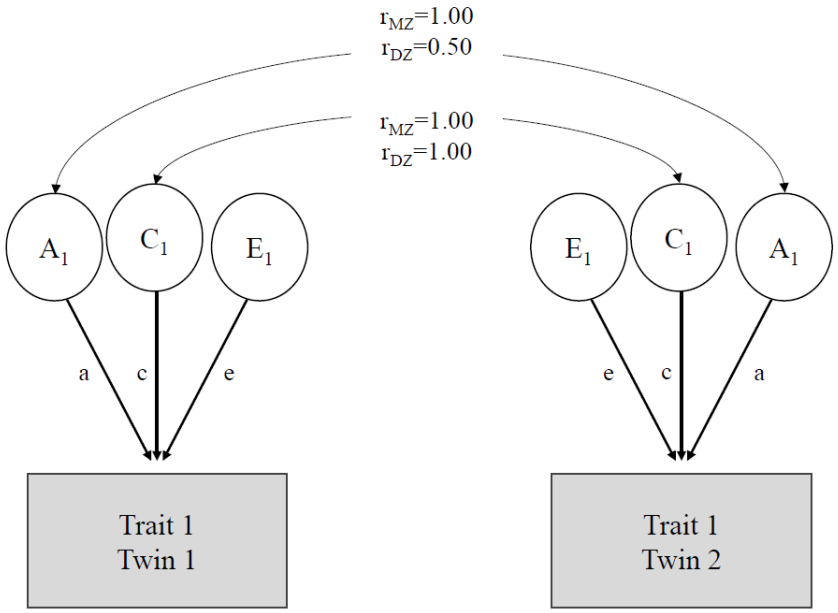

Figure 1.7: Univariate Twin Design. Depicts the structural equational modeling of classical twin designs, showing the additive genetics, common environment, and unique environment components in a single trait. The squares reflect measured traits, whereas the circles reflect latent variables.

Quantifying the variance attributed to additive genetics, common environment, and unique environment allows us to calculate the narrow-sense heritability (h^2) of a trait. h^2 is the proportion of the total phenotypic variance (V_p) that is attributed to the genetic variance (V_A) and is expressed as $h^2 = \frac{V_A}{V_p}$. The h^2 ranges between 0 and 1 where 0 indicates no genetic influences in a trait and 1 indicates that the genetic influences explain all of the variation in the trait [225].

While univariate models can decompose the A, C, and E components in a given trait, multivariate models can estimate the sources of covariation between two different traits. One way to investigate the covariation is through cross-twin cross-trait correlations for MZ and DZ twins. For example, if we have two traits, X and Y, then the correlation between trait X in twin one and trait Y in twin 2 will give us the cross-twin cross-trait correlation. When the cross-twin cross-trait

correlations are higher in MZ twins compared to DZ twins, this suggests common genetic influences between the two traits. If the correlation coefficients are similar between the MZ and DZ twins, this suggests common environmental influences between the two traits [226] [227].

A more sophisticated way to examine covariance between traits is through multivariate twin modeling. Bivariate twin modeling allows us to understand the extent to which genetic and environmental factors that influence one trait also influence another (See Figure 1.8). It uses the differences in correlations between the MZ and DZ twins to estimate the genetic (r_g), shared environmental (r_c), and unique environmental (r_e) correlations between two traits. These correlations indicate the extent to which the same genetic, shared environmental, and unique environmental factors influence both traits. Furthermore, by integrating these correlations with the h^2, shared environmental (c^2), and unique environmental (e^2) components of each trait, we can measure the genetic ($r_{\text{ph-a}}$), shared environmental ($r_{\text{ph-c}}$), and unique environmental ($r_{\text{ph-e}}$) contributions to the total phenotypic correlation (r_{ph}) between two different traits [228].

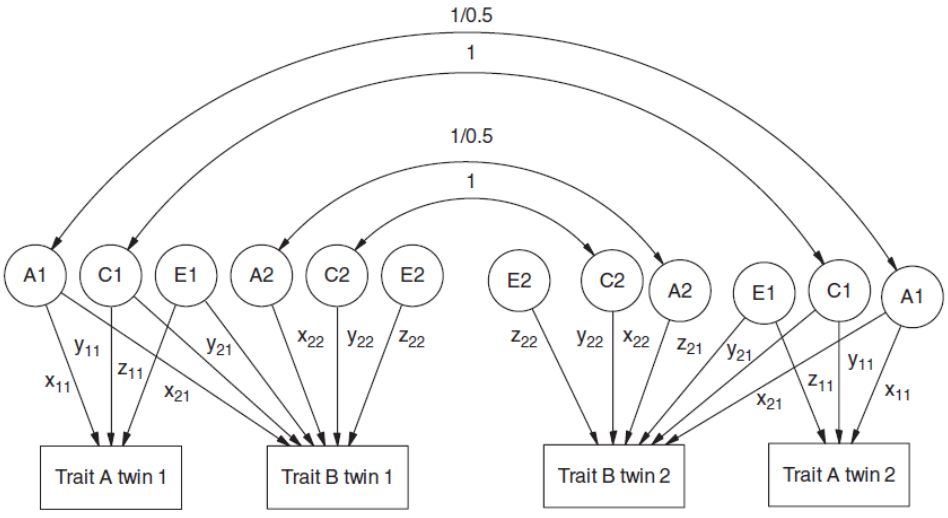

Figure 1.8: Bivariate Cholesky Decomposition. Depicts the structural equational modeling of two different traits. The squares reflect measured traits, whereas the circles reflect latent variables.Reprinted, with permission, from ref. [228]

Twin studies have greatly contributed to our understanding of the sources of variation in complex human traits. A meta-analysis study has demonstrated that around 49% of all human traits are under genetic influences, whereas the rest are influenced by the environment [229]. Moreover, they have informed our understanding of the genetic and environmental influences in complex psychotic disorders such as schizophrenia. Over the years, twin studies have consistently reported heritability estimates of around 80-90% for psychotic disorders [230] [231] and around 81% for schizophrenia [198]. In addition, the concordance rate for schizophrenia was reported to be around 33% for MZ twins and 7% for DZ twins [232]. Furthermore, via twin designs, researchers demonstrated that PLEs were also heritable to some extent. One study reported heritability estimates of 42-53% for participants aged between 11-13 years and 38-47% for participants aged between 14-16 years for schizotypal traits [233]. Another study showed that during adolescence, PLEs showed heritability estimates of around 15-59%, with the highest heritability estimates for paranoia and the lowest for hallucinations [234]. Multivariate twin studies have also reported covariance between PLEs and psychotic disorders [235]. However, it should be noted that heritability is not a fixed construct and is known to change with increasing age or exposure to the environment [236] [237].

Taken together, the heritability studies of PLEs contribute to the view of the psychosis continuum, with PLEs showing significant but less heritability and more unique environmental effects compared to estimates for psychotic disorders.

1.6 The Current Study

Adolescence reflects a window of vulnerability for psychotic disorders [92]. The current state of the literature suggests that environmental and genetic risk factors influence the cognitive circuitry of the brain even before manifest illness and indicate a risk mechanism for psychotic disorders [17] [238]. Moreover, psychotic-like experiences are relatively common during adolescence, with distress associated

with these experiences playing an essential role in determining their clinical significance [26] [27]. Despite their prevalence, the neural mechanisms behind these experiences remain underexplored, particularly in young individuals, including some who find them distressing but are not currently seeking help. In addition, there is a paucity of these studies in non-western non-European populations.

The first study in this thesis aimed to investigate the relationship between PLEs and frontal connectivity during a working memory task in a healthy Turkish adolescent and young adult twin sample between ages 14 and 23 (474 twins and siblings). First, we used linear mixed models to examine the relationship between PLEs for frequency and distress and the frontal connectivity indices. Then, for the connectivity variables that showed significant associations with PLEs, we used twin modeling to quantify the genetic and environmental contributions and assess the nature of the covariance between these traits. Furthermore, to the best of our knowledge, the genetic and environmental influences of distressing and frequent PLEs and task-based connectivity measures have not been investigated before in a Turkish adolescent sample. Therefore, we used twin modeling to quantify the genetic and environmental contributions to PLEs and functional connectivity and assess the covariance between the two traits.

Another recent and important risk factor for psychotic disorders is the COVID-19 [175]. Studies have reported that individuals who had COVID-19 report more PLEs and altered functional connectivity [189] [190] [192] [193]. However, how COVID-19 affects brain mechanisms and PLEs during the critical time period of adolescence is not well known. Previous studies have mainly focused on adult samples. Therefore, in the second study, we investigated the changes in functional connectivity between COVID-19 participants and healthy controls. Next, we wanted to examine whether these changes were related to the level of positive PLEs and inflammation markers.

Chapter 2

Study 1

Psychotic-Like Experiences and Working Memory Connectivity in Adolescents and Young Adults: A Study on Turkish Twins

2.1 Introduction

The continuum model of psychosis proposes that the phenotype ranges from psychotic-like experiences that can be seen in the general population to full-blown disorders such as schizophrenia [239]. Around 8% of individuals report experiencing PLEs in their lifetimes, with a peak during adolescence [240]. However, many psychotic symptoms experienced during this time are transient in nature [26]. One criterion used to distinguish clinically relevant PLEs from those more innocuous is the level of distress associated with them [241]. For example, individuals with distressing PLEs showed impairments in brain volume and structure regardless of the persistence of these experiences [34] and impaired cognitive functioning, particularly when accompanied by higher levels of distress [35].

Indeed, low premorbid cognitive functioning is associated with and predates the onset of a psychotic disorder [48] [242]. Working memory deficits and alterations in prefrontal connections are repeatedly seen in psychosis patients, their unaffected first-degree relatives, and clinically high-risk individuals [50] [78] [87]. Recent studies have also found poor working memory performance [59], abnormal activation patterns in frontal regions [85], and impaired connectivity in functional networks during resting state [243] [244] in individuals with PLEs. In a small group, researchers showed that individuals with high delusional ideations had reduced effective connectivity in frontoparietal regions during a working memory task [88]. Although working memory-related connectivity impairments in psychosis and high-risk individuals are well established, whether the same impairments are also found in young and currently non-help-seeking populations with PLEs remains less understood. Furthermore, it remains unclear whether these connectivity impairments are associated with the level of distress accompanying PLEs.

Psychosis is a highly heritable disorder, with heritability estimates reaching around 80% [212]. Genome-wide association studies have shown that PLEs share genetic liability for psychotic and other mental health disorders [245]. Twin studies of adolescents also show moderate heritability estimates and significant

nonshared environmental influences for PLEs [234] [246]. For instance, one study reported heritability estimates of 42-53% for participants aged between 11-13 years and 38-47% for participants aged between 14-16 years for schizotypal traits [233]. These studies highlight the interplay between genetic and environmental factors in the etiology of PLEs.

Studies investigating heritability estimates of task-related connectivity measures are very limited. In a recent study, researchers reported heritability estimates of around 30% for working memory task-related functions using multivariate methods [247]. However, this study focused on Australian adult twins examining different emotional and cognitive tasks and investigated working memory measures in isolation. Moreover, the authors focused on the maintenance component of working memory. Previous research indicates that individuals with psychosis and their first-degree relatives often exhibit difficulties with tasks that necessitate the updating and manipulation of contextual information in working memory [248]. These individuals also tend to show abnormal connectivity patterns during such tasks, particularly within frontal brain regions [87]. Given that the overarching aim of the current study was to investigate the relationship between PLEs and working-memory related connectivity for the purposes of this paper, we focused on the manipulation of working memory.

Recently, there has been a pressing need in the field of psychosis research to include more diverse ethnic and racial groups, as most studies have been mainly conducted in Western populations [249]. For example, previous research has reported that around 15-30% of the frequency of psychotic symptoms was due to cultural differences [250]. Given that the phenotypic variance in a trait is partitioned into genetic and environmental components, with the latter including the culture of the population, it is of utmost importance to study non-European populations in twin research [251] [252]. Our study addresses this gap by examining the heritability estimates of PLEs and frontal connectivity measures in an adolescent Turkish sample.

Investigating the covariance between genetic and environmental influences on PLEs and frontal functional connectivity (FC) during adolescence is particularly

important, as this developmental stage represents a critical period for the emergence of psychotic disorders. However, to the best of our knowledge, no study has yet explored the shared genetic and environmental influences between PLEs and task-related frontal functional connectivity during adolescence. To this aim, twin studies offer a unique opportunity to decompose the variance of phenotypes like PLEs and functional connectivity into genetic and environmental factors and, crucially, to decompose the covariance between two different traits to observe the extent to which genetic and environmental factors that influence one trait also influence another [226].

The current study aimed to first investigate the relationship between PLEs and frontal functional connectivity during a working memory task in a healthy, currently non-help-seeking adolescent and young adult twin sample separately for the distress and frequency of PLEs. For this aim, we used linear mixed models that examined the relationship between working-memory related connectivity and the PLEs, focusing separately on the PLE frequency and distress. We then went further and quantified the genetic, common, and unique environmental influences contributing to the variance in PLEs and the brain connectivity measures identified in the earlier step through the linear mixed models. Additionally, for the first time, we assessed the degree of genetic and environmental covariance between these traits. For this step, we use twin modeling to disentangle and quantify the shared genetic, common environmental, and unique environmental influences contributing to the covariation between PLEs and working memory connectivity measures. We hypothesized that the alterations in frontal connectivity during a working memory task would be associated with higher frequency and distress of PLEs. Moreover, we hypothesized that the variations in PLEs and connectivity measures would be explained by both environmental and genetic factors and that there would be some covariation between PLEs and frontal connectivity measures.

2.2 Methods

2.2.1 Participants

The sample consisted of 474 healthy twins (214 pairs) and siblings (23 pairs). The siblings had an age difference of no more than two years. All participants were between 14 and 23 years old. Zygosity and demographic characteristics of participants are presented in Table 2.1. The zygosity of the participants was primarily determined through DNA analysis. For 40 twin pairs where genetic zygosity analysis was not completed, zygosity was assessed based on the Zygosity Questionnaire [253]. Exclusion criteria were an IQ below 70, a history of head trauma, a diagnosis of neurological or psychiatric disorders, serious visual impairment, and non-native Turkish speakers. All participants provided written informed consent before participating in the study. For participants under the age of 18, written consent was obtained from their parents or legal guardians. The Ethics Committees of Ankara University Medical Faculty and İhsan Doğramacı Bilkent University approved the study. The study adhered to the principles outlined in the Helsinki Declaration.

2.2.2 Assessments

2.2.2.1 Community assessment of psychic experiences-42 (CAPE-42)

The Community Assessment of Psychic Experiences is a self-report tool designed to evaluate the lifelong prevalence of psychotic-like experiences and tendencies in the general population [37]. The CAPE-42 has demonstrated good reliability and stability [254]. Additionally, it has been found to be particularly reliable for younger populations [33]. We calculated the total frequency score (ranges from 42 to 168) and the weighted distress scores following the methodology outlined by [255]. This method combines each score's frequency and distress into a composite score. The weighted score was calculated by multiplying frequency and distress

associated with PLEs divided by the number of questions answered. All subsequent analyses entered total CAPE-42 frequency and weighted CAPE-42 distress scores as continuous variables.

2.2.2.2 The Wechsler Abbreviated Scale of Intelligence

Block-Design and Matrix Reasoning subscales of the revised Wechsler Abbreviated Intelligence Scale, Second Edition (WASI-II), were used to estimate intelligence using standard procedures. Based on the ages of the participants, the raw scores from the Block Design and Matrix Reasoning were calculated and converted into individual T-scores. A composite score was created by the sum of the two T (Perceptual Reasoning) values as a proxy of IQ using standard procedures [256].

2.2.3 Neuroimaging Data Acquisition and Processing

2.2.3.1 fMRI acquisition

MRI data were acquired using a 3 Tesla MRI scanner (Magnetom Trio, Siemens AG, Erlangen, Germany) equipped with a 32-channel head coil at the National Magnetic Resonance Research Center, Bilkent University, Türkiye. High-resolution T1-weighted anatomical images were collected with the following parameters: echo time (TE) = 3.02 ms, repetition time (TR) = 2600 ms, inversion time (TI) = 900 ms, flip angle = 8°, slice thickness = 1.0 mm across 176 slices, matrix size = 256 x 256, yielding a voxel size of 1 x 1 x 1 mm^3. Functional MRI data were acquired using blood oxygenation level-dependent (BOLD) contrast with T2*-weighted Echo-Planar Imaging (EPI). The EPI parameters were: TR = 2000 ms, TE = 30 ms, 24 slices with a slice thickness of 5 mm, tilt angle = 90°, voxel size = 3.7 x 3.7 x 5.0 mm^3, and a field of view (FOV) = 64 x 64 mm.

2.2.3.2 fMRI Working Memory Task

During the functional imaging session, participants underwent a well-established working memory task described here [204] and here [87]. Briefly, the event-related paradigm employed in this study was established to evaluate working memory and cognitive control processes. The task began with an encoding phase where participants were shown two integers for 500 ms. Following this, participants experienced a jittered interval of 3-6 seconds with a fixation point, during which the information had to be retained in working memory. In the manipulation task, participants were required to subtract either 2 or 3 from one of the remembered numbers before making a judgment on which number was smaller or larger. In the motor task, participants were presented with left- or right-pointing arrows and were asked to press the corresponding button to indicate the direction of the arrow. Each response phase lasted three seconds. For the purposes of this paper, we focused on the manipulation task (ECJ) (See Figure 2.1).

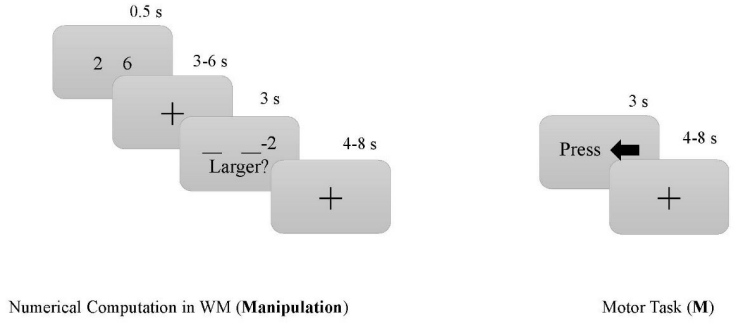

Figure 2.1: The Manipulation and Motor task in the working memory paradigm adapted from [204]

2.2.3.3 Task-based fMRI Preprocessing

The anatomical and functional MRI data were preprocessed and analyzed using the Conn Toolbox [257] implemented in MATLAB R2022b [258]. The default preprocessing steps for the functional data included slice timing correction, realignment, coregistration to the structural images, normalization to the Montreal Neurological Institute (MNI) template, and smoothing (full width at half maximum: FWHM: 8 mm). To reduce the noise, a component-based noise correction (CompCor) method was applied, followed by band-pass filtering.

2.2.3.4 Task-based fMRI Data Analysis

First, onset times for the working memory tasks were extracted, and events were modeled. Movement parameters from the preprocessing step were added as regressors of no interest. To isolate the cognitive processes of working memory from motor and visual components of the task, such as button pressing, the contrast was defined as manipulation > motor task (ECJ>M).

Next, a Seed Based Connectivity (SBC) analysis was conducted using the Conn Toolbox, modeling the bivariate regression coefficients of the general linear model (GLM) for each seed region and every other voxel in the brain. In the second level analysis, we conducted SBC analyses using a GLM to determine how activity in a specific seed region correlated with activity across the entire brain during the ECJ>M contrast. Statistical tests were performed to identify significant connectivity patterns associated with the target contrast across the entire sample. Bivariate correlation coefficients between the BOLD time series of the seed regions and each voxel of the brain were generated and Fisher-transformed. The prefrontal regions were chosen from the predefined ROIs in the CONN Toolbox, derived from the Harvard-Oxford Cortical and Subcortical Structural Atlases. Specifically, prefrontal regions were chosen as seed regions due to their known involvement in working memory processes during adolescence [259]. The voxel-wise significance threshold was set at $p < 0.001$, with a False Discovery Rate

(FDR) correction applied at the cluster level ($p < 0.05$) to account for multiple comparisons.

2.2.4 Statistical Analysis

2.2.4.1 Associations between psychotic-like experiences and brain connectivity

Associations among PLEs and frontal connectivity measures were calculated using bivariate correlations and linear mixed-effects (LMM) models using R version 4.4.1 [260]. LMMs were fitted using the *lmer*() function from the lme4 package [261] and model diagnostic plots were obtained via the *checkmodel*() function from the performance package [262]. In the LMMs, family ID was included as a random intercept to account for within-family correlations for twins. The Likelihood Ratio Test (LRT) was applied to determine the necessity of including a random intercept in the model. This was performed using the *anova*() function in R.

2.2.4.2 Univariate and Bivariate ACE models

All twin models and correlations were performed in R version 4.4.1 [260] with the OpenMx package version 2.20.6 [263] [264]. Twin analyses were completed for the variables that showed significant associations in the LMMs established in the previous step. Before twin analyses, the effects of age, sex, and IQ were regressed from all the variables, and the resulting residuals were standardized. We conducted classical twin modeling using the ACE model framework to analyze the CAPE-42 and fMRI connectivity indices identified by the two LMMs.

The ACE model decomposes the total variance in a phenotype into three components: additive genetic factors (A), shared environmental factors (C), and unique environmental factors or measurement error (E) [265]. In twin studies,

the shared environmental factors (C) refer to environmental influences that affect both members of a twin pair similarly, regardless of their zygosity. Examples include family upbringing and socioeconomic status. In contrast, the unique environmental factors (E) encompass influences that differ between members of a twin pair, such as individual life experiences. The E component also includes residual variance, which accounts for measurement error [226]. The classical twin design is based on the assumption that monozygotic (MZ) twins share 100% of their genes, while dizygotic (DZ) twins or siblings share, on average, 50% of their segregating genes. Consequently, the correlation of the A component is expected to be 1 for MZ twins and 0.5 for DZ twins. The C component is assumed to be equal for both MZ and DZ twins. The E component is unique to each twin and is calculated as the total variance minus the MZ correlation [226].

Model fit was evaluated using goodness-of-fit indices, including the chi-square test. The full-information maximum likelihood method was used to generate the expected covariance matrix and estimate the free parameters. The model fit was assessed by the χ^2 goodness-of-fit, where more parsimonious models did not lead to a decline in model fit, the best fitting model was selected based on the lowest Akaike Information Criterion (AIC) [266]. The narrow-sense heritability (h^2) was calculated using the variance components estimated by the ACE model. Narrow-sense heritability refers to the proportion of the total phenotypic variance in a trait that can be attributed to additive genetic factors.

While the univariate ACE model decomposes the variance of a trait into genetic and environmental factors, this model can be extended into a bivariate model to decompose the covariance between two different traits. To decompose the shared environmental and genetic influences between two traits, first, we calculated cross-twin/sibling cross-trait correlations. The cross-twin/sibling cross-trait measures the correlation between different traits across twin/sibling pairs for MZ and DZ twins. If a trait is under genetic influence, we would expect the MZ correlation to be twice the size of the DZ correlation. If the correlation coefficients are similar, we would assume the influence of common environmental factors. If the correlation coefficients are not significant, unique environmental factors likely play a role in the trait's variance. Further, to examine the covariance between

PLE distress and frequency and the connectivity measures that were significantly associated with them we established bivariate twin models. Bivariate twin modeling allows us to understand the extent to which genetic and environmental factors that influence one trait also influence another. It uses the differences in correlations between the MZ and DZ twins to estimate the genetic (r_g), shared environmental (r_c), and unique environmental (r_e) correlations between two traits. Furthermore, by integrating these correlations with the h^2, shared environmental (c^2), and unique environmental (e^2) components of each trait, we can measure the genetic ($r_{\text{ph-a}}$), shared environmental ($r_{\text{ph-c}}$), and unique environmental ($r_{\text{ph-e}}$) contributions to the total phenotypic correlation (r_{ph}) between two different traits [228].

2.3 Results

2.3.1 Sample Characteristics

Sample characteristics and descriptive statistics for quantitative variables are presented in Table 2.1. In the fMRI analysis, seven individuals were excluded due to head movement exceeding 2.5 mm during MRI scanning. Additionally, forty-five individuals were excluded for reasons such as claustrophobia, inability to complete the MRI scan, and the presence of non-removable metal objects in their bodies. This resulted in a final sample size of four hundred twenty-two participants for fMRI analysis, comprising twelve sibling pairs (n=24) and one hundred ninety-nine twin pairs (n=398).

Table 2.1: Demographic and clinical characteristics of participants

	Participants (N=474)
Age, mean (SD)	19.64 (2.65)
Sex	
Females, *n* (%)	299 (63.00)
Males, *n* (%)	175 (37.00)
Zygosity	
Monozygotic, *n* (%)	160 (33.75)
Dizygotic, *n* (%)	268 (56.54)
Sibling, *n* (%)	46 (9.71)
IQ, *mean* (SD)	101.83 (13.21)
Education (years), *mean* (SD)	13.69 (2.40)
CAPE-42 Frequency, *mean* (SD)	74.3 (16.05)
CAPE-42 Distress, *mean* (SD)	3.3 (1.71)

2.3.2 Seed-Based Connectivity Analysis

Significant seed-to-voxel connections during the manipulation contrast were found for the right middle frontal gyrus (MFG R), bilateral inferior frontal gyrus triangular (IFG tri), and bilateral inferior frontal gyrus pars opercularis (IFG Oper). The complete list of significant connections and their clusters are presented in Table 2.2.

Table 2.2: SBC seed-to-voxel brain connectivity for manipulation>motor contrast.

Seed Region	**Cluster (x, y, z)**	**Cluster no**	**Size**	**Size p-FDR**	**Size p-unc**	**Peak p-unc**
MFG R	-34, -44, 32	-	267	0.019	0.0011	<0.0001
IFG tri R	-14, 38, 10	-	469	0.001	<0.0001	<0.0001
IFG tri L	-52, -54, -18	Cluster 1	2196	<0.0001	<0.0001	<0.0001
	30, -66, -18	Cluster 2	1681	<0.0001	<0.0001	<0.0001
	02, 44, 12	Cluster 3	697	<0.0001	<0.0001	<0.0001
	-60, -38, 32	Cluster 4	299	0.005	0.0008	<0.0001
IFG Oper R	44, 14, 22	-	396	0.0007	<0.0001	<0.0001
IFG Oper L	-62, -44, -10	Cluster 1	1345	<0.0001	<0.0001	<0.0001
	-04, 30, 10	Cluster 2	728	<0.0001	<0.0001	<0.0001
	32, -62, -22	Cluster 3	613	<0.0001	<0.0001	<0.0001
	-64, -38, 26	Cluster 4	252	0.006	0.0009	<0.0001

Note: Cluster coordinates are reported in MNI space.
Abbreviations: a:anterior; ACG: Anterior Cingulate Gyrus; IFG oper: Inferior Frontal Gyrus pars Opercularis; IFG tri : Inferior Frontal Gyrus pars triangularis; TOFusC: Temporal Occipital Fusiform Cortex; toITG: Inferior Temporal Gyrus, temporooccipital part; L: Left; MFG:Middle Frontal Gyrus; R:Right; OFusGr: Occipital Fusiform Gyrus; SMG: Supramarginal Gyrus; SPL: Superior Parietal Lobule

2.3.3 Associations between psychosis-proneness and brain connectivity

Two comprehensive LMMs were developed to explain variability in CAPE-42 frequency and distress separately. The full models were constructed where connectivity indices, age, years in education, IQ, and gender were considered as fixed effects, and family ID representing twin pairs was added as a random intercept term to control the variability within twins. For the frequency of PLEs when comparing the model with and without random effects, the inclusion of the random intercept for family ID significantly improved model fit ($\chi^2_1 = 22.57, \text{p-value} < 0.001$). This result confirms the importance of accounting for the clustering of twins within families. The results of the CAPE-42 frequency model indicate that the hypoconnectivity between left inferior frontal gyrus opercularis and anterior supramarginal gyrus (aSMG) exhibited a negative association (Estimate $= -2.71, \text{p-value} = 0.03$). The marginal R^2 of 0.029 indicates that 2.9% of the variability in CAPE-42 frequency is explained by the fixed effects, while the conditional R^2 of 0.353 suggests that the full model, including both fixed and random effects, explains 35.3% of the total variability in CAPE-42 frequency. A detailed summary of the final model, including all statistically significant variables, is provided in Table 2.3.

Table 2.3: Linear mixed model results for frequency of PLEs.

Predictors	**Estimates**	**Std. Error**	**95% CI**	***p*-value**
(Intercept)	67.70	7.80	52.37 – 83.03	<0.001
IFG Oper L Cluster4	-2.71	1.28	-5.22 – -0.20	**0.034**
Wechsler IQ class [Borderline]	-3.31	4.11	-11.39 – 4.77	0.421
Wechsler IQ class [Low Average]	-2.16	2.33	-6.74 – 2.42	0.355
Wechsler IQ class [High Average]	3.65	2.15	-0.58 – 7.88	0.090
Wechsler IQ class [Superior]	4.39	3.05	-1.61 – 10.39	0.151
Wechsler IQ class [Very Superior]	-1.11	5.29	-11.50 – 9.28	0.833
gender [Male]	-2.65	1.70	-5.99 – 0.69	0.120
age	0.61	0.77	-0.90 – 2.11	0.427
ed yrs	-0.39	0.80	-1.96 – 1.19	0.629
Random Effects				
σ^2	174.33			
τ_{00} *famid*	87.25			
ICC	0.33			
N famid	218			
Observations	415			
Marginal R^2 / **Conditional** R^2	0.029 / 0.353			

For the model explaining the variability in CAPE-42 distress, the inclusion of the random intercept for family significantly improved model fit ($\chi^2_1 = 16.89$, p-value < 0.001). The model, constructed with brain connectivity measures, age, years in education, IQ, and gender, showed significant associations with CAPE-42 Distress. Notably, the hypoconnectivity between the left inferior frontal gyrus triangularis and the left inferior temporal gyrus (ITG) (Estimate $= -0.41$, p-value $= 0.048$) and the hypoconnectivity between left inferior frontal gyrus opercularis and anterior supramarginal gyrus (Estimate $= -0.28$, p-value $= 0.025$) was negatively associated with CAPE-42 distress, while the hypoconnectivity between the left inferior frontal gyrus opercularis and left temporal occipital fusiform cortex (TOFusC) (Estimate $= 0.36$, p-value $= 0.035$) showed positive associations. The marginal R^2 value of 0.052 suggests that 5.2%

of the variability in distress is explained by the fixed effects, while the conditional R^2 of 0.325 shows that the complete model, accounting for both fixed and random effects, explains 32.5% of the overall variability in distress. The summary of the final model results, including statistically significant variables, is provided in Table 2.4.

Table 2.4: Linear mixed model results for distress of PLEs.

Predictors	**Estimates**	**Std. Error**	**95% CI**	***p*-value**
(Intercept)	1.95	0.78	0.41 – 3.49	**0.013**
IFG tri l cluster1	-0.41	0.21	-0.82 – -0.00	**0.048**
IFG Oper L Cluster1	0.36	0.17	0.03 – 0.70	**0.035**
IFG Oper L Cluster4	-0.31	0.14	-0.59 – -0.04	**0.025**
Wechsler IQ class [Borderline]	-0.28	0.44	-1.14 – 0.59	0.533
Wechsler IQ class [Low Average]	-0.32	0.25	-0.81 – 0.17	0.201
Wechsler IQ class [High Average]	0.46	0.23	0.00 – 0.91	**0.049**
Wechsler IQ class [Superior]	0.30	0.33	-0.34 – 0.94	0.356
Wechsler IQ class [Very Superior]	-0.05	0.56	-1.16 – 1.06	0.933
gender [Male]	-0.36	0.18	-0.72 – -0.00	**0.047**
age	0.07	0.04	-0.01 – 0.15	0.068
Random Effects				
σ^2	2.10			
τ_{00} (famid)	0.85			
ICC	0.29			
N (famid)	218			
Observations	415			
Marginal R^2 / Conditional R^2	0.052 / 0.325			

2.3.4 Twin Analysis

The cross-twin/sibling within-trait correlations and the results of the univariate twin models, including the heritability and environmental estimates for PLEs and connectivity measures, are presented in Table 2.5. The univariate twin models were established with the best-fitting model (See Tables A.1–A.5 for details). The correlations showed higher values for MZ twins compared to the DZ twins/siblings for the distress associated with PLEs, indicating genetic influences. In contrast, the frequency of PLEs showed similar correlations for MZ and DZ twins, suggesting the role of environmental influences. Notably, the frequency of the PLEs did not show significant heritability estimates, whereas the distress associated with the PLEs $h^2 = 0.54$ [0.40−0.67]; $e^2 = 0.45$ [0.33−0.60] showed moderate heritability estimates. The functional connectivity measures related to working memory mechanisms were under significant influences of unique environmental factors.

Table 2.5: Cross-Twin/Sibling Within-Trait Correlations and Univariate Twin Models

Measures	MZ	DZ	Best-fitting Model	h^2 (95% CI)	c^2 (95% CI)	e^2 (95% CI)
CAPE-42 Frequency	0.38 (0.18, 0.56)	0.40 (0.25, 0.52)	CE	-	0.38 (0.27, 0.49)	0.61 (0.51, 0.73)
CAPE-42 Distress	0.51 (0.32, 0.66)	0.32 (0.17, 0.46)	AE	0.54 (0.40, 0.67)	-	0.45 (0.33, 0.60)
IFG tri L Cluster #1	0.05 (-0.18, 0.28)	-0.01 (-0.19, 0.16)	E	-	-	1 (1, 1)
IFG Oper L Cluster #1	-0.21 (-0.42, 0.02)	-0.11 (-0.28, 0.07)	E	-	-	1 (1, 1)
IFG Oper L Cluster #4	0 (-0.23, 0.23)	-0.1 (-0.27, 0.08)	E	-	-	1 (1, 1)

To assess the covariance between the connectivity measures and PLEs, within-twin/sibling cross-trait and cross-twin/sibling cross-trait correlations were calculated. While none of the connectivity measures showed significant correlations with distress or the frequency of CAPE-42 (See Table 2.6), we proceeded to calculate the frequency and distress of PLEs in relation to the connectivity measures using bivariate models. This approach also revealed no phenotypic correlations

between the connectivity measures and the PLEs (See Table 2.7).

Table 2.6: Twin correlations between PLEs and brain connectivity measures

	Within-Twin Cross-Trait Correlations	**Cross-Twin Cross-Trait Correlations**	
		MZ	**DZ**
CAPE-42 Frequency			
IFG tri L Cluster #1	-0.17 (-0.39, 0.07)	-0.20 (-0.41, 0.03)	0.14 (-0.03, 0.30)
IFG Oper L Cluster #1	-0.09 (-0.32, 0.15)	-0.14 (-0.35, 0.09)	0.13 (-0.03, 0.29)
IFG Oper L Cluster #4	-0.02 (-0.27, 0.23)	0.14 (-0.09, 0.36)	-0.17 (-0.32, 0.00)
CAPE-42 Distress			
IFG tri L Cluster #1	-0.07 (-0.30, 0.16)	-0.16 (-0.37, 0.07)	0.17 (0.01, 0.33)
IFG Oper L Cluster #1	0.04 (-0.20, 0.26)	-0.10 (-0.32, 0.12)	0.12 (-0.04, 0.28)
IFG Oper L Cluster #4	-0.04 (-0.26, 0.19)	0.13 (-0.10, 0.35)	-0.17 (-0.32, -0.00)

Table 2.7: Bivariate Twin Models

	$\mathbf{r_{ph\text{-}a}}$	$\mathbf{r_{ph\text{-}c}}$	$\mathbf{r_{ph\text{-}e}}$	$\mathbf{r_{ph}}$	$\mathbf{r_g}$	$\mathbf{r_c}$	$\mathbf{r_e}$
CAPE-42 Frequency							
IFG tri L Cluster #1	-0.03 (-0.17/0.15)	0.03 (-0.12/0.14)	-0.03 (-0.16/0.08)	-0.03 (-0.13/0.06)	-1 (-1/1)	1 (-1/1)	-0.04 (-0.21/0.11)
IFG Oper L Cluster #1	-0.02 (-0.15/0.1)	-0.01 (-0.12/0.1)	0.09 (-0.02/0.2)	0.06 (-0.04/0.15)	-1 (-1/1)	-1 (-1/1)	0.12 (-0.02/0.26)
IFG Oper L Cluster #4	0.01 (-0.13/0.12)	-0.04 (-0.14/0.06)	-0.06 (-0.17/0.05)	-0.09 (-0.19/0)	1 (-1/1)	-1 (-1/1)	-0.07 (-0.22/0.07)
CAPE-42 Distress							
IFG tri L Cluster #1	-0.1 (-0.23/0.11)	0.05 (-0.09/0.13)	0.01 (-0.12/0.12)	-0.05 (-0.14/0.05)	1 (-1/1)	1 (-1/1)	0.01 (-0.17/0.19)
IFG Oper L Cluster #1	-0.06 (-0.19/0.09)	0.01 (-0.08/0.1)	0.09 (-0.02/0.2)	0.05 (-0.05/0.14)	-1 (-1/1)	-1 (-1/1)	0.14 (-0.03/0.3)
IFG Oper L Cluster #4	-0.06 (-0.21/0.1)	-0.01 (-0.12/0.07)	-0.02 (-0.15/0.09)	-0.1 (-0.19/0)	-1 (-1/1)	-1 (-1/1)	-0.04 (-0.21/0.14)

2.4 Discussion

The current study investigated the association between PLEs and working memory-related functional connectivity measures in an adolescent and young adult twin sample. There is limited understanding of how the distress caused by PLEs affects working-memory related connectivity in young people. In addition, the degree to which this relationship may be influenced by environmental and genetic factors is underexplored. Building on these gaps in the literature, the current study investigated the relationship between working-memory related connectivity and the frequency and distress of PLEs. We found that a higher frequency of PLEs was associated with increased connectivity between the frontal and parietal lobes, specifically the left inferior frontal gyrus opercularis and anterior supramarginal gyrus. Similarly, this pattern of increased connectivity was also observed in individuals reporting more distressing PLEs, suggesting a shared neural mechanism underlying both the frequency and distress of PLEs. In addition, increased connectivity between regions associated with executive control, and cognitive and emotional processing in the frontal and temporal lobes, such as the left inferior frontal gyrus triangularis and left temporo-occipital inferior temporal gyrus, and decreased connectivity between the left inferior frontal gyrus opercularis and the temporo-occipital fusiform cortex, was specifically linked to higher distress associated with PLEs. These findings may suggest that distress associated with PLEs may engage broader functional circuits compared to frequency.

Our findings align with the well-established role of the inferior frontal gyrus, which is heavily involved in higher-order cognitive functions such as language processing, executive control, and working memory [251] [252]. Numerous studies have consistently demonstrated the involvement of inferior frontal gyrus in psychosis. Structural [267] [268] and functional [78] [269] abnormalities in the inferior frontal gyrus have been reported in psychosis patients and their first-degree relatives. Additionally, several studies have shown that inferior frontal gyrus is associated with the genetic risk for psychosis [61] [270]. In a recent study, researchers found both hyper- and hypoconnectivity patterns in the inferior frontal

gyrus in patients with bipolar disorder, reflecting trait-like impairments [271]. Furthermore, Nielsen et al. [272] found decreased effective connectivity from the left parietal lobe to left inferior frontal gyrus in first-episode schizophrenia patients during an n-back working memory task. Similar results have also been observed in healthy populations with PLEs. For example, Evermann et al. [273] found that individuals with higher distress associated with PLEs had reduced gyrification in the inferior frontal gyrus. These findings together support our results by highlighting the impairments in working memory-related connections of the frontal regions, such as the inferior frontal gyrus within the psychosis spectrum. However, most studies focused on adult populations, whereas our study investigates adolescents and young adults. The inferior frontal gyrus, as part of the frontal lobe, undergoes functional changes during adolescence, which might influence the connectivity patterns in this age group. Moreover, previous studies have shown that working memory manipulation tasks place greater cognitive demands on the participants, with psychosis patients and clinically high-risk individuals performing worse on these tasks and exhibiting altered connectivity patterns [87]. Therefore, the current findings of increased connectivity from the inferior frontal gyrus to parietal, visual, and limbic regions in individuals with more frequent and distressing PLEs may suggest the role of compensatory mechanisms and connectivity patterns unique to adolescence.

PLEs are believed to share similar environmental and genetic risk factors with psychosis [235]. Therefore, the current study also decomposed the variance in PLEs and connectivity measures into additive genetics and shared and unique environmental factors. We found moderate heritability estimates ($h^2 = 0.43$) for the distress associated with psychotic-like experiences, similar to what was reported by Ronald [274]. However, we extend these findings to a non-Western population. In contrast, the frequency of PLEs was primarily influenced by environmental factors. These findings emphasize the substantial role of genetic factors in shaping distress associated with PLEs and the importance of investigating distress separately from frequency, as they may have distinct underlying influences. In an adolescent twin sample, researchers [236] found that environmental factors may play a greater role than genetic factors in the development of psychotic

experiences. Their findings suggest that during adolescence, the heritability of psychotic symptoms varies depending on the level of environmental exposures, indicating important gene-environment interactions (GxE). Our results support such findings. Similarly, a recent study conducted on youth and adults reported that the variation in schizotypal experiences was due to unique environmental effects [275]. Further, recent findings from the Adolescent Brain Cognitive Development Study (ABCD) demonstrate that only the distressing PLEs and not the frequency of PLEs were associated with the genetic risk for psychosis [218]. Our findings suggest that while distress associated with PLEs may be more influenced by genetic factors, perhaps more closely related to the risk for psychosis, the frequency of PLEs during adolescence may represent an early part of the continuum and may not share the same genetic influences with psychosis.

On the other hand, several studies on adolescents have reported moderate heritability estimates for the frequency of PLEs [233] [234] [246]. As this is the first study done in an adolescent Turkish sample, the differences between our results and the literature may reflect ethnic and cultural differences. For instance, certain PLEs may be more culturally accepted in some societies as compared to others, influencing how they are perceived and reported. The CAPE-42 questionnaire, which captures a broad spectrum of psychotic-like symptoms, may reflect a wider range of experiences that are not necessarily associated with distress.

We also found that the working memory-related connectivity measures in the frontal regions were under unique environmental influences. Few studies have investigated task-related working memory connectivity, especially in youth, but our results differ from the limited earlier findings that showed low to moderate heritability estimates in adults [247]. However, given that heritability estimates vary with age, more studies are needed to study the genetic and environmental influences in adolescent samples [276]. On the other hand, in a recent study on adolescents, researchers have found resting-state functional connectivity measures to be under unique environmental influences similar to our findings [277]. Our findings may also reflect the heightened sensitivity of the executive functions to the environment during adolescence. Indeed, it is known that during adolescence,

brain networks are under the influence of environmental factors [278]. For example, different environmental exposures during developmental trajectories, such as exposure to stressors, may play a role in shaping the functional connectivity measures in individuals. However, studies directly investigating the mediating role of the environment to the heritability of brain networks in adolescents are required to make such inferences.

Finally, contrary to our hypothesis, we did not find covariance between the PLEs and functional connectivity measures. This suggests that within our sample, the unique environmental factors that affect the functional connectivity measures are not shared with the factors affecting the PLEs. They may be influenced by a distinct set of environmental factors. If the finding is confirmed, future research can explore unique environmental factors that influence PLEs and functional connectivity measures.

Overall, the current study's findings emphasize the importance of unique environmental factors in shaping brain connectivity mechanisms and the frequency and distress of PLEs during adolescence. This period is crucial as the brain undergoes rapid developmental changes in both structure and function and is highly receptive to external influences [92]. These results have implications for developing prediction-based strategies aiming at reducing the risk of psychosis. Importantly, as environment is the most easily accessible factor to change, it provides opportunities for early intervention and prevention strategies aimed at reducing the risk of distressing PLEs through targeted modifications. Moreover, the findings make a distinction between the frequency of PLEs and the distress associated with them, suggesting that distressing PLEs may have a stronger genetic influence than the frequency.

The limitations of the current study should be considered when interpreting the findings. First, although using a Turkish sample allows us to study functional connectivity measures and heritability estimates in a non-Western sample, the generalizability of the findings is limited as heritability estimates may change across different ethnicities and cultures. Second, PLEs were assessed using the CAPE-42 questionnaire, which is a self-report questionnaire and, therefore, may

be less accurate than clinician-rated interviews of PLEs. Additionally, it should be noted that the unique environmental variance component also includes measurement errors, and thus, the results should be interpreted carefully. This places an upper limit on heritability estimates as the presence of measurement errors may reduce the amount of variance that can be attributed to genetic factors [226]. Finally, this is a cross-sectional study, and future studies might benefit from investigating the heritability estimates of connectivity measures and PLEs along the developmental trajectories.

2.5 Conclusion

In conclusion, the current provides novel insights into the relationship between working memory-related functional connectivity, and PLEs, as well as the genetic and environmental influences of these traits in an adolescent Turkish twin sample. Our findings suggest that the frequency and distress associated with PLEs were associated with the functional connectivity of the inferior frontal gyrus. Moreover, the findings indicate that the distress related to PLEs has a significant genetic influence, while the occurrence of PLEs is mostly determined by environmental factors. This study has implications in terms of developing targeted interventions that focus on modifying environmental stressors during early development and adolescence to mitigate the risk of psychosis.

Chapter 3

Study 2

The effect of SARS-CoV-2 virus on resting-state functional connectivity during adolescence: Investigating brain correlates of psychotic-like experiences and SARS-CoV-2 related inflammation response

This chapter is based on the publication by Kafali, H. Y., Dasgin, H., Sahin Cevik, D., Sozan, S. S., Oguz, K. K., Mutlu, M., Parlakay, A. O., & Toulopoulou, T. (2023). The effect of SARS-CoV-2 virus on resting-state functional connectivity during adolescence: Investigating brain correlates of psychotic-like experiences and SARS-CoV-2 related inflammation response. *Psychiatry Research: Neuroimaging, 336,* 111746. https://doi.org/10.1016/j.pscychresns.2023.111746 [279].

3.1 Introduction

COVID-19 is an infectious disease accompanied by acute respiratory distress [280]. There is emerging evidence that COVID-19 is associated with neurological symptoms and cognitive impairment [281] [282]. In a meta-analysis study, researchers reported associations between COVID-19 and impairments in executive function, attention, and working memory [283]. In addition to cognitive impairments, recent studies demonstrate that COVID-19 may increase the risk of PLEs [189]. In a Turkish adolescent sample, researchers found that individuals who had COVID-19 experienced more PLEs than those who were never diagnosed. Additionally, adolescents who had more severe COVID-19 symptoms experienced more PLEs, and this relationship was mediated by depressive and anxiety symptoms [284].

Moreover, studies have found that individuals who are diagnosed with COVID-19 show alterations in brain structure and functional connectivity [192]. In a longitudinal study, researchers examined UK Biobank participants, each with two MRI scans. Those in the COVID-19 group were diagnosed with COVID-19 between scans, while healthy controls remained uninfected. They found that between the two scans, the COVID-19 group showed impairments in cognitive functions and significant impairments in brain structures, such as reductions in brain volume. Moreover, their findings remained significant even after removing the patients with severe symptoms [285]. Therefore, the findings of the study demonstrate that even in milder cases of COVID-19 infection, longitudinal changes are seen in the brain and cognitive abilities. Taken together, these findings suggest that COVID-19 might be a risk factor for psychosis risk, potentially altering underlying functional connectivity mechanisms.

However, most of the studies have focused on adult populations, and thus, the effects of COVID-19 on functional connectivity measures during adolescence are not well-established. Adolescence represents a critical window of vulnerability to psychopathology, making it crucial to investigate how infections such as COVID-19 might influence functional connectivity measures during this time. In the

current study, in an adolescent Turkish sample, we investigated the resting state functional connectivity (rs-FC) differences in individuals who had COVID-19 and healthy controls. Furthermore, we examined the effects of PLEs and inflammation markers on rs-FC.

3.2 Methods

3.2.1 Participants

COVID-19 participants (n=35) were recruited from the Ankara City Hospital Department of Child Infectious Diseases. The healthy control (HC) participants (n=47) were recruited from a larger research project. For details, refer to Chapter 2, See Section 2.2.1 'Participants'. Inclusion criteria required participants to be between the ages of 14-24, have a positive reverse transcriptase polymerase chain reaction test (RT-PCR), and have a recovery period of between two to four months following COVID-19 infection. Exclusion criteria were an IQ below 70, a history of head trauma, a diagnosis of neurological or psychiatric disorders, serious visual impairment, and non-native Turkish speakers. All participants provided written informed consent before participating in the study. For participants under the age of 18, written consent was obtained from their parents or legal guardians. The ethics committee of Bilkent University approved the study.

3.2.2 Assessments

For details of the assessments, refer to Chapter 2, Section 2.2.2.1 'Community assessment of psychic experiences (CAPE-42)' and Section 2.2.2.2 'The Wechsler Abbreviated Scale of Intelligence'.

3.2.2.1 Inflammation markers

The inflammation markers of neutrophil/lymphocyte ratio (NLR) ($N = 14$) and thrombocyte∗neutrophil/lymphocyte ratio (T-NLR) ($N = 14$) during COVID-19 infection were assessed for the COVID-19 participants during their admission to the hospital.

3.2.3 Neuroimaging Data Acquisition and Processing

3.2.3.1 rs-fMRI Data Acquisition and Preprocessing

For details of the scanner and the acquisition of anatomical images, refer to Chapter 2, Section 2.2.3.1 'fMRI Acquisition'.

The rs-fMRI images were acquired with an echo-planar imaging (EPI) sequence using these parameters: repetition time: 2000 ms; echo time: 35 ms; flip angle: 75°; matrix: 64 × 64; field of view: 192 mm; slice thickness: 3 mm; number of slices: 28. A total of 150 images were collected with a voxel size of 3 × 3 × 3 mm^3.

Standard preprocessing procedures were applied in Conn Toolbox [257], as described in detail in Chapter 2, Section 2.2.3.3 'Task-based fMRI Preprocessing'.

3.2.3.2 rs-fMRI Data Analysis

A Seed-Based Connectivity analysis was applied to the rs-fMRI data, including the predefined networks in Conn Toolbox. For details of SBC analysis, refer to Chapter 2, Section 2.2.3.4.

In this analysis, the Default Mode Network, Salience Network, Visual Network (VN), Central Executive Network (CEN), Language Network (LN), Dorsal Attention Network (DAN), and Sensorimotor Network (SMN) were chosen as seeds.

SBC maps were generated as the Fisher-transformed bivariate correlation coefficients of the time series between the selected seed networks and each individual voxel. Functional connectivity values were compared between the two groups, COVID-19 and healthy controls, using a two-sample t-test. Next, to investigate the effects of PLEs and the functional connectivity, the CAPE-42 positive subtest scores were added as covariates to the analysis using a one-way ANCOVA. The same method was used to investigate the effects of the inflammation markers in the COVID-19 group. The voxel-wise significance threshold was set at $p < 0.001$, with FDR correction applied at the cluster level ($p < 0.05$) to account for multiple comparisons.

3.3 Results

3.3.1 Sample Characteristics

Sample characteristics are presented in Table 3.1

Table 3.1: Demographic and clinical characteristics of COVID-19 group and HC (N=82)

	Group		**t/U**	**df**	**p**
	COVID-19 (N=35)	**Healthy Controls (N=47)**			
Age, mean (SD)	17.00 (3.00)	17.40 (2.10)	U=747.00	–	0.22
IQ, mean (SD)	98.80 (13.00)	98.60 (12.60)	$t = -0.06$	76	0.40
Education (years), mean (SD)	11.50 (2.50)	11.80 (2.20)	$t = -0.60$	75	0.27
CAPE-Positive	30.58 (6.58)	29.52 (6.21)	$t = 0.71$	76	0.24
Sex			$\boldsymbol{\chi^2}$	**df**	**p**
Female (%)	12 (34.30)	29 (61.7)	3.54	2	0.06

χ^2: Chi-square, df: degree of freedom, t: t-test, SD: Standard deviation, U: Mann-Whitney U test

3.3.2 rs-fMRI results

Significant differences in rsfMRI functional connectivity were identified between the COVID-19 and healthy controls. When the SMN was chosen as the seed region, the COVID-19 participants exhibited reduced connectivity compared to healthy controls ($p - FDR = 0.019, T = -4.18$) in a cluster including the left precentral gyrus ($-42, 00, 25; k = 128$). Likewise, reduced connectivity for COVID-19 participants was found in the right precentral gyrus (PCG) ($12, -24, 66; k = 186$) with the CEN ($p - FDR = 0.003, T = -4.60$). Moreover, with the LN, a cluster including the left SMG and left angular gyrus ($-54, -54, 50; k = 213$) exhibited reduced connectivity for the COVID-19 group ($p - FDR < 0.001, T = -4.38$). On the other hand, a cluster including the left superior frontal gyrus and left middle frontal gyrus ($-18, -04, 56; k = 197$) and the VN exhibited increased connectivity in the COVID-19 group when compared to healthy controls ($p - FDR = 0.003, T = 4.51$).

Next, the effects of CAPE-positive symptoms and inflammation markers on rs-fMRI functional connectivity were investigated. Again, significant differences were observed between the groups when CAPE-positive scores were added as covariates. The COVID-19 group exhibited increased functional connectivity with the CEN in a cluster including bilateral supramarginal gyrus and right superior frontal gyrus($10, 06, 56; k = 114$) ($p - FDR = 0.005, T = -4.48$) as well as with a cluster including the right caudate, right putamen and right accumbens ($18, 14, -04; K = 82$) ($p - FDR = 0.011, T = -4.86$). Further, increased connectivity in COVID-19 participants was also observed in the left postcentral gyrus with the SN ($-48, -24, 54; k = 99$) ($p - FDR = 0.021, T = -4.48$).

The effects of the inflammation markers were only observed in the COVID-19 group. When the T-NLR was added to the analysis, the functional connectivity within the DMN ($24, -92, 32; k = 145$) showed decreases ($p - FDR = 0.002, T = -7.51$). Moreover, increases in functional connectivity ($p - FDR = 0.002, T = 7.38$) were observed within the SN in a cluster including the left frontal operculum cortex ($-38, 08, 08; k = 143$) and decreased connectivity was observed

in a cluster including the left central operculum cortex $(-66, -16, 00; k = 133)$ $(p - FDR = 0.02, T = -4.48)$ and the right precentral gyrus $(54, -04, 36; k = 121)$ $(p - FDR = 0.002, T = -5.89)$. Finally, increased connectivity was observed within the CEN in a cluster, including the left PCG $(-06, -30, 48; k = 202)$ $(p - FDR < 0.001, T = 6.81)$, and in a cluster including the thalamus $(12, -16, 18; k = 66)$ $(p - FDR = 0.037, T = 5.53)$. When NLR was added to the analysis, increased connectivity within the DMN in a cluster, including the right PCG $(4, -22, 48; k = 151)$, was found $(p - FDR = 0.001, T = 6.33)$.

3.4 Discussion

The current study investigated the effects of COVID-19 on resting-state functional connectivity mechanisms in a Turkish adolescent sample. Moreover, we sought to explore how PLEs and inflammatory markers affected the functional connectivity measures during rest. Significant differences were observed for COVID-19 participants, and the healthy controls in several major networks, including the SMN, VN, CEN, and LN, were observed.

Our findings of altered functional connectivity in the precentral gyrus for COVID-19 participants are in line with previous studies. In an rs-fMRI study, researchers followed up with patients a year after their discharge from the hospital and found that the COVID-19 group had an increased amplitude of low-frequency fluctuation (ALFF) in the precentral gyrus. Another study examining SBC reported that COVID-19 participants who indicated having cognitive difficulties showed increased connectivity in the precentral gyrus [286]. Moreover, we found increased connectivity with the VN and frontal regions. Other studies have also reported alterations in the frontal regions and the occipital regions in COVID-19 patients. One study showed that at 6 months follow-up, COVID-19 patients found alterations both in the ALFF and the functional connectivity in the frontal and visual regions [287]. Another study showed increased dynamic functional network connectivity between the motor and visual networks [197]. Finally, we observed decreased functional connectivity within the language-related

networks in COVID-19 participants during rest. Recent studies have reported that impaired verbal abilities and verbal memory were some of the most implicated cognitive functions after COVID-19 diagnosis [288]. Moreover, we found that the frequency of PLEs and the inflammation markers affected the functional connectivity within the major networks in the brain. Individuals with more frequent symptoms showed increased connectivity of the CEN with the motor and striatal regions, as well as increased connectivity of the SN with the postcentral gyrus. Previous studies have reported an increase in the frequency of PLEs in individuals with COVID-19 [175] [284], whereas other studies have reported both increased and decreased functional connectivity patterns in individuals with PLEs [289] [290]. Lastly, our findings suggest that neuroinflammation markers such as the T-NLR and NLR were associated with both hypo- and hyperconnectivity within the DMN and SN and with hyperconnectivity of the CEN. These findings suggest that systematic inflammation due to the disease may alter functional connectivity mechanisms in patients. Previous literature has argued that the neuroinflammation due to COVID-19 may affect cognitive mechanisms [291]. In a study, researchers demonstrated that neuroinflammation markers in COVID-19 patients predicted abnormal functional connectivity in rs-fMRI [292]. In conclusion, our findings are in line with the literature and suggest that COVID-19 may be a risk factor for altered functional connectivity within the major networks of the brain in adolescents.

Chapter 4

General Discussion

The first study investigated the association between working memory-related functional connectivity measures and PLEs in an adolescent and young adult twin sample. Specifically, we examined the frequency and the distress associated with PLEs separately. Although the associations between brain connectivity and PLEs have been documented, the relationship between distress of PLEs and task-based connectivity measures has been less examined. Furthermore, most twin studies have predominantly focused on structural brain measures rather than task-evoked functional connectivity. In this study, using a healthy twin sample, the heritability estimates of working-memory-related connectivity measures and the frequency and distress of PLEs were studied. Our findings revealed that altered connectivity in the inferior frontal gyrus was associated with increased frequency and distress of PLEs during adolescence. Moreover, distress associated with PLEs showed moderate heritability, while the frequency of PLEs was predominantly shaped by environmental factors. The functional connectivity measures during the working memory task were mainly influenced by unique environmental factors. However, no significant genetic or environmental covariance was found between PLEs and brain connectivity measures, suggesting distinct underlying mechanisms for these traits. These results emphasize the importance of environmental factors in psychosis risk, highlighting the potential for early intervention strategies aimed at

modifying environmental exposures. Moreover, the results emphasize the substantial role of genetic factors in shaping distress associated with PLEs and the importance of investigating distress separately from frequency, as they may have distinct underlying influences.

The second study investigated the functional connectivity of the major brain networks in a Turkish adolescent sample. Moreover, we aimed to investigate the association of CAPE-positive symptoms and inflammation markers with the functional connectivity differences between groups. The majority of the studies of COVID-19-related functional connectivity have focused on adult samples. Therefore, the effect of COVID-19 during adolescence is not well studied. The findings of our study demonstrate alterations in the functional connectivity of the major networks in COVID-19 participants. Moreover, when positive PLEs were added as covariates in the analysis, COVID-19 patients showed increased connectivity in SN and CEN. As the brain goes under functional reorganization during adolescence, it may be more vulnerable to both inflammatory markers of the disease and the psychosocial stress associated with the disease, such as the lockdowns. Our results suggest that exposure to COVID-19 during adolescence may alter the functional connectivity of the brain and thus make individuals more susceptible to psychosis risk.

4.1 Limitations and Future Directions

The limitations of the studies should be considered when interpreting the findings. In the first study, although using a Turkish sample allows us to study FC measures and heritability estimates in a non-Western sample, the generalizability of the findings is limited as heritability estimates may change across different ethnicities and cultures. Second, PLEs were assessed using the CAPE-42 questionnaire, which is a self-report questionnaire and, therefore, may be less accurate than clinician-rated interviews of PLEs. Additionally, it should be noted that the unique environmental variance component also includes measurement errors, and thus, the results should be interpreted carefully. This places an upper limit

on heritability estimates as the presence of measurement errors may reduce the amount of variance that can be attributed to genetic factors [226]. Finally, this is a cross-sectional study, and future studies might benefit from investigating the heritability estimates of connectivity measures and PLEs along the developmental trajectories.

In the second study, our main limitation was the sample size, especially for the COVID-19 group. Moreover, the inflammation markers were only measured for the COVID-19 group, which further reduced the sample size for the analysis, including these markers. Studies with larger sample sizes are needed to confirm our results. In addition, we could not measure the psychosocial stressors associated with the disease, such as the lockdowns. Therefore, our results of altered functional connectivity may not only reflect the COVID-19 related systematic inflammation but may also be due to factors such as lockdowns and stress associated with the disease. Future studies can benefit from longitudinal studies investigating the rs-fMRI functional connectivity measures in larger populations and account for the disease-related psychosocial stressors.

4.2 Conclusion

Overall, the findings highlight the importance of considering the distress and frequency associated with psychotic-like experiences separately. Moreover, the results of both of the studies emphasize the importance of unique environmental factors such as exposure to the coronavirus, in shaping brain connectivity mechanisms and PLEs during adolescence. This is a critical period of time in which the brain undergoes rapid developmental changes both in structure and function and is vulnerable to exogenous influences [92]. These results have implications for developing prediction-based strategies aiming at reducing the risk of psychosis. Importantly, since environment is the most easily accessible factor to modify, it provides opportunities for early intervention and prevention strategies aimed at reducing the risk of PLEs through targeted modifications.

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Appendix A

Study 1: Psychotic-Like Experiences and Working Memory Connectivity in Adolescents and Young Adults: A Study on Turkish Twins

Model Diagnostic Plots

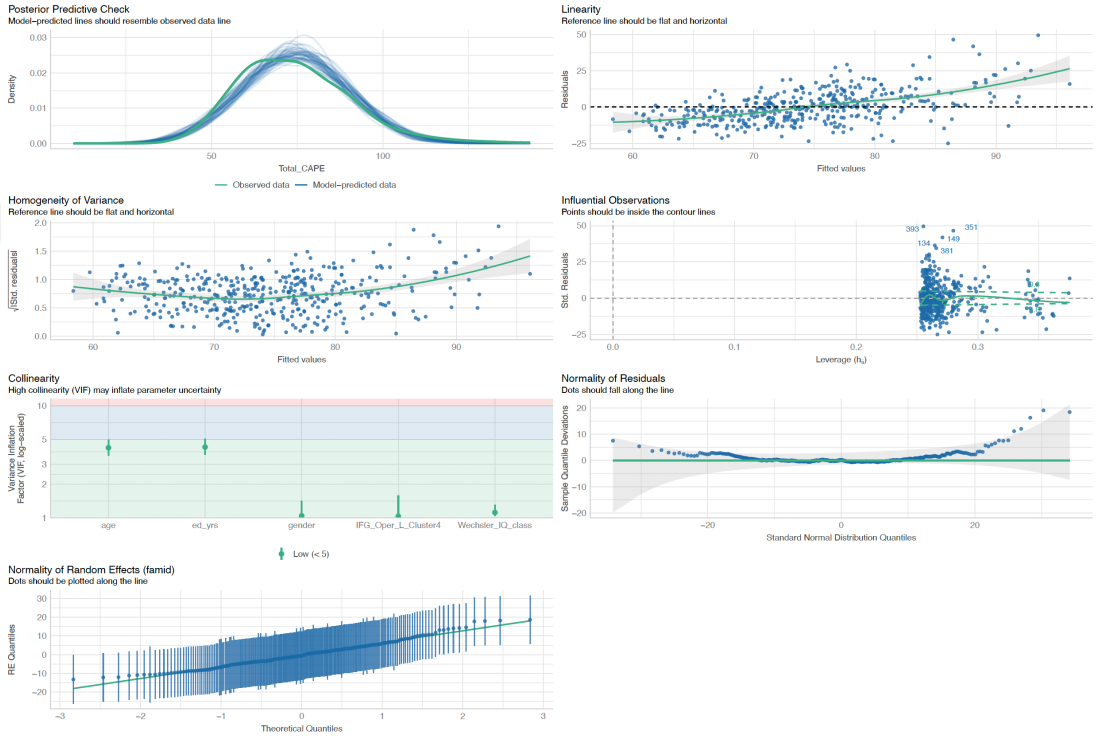

Figure A.1: Model Diagnostic Plot for CAPE-42 Frequency

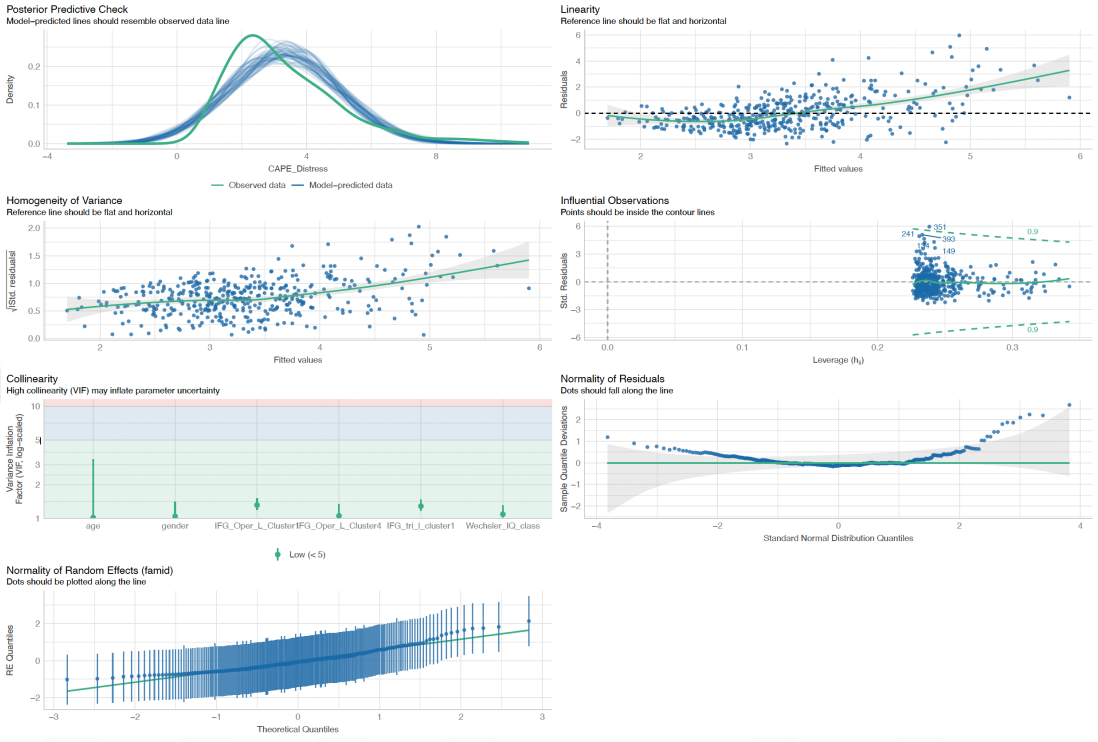

Figure A.2: Model Diagnostic Plot for CAPE-42 Distress

Model Parameters for Univariate Models

Table A.1: CAPE-42 Frequency

Base	Comparison	ep	-2LL	df	AIC	diffLL	diffdf	p-value
oneACEvc	*NA*	4	1262.0860	6	1270.0860	*NA*	*NA*	*NA*
oneACEvc	oneAEvc	3	1267.3737	7	1273.3737	5.287668	1	0.02147
oneACEvc	oneCEvc	3	1262.0885	7	1268.0885	0.002514	1	0.96000
oneACEvc	oneEvc	2	1298.6674	8	1302.6674	36.58138	2	<0.0001

Table A.2: CAPE-42 Distress

Base	Comparison	EP	-2LL	DF	AIC	DiffLL	DiffDF	p-value
oneACEvc	*NA*	4	1246.7704	6	1254.7704	*NA*	*NA*	*NA*
oneACEvc	oneAEvc	3	1246.9759	7	1252.9759	0.205490	1	0.65032
oneACEvc	oneCEvc	3	1250.9504	7	1256.9504	4.180049	1	0.04090
oneACEvc	oneEvc	2	1283.5240	8	1287.5240	36.75366	2	<0.0001

Table A.3: IFG tri L Cluster #1

Base	Comparison	EP	-2LL	DF	AIC	DiffLL	DiffDF	p-value
oneACEvc	*NA*	4	1176.4861	6	1184.4861	*NA*	*NA*	*NA*
oneACEvc	oneAEvc	3	1176.6549	7	1182.6549	0.168854	1	0.68113
oneACEvc	oneCEvc	3	1176.7033	7	1182.7033	0.217254	1	0.64113
oneACEvc	oneEvc	2	1176.7108	8	1180.7108	0.224692	2	0.89373

Table A.4: IFG Oper L Cluster #1

Base	Comparison	EP	-2LL	DF	AIC	DiffLL	DiffDF	p-value
oneACEvc	*NA*	4	1156.1663	6	1164.1663	*NA*	*NA*	*NA*
oneACEvc	oneAEvc	3	1156.8375	7	1162.8375	0.671216	1	0.41262
oneACEvc	oneCEvc	3	1156.4533	7	1162.4533	0.287052	1	0.59211
oneACEvc	oneEvc	2	1157.3973	8	1161.3973	1.231054	2	0.54035

Table A.5: IFG Oper L Cluster #4

Base	**Comparison**	**EP**	**-2LL**	**DF**	**AIC**	**DiffLL**	**DiffDF**	**p-value**
oneACEvc	*NA*	4	1175.3293	6	1183.3293	*NA*	*NA*	*NA*
oneACEvc	oneAEvc	3	1176.1858	7	1182.1858	0.85645	1	0.35473
oneACEvc	oneCEvc	3	1175.7286	7	1181.7286	0.39929	1	0.52745
oneACEvc	oneEvc	2	1176.7059	8	1180.7059	1.37658	2	0.50243

Appendix B

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Last updated October 2022

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