

**THE IMPACT OF ENVIRONMENTAL RISK
FACTORS ON PSYCHOSIS PRONENESS
AND NEURAL CORRELATES OF WORKING
MEMORY AND RESTING-STATE IN
ADOLESCENTS AND YOUNG ADULTS**

A DISSERTATION SUBMITTED TO
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By
Tuba Şahin İlikoğlu
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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.

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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 Touloupoulou. 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 236 participants. I contributed to data collection or scoring for 188 of these participants. The remaining data were gathered by other graduate students supervised by Professor Touloupoulou, including Timucin Bař, Rabia Sen, Kübra Çelikbař, Seda Arslan, Didenur Sahin Cevik, 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 Chapter 4 and parts of Chapter 2. The work presented in Chapter 4 and parts of Chapter 2 was previously published as a multi-author manuscript included in the journal *Psychiatry Research: Neuroimaging* as “Causal Discovery Analysis Reveals Insights into Psychosis Proneness, Brain Function, and Environmental Factors among Young Individuals” by Tuba Sahin-Ilikoglu, Sisi Ma, Erich Kummerfeld, Eric Rawls, Hao Yang Tan and Timothea Touloupoulou (2025). This paper included my supervisor, Prof. Dr. Timothea Touloupoulou and the following collaborators: Sisi Ma, Erich Kummerfeld, Eric Rawls, Hao Yang Tan. I contributed by collecting and analyzing data and by writing the first draft of the manuscript. All co-authors contributed to the write-up. All co-authors made substantial contributions to the conception, statistical analysis, and writing of that paper.

Tuba Şahin İlikođlu

ABSTRACT

THE IMPACT OF ENVIRONMENTAL RISK FACTORS ON PSYCHOSIS PRONENESS AND NEURAL CORRELATES OF WORKING MEMORY AND RESTING-STATE IN ADOLESCENTS AND YOUNG ADULTS

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Experiencing symptoms of psychosis, such as delusions and hallucinations, is sometimes observed in the general, nonclinical populations in a mild form, and is often termed psychosis proneness (PP), potentially as part of the psychosis continuum. Understanding the neural, environmental and cognitive factors contributing to PP in young individuals during critical developmental periods remains unclear. Environmental risk correlations, causal factors, and neural correlates of psychosis proneness were investigated using fMRI during both task performance and resting state. To this end, three different studies were conducted. The first study examined the relationship between environmental risk factors including ethnic minority or migration history, obstetric complications, paternal age, urbanicity, trauma, cannabis use, and psychosis proneness and schizotypy using multilevel mixed effects linear regression. Additionally, schemas about the self and others were used to predict psychosis proneness and schizotypy, alongside an exploration of its neural correlates during working memory performance. In the second study, we used a data-driven approach, causal discovery analysis (CDA), a novel machine learning algorithm, to explore directional relationships among variables. The analysis identified negative self-schema as having the largest causal effect on psychosis proneness among all assessments. Furthermore, experiencing low levels of social cohesion and trust had a causal effect on psychosis proneness. Although our analysis could not exclude the possibility that other unmeasured factors may confound these relationships, the effect sizes (ES) were substantial: negative self-schema & PPS (ES= 0.54) and social cohesion and trust & PPS (ES= -0.18). Moreover, PPS was identified as a direct cause of increased activation in the dorsolateral prefrontal cortex (DLPFC) during working memory (ES= 0.12). CDA provided simultaneous directionality for 37 variables measured in the same individuals. Finally, in the third study, we applied CDA to a dataset that included resting-state fMRI functional connectivity (FC) indices, with two different configurations of prior knowledge. Negative self-schema and social cohesion

& trust again emerged as a direct causal factor for psychosis proneness. However, psychosis proneness did not appear to influence mean FC indices during rest. Instead, it directly affected specific functional connections within the dorsal attention network. These findings highlight the significance of negative self-schema and social cohesion and trust in the general population with psychosis proneness, suggesting potential preventive interventions targeting these factors. Furthermore, the results highlight the roles of the DLPFC during working memory and the dorsal attention network during rest as potential targets for understanding and addressing psychosis proneness. These findings represent the first data-driven analysis modelling causal mechanisms underlying psychosis proneness in the general population and further supports the hypothesis of continuum of psychosis.



Keywords: psychosis proneness, environmental risk factors, self-schema, fMRI, working memory, schizophrenia, CDA, GFCI.

ÖZET

ERGEN VE GENÇ ERİŞKİN NÜFUSTA ÇEVRESEL RİSK FAKTÖRLERİN ÇALIŞMA BELLEĞİ SIRASINDAKİ NÖRAL AKTİVASYON VE DİNLENİM HALİNDEKİ FONKŞİYONEL BAĞLANTI ÜZERİNDEKİ ETKİŞİ İLE PSİKOZ EĞİLİMİNE İLİŞKİN ETKİLERİ

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Sanrılar ve halüsinasyonlar gibi psikoz belirtileri, genel, klinik olmayan popülasyonda bazen hafif bir formda gözlemlenebilir ve genellikle psikoz eğilimi (PP) olarak adlandırılır, bu durum potansiyel olarak psikoz sürekliliğinin bir parçası olarak değerlendirilir. Genç bireylerde, özellikle kritik gelişimsel dönemlerde psikoz eğilimine katkıda bulunan nöral, çevresel ve bilişsel faktörlerin anlaşılması ise belirsizliğini korumaktadır. Bu tez psikoz eğiliminin çevresel risk korelasyonlarını, nedensel faktörlerini ve nöral korelasyonlarını, hem görev sırasında hem de dinlenme durumunda fMRI verilerini kullanarak araştırmayı amaçlamaktadır. Bu amaçla, üç farklı çalışma gerçekleştirilmiştir. İlk çalışmada, etnik azınlık veya göç geçmişi, obstetrik komplikasyonlar, baba yaşı, kentsel yaşam, travma ve esrar kullanımı gibi çevresel risk faktörleri ile psikoz eğilimi ve şizotipiklik arasındaki ilişki çok düzeyli karma etkili doğrusal regresyon yöntemiyle incelenmiştir. Ayrıca, benlik ve diğerleri hakkındaki şemalar, psikoz eğilimi ve şizotipiklik öngörüsü için kullanılmış ve çalışma belleği performansı sırasında gözlemlenen nöral korelatlar araştırılmıştır. İkinci çalışmada değişkenler arasındaki nedensellik ve etki yönünü keşfetmek için veri odaklı bir yaklaşım olan, yeni bir makine öğrenimi algoritması olan nedensel keşif analizi (CDA) kullanılmıştır. Bu analiz, negatif benlik şemasının psikoza yakınlık üzerinde tüm değerlendirmeler arasında en büyük nedensel etkiye sahip olduğunu ortaya koymuştur. Ayrıca, zayıf seviyede deneyimlenen sosyal uyum ve güvenin de psikoz eğilimi üzerinde nedensel bir etkisi olduğu belirlenmiştir. Analizimiz, bu ilişkileri etkileyebilecek başka ölçülmemiş faktörlerin varlığını dışlayamasa da, etki büyüklükleri (ES) anlamlıydı: negatif benlik şeması & PPS (ES= 0.54) ve sosyal uyum ve güven & PPS (ES= -0.18). Ek olarak, PP'nin, çalışma belleği sırasında dorsolateral prefrontal korteksteki (DLPFC) aktivasyon artışına doğrudan neden olduğu tespit edilmiştir (ES= 0.12). CDA aynı bireylerde ölçülen 37 değişken için eş zamanlı yönlü nedensellik ilişkilerinin ortaya çıkmasını sağlamıştır. Son

olarak, üçüncü çalışmada CDA, dinlenme durumundaki fMRI (rsfMRI) ortalama fonksiyonel bağlantı (FC) indekslerini içeren bir veri setine, iki farklı ön bilgi yapılandırmasıyla uygulanmıştır. Negatif benlik şeması ve sosyal uyum & güven, tekrar psikoz eğiliminin doğrudan nedensel faktörü olarak ortaya çıkmıştır. Ancak, psikoz eğiliminin dinlenme sırasındaki ortalama FC indekslerini etkilediği gözlemlenmemiştir. Bunun yerine, dorsal dikkat ağı içindeki bölgesel FC indekslerini doğrudan etkilediği belirlenmiştir. Bu bulgular, PP'li genel popülasyonda negatif benlik şeması ve sosyal uyum ve güvenin önemini vurgulamakta ve bu faktörlere yönelik önleyici müdahalelerin potansiyelini ortaya koymaktadır. Ayrıca, sonuçlar çalışma belleği sırasında DLPFC'nin ve dinlenme sırasında dorsal dikkat ağının, psikoz eğilimini anlamada ve ele almada potansiyel hedefler olarak rolünü vurgulamaktadır. Bu tez, genel popülasyonda PP'nin altında yatan nedensel mekanizmaları modelleyen ilk veri odaklı analiz olup, psikoz sürekliliği hipotezini de desteklemektedir.

Anahtar sözcükler: psikoz, psikoza yatkınlık, şizofreni, fMRI, çevresel risk faktörleri, benlik şeması, CDA, GFCI.



To my beloved sister Merve Şahin...

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Contents

1	Introduction	1
1.1	Psychosis Proneness	2
1.2	Environmental Risk Factors of Psychosis	3
1.2.1	Obstetric and Birth Complications	4
1.2.2	Migration and Ethnicity	4
1.2.3	Urbanicity	5
1.2.4	The Role of Early Life Experiences in Psychosis	7
1.2.5	Cannabis Use	7
1.2.6	Paternal Age	8
1.3	Cognitive Deficits in relation to Psychosis and Psychotic-Like Experiences	8
1.3.1	Cognitive Biomarkers of Psychosis Proneness	8
1.3.2	Working Memory as an Intermediate Phenotype	9
1.3.3	Self-Schema in relation to Psychosis Proneness	10
1.4	Functional Imaging Markers for Psychosis Proneness	11
1.5	Aims and Hypotheses	12
2	Methods	15
2.1	Participants	15
2.2	Psychological Assessments	16
2.2.1	Psychosis Proneness	16
2.2.2	Brief Core Schema Scales (BCSS)	17
2.3	Environmental Assessments	19
2.3.1	Urbanicity	19
2.3.2	Obstetric Complications	20
2.3.3	Cannabis and Other Drug Use	20
2.3.4	Childhood Trauma	20
2.3.5	Parental Discord Ratings Scale	23

2.3.6	Alcohol Usage	23
2.3.7	Discrimination	24
2.3.8	Life-Threatening Events	24
2.3.9	Social Cohesion and Trust (SC&T)	24
2.3.10	Maudsley Environmental Risk Score Calculation	25
2.4	Family Interview for Genetic Studies (FIGS)	26
2.5	Psychiatric Medication Usage	26
2.6	Cognitive Assessments	26
2.6.1	Wechsler Abbreviated Scale of Intelligence — Second Edition (WASI-II)	26
2.6.2	Verbal Fluency	27
2.7	Neuroimaging	27
2.7.1	MRI Apparatus	27
2.7.2	Structural Magnetic Resonance Imaging (sMRI)	27
2.7.3	Task-based Functional Magnetic Resonance Imaging (fMRI)	28
2.7.4	Resting State Functional Magnetic Resonance Imaging (rsfMRI)	30
2.8	Data Analysis	30
2.8.1	Task based fMRI Preprocessing and Data Analysis	30
2.8.2	Resting-state fMRI (rsfMRI) Image Preprocessing	33
2.8.3	Multilevel Mixed-Effects Linear Regression	34
2.8.4	Causal Discovery Analysis	34
3	The Influence of Individual and Aggregate Environmental Risk Factors and Cognitive Schemas on Psychosis Proneness and Schizotypy: Implications for Neural Correlates During Working Memory	40
3.1	Descriptive Statistics	41
3.2	Aggregated Environmental Risk Score Predicts Psychosis Proneness	44
3.3	The Relationship between Individual Environmental Risk Factors and Psychosis Proneness	45
3.3.1	Ethnic Minority and Migration History	48
3.3.2	Paternal Age	48
3.3.3	Obstetric Complications	49
3.3.4	Urbanicity	49
3.3.5	Childhood Trauma	50
3.3.6	Cannabis Use	51

3.4	Schema about Self and Others Predicts Psychosis Proneness . . .	51
3.5	Negative Self-Schema Predicts VLPFC Activation during Working Memory	56
3.6	Discussion and Conclusions	56
4	Causal Discovery Analysis Reveals Insights Into Psychosis Pro- nenss, Brain Function, and Environmental Factors Among Young Individuals	62
4.1	Sample Characteristics	62
4.2	Causal Discovery Analysis	63
4.3	Causal Model Results	71
4.3.1	The Partial Ancestral Graph (PAG) Suggests Possibly Causal Relationships Between Negative Self-Schema, So- cial Cohesion and Trust and Psychosis Proneness Score . .	71
4.3.2	Psychosis Proneness Score as a Causal Factor in Activation of the Dorsolateral Prefrontal Cortex	73
4.3.3	The Partial Ancestral Graph Suggests Causal Relationships Between Cognitive Variables and Other Variables	74
4.3.4	The Partial Ancestral Graph Suggests Causal Relationships between fMRI Indexes and Other Variables	74
4.3.5	Additional Partial Ancestral Graph with Negative Others Schema Included	81
4.4	Sensitivity Analysis	87
4.4.1	Alternative Variable Coding of Environmental Risk Factors	87
4.4.2	Structural Equation Modelling of the Sensitivity Analysis .	88
4.5	Results of the Sensitivity Analysis and SEM Comparison with the Main Results	94
4.6	Discussion and Conclusions	95
4.7	Limitations and Strengths	100
4.8	Conclusion	102
5	Causal Discovery Analysis to Find Pathways to Psychosis Prone- ness During Rest: rsfMRI	103
5.1	Introduction	103
5.2	Sample Characteristics	105
5.3	Causal Discovery Analysis with rsfMRI Connectivity Indices . . .	107

5.4	Exploring the Relationship Between Psychosis Proneness Score and Seed-based Resting-State Functional Connectivity	114
5.5	Discussion	115
6	Overall Conclusions and Future Prospects	122
6.1	Limitations and Future Directions	128
6.2	Conclusion	130
A	Supplementary Results	159
B	Permisson to Re-use Brain Figure	193



List of Figures

2.1	The Working Memory Paradigm	29
2.2	Working Memory Encoding and Manipulation. In the encoding phase, two digits appeared on the left and right sides of the screen. Participants were instructed to retain both digits and their spatial locations in working memory for a duration of 3 to 6 seconds. During the manipulation phase, they mentally subtracted from the digit on the cued side and indicated whether the resulting number was larger or smaller than the number on the opposite side. Adapted from Sahin-Ilikoglu et al., 2025 [1].	30
4.1	Causal Discovery Analysis for all variables and Manipulation phase of the Working Memory Paradigm. Causal Discovery Analysis was performed using GFCI for activations in ROIs when manipulating information during fMRI, environmental and psychological variables. (B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus; I.P.: Intraparietal Sulcus; a9-46v: frontal mid; FOP4: frontal operculum; IFJa: anterior inferior frontal gyrus; p47r: the orbital prefrontal cortex; a32pr: refers to a narrow strip of the anterior midcingulate cortex; FEF: frontal eye fields; SES: socioeconomic status; W.M.: working memory). Adapted from Sahin-Ilikoglu et al., 2025 [1].	64

- 4.2 **Complete Partial Ancestral Graph with Effect Sizes and p-value Information.** Causal Discovery Analysis was conducted with GFCI, incorporating fMRI activation data from ROIs during information manipulation, along with environmental and psychological factors. (B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus; I.P.: Intraparietal Sulcus; a9-46v: frontal mid; FOP4: frontal operculum; IFJa: anterior inferior frontal gyrus; p47r: the orbital prefrontal cortex; a32pr: refers to a narrow strip of the anterior midcingulate cortex; FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory.) [0.5em] ** $p < 0.01$; * $p < 0.05$ [0.5em] (Created in BioRender. Sahin, T. (2025). <https://BioRender.com/gj42q12>) 65
- 4.3 **Psychosis Proneness Subgraph.** GFCI returns a partial ancestral graph (PAG) depicting causal relationships between a set of variables, while assessing for unmeasured third variables in relationships (confounders). BA9: DLPFC; BA46: MPFC; P47r: Orbital Prefrontal Cortex. Adapted from Sahin-Ilikoglu et al., 2025 [1]. . 72
- 4.4 **Causal Discovery Analysis including Negative Others Schema and Manipulation phase of the Working Memory Paradigm.** Causal Discovery Analysis was performed using GFCI for activations in ROIs when manipulating information during fMRI, environmental and psychological variables including the negative others schema. (B.A.:Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus, I.P.: Intraparietal Sulcus; a9-46v: frontal mid, FOP4: frontal operculum, IFJa: anterior inferior frontal gyrus, p47r: the orbital prefrontal cortex, a32pr: refers to a narrow strip of the anterior midcingulate cortex, FEF: frontal eye fields; SES: socioeconomic status; W.M.: working memory). Adapted from Sahin-Ilikoglu et al., 2025 [1]. 82

4.5	Sensitivity Analysis: Causal Discovery of Environmental Risk Factors and the Working Memory Manipulation Phase. Causal Discovery Analysis was performed using GFCI for activations in ROIs during the manipulation phase of working memory in fMRI. Variables included environmental risk factors from Vassos et al. (2020) [2], multidomain risks, and psychological variables. (B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus; I.P.: Intraparietal Sulcus; a9-46v: frontal mid; FOP4: frontal operculum; IFJa: anterior inferior frontal gyrus; p47r: orbital prefrontal cortex; a32pr: anterior midcingulate cortex; FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory). ** $p < 0.01$, * $p < 0.05$. (Created in BioRender. Sahin, T. (2025). https://BioRender.com/jblr2km)	92
4.6	Psychosis Proneness Subgraph of the Sensitivity Analysis. GFCI returns a partial ancestral graph (PAG) depicting causal relationships between a set of variables, while assessing unmeasured third variables in relationships (confounders). (<i>BA9: dorsolateral prefrontal cortex (DLPFC); BA46: medial prefrontal cortex (MPFC); P47r: orbital prefrontal cortex.</i>) Adapted from Sahin-Ilikoglu et al., 2025 [1].	93
5.1	Partial Ancestral Graph depicting causal relationships among rsfMRI FC Indices and all variables. The PAG displays estimated causal links among rsfMRI FC indices, environmental exposures, demographic and cognitive factors, and psychological variables. Causal Discovery Analysis was performed using GFCI for rsfMRI FC indexes, environmental and psychological variables. (FC: functional connectivity) (Brain illustration adapted with courtesy of https://www.mindmedia.com). ** $p < 0.01$; * $p < 0.5$	108
5.2	Causal Discovery Analysis with five levels of hierarchy for all variables and rsfMRI FC Indexes with Effect Sizes and p-value Information. Causal Discovery Analysis was performed using GFCI for rsfMRI FC indexes, environmental and psychological variables. (FC: functional connectivity) (Brain illustration adapted with courtesy of https://www.mindmedia.com). ** $p < 0.01$; * $p < 0.5$	114

- A.1 **Supplementary Figure 1.** The anatomical location of MNI coordinates $x = +0$, $y = -8$, $z = +4$. Although the CompCor in the CONN toolbox was used to reduce cerebrospinal fluid (CSF)-related noise, the potential confounding influence of CSF on the observed resting state FC between this region and the right frontal eye fields (FEF) of the dorsal attention network was further evaluated. The CSF map derived from a participant overlaid onto MNI152 T1 anatomical template in MRICron. At the $x = 0$, $y = -8$, $z = 4$ coordinates, the CSF mask did not show any signal intensity, suggesting that observed functional connectivity at this location is unlikely to be contaminated by CSF signal. In the image, CSF appears in red, while surrounding anatomical structures are displayed in grayscale. 190

List of Tables

2.1	The Structured Interview for Schizotypy-Revised (SIS-R) Schizotypal Signs	18
2.2	Cut-off Points for the Subscales of the Childhood Trauma Questionnaire (CTQ)	21
2.3	Severity Classification for the Psychological Abuse Rating Questionnaire	22
2.4	Severity Classification for the Parental Discord Rating Scale . . .	24
2.5	Regions of Interest (ROIs) for Task-Based fMRI During Working Memory	32
3.1	Sample Characteristics	41
3.2	Descriptive Statistics of Childhood Trauma Questionnaires	43
3.3	Distribution of Participants Based on Percentile Ranks of Psychosis Proneness Measured by Total CAPE-42 Score	43
3.4	Multilevel mixed-effects linear regression results predicting CAPE-42 and SIS-R subscale scores from the aggregated environmental risk score. Adjusted p-values were calculated using the Benjamini-Hochberg FDR. SE = Standard Error, CI = Confidence Interval. (* $p < .05$)	44
3.5	Multilevel mixed-effects linear regression results showing associations between individual environmental risk factors and CAPE-42 and SIS-R subscales. SE = standard errors, CI = confidence intervals, (* $p < .05$)	45
3.6	Multilevel mixed-effects linear regression results showing associations between schema about self/others and CAPE-42 and SIS-R subscales. SE = standard errors, CI = confidence intervals, * $p < .05$	52
4.1	Effect Sizes of Variables Estimated via SEM for Relationships Suggested by PAG	66

4.2	Resampling with Replacement Analysis for Main Results	76
4.3	Effect Sizes Estimated via SEM for Relationships Suggested by the PAG Involving Negative Others	83
4.4	Effect Sizes Estimated via SEM for the Sensitivity Analysis	88
4.5	Comparison of SEMs between the Main Model and Alternative Model	94
4.6	Changed Edges in the Alternative Model	94
5.1	Sample Characteristics	105
5.2	SEM Results for the PAG Derived from rsfMRI FC Indices and Additional Factors	109
A.1	Rounded Ratios Calculated for Obstetric and Birth Complications	160
A.2	Resampling with Replacement Analysis for Sensitivity Results . .	162
A.3	SEM Results for Negative Self-Schema and SC&T as Di- rect Edges to Psychosis Proneness	166
A.4	RsfMRI FC Indices and Corresponding Coordinates	170
A.5	Resampling with Replacement Analysis of rsfMRI Functional Con- nectivity Indices	191

Chapter 1

Introduction

One of the important concepts what keeps people continuing their lives healthy and persisting in good mental health is the correct perception of self and the environment around them. Let's imagine a case where a person thinks some thoughts are being inserted into oneself' mind and consistently watched and gazed at by a stranger. This is often what people with psychosis experiences, where the mind is affected, and series of symptoms accompany and the connection with reality got distorted. Psychosis can be described as an episode of losing contact with reality such as hallucinations and delusions together with disorganized thoughts and feelings. Psychosis can occur in various psychological disorders such as schizophrenia, bipolar disorder, severe depression, and schizoaffective disorder. Additionally, neurological conditions like brain tumors, multiple sclerosis, epilepsy, dementia, and substance abuse can also lead to psychotic episodes. Psychosis can also be experienced in the non-clinical population, especially among adolescents and young adults. These early experiences may increase the risk of developing full-blown psychosis, although some individuals may continue their lives without serious problems or receiving any diagnosis.

The current thesis focuses on understanding vulnerability to psychosis and how risk factors may contribute to higher levels of vulnerability during critical stages, specifically adolescence and young adulthood, in the general population. Additionally, it examines whether there are neural correlates of vulnerability to psychosis. To discover these relationships, both traditional and novel methods were applied, and the results are presented in the following sections.

1.1 Psychosis Proneness

Some symptoms of schizophrenia such as hallucinations, delusions, social isolation can also be observed in non-clinical population [3]. These experiences are often called as either psychotic-like experiences (PLEs) or schizotypal traits. In Meehl's model, Schizotypy is defined as a latent personality structure reflecting a liability for psychotic-spectrum disorders and this liability can be present in 10% of the general population [4]. On the other hand, PLEs are more transitory and mostly observed during adolescence which is a critical point during development and can disappear over time [5]. Thus, the difference between the schizotypy and PLEs is the “stability” in the nature while schizotypy forms more “trait-like” structure, PLEs form “symptom approach” [6].

Both schizotypy and PLEs constitute parts of the hierarchical continuum of the psychosis without any clinical manifestations. In this thesis, “Psychosis Proneness” was used to refer any experiences of PLEs, Schizotypy in the general population that can arise either from genetic liability or more transitory experiences occurring especially during the developmental trajectory. Psychotic-like experiences are particularly reported during adolescence and young adulthood [7, 3]. Capturing the reasons of the origin of these experiences may be crucial, as their occurrence during adolescence has been linked to a heightened risk of developing psychotic disorders [8, 9], and other mental health conditions [10] in later stages of life. Prevalence rate for the PLEs is reported at 17 % in children aged 9-12 and in adolescents aged 13-18 [7], which depicts that an individual does not have to have a clinical diagnosis to experience such symptoms. Therefore, a continuum of a psychosis-spectrum can be observed across the lifespan in which some individuals receive clinically significant diagnoses while others are somehow able to resist and overcome previous symptoms without getting any diagnoses in their lifetime. The prevalence rate for such non-clinical psychosis symptoms is 5% which is more frequent compared to clinical disorders [3]. It is still not entirely understood what drives some individuals to be diagnosed with clinical mental disorders, such as schizophrenia and bipolar disorder, while others who experience mild psychotic symptoms do not. Many approaches were taken into consideration while understanding such complex mental disorders and psychosis. Previous research was focused mainly on the patients but soon then it was realized that the research results were biased by the medication usage such as antipsychotics.

Not just because of medication effect but also low intelligence quotient (IQ) of patients (generally) with schizophrenia and its effect on cognitive performance, patient data do not exactly enable us pure course of the disorder and the trajectory of the psychosis-related disorders. To understand schizophrenia, it could be a better approach to understand its symptoms and how they are neurologically implicated in the brain. Flat affect, social withdrawal, poor judgment and poor executive functions are other symptoms of schizophrenia besides hallucinations and delusions and these intellectual impairments in the general population can give insight into psychosis in part.

1.2 Environmental Risk Factors of Psychosis

The prevalence of schizophrenia in the general population is approximately 1 %. The elevated likelihood of schizophrenia among the relatives of patients was supported by the evidence from the heritability research. Evidence from heritability research indicates an elevated likelihood of psychotic disorders in the relatives of patients. The risk can further increase to approximately 50 % in concordant monozygotic twins. Genes only cannot explain the vulnerability to schizophrenia even though the elevated risk observed in relatives of patients. One of the reasons why relatives of patients have higher risk for psychosis could be due to shared environment in addition to shared genetics. Psychosis is present only for the twin who is exposed to certain environmental experiences who also share genetic vulnerability [11].

Findings from previous research suggest that environmental challenges not only increase the likelihood of developing schizophrenia but also affect subclinical psychotic-like experiences within the psychosis spectrum among unaffected siblings and healthy individuals [12, 13]. Numerous environmental risk factors for psychosis have been identified, including obstetric complications [14, 15, 16, 17], migration, minority group position [18, 19], urban birth and urban upbringing [20, 21, 11], childhood trauma [13], and cannabis use [22, 23, 24]. Exposure to environmental risk factors has been linked to neural deviations, increasing the susceptibility to altered brain function and structure, particularly in the prefrontal cortex [25, 26, 27, 28, 29, 30, 31, 32]. In the following section, these psychosis risk factors which are relevant to the current thesis will be introduced.

1.2.1 Obstetric and Birth Complications

Obstetric complications (OCs) are one of the perinatal risk factors for psychosis and the term refers to “somatic deviations from the normal course of events over the pregnancy, delivery, and early neonatal periods” [14]. OCs have a modest but consistent relationship with psychosis-related disorders across the studies in which odds ratios (ORs) remained between 1.5 to 2.0 [14]. Recent studies revealed that rather than focusing on the individual OCs, evaluating the OCs as a category of risk factor revealed more prominent results especially when it was an additive component to the “polyenviromic risk score” [33].

Perinatal hypoxia is one of the complications observed during pregnancy and after birth and defined as the lack of oxygen or inadequate utilization of oxygen by the fetus or a newborn. Perinatal hypoxia may lead to enduring changes in dopaminergic activity [34]. Gene-environment interaction studies found that several schizophrenia related genes AKT, BDNF, GRM3 and DTNBP were associated with the obstetric complications (bleeding during pregnancy, prolonged labor, complications during delivery problems and neonatal respiratory distress) which are potential complications to cause hypoxia. Consequently, obstetric complications and their relation to psychosis risk might not only be due to the environmental risk factor but also combined effect with underlying genetic vulnerability.

Longitudinal studies conducted on the PLEs during adolescence and the OCs in 6,356 children found that there were significant associations between maternal tobacco and alcohol use, low birth weight and ponderal index, maternal infection during pregnancy, maternal diabetes, the requirement for resuscitation and 5-minute Apgar score [15, 16, 17].

1.2.2 Migration and Ethnicity

Literature on the ethnic minority groups and migration revealed there is a high incidence rate of psychosis [19, 18]. The relative risk differs for each country and each ethnic minority group. For example, relative risk rate is higher for Moroccan and Surinamese populations but less for Turkish population living in Netherlands [35, 36]. The possible misleading concept is the overdiagnosis of schizophrenia for the migrant population. It could be that migrant population might go through a

difficult time or mood changes which might mislead professionals for the diagnosis process. Additionally, cultural aspects might play a role here for which local professionals do not have much information or understanding. Many countries such as Germany try to recruit for example Turkish mental health professionals for Turkish minority group to avoid any misleading due to the cultural aspects. On the other hand, research comparing diagnostic assessments made by Jamaican and British mental health professionals evaluating the same patients found no differences [37].

The high relative risk of psychosis for ethnic minority populations and migrants could rise from several reasons such as external social conditions including socioeconomic disadvantages, bullying, discrimination, childhood adversity, living in densely populated areas which then have an impact on the biological and psychological mechanisms to be resulted in paranoia, hallucinations and thought disturbances [38]. Therefore, in the current thesis, the risk effect of psychosis vulnerability on ethnic minority groups is going to be evaluated.

1.2.3 Urbanicity

Urban living brings many advantages such as better health-care, better education opportunities and social activities, but it is now inevitable that “Urban Birth”, “Urban Upbringing” and “Current Urban Living” is associated with increased risk for psychiatric disorders including schizophrenia [39, 26] and were shown as a risk factor for vulnerability to psychosis [20]. Between 16-34% of cases of psychosis is related to urban living and urban upbringing [21, 11]. Exposure to early environmental risk factors makes individuals more susceptible to later illnesses, such as vulnerability to psychosis-related disorders likely by disrupting critical period of brain development [40, 41]. Environmental risk factors such as urban birth are also possibly mediated by viral infections which is the risk increasing factor [42].

The intermediate risk factors between exposure to urban living and increased prevalence of psychosis in urban environment might reflect the effect of various social adversity such as social isolation, social status [43]. The source of these results could arise from stressful daily life situations such as air pollution, high population density, negative social environment [26]. Lederbogen et al. (2011)

investigated how urban residency and upbringing relate to brain activity during acute social stress among healthy population. Throughout the experiment, participants with current urban living resulted in modulated activity in amygdala which was independent of the stress-paradigm task. Similar results were observed in the replication study with n-back task with different subjects [44].

The effect of urbanicity in different countries might differ [45]. Many urbanicity studies mostly were carried out in western countries with lower population densities in comparison to Türkiye. In Türkiye, studies examining how environmental risks relate to psychotic symptoms have been restricted to limited number of cities. For example, 1,268 individuals from were examined and results have shown that alcohol use, lack of social support, having a first-degree family history were related to psychotic symptoms [46]. Furthermore, the relationship with urbanicity and social life adversity were found in İzmir, Türkiye [47]. Based on the State Institute of Statistics, Republic of Türkiye (<http://www.tuik.gov.tr/Start.do>), the estimated population of Türkiye is 85.279 million by 2022 and the overall population density is approximately 111 people per square kilometer. The most densely populated city in Türkiye is İstanbul with 3,062 and Ankara is in the 8th order with 228 people per kilometer density. In the current thesis, participants were mostly recruited from the city Ankara.

One of the important factors in urbanization is how it is defined, as there are various ways to define urbanization. While some studies defined urbanization level using measures such as population concentration per square kilometer[48] or the ratio of inhabitants to land area [49], in other studies it were either defined with categorization such as labelling areas with more than 100,000 residents as “city”, between 10,000 and 100,000 as town, and 10,000 or fewer as rural in Australia [50]. Alternatively, some research defined urbanicity more contextually, such as defining Munich as urban and the surroundings of Munich was defined as rural areas [51]. According to previous research, the definition of urbanization immensely differs between regions and countries due to several reasons such as overall population density, defining cities, towns, and suburbs are hugely based on the environment and urban planning of governments. In Türkiye, there are not many studies conducted for the effect of urbanization on human mental health. Moreover, the application of the Organization for Economic Cooperation and Development (OECD) classification systems to cities of Türkiye and suburbs might not be relevant.

1.2.4 The Role of Early Life Experiences in Psychosis

Wide range of research investigated the association between early life experiences, such as childhood trauma and psychosis. Usually, sexual abuse, physical abuse, physical neglect and similar factors were individually examined for the association with psychosis. In 2012 Varese and colleagues conducted meta-analysis by combining several childhood abuses and it was revealed trauma experiences during childhood was significantly related to increased vulnerability to develop psychosis during adulthood. The results were replicable across many studies. Furthermore, a study conducted for patients and healthy controls revealed that the lifetime occurrence of sexual abuse among patients were reported as 47.7% for females and 28.3% for males and for physical abuse 47.8% (females), 50.1% (males) [52]. In addition, first episode psychosis (FEP) patients reported significantly more bullying experiences than the control group [53].

A study by McGrath and colleagues identified a dose-response association between traumatic experiences in childhood and adulthood in relation to hallucinations and delusions among the 24,464 respondents [54]. While the single trauma effect was $OR=3.1$, the cumulative trauma (experiencing five or more exposures to trauma) effect was $OR=7.6$ [54]. Although individual traumas were associated with psychosis, collective traumas such as living in a war zone were not [54].

1.2.5 Cannabis Use

The use of cannabis represents one of the environmental factors linked to elevated risk for psychosis. Cannabis is widely used drug especially among the young population and half of the users start the consumption before the age of 18 [24]. The lifetime occurrence of cannabis use disorder in schizophrenia patients ranges from 13% to 64% [24]. Previous research revealed the association between the earlier onset of psychosis (1.8 years) and cannabis usage [23]. Usage of cannabis at critical time points of the development accelerates the risk to develop psychotic disorders. For example, in a study, using cannabis by 15 years of age had a fourfold increase in the likelihood of developing psychotic disorders, relative to individuals who used cannabis at age 18 or older [22].

1.2.6 Paternal Age

In the 1950s, advanced paternal age at conception was suggested to introduce de novo mutations, and it has since been recognized as contributor to offspring developing various diseases, including psychiatric conditions such as schizophrenia [55]. This assertion remained mainly ignored prior to the early 2000s, as studies start to provide stronger evidence linking increased paternal age with a heightened risk of psychiatric disorders in offspring [56, 57, 58]. The study showed that the risk of developing schizophrenia was the lowest for the children with ≤ 25 years of paternal age and the risk increases to 4 fold with paternal age ≥ 50 years [58]. The sharp increase for risk for paternal age ≥ 50 years old was also replicated in meta-analysis study [59].

1.3 Cognitive Deficits in relation to Psychosis and Psychotic-Like Experiences

1.3.1 Cognitive Biomarkers of Psychosis Proneness

Cognitive deficits have emerged as a key feature of psychotic disorders, together with environmental influences. Cognitive dysfunction represent a fundamental aspect of psychotic disorders, and some form of cognitive dysfunction precedes psychotic symptoms and shows liability to schizophrenia [60]. Studies indicated that generalized cognitive dysfunction are evident from the first onset of the disorder such as first-episode psychosis and continues across the psychosis spectrum independent from the clinical status and medication usage [61, 62]. For example, patients with bipolar disorder with psychosis showed significantly more cognitive deficits compared to counterparts without psychosis [63]. Retrospective studies on developmental trajectories of cognitive dysfunction revealed a divergence between patients who were diagnosed with schizophrenia and their peers at the age of 13, which was several years before the disease onset [64, 65]. Moreover, a prospective 30 years study found poor cognitive performance were present at the age of 7 and onwards for children who subsequently diagnosed with schizophrenia [66]. Such findings suggest the neurodevelopmental lag hypothesis which supports the idea that during the development, children who later develop schizophrenia

falls behind their peers because of lack of normal developmental progress.

In this context, intermediate phenotypes are crucial to understand the heritability and genetic architecture of the psychosis spectrum. Compared to the clinical construct of schizophrenia, intermediate phenotypes are characterized by higher uniformity and reduced phenotypic complexity [60]. Genes encode for molecular structures, not for particular forms of psychopathology. The progression from genetic variation to behavior requires intermediate stages, including alterations in neural circuits and biological systems [67]. In fact, variation in cognitive function accounts for 23% of the variance in liability to schizophrenia [60].

Furthermore, cognitive deficits, commonly found among healthy relatives of people with schizophrenia [68, 69, 70, 71], are considered to predate the onset of psychotic symptoms [64, 66, 65] and may have a causal influence [60, 72]. Cognitive impairments could thus act as early indicators of individuals at heightened risk for developing psychosis, even before the disorder fully manifests [73].

1.3.2 Working Memory as an Intermediate Phenotype

Intermediate phenotypes are crucial concept while explaining complex disorders such as schizophrenia. In this context, cognitive symptoms and cognitive deviations are better at explaining neural deviations related to disorders such as schizophrenia [67]. Extensive research on the prefrontal cortex, more specifically the dorsolateral prefrontal cortex (DLPFC) revealed the main function in pathological mechanisms involved in schizophrenia. Although it is not specifically linked to the positive symptoms of schizophrenia, it shows more association with cognitive symptoms such as poor judgment and poor working memory performance [74]. The prefrontal cortex receives dopaminergic inputs via mesocortical pathway which originates from the ventral tegmental area (VTA) [75, 76]. Dopamine inputs to the prefrontal cortex regulate many executive functions including working memory and any dysfunction in this projection is related to cognitive dysfunction seen in schizophrenia [76]. In fact, organization, information control in short-term memory is manipulated by PFC to create future action or thought [76]. As a result, PFC plays a bridge role between the perception and action cycle by manipulating the former memory information to generate

future-based thought or action [76].

Individuals diagnosed with schizophrenia, as well as their first-degree relatives, tend to show poor performance on tasks assessing working memory, such as n-back paradigm [77]. The reason behind the poor performance could be the reduced cost-efficiency (balancing efficiency and metabolic cost in achieving optimal brain network organization) in schizophrenia networks [78]. Performance on the n-back working memory task has been associated with elevated beta (15-30 Hz) and gamma (30-60 Hz) bands, primarily within the frontal and parietal cortices and these regions are part of the neurocognitive network for “higher-order” mental functions as working memory. Examining the function of these “higher-order” cognitive functions which are disrupted in schizophrenia will boost the power of traditional clinical assessments and may be the best candidates for the biomarkers for schizophrenia before even the mental illness fully progress to prevent earlier [79].

1.3.3 Self-Schema in relation to Psychosis Proneness

Self-schema refers to the cognitive framework that encompasses information and beliefs about the self and can also involve the interpretation of the world around them. It significantly affects how people understand their surroundings and guide their behaviour. Real-time monitoring of one’s self-perception could be influenced by both past and current experiences [80]. During adulthood, self-evaluation tends to become more rigid and trait like [81]. Psychotic disorders have frequently been associated with disruptions in self-schemas, cognitive frameworks that underlie beliefs about the self. Negative self-perceptions and self-concepts, in particular, are associated with the development of paranoid ideation [82, 83, 84], hallucinations [85, 86] and delusional thinking [87]. These cognitive patterns could also interact with environmental factors [88, 89, 90], although it remains uncertain how and in which direction this interaction unfolds. A recent study evaluated individuals with schizophrenia, their unaffected siblings and a healthy control group to examine whether self-schema served as a mediator between childhood trauma and psychotic symptoms [81]. The study found that all types of traumas were associated with negative self-schema in both the patients and their siblings [81]. Self-schema is a key factor in maintaining psychological because it

may serve as a psychological resource for coping with stressful life events during adulthood [91]. Hence, self-schema plays a crucial role in the well-being of individuals, including their vulnerability to psychosis.

1.4 Functional Imaging Markers for Psychosis Proneness

In addition to cognitive deviations, structural and functional neural deviations are also seen as potential intermediate phenotypes for vulnerability to psychosis [92]. Although brain structure and function are ideally reviewed together, the scope of this thesis will focus exclusively on potential functional neural correlates, both during task performance and at rest.

A large body of research has focused on identifying functional markers of psychosis preceding clinical onset by investigating the well-known schizophrenia-related cognitive deficits [93]. Research on individuals at clinically-high risk state (CHR), prior to the manifestation of full psychotic disorders, has revealed that only about one-third eventually transition to psychosis. Neuroimaging studies have demonstrated reduced activation in the middle frontal gyrus during verbal working memory task, while the same region shows increased activation during verbal fluency tasks in this population. Additionally, resting-state findings in CHR patients indicated disruptions in key neural networks, including the superior temporal, salience network and thalamic dysconnectivity, as well as abnormal activity in the default mode network which are features also observed in psychotic disorders [93].

The studies not only focused on the clinically high-risk groups or at-risk mental state groups but also investigate the vulnerability to psychosis by focusing on the general population who might experience PLEs. For instance, Papanastasiou et al. (2020) [94] investigated whether PLEs during adolescence are linked to changes in the activation of frontal and limbic regions within a brain network involved in facial emotion processing, a process often impaired in psychosis [94]. The study included 1,434 adolescents who were assessed at age 14 and at age 19 and groups were divided based on the CAPE-42 (the Community Assessment of Psychotic Experiences-42), a tool assesses lifetime psychotic experiences and

susceptibility to psychosis across affective and non-affective domains [95]. Overall, the results showed that adolescents with lower CAPE scores exhibited greater activation than those with higher scores in the left insula at age 14, and in the left caudate, right prefrontal, and the right parahippocampal region at age 19. Notably, the high CAPE score group showed stronger activation only in the right insula at age 14. The findings indicated the role of frontal and limbic systems in the psychosis continuum model among the samples without any clinical phenotype [94]. The study also highlighted a potentially atypical neurodevelopmental course in key limbic regions among individuals with high levels of PLEs.

1.5 Aims and Hypotheses

The main aim of this thesis is to characterize the contributing factors and pathways to psychosis proneness, as well as its neural correlates, in adolescents and young adults from the general population in order to identify targets for early intervention. While previous research has largely concentrated on the effects of isolated environmental risk factors on psychosis and their effects on mental health brain, few studies have investigated the impact of aggregated environmental risk factors on psychosis proneness. Moreover, to current knowledge no studies have examined the relationship between aggregated risk, individual risk factors and brain function during both cognitive performance and at rest in general population at critical developmental stage. To address this gap, the current thesis explores the relationship between both individual and aggregated environmental risk factors for psychosis and psychosis proneness was researched, along with the implications for possible neural correlates during task and rest states. In this respect, two different approaches were employed. The first approach, detailed in Chapter 3, involved traditional analysis to test the established aims and hypotheses. The second approach, covered in Chapters 4 and 5, was more exploratory and utilized machine learning algorithm to understand the potential pathways to and from psychosis proneness.

The scope of this thesis was based on understanding the risk factors of psychotic-like experiences during the critical developmental period by focusing on healthy young population. Focusing on healthy adolescents and young adults offers several methodological advantages in comparison to patient population.

Studying patient populations with psychosis-spectrum disorders introduces confounding factors such as lower IQ levels, which can affect working memory performance. Furthermore, patients are often prescribed anti-psychotic medications which affect dopaminergic activity in the brain which in turn can affect the brain function during working memory performance during fMRI. Therefore, assessing individuals from the general population during a sensitive neurodevelopmental window allows for better understanding of how environmental, cognitive factors contribute to psychosis proneness and changes in the brain function.

The following aims were addressed using two methodological approaches, multilevel mixed effects linear regression and data-driven approach, causal discovery analysis:

AIM 1: Identifying the effect of the aggregated and individual environmental risk factors for psychosis and schema about self and others to psychosis proneness

AIM 2: Identifying the core effect of vulnerability to psychosis to functional activity in prefrontal-parietal-striatal brain systems during working memory.

AIM 3: Identifying the core effect of vulnerability to psychosis to functional activity in prefrontal-parietal-striatal brain systems at rest.

Based on aim 1, it was primarily hypothesized that higher levels of aggregated environmental risk factors, individual environmental risk factors and more negative cognitive schemas about self and others will be associated with increased psychosis proneness. In line with aim 2, it was hypothesized that higher levels of psychosis proneness will be associated with altered functional activation in prefrontal-parietal-striatal brain regions during working memory performance. Finally, based on aim 3, it was hypothesized that higher psychosis proneness will be associated with altered functional connectivity within resting state networks. In this respect, the predictive effects of both individual and aggregated environmental risk factors, as well as cognitive schemas, on psychosis proneness were examined. In addition, potential neural correlates of the aggregated risk score and psychosis proneness were further analyzed.

Despite progress in understanding the mechanisms that underlie psychosis proneness, comprehensive assessments are lacking. To address this gap, in this thesis, two methodological approaches were used: multilevel mixed-effects linear regression (Chapter 3) and a comprehensive assessment approach covering

clinical, cognitive, environmental, and neurobiological measures by using causal discovery analysis (CDA) (Chapter 4,5). CDA, an emerging approach designed to distinguish causality from mere associations, was utilized to uncover potential causal pathways leading to psychosis proneness in the general population. In contrast to structural equation modeling (SEM), which relies on pre-established expert assumptions, CDA is primarily data-driven, though it allows for the integration of expert knowledge.

Previous research investigating psychosis proneness largely employs traditional statistical methods, which fall short of capturing potential causal factors. Furthermore, traditional methods, such as regression analysis, often require the reduction of variables, which also requires a priori human-driven hypothesis. In contrast, CDA incorporates machine learning algorithms that simultaneously facilitate the input of all relevant variables, generating causal models [96] that are challenging to achieve accurately using SEMs. CDA enables the identification of the most suitable causal network structure for a given dataset, while accounting for the presence of latent (unobserved) variables [97]. Given the data-driven nature of this approach, although connections among psychosis proneness, environmental risk, negative self-schema and neurobiological alterations were expected, no prior assumptions were made about causal direction. In both Chapter 4 and Chapter 5, CDA was employed, with a main aim of comparing task-based fMRI activation (Chapter 4) and resting-state functional connectivity (Chapter 5) in relation to psychosis proneness.

Through a combination of hypothesis-driven and data-driven analyses, this thesis aims to advance our understanding of how environmental and cognitive risk factors contribute to psychosis proneness, and how these influences are reflected in functional brain during a critical developmental period.

Chapter 2

Methods

2.1 Participants

Participants were drawn from a broader research project on brain development and psychosis, which targeted a non-clinical sample of adolescents and young twin and sibling pairs (Tubitak 1001, 119K410, PI TT). Only pairs in which both individuals provided usable MRI data, head movement below 2 mm in both translation and rotation were included. Exclusion criteria involved intellectual disability, neurological conditions, history of head trauma, loss of consciousness, any psychiatric diagnosis, use of dental braces and medical conditions such as heart disease and pregnancy. All participants were native Turkish speakers and citizens of Turkey. For those under 18 years of age, written informed consent was obtained from legal guardian, and verbal assent was provided by the child. The study received ethical approval from the Human Research Ethics Committee of Ihsan Dogramaci Bilkent University (Decision/Meeting No: 2016_08_02.01) and all procedures complied with the Helsinki Declaration. Participants were recruited through university and high school advertisements and social media platforms. Upon completion of the study, participants received compensation for their participation.

Participants included in this thesis were from the same study and were collected between April 20, 2017, and August 11, 2022. However, the total number of participants varied between the task-based fMRI study (Chapters 3 and 4) and

the resting-state fMRI study (Chapters 5) due to differences in head movement criteria and data availability.

In Chapter 3, multilevel mixed effects linear regression was applied to 194 participants. The participants ranged in age from 14 to 24, with a mean age of 19.8 (SD=2.34).

In Chapter 4, CDA was applied to the same population as in Chapter 3.

In Chapter 5, CDA was applied to find pathways to psychosis proneness with rsfMRI indices. 236 participants were included ($M = 19.68$, $SD = 2.36$).

2.2 Psychological Assessments

2.2.1 Psychosis Proneness

2.2.1.1 Community Assessment of Psychic Experiences (CAPE-42)

Psychosis proneness was assessed using the Community Assessment of Psychic Experiences (CAPE-42). CAPE-42 is a self-report instrument consisting of 42 items designed to assess lifetime psychotic experiences and vulnerability to psychosis across both affective and non-affective domains [95]. CAPE-42 assesses three types of psychotic experiences: positive, negative and depressive on frequency and distress dimensions, resulting in six subscales in total. The total score can range from 42 to 168 on both dimensions [98]. The presence of psychotic symptoms in the general population supports a dimensional view, indicating that such experiences lie on a continuum and are not always clinically significant [95]. A meta-analysis evaluating the psychometric properties of CAPE-42 confirmed its reliability and validity, particularly in younger populations, for assessing psychosis proneness [99]. CAPE-42 was used as a continuous measure, referred to as the psychosis proneness score (PPS).

2.2.1.2 SIS-R (Structured Interview for Schizotypy– revised)

The SIS-R is a semi-structured interview comprising 20 schizotypal symptoms and 11 schizotypal signs rated on a four-point scale [100, 101]. SIS-R measures schizotypal personality traits (Table 2.1). Most of the items of SIS-R are closed-ended multiple-choice questions, and SIS-R assesses mainly the frequency of each subsection and the duration of the experience. SIS-R consists of 15 global assessments, and each global assessment is rated on a Likert scale of 1 to 4 (1: Absent; 2: Mild; 3: Moderate; 4: Severe) and comprises the central scoring of the SIS-R. Meehl’s schizotypal construct is being used to construct the schizotypal traits. 11 signs of SIS-R were evaluated by three researchers. When there was disagreement among the researchers, the clinical evaluation was determined based on consensus. Additionally, SIS-R scores were categorized into two dimensional scores [102]: Positive Schizotypy and Negative Schizotypy. Positive Schizotypy calculated by the average sum scores of referential thinking, psychotic phenomena, derealization, magical ideation, illusions, and suspiciousness. Negative Schizotypy was calculated by means of social isolation, introversion, hypersensitivity, restricted affect. The following items were excluded from the negative schizotypy disturbances in associative and goal-directed thinking, poverty of speech, and eccentric behaviour because the data were unreliable.

2.2.2 Brief Core Schema Scales (BCSS)

The Brief Core Schema Scales (BCSS) [80] is a 24-item self-report questionnaire designed to assess belief about the self and others, using a five-point scale (0–4). It captures four schema dimensions, each represented by six items: Negative Self (e.g. “I am unloved”), Positive Self (e.g. “I am respected”), Negative Others (e.g. “Other people are bad”), Positive Others (e.g. “Other people are good”). Severe negative beliefs about self and others are commonly observed in individuals with chronic psychosis and have also been linked to grandiose and paranoid symptoms in non-clinical population. For every subscale the scores are Min=0, Max=24.

Table 2.1: The Structured Interview for Schizotypy-Revised (SIS-R) Schizotypal Signs

Number	Name of the Schizotypal Sign	Description
1	SOCIAL ISOLATION (lifelong)	Evaluation of social isolation during the entire life.
2	INTROVERSION	Evaluation of the extent to which an individual exhibits inward-focused or self-directed tendencies.
3	HYPERSENSITIVITY	The degree to which someone is hypersensitive.
4	REFERENTIAL THINKING (being watched)	Evaluation of the feeling that the person is being watched by others. The feeling usually comes from within.
5	REFERENTIAL THINKING (being talked about)	Evaluation of the idea that others are speaking critically about the person.
6	SUSPICIOUSNESS	General doubt and distrust toward others, involving feelings of mistrust and alertness to protect against possible harm.
7	RESTRICTED AFFECT	Assesses limitations in expressing tenderness, warmth, and affection.
8	MAGICAL IDEATION	Beliefs in implausible causal relations (e.g., special meaning in numbers, black magic), considering cultural context.
9	ILLUSIONS	Misinterpretations of external stimuli in sensory domains (e.g., visual, tactile, auditory), which must be present.
10	PSYCHOTIC SYMPTOMS	Evaluation of traits like thought blocking, insertion, extraction, or broadcasting.
11	DEREALIZATION / DEPERSONALIZATION	Feelings of unreality regarding the environment or oneself (e.g., feeling like a robot).

2.3 Environmental Assessments

Ten environmental risk factors associated with psychosis were assessed, including urbanicity, obstetric complications, cannabis consumption, use of other substances, childhood trauma, parental discord, alcohol use, experiences of discrimination, exposure to life-threatening events within the past year and, social cohesion and trust.

2.3.1 Urbanicity

Urbanicity was assessed using an amended version of the Medical Research Council sociodemographic schedule [103]. Urbanicity was determined as the "place of birth". The level of urban/rural classification was determined through an open source "European Commission Global Human Settlement (GHS)" (<https://ghsl.jrc.ec.europa.eu/ESMVisualisation.php>). GHS depicts global spatial information about the human settlement on the planet. The map is generated by using fine-scale satellite imagery with the combination data sources of population density maps and built-up areas. Urbanization levels were defined in three categories: Urban center, Urban Cluster and Rural Grid Cell (transparent/light gray). Urban center refers to a city, and is composed of adjacent 1 sq km grid cells with a population density of at least 1,500 individuals per sq km and a total population of no less than 50,000. Urban clusters, representing towns and suburbs, are formed by contiguous 1 sq km grid cells with a minimum density of 300 people per sq km and a total population of at least 5,000. Rural areas defined as grid cells with fewer than 300 inhabitants per sq km and include all other cells not part of urban centers or clusters. an urban center consists of contiguous grid cells of 1 sq km with a density of at least 1500 inhabitants per sq km and a minimum total population of 50 000. Urban cluster defines towns and suburbs and consists of contiguous grid cells of 1 sq km with a density of at least 300 inhabitants per sq km and a minimum total population of 5 000. Rural grid cells define rural areas and encapsules grid cells of 1 sq km with a density below 300 inhabitants per sq km and other grid cells outside urban clusters or centers.

2.3.2 Obstetric Complications

Obstetric complications include complications during pregnancy or delivery. Information on the obstetric and delivery complications were collected using the ERI-RAOS risk factors questionnaire [104]. Risk factors during pregnancy include the following symptoms and conditions: preeclampsia (with at least one of the following, edema, hypertension, proteinuria) and subsequent symptoms such as restlessness, altered consciousness, visual disturbances, and upper abdominal discomfort; preterm placental abruption or threatened abortion; blood incompatibility; rubella or syphilis; bleeding; and febrile infections, including viral infections like influenza.

Risk factors during birth include the following conditions: preterm rupture of fetal membranes, preterm contractions, prolonged labor, twin birth, preterm delivery, breech or abnormal presentation, forceps delivery, asphyxia due to cord entanglement, low birth weight ($< 2500\text{g}$), infections, and birth trauma. Information on complications was collected by asking either parent of the participant.

2.3.3 Cannabis and Other Drug Use

The questionnaire includes tools that assess not only cannabis use but also the use of other drugs, such as inhalants (e.g., glue, petrol, gas); crack; cocaine; amphetamines/stimulants (e.g., speed, ecstasy); sedatives (e.g., sleeping pills, valium, when not prescribed by a doctor); opioids (e.g., heroin, morphine, methadone); hallucinogens (e.g., LSD, mushrooms, PCP); ketamine; and other drugs (e.g., mephedrone, legal highs) [105]. Data on cannabis and other drug use were collected in terms of frequency, type, and duration of use [105].

2.3.4 Childhood Trauma

Childhood trauma was assessed by combining information from the following scales: Childhood Trauma Questionnaire (CTQ) [106] and abuse rating questionnaires. Abuse questionnaires consisted of ratings of sexual abuse, physical abuse, psychological abuse, and bullying. All rating questionnaires included indexes of

the perpetrator, frequency, ratings on the overall support received, and whether any official contact was processed.

2.3.4.1 Childhood Trauma Questionnaire (CTQ)

The Childhood Trauma Questionnaire (CTQ) is a self-report instrument consisting of 28 items that assess the severity of emotional abuse and neglect, physical abuse and neglect and sexual abuse [106]. Childhood emotional abuse is characterized as childhood exposure to behaviors likely to induce trauma, such as being subjected to harsh discipline or verbal insults by parents. Physical neglect refers to the failure of caregivers to provide necessary physical care, such as food or clothing. Emotional neglect is defined as the failure of caregivers to meet a child’s emotional needs, such as being unresponsive to the child’s emotional cues. The total CTQ score was calculated and based on the established cut-off scores (Table 2.2), each subscale was categorized as None, Low, Moderate, or Severe.

Table 2.2: Cut-off Points for the Subscales of the Childhood Trauma Questionnaire (CTQ)

Subscale	None	Low	Moderate	Severe
Emotional Abuse	5–8	9–12	13–15	16+
Physical Abuse	5–7	8–9	10–12	13+
Sexual Abuse	5	6–7	8–12	13+
Emotional Neglect	5–9	10–14	15–17	18+
Physical Neglect	5–7	8–9	10–12	13+

2.3.4.2 Sexual Abuse Ratings Questionnaire

Sexual Abuse Ratings Questionnaire assesses sexual acts towards a person, including intercourse, touching. During teenage years, willing contact with peers is excluded from being defined as sexual abuse. However, if any coercion or force is used, then it is included. Additionally, verbal sexual advances without physical contact are included if the perpetrator is a relative, known adult or an authority figure. Instances in which individuals are coerced into viewing sexual acts or pornography. are also included. In accordance with the EU-GEI study protocol, self-report of sexual abuse was considered valid regardless of specific age difference between the participant and perpetrator.

The Sexual Abuse Ratings questionnaire includes indices for the perpetrator (1. Both parents, 2. Mother, 3. Father, 4. Sibling, 5. Other relative, 6. Family friend, 7. Other), frequency, and severity. The tool also includes ratings for "overall support received" and "official contact" (None, Social Services, General Practitioner, Police, and other official contacts).

2.3.4.3 Physical Abuse Ratings Questionnaire

Physical abuse includes aggressive behaviors resulting in bodily harm or injury, including several physical such as harsh physical punishment and other forms of aggressive physical behavior. The questionnaire includes the same coding system as seen in sexual abuse ratings questionnaire for the perpetrator. The frequency, severity, support, and official contact are also included as indexes.

2.3.4.4 Psychological Abuse Ratings Questionnaire

Psychological Abuse Ratings Questionnaire assesses experiences of humiliation, degradation such as being exposed to spreading lies about oneself by the perpetrator or shaming oneself in public or being exposed to terrorization such as invoking fear in the subject, in a calculated way. Furthermore, deprivation of basic needs such as light, sleep or lacking company of significant others, deprivation of social contact etc. Extreme rejection and emotional blackmail are also rated as psychological abuse. The coding of severity of incidences is shown in Table 2.3.

Table 2.3: Severity Classification for the Psychological Abuse Rating Questionnaire

Severity Level	Description
NONE	No experiences of abuse, or only minimal exposure
SOME	Single abusive event or rare occurrences with low severity
MODERATE	Frequent or consistent exposure to one form of abuse (e.g., humiliation)
MARKED	Frequent or widespread exposure to multiple types of abuse (e.g., humiliation and terrorizing)

2.3.4.5 Bullying Ratings Questionnaire

Bullying is an act of repeated aggressive behavior by a peer with the intention to harm the child, including actions such as physical assault, intimidation, or repeated name-calling [13]. The Bullying Rating Questionnaire includes questions about teasing and bullying that participants may have experienced before the age of 17 from a perpetrator of similar age. Examples of incidents include the perpetrator using insulting or emotionally damaging language, mocking the participant, or assigning them hurtful labels; socially isolating the participant by ignoring them or intentionally excluding them from peer groups and activities; engaging in physical aggression such as hitting, kicking, shoving, or confining them; spreading false information or harmful rumour about them; and other hurtful behaviors.

All categories of the questionnaires were combined, and any severe level of trauma, regardless of type or scale, was considered as exposure and coded as trauma present (1). Participants with no exposure or exposures below the severe level were coded as no trauma (0).

2.3.5 Parental Discord Ratings Scale

Participants were asked about the level of argument and fighting in the family during their lifetime. The level of severity (None, Some, Moderate, Marked, Violence) was used as an indicator of the intensity of parental discord in the family (Table 2.4).

2.3.6 Alcohol Usage

Current alcohol use was measured based on the consumed alcohol more than 12 times in 12 months [107]. Participants were divided based on the ones who consume alcohol more than 12 times in the last 12 months and participants who do not.

Table 2.4: Severity Classification for the Parental Discord Rating Scale

Code	Severity	Description
0	None	No signs of conflict or tension, or only in extremely rare cases
1	Some	Occasional disagreements or signs of tension, occurring infrequently (e.g., less than once a month)
2	Moderate	Regular disputes, verbal arguments, or a consistently tense environment occurring monthly or more often; may be intense or recurrent
3	Marked	Frequent and intense verbal conflicts or arguments; additionally, a persistently tense atmosphere, such as prolonged periods of silence among household members
4	Violence	Repeated instances of physical violence between parents

2.3.7 Discrimination

The scale consists of 12 yes or no questions and participants were asked about the lifetime exposure to discrimination [108]. The total score was determined by summing up the yes answers. Summed score was used for the subsequent analysis.

2.3.8 Life-Threatening Events

Participants were asked about stressful life events within the past year before the interview. The interview included 12 yes or no questions [109]. The overall score was calculated by adding together all ‘yes’ responses.

2.3.9 Social Cohesion and Trust (SC&T)

SC&T is one of the subdomains of the Social Environment Assessment Tool (SEAT)’s subdomains, and it looks at how people feel about being part of the community [110]. Additionally, SC&T assesses whether people can be trusted and whether they are willing to help. A stronger sense of belonging and trust are indicated by higher SC&T scores.

2.3.10 Maudsley Environmental Risk Score Calculation

The aggregated environmental risk factor was calculated using a validated and recently published method known as the ‘Maudsley Environmental Risk Score’ for psychotic disorders [2].

Numerous studies examined the individual environmental risk factors such as urbanicity, urban upbringing, social adversity and their association to the heightened risk of psychosis [39, 111, 20, 26, 112, 13]. However, the combined impact of all environmental risk factors may provide a more accurate estimate of overall risk. For the Maudsley Environmental Risk Score, Vassos and colleagues (2020) included the following six environmental risk factors: minority ethnic group, urbanicity, high paternal age, obstetric complications, cannabis use and childhood adversity. Due to overlapping risk estimates among certain age groups, paternal age was categorized into three groups: under 40 (baseline), 40-50 and over 50. Obstetric complications include complications during pregnancy or delivery and because of the challenges in obtaining accurate data, in the study by Vassos et al., 2020, only birth weight was considered as the existence of the obstetric complications. The authors of the original study only opted for the birth weight [2]. However, the current study has reliable data on both obstetric and delivery complications by using the ERI-RAOS Risk Factors questionnaire [104]. Therefore, the corresponding author of the study by [2] was consulted regarding obstetric complications in our available data. Based on this, rounded ratios for each complication were calculated using formula below. The detailed odds ratios are presented in the Table A.1.

$$\text{incidence_no_risk} = \frac{\text{incidence_pop}}{(\text{RR_risk} \times \text{pRF}) + (1 - \text{pRF})}$$

$$\text{incidence_risk} = \text{incidence_no_risk} \times \text{RR_risk}$$

For cannabis usage, 70% of the population was categorized as having no or minimal use and the remaining population were split into two equal parts and they fit $\log(\text{OR}) = 0$ for the non-users, and $\log(\text{OR}) = \log(3.9) \times u$ with u taking the values of 0.25 and 0.75 for the little to moderate and the high exposure group [2]. ERS was calculated by adding up the rounded log ratios and the range was

-4.5 (lowest risk) and 13 (maximum risk).

2.4 Family Interview for Genetic Studies (FIGS)

To evaluate if participants had first-degree relatives (parents, siblings, children) affected by psychosis or schizophrenia, the structured interview FIGS was administered [113].

2.5 Psychiatric Medication Usage

Participants were asked whether they had used any psychiatric medication in their lifetime and type of medication. Since the sample was drawn from the general population and the primary aim was to examine overall exposure to psychiatric medication rather than dose-response relationships, a binary variable (ever used vs never used) was used without conversion to chlorpromazine equivalents.

2.6 Cognitive Assessments

2.6.1 Wechsler Abbreviated Scale of Intelligence — Second Edition (WASI-II)

Intelligence quotient (IQ) was quickly assessed using the Block-Design and Matrix-Reasoning subtests of the Revised Wechsler Abbreviated Scale of Intelligence (WASI-II) [114]. Block Design assesses an individual's skill in analyzing and integrating abstract visual patterns, while matrix reasoning evaluates fluid intelligence, visual-spatial reasoning, categorization, part whole comprehension, and the capacity for simultaneous and organized perceptual processing. The raw scores of the Block Design and Matrix Reasoning subscores were converted into age-adjusted scale scores. These scores were combined to calculate T scores. The sum of these T scores yielded the Perceptual Reasoning composite score.

2.6.2 Verbal Fluency

Verbal fluency was evaluated through two types of tasks: letter fluency (Turkish version) and category fluency, following standardized evaluation and scoring guidelines [115]. For phonemic fluency (letter fluency), words had to begin with a specified letter, such as ‘a’ or ‘s’. In the semantic (category) fluency task, participants were instructed to generate as many words as possible within 60 seconds that belonged to specific semantic groups, such as animals or vegetables [115].

2.7 Neuroimaging

2.7.1 MRI Apparatus

Magnetic resonance imaging was performed using a 3-Tesla Siemens Magnetom Trio MRI scanner with an echo-planar imaging (EPI) sequence to acquire both anatomical images and blood oxygen level-dependent (BOLD) functional MRI data. A 32-channel head coil delivered the radio-frequency pulses. While in the scanner, participants viewed stimuli on a 31.5” telemedicine LCD screen (1920 x 1080-pixel resolution and 59 Hz refresh rate). Stimulus presentation, response accuracy, and reaction times were conducted using neurobehavioral systems (<https://www.neurobs.com/>).

2.7.2 Structural Magnetic Resonance Imaging (sMRI)

High-resolution T1-weighted images were acquired with TE=3.02 s; RT=2.6 s; Slice number =176; slice thickness = 1 mm; flip angle= 8°, field of view =256 mm; matrix=256 *256; voxel size= 1.0 x1.0x1.0 mm in 7 min 18 s.

2.7.3 Task-based Functional Magnetic Resonance Imaging (fMRI)

Functional images were recorded with T2* weighted echo-planar imaging (EPI). The recording time was 11:42 minutes and TR = 2000 ms, TE=30 ms, tilt angle = 90 °, number of sections = 24, slice thickness: 5 mm; voxel size: 3.7 x 3.7 x 5.0 mm, FOV = 64x64 mm. All participants completed a working memory task while undergoing functional MRI acquisition.

2.7.3.1 Working Memory Paradigm

The event-related paradigm employed in this study (Figure 2.1) has previously been shown to detect changes in cortical activation and behavioral responses in both individuals with schizophrenia [77] and susceptible healthy people [116]. Among the several working memory conditions in this paradigm, the manipulation condition involving subtraction (Figure 2.2) was selected because it requires more cognitive and neuronal demand, encoding, active transformation and temporal integration of numerical information. Previous research has shown that arithmetic performance engages dopaminergic signaling in regions such as the DLPFC [77], a region that continues to undergo maturation during adolescence and young adulthood. It is especially sensitive to working memory (WM) manipulation, which is the main focus of the current fMRI analysis. While other working memory paradigms may also be considered, this specific paradigm was selected due to its task simplicity, clear separation of different cognitive phases, and well-validated behavioral and neural markers. Importantly, the task design minimizes sensory confounds by using visually simple stimuli, ensuring the activations are more likely attributable to cognitive rather than perceptual processes and motor function. Therefore, this task is well-suited for identifying neural and cognitive deviations associated with psychosis vulnerability in both clinical and at-risk populations [116]. A comprehensive description of the paradigm are provided in [77].

Briefly, six different events comprised the paradigm ((Estimate without working Memory (J), Compute/estimate without working memory (CJ), Estimate after encoding (E-RJ), Compute/estimate after encoding (E-CJ) in which subjects

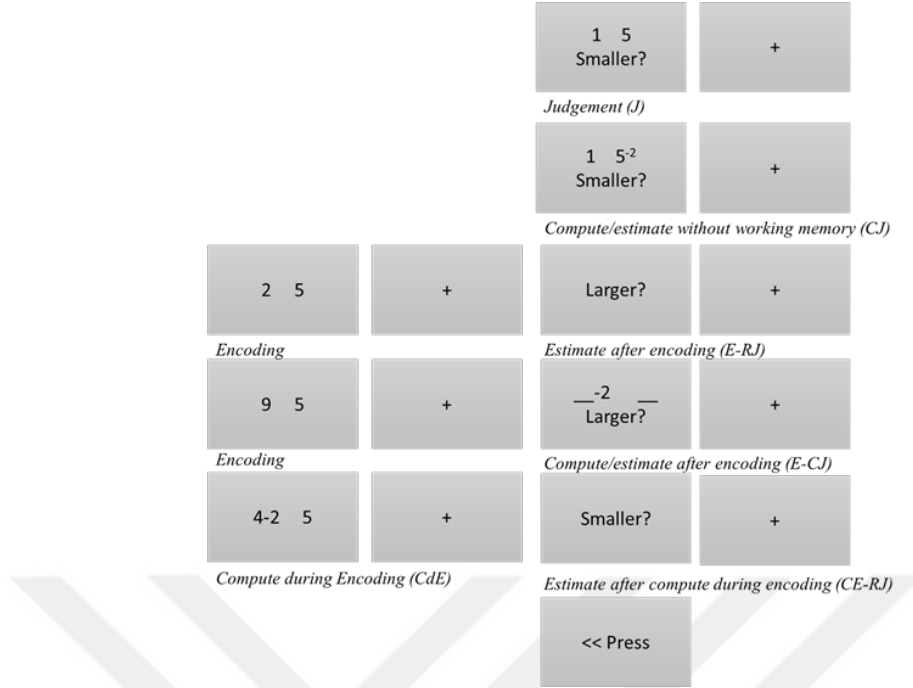


Figure 2.1: The Working Memory Paradigm

performed subtraction on the retrieved number of the indicated side in working memory, Estimate after compute during encoding (CE-RJ), Control Motor Task (M) in which participants only asked to indicate the direction of an arrow (left or right), and each event has ten trials (Figure 2.1). Two number digits were presented on the left and right side of the screen, and participants were asked to respond which side of the number was larger or smaller. Depending on the specific event, participants were asked to either judge and respond without encoding (e.g., J, CJ) or with encoding (e.g., E-CJ, E-RJ) or without subtraction (e.g., J, E-RJ) or with subtraction (e.g., CJ, E-CJ, CE-RJ) on the retrieved number. The paradigm distinguishes well between encoding and response phases. The rest interval between encoding and response phases (the working memory interval) were jittered between 3 to 6 seconds and rest interval between each consecutive task were jittered between 10 seconds to 13 seconds.

To assess working memory, with a focus on manipulation rather than encoding, results from the manipulation phase of the paradigm were analyzed further (Figure 2.2).

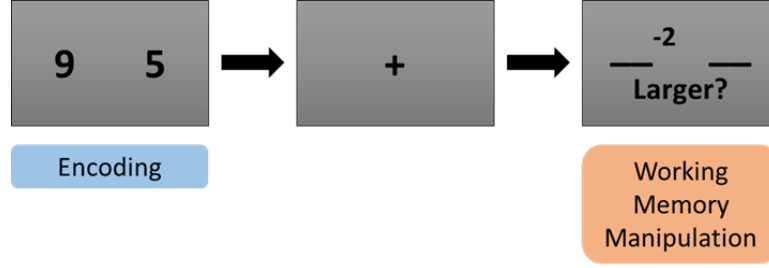


Figure 2.2: Working Memory Encoding and Manipulation. In the encoding phase, two digits appeared on the left and right sides of the screen. Participants were instructed to retain both digits and their spatial locations in working memory for a duration of 3 to 6 seconds. During the manipulation phase, they mentally subtracted from the digit on the cued side and indicated whether the resulting number was larger or smaller than the number on the opposite side. Adapted from Sahin-Ilikoglu et al., 2025 [1].

2.7.4 Resting State Functional Magnetic Resonance Imaging (rsfMRI)

rsfMRI images were collected with EPI sequence. The recording time was 5:04 minutes and $TR = 2000$ ms, $TE = 35$ ms, slices = 28, slice thickness = 3 mm, $FA = 75$, $FOV = 192$ mm, slice thickness = 3 mm, voxel size: $3 \times 3 \times 3$ mm. During the entire session, participants were asked to close their eyes and avoid falling asleep.

2.8 Data Analysis

2.8.1 Task based fMRI Preprocessing and Data Analysis

The fMRI data were preprocessed and analyzed using SPM12 (Statistical Parametric Mapping 12, Wellcome Centre for Human Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab R2017b or R2020b. The initial step involved converting DICOM files to NIFTI format. Subsequently, slice timing correction was applied, and images were realigned to the first image in the series to account for motion across three translational and rotational axes. Following coregistration, images were spatially normalized into the Montreal Neurological Institute (MNI) space using a 12-parameter affine model and resampled to a voxel size of $2 \times 2 \times 2$ mm. To enhance the signal-to-noise ratio (SNR), spatial

smoothing was conducted using an 8 mm full width at half-maximum (FWHM) Gaussian kernel. Finally, to eliminate low frequency noise, a high-pass filter with a 128 seconds cutoff was applied.

At the first level analysis, each task condition’s event onsets and duration (Figure 2.1) were convolved with a canonical hemodynamic response function (HRF) and modeled using a Generalized Linear Model (GLM) implemented in SPM12 on an individual subject basis. The GLM assessed the relationship between experimental manipulations and changes in the BOLD (blood-oxygen-level-dependent) signal, which serves as an indirect measure of neural activity [117]. Events corresponding correct and incorrect trials within each task phase of the event-related paradigm were separately modeled. Additionally, the residual movement and incorrect response parameters were modeled as regressors of no interest. A group-level (second level) analysis was conducted using a one-sample t-test on the statistical parametric maps from each individual participant. To estimate the effect of manipulating information in the working memory on activation of regions of interest, the contrast for the “Manipulation” was generated by removing the effect of “Motor task (M)” from Compute/estimate after encoding (E_CJ), resulting in the contrast

$$[E_{CJ} > M]$$

(Figure 2.1; Figure 2.2). This contrast controls for basic motor and response related processes, allowing neural activation associated with cognitive manipulation to be measured. Participants exhibiting more than 2 mm of motion in either translation or rotation were excluded from further analysis.

2.8.1.1 Regions of Interest (ROI) Analysis

Following the second-level analysis in SPM12, regions of interest (ROIs) were defined for the manipulation contrast of the task-based fMRI paradigm. The primary goal of ROI selection was to include as many informative regions possible for subsequent use in the causal discovery analysis. ROIs were selected by both theoretical interest and previously reported studies. To ensure that the selected regions were actively engaged during the task, the second-level contrast maps were overlaid onto the Human Connectome Project MMP extended Atlas, HCPex [118] using MRICron. If the specified ROIs passed a peak-level activation threshold of $p < 0.05$, with family-wise error (FEW) correction for multiple comparisons, then

they were included for further analysis. In total 16 ROIs were identified and listed in Table 2.5.

Masks for each ROI were created using MarsBar [119] implemented in SPM12. Each edge (ROI) constitutes the value derived from contrast estimates for each subject averaged over all the voxels in ROI during the manipulation phase of working memory paradigm. Average activation values during manipulation phase of the working-memory paradigm were extracted from 16 ROIs (Table 2.5). ROIs from the left hemisphere were included, while those from the right hemisphere were excluded. Focusing on one hemisphere might neglect important interactions that occur across hemispheres. However, neuroimaging studies have demonstrated that certain aspects of working memory, such as verbal manipulation tasks, often exhibit lateralization towards the left hemisphere due to its language processing functions. By restricting the analysis to the left hemisphere, the study concentrated on the neural circuits involved in language-related manipulation within working memory, thereby reducing the number of comparisons. Time course normalization to raw fMRI data was applied with z-standardization to avoid signal changes between voxels due to physical and physiological aspects of MRI scan.

Table 2.5: Regions of Interest (ROIs) for Task-Based fMRI During Working Memory

#	Hemisphere	ROI Name - HCP	BA	MNI Coordinates
1	Left	Left BA 45	BA 45	-40 22 2
2	Left	L 9-46d 173		-33 50 13
3	Left	L BA46	BA46	-34 38 30
4	Left	BA6 (L 6a 42)	BA6	-27 1 55
5	Left	L SFL		-1 10 61
6	Left	L AIP (BA40)	BA40	-40 -46 42
7	Left	L IP2		-34 -53 43
8	Left	Insula_L (L FOP4 72)		-42 12 0
9	Left	BA9 (9a 174)	BA9	-30 55 13
10	Left	L-a9-46v (176)		-38 50 10
11	Left	L-FOP4 (Frontal Operculum)		-36 16 8
12	Left	L-IFJa (Anterior Inferior Frontal Junction)		-45 14 27
13	Left	L-8C (172)	BA8	-44 19 31
14	Left	L-p47r (167)	BA47	-44 44 4
15	Left	L-a32pr (142)		-3 27 38
16	Left	L-FEF (46)		-34 -3 56

2.8.2 Resting-state fMRI (rsfMRI) Image Preprocessing

The rsfMRI data were analyzed using the SPM12 software (Statistical Parametric Mapping 12, Wellcome Centre for Human Neuroimaging, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and CONN software [120] implemented in Matlab R2020b. The initial pre-processing step involved removing the first three images from the dataset to achieve a stable magnetization state. Both anatomical and functional MRI data were preprocessed by using CONN’s default pipeline. This process included realignment to the first scan of each session, slice time correction, and detection of outlier using ART. Direct segmentation into grey matter, white matter, and CSF tissue classes and MNI- space normalization, and smoothing using spatial convolution with a Gaussian kernel of 8 mm full width half maximum (FWHM), and a band-pass filter [0.008-0.09 Hz] were applied. In addition, functional data were denoised using an anatomical component-based noise correction procedure (CompCor), and integrating noise components from cerebral white matter and cerebrospinal areas [121], estimated subject-motion parameters [122], identified outlier scans or scrubbing [123], and considering constant and first-order linear session effects [120].

2.8.2.1 Resting state fMRI (rsfMRI) Statistical Analysis

Seed based connectivity (SBC) analysis was applied to the data. Connectivity analysis was performed between the networks Default Mode Network, Sensorimotor, Visual, Salience, Dorsal Attention, Frontoparietal and Language and every voxel in the brain. SBC was performed at single subject level and group level. To extract functional connectivity (FC) indices, one sample t-test was performed in CONN toolbox. Z-standardization was performed for each functional connectivity (FC) index. Afterwards, a multilevel mixed-effects linear regression (“mixed”) model was applied in Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) to predict and subtract family-level unobservables (estimated random effects) from the original FC indices. Each network had subcomponents (e.g., Default Mode MPFC, Left DefaultMode LP, Right DefaultMode LP, etc.; See Table A.4 for details). The connectivity metrics of these network subcomponents were then averaged to derive a comprehensive

and summary statistic functional connectivity index for within network connectivity for each subject.

2.8.3 Multilevel Mixed-Effects Linear Regression

A multilevel mixed-effects linear regression (“mixed”) model was applied in Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) to predict effects on psychosis proneness and other dependent variables. Multilevel mixed-effects linear regression models contain both fixed effects (independent variables) and random effects for clusters such as members of the same family as we have in the current study (e.g., sibling pairs). The model assumes that individuals are nested in families. Independent variables were environmental risk factors such as urbanicity, cannabis and schema subscales. The p-value to indicate significance was set to $p < 0.05$. All variable distributions were checked for skewness and kurtosis. Z-standardization was conducted before the multilevel mixed-effects linear regression was applied.

2.8.4 Causal Discovery Analysis

This study employed two complementary methods for causal discovery: the Greedy Fast Causal Inference (GFCI) algorithm [97] was utilized to learn the causal structure from the data, while structural equation modeling (SEM) estimated the effect sizes for the directed edges in the partial ancestral graph (PAG) generated by GFCI. Because GFCI does not compute effect sizes, SEM was essential for quantify these associations. Together, GFCI enabled identification of the causal framework, and SEM provided numerical estimates of the causal effects, offering a thorough understanding of both structural and quantitative dimensions.

2.8.4.1 Arrangement of Variables

Variables were arranged as the following; urbanicity were divided into two categories: urban center (1) and suburb/rural areas (0); obstetric complications score were calculated into two categories; no complications (0), any complication during pregnancy or birth (1); cannabis use were divided into two categories; no

exposure in a lifetime (0), little/moderate exposure (little or a few times a year), and high exposure (a few times a month and above) (1) ; childhood trauma were divided into two categories; no childhood trauma (0), existence of trauma (1). For FIGS, participants received a score of 0 in the absence of a family history of psychosis and a score of 1 if they had a first-degree family history of psychosis. Participants who used psychiatric medication in their lifetime received a score of 1 and participants who used no psychiatric medication in their lifetime received a score of 0.

2.8.4.2 Adjusting Observed Variables for Family-Level Clustering using Linear Mixed Model

Since the sample contained family members and accounting for familial relationships was not within the aims of this thesis, adjustments were made for family-level clustering to preserve the independence of observations from family effects. A multilevel mixed-effects linear regression (“mixed”) model was applied in Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) to predict and subtract family-level unobservables (estimated random effects) from the original scores of environmental, psychological, and fMRI variables before they were introduced to CDA. Data were Z-standardized before this analysis. The residuals from the constant only model with a random intercept at the family level were included in the CDA analysis:

Example for a constant-only model with a random intercept at the family level; for example, using the `mixed` command in Stata:

```
mixed depvar || FamilyID:
```

This command fits the following equation:

$$\text{depvar}_{ij} = \beta_0 + V_j + e_{ij} \quad (2.1)$$

where:

- i – individual i ,

- j – family j ,
- V_j – family-level unobserved heterogeneity (random intercept),
- e_{ij} – individual-level random noise.

The `|| FamilyID:` notation implements a random intercept model at the family level. It assumes that there is unobserved information specific to each family (V_j), which remains constant across individuals within the same family. The random-effects model is fitted using the `mixed` command, which estimates the variance of V_j .

2.8.4.3 Causal Structure Discovery with Greedy Fast Causal Inference

In Chapter 4 and Chapter 5, data-driven causal discovery analysis was applied to examine the relationship between set of variables. In Chapter 4, the following variables were included in CDA: Age, Gender, Education in years, socioeconomic status (SES), First-degree family history of psychosis, Cannabis use, Other Drug use, Alcohol use, Psychiatric medication, IQ, Working memory reaction time, verbal fluency, obstetric complications, Urbanicity, Parental Discord, Trauma, Discrimination, Life-Threatening Events, Social Cohesion and Trust, Negative Self-Schema, Psychosis Proneness Score presented in Table 3.1 and ROIs presented in Table 2.5. A total of 37 variables were included in the CDA presented in Chapter 4. In Chapter 5, the following 24 variables were introduced in the Causal Discovery Analysis (CDA): Age, Gender, Years of Education, Socioeconomic Status, Paternal Age, First-Degree Family History of Psychosis, Cannabis Use, Other Drug Use, Alcohol Use, Psychiatric Medication, IQ, Verbal Fluency, Urbanicity, Parental Discord, Trauma, Discrimination, Life-Threatening Events, Social Cohesion and Trust, Negative Self-Schema, Psychosis Proneness Score, and six mean rsfMRI functional connectivity indices (DFMN, Fronto-Parietal, Dorsal Attention, Sensorimotor, Salience, and Visual Lateral).

CDA was conducted using the Greedy Fast Causal Inference (GFCI) algorithm [97] available in the Tetrad software (version 6.9; <https://cmu-phil.github.io/tetrad/manual/>). GFCI uses the Greedy Equivalence Search (GES) algorithm and the Fast Causal Inference (FCI) algorithm. A detailed

explanation can be found in previous work [124]. In short, it first uses GES to identify the basic structure of causal relationships, then applies FCI to detect possible error due to hidden shared influences (confounders) between variables. The GES algorithm begins its search for a Causal Bayesian Network with an empty graph, meaning no initial connections between variables. It then adds edges between variables one at a time, continuing this process until no further additions or removals enhance the model's fit to the data. GFCI then produces a graph called a PAG, which shows possible causal associations between variables. In this graph, each node corresponds to a variable and each edge reflects a potential causal connection. In the GES step, evaluation for model fit is conducted by utilizing the Bayesian Information Criterion (BIC) [125] with a penalty discount of 1 (that is, the standard BIC score). The use of BIC in this context is important, as it serves a similar purpose to multiple comparison corrections by discouraging overly complex models and helping to eliminate weaker, potentially spurious connections. The second part of the GFCI involves FCI, which begins with the undirected graph built during the earlier GES step. FCI then examines adjacent variable pairs to determine whether they are conditionally independent. If a pair is found to be independent given a specific set of other variables, the connection between them is eliminated. These evaluations rely on Fisher's Z test with an alpha threshold specified at 0.01. After pruning unnecessary connections, FCI works to determine the direction of the remaining edges by integrating both its own dependence tests and the structural information produced by GES. GFCI also identifies potential hidden (latent) variables by recognizing patterns of conditional independence when certain variables become independent given another set of variables. GFCI was used to explore possible causal pathways among psychosis proneness score, self-schema, environmental and cognitive factors, demographic variables, and fMRI indices. GFCI was applied using its default settings. This algorithm is capable of identifying potential causal links as well as hidden shared causes between variables, within the bounds of statistical equivalence and under general assumptions. The stability of the generated PAG was evaluated by applying GFCI to resamples of the original dataset, with replacement, at a 90 % resampling rate, repeated 1000 times. This resampling procedure evaluates how consistently each edge appears, treating the presence or absence of connections as binary outcomes. The proportion of times each edge is retained across resamples serves as an indicator of its stability, a method commonly used in CDA research [126].

Unlike expert-defined models (e.g., SEM), which relies on pre-established theoretical models, CDA can include all relevant variables, allowing the algorithm to uncover the most suitable model without relying on prior assumptions or reducing the variables [96]. GFCI explores causal patterns directly from the observed data, avoiding the need to explicitly model hidden variables [97]. In contrast, SEM is designed to test a specified model based on a selected subset of variables.

Although GFCI functions to explore directly from the data, operates in a purely data-driven fashion, prior knowledge such as the fact that cannabis use cannot influence a person’s biological sex, can be incorporated to help guide and improve the model fit. In Chapter 4 and Chapter 5, the same background knowledge was used. The background knowledge included four levels. The first level included age, sex, urban birth, obstetric complications, family history of psychosis and paternal age. No other variable could cause these variables, and causation to each other in the first level was forbidden. The second level included education in years and socioeconomic status. The third level included parental discord. Participants were asked to indicate the earliest period they could remember parental discord, and these periods were temporally earlier than other factors. The remaining variables were included in the fourth level. No variable in the lower hierarchy could cause a variable in the higher hierarchy.

2.8.4.4 Causal Effect Size Estimation

The SEM was fitted to the identified PAG using the R package Lavaan version 0.6.9 [127] in order to obtain standardized effect sizes for each edges observed. Directed causal links were represented by linear regressions, where the predictor (independent) variable represents the cause, and the outcome (dependent) variable represents the effect. The regression model follows the equation:

The standard linear causal model can be represented as:

$$y = X\beta + \epsilon \quad (2.2)$$

where:

- y – the effect variable,
- X – the cause variable (predictor),
- β – the standardized effect size,
- ϵ – the error term.

The causal effect size (β) reflects the expected change in the effect (y) when the cause (X) is changed by one standard deviation, while holding all other variables constant.

Edges in the Partial Ancestral Graph (PAG) correspond to these causal links, with edge weights representing the magnitude of the standardized effect size (β).

Edges labeled as $o \rightarrow$ type represent uncertain causal directions, implying that the causal discovery approach cannot definitively distinguish whether the relationship is causal, confounded, or both. This ambiguity arises due to statistical equivalence, where each of these scenarios fits the observed data equally well. Such edges were found between *Psychosis Proneness Score*, *Negative Self-Schema*, and *Social Cohesion & Trust*. Similar ambiguous edges are observed elsewhere in the Partial Ancestral Graph (PAG). In general, we instantiate the SEM for the $o \rightarrow$ and $o - o$ edges as covariances, i.e., treating these edges as confounding. However, given the central role of *Psychosis Proneness Score*, alternative models were also considered by assuming directed causal effects from *Negative Self-Schema* and *Social Cohesion & Trust* to *Psychosis Proneness Score* [128, 129, 130, 81], although the literature does not conclusively determine this direction. The model fit was assessed using the Tucker–Lewis Index (TLI) and Root Mean Square Error of Approximation (RMSEA).

Chapter 3

The Influence of Individual and Aggregate Environmental Risk Factors and Cognitive Schemas on Psychosis Proneness and Schizotypy: Implications for Neural Correlates During Working Memory

3.1 Descriptive Statistics

Demographic, environmental and psychological variables are reported in Table 3.1.

Table 3.1: Sample Characteristics

Sample Characteristics	N=194	Min	Max
Demographic Variables			
Age, mean (SD)	19.8 (2.34)	14	24
Gender: Female, n (%)	80 (40.82%)		
Gender: Male, n (%)	116 (59.18%)		
Sibling Type			
M.Z, n (%)	64 (32.9%)		
D.Z., n (%)	98 (50.52%)		
Sibling, n (%)	32 (16.9%)		
Socioeconomic Status of Parent			
Never worked / long-term unemployed	2 (1.03%)		
Routine work	4 (2.06%)		
Lower-level technical job	18 (9.28%)		
Lower-level service/sales/secretarial	14 (7.22%)		
Lower-level admin/technician	12 (6.19%)		
Self-employed	25 (12.89%)		
Small-medium business owner	12 (6.19%)		
Intermediate level	67 (34.54%)		
Middle-level manager	32 (16.49%)		
Senior manager	8 (4.12%)		
Years of Education, mean (SD)	13.89 (2.12)	9	18
Psychological Variables			
Psychosis Proneness Score, mean (SD)	74.32 (15.4)	42	122
Negative Self-Schema, mean (SD)	5.33 (4.74)	0	22
Environmental Variables			
Ethnic Minority: Turkish, n (%)	170 (87.63%)		
Ethnic Minority: Other, n (%)	24 (12.37%)		
Paternal Age < 40, n (%)	174 (89.69%)		
Paternal Age 40–50, n (%)	18 (9.28%)		
Paternal Age > 50, n (%)	2 (1.03%)		

Sample Characteristics	N=194	Min	Max
Obstetric Complications, mean (SD)	0.52 (0.98)	-0.5	2.5
Parental Discord: None, n (%)	74 (38.14%)		
Parental Discord: Some, n (%)	15 (7.73%)		
Parental Discord: Moderate, n (%)	45 (23.20%)		
Parental Discord: Marked, n (%)	42 (21.65%)		
Parental Discord: Violence, n (%)	18 (9.28%)		
Urban Birth: Urban center, n (%)	139 (71.65%)		
Urban Birth: Urban Cluster, n (%)	48 (24.74%)		
Urban Birth: Rural, n (%)	7 (3.61%)		
Childhood Trauma: Trauma, n (%)	51 (26.29%)		
Childhood Trauma: No Trauma, n (%)	143 (73.71%)		
Discrimination, mean (SD)	1.42 (1.67)	0	8
Life-threatening events (12 mo), mean (SD)	2.52 (1.9)	0	8
Social Cohesion and Trust, mean (SD)	30.1 (8.6)	0	50
Alcohol Usage > 12 drinks/year, n (%)	100 (51.55%)		
Alcohol Usage < 12 drinks/year, n (%)	94 (48.45%)		
Cannabis: No exposure, n (%)	147 (75.77%)		
Cannabis: Little/moderate, n (%)	33 (17.01%)		
Cannabis: High exposure, n (%)	14 (7.22%)		
Other Drug Use: Used, n (%)	14 (7.22%)		
Other Drug Use: Not used, n (%)	180 (92.78%)		
Psychiatric Medication: Used, n (%)	31 (15.98%)		
Psychiatric Medication: Not used, n (%)	163 (84.02%)		
Family History of Psychosis: Yes, n (%)	12 (6.19%)		
Family History of Psychosis: No, n (%)	182 (93.81%)		
Cognitive Variables			
IQ, mean (SD)	102.39 (13.65)	72	154
Working-memory reaction time, mean (SD)	0.95 (0.3)	0.19	1.92
Verbal Fluency, mean (SD)	13.09 (3.41)	4.25	24.5

Detailed descriptive statistics of scales on childhood trauma including subscales

of the Childhood Trauma Questionnaire (CTQ), abuse rating questionnaires on psychological, physical, sexual abuse and bullying are reported in Table 3.2. The distribution and the percentile rank of psychosis proneness measured by Total CAPE-42 score is reported in Table 3.3. For example, 15 participants were above the 90 % percentile out of 194 participants in total and the mean score was 96.

Table 3.2: Descriptive Statistics of Childhood Trauma Questionnaires

Scale of Trauma	Mean	Std. dev.	Min	Max
CTQ Total Score	34.48	9.35	15	71
CTQ Emotional Abuse	2.13	3.71	0	17
CTQ Physical Abuse	1.33	2.53	0	16
CTQ Physical Neglect	1.71	3.02	0	16
CTQ Emotional Neglect	3.05	5.00	0	21
CTQ Sexual Abuse	1.25	2.19	0	8
Psychological Abuse	0.66	1.03	0	3
Physical Abuse (scale)	0.33	0.71	0	3
Bullying	0.73	1.01	0	4
Sexual Abuse (scale)	0.16	0.44	0	2

Table 3.3: Distribution of Participants Based on Percentile Ranks of Psychosis Proneness Measured by Total CAPE-42 Score

Percentile	Mean Score at the Percentile	N Above the Percentile
50%	73	96
75%	85	44
90%	96	15
95%	99	9
99%	117	1

3.2 Aggregated Environmental Risk Score Predicts Psychosis Proneness

A multilevel linear mixed-effects analysis was conducted to examine whether the aggregated Environmental Risk Score (ERS) predicts psychosis proneness, with adjustments made for family-relatedness. The results are presented in Table 3.4. Results revealed that the ERS significantly predicted CAPE-42 Total Score ($z=2.50$, $p=0.012$); CAPE-42 depressive frequency ($z= 3.36$, $p=0.001$); CAPE-42 negative dimension ($z = 2.63$, $p = 0.0084$); CAPE-42 Depressive Dimension Distress Score ($z=2.88$, $p=0.004$); SIS-R total score ($z = 3.85$, $p = 0.0001$); SIS-R positive schizotypy ($z = 3.12$, $p = 0.002$); SIS-R negative schizotypy ($z = 3.16$, $p = 0.002$).

Table 3.4: Multilevel mixed-effects linear regression results predicting CAPE-42 and SIS-R subscale scores from the aggregated environmental risk score. Adjusted p-values were calculated using the Benjamini-Hochberg FDR. SE = Standard Error, CI = Confidence Interval. (* $p < .05$)

Dependent Variable	Coefficient	SE	95% CI	z-value	p-value	Adjusted p-value
CAPE-42 Total Score	1.14	0.45	[0.24–2.03]	2.50	0.012*	0.017*
CAPE-42 Negative Frequency	0.41	0.22	[-0.02–0.84]	1.85	0.065	0.081
CAPE-42 Positive Frequency	0.33	0.18	[-0.02–0.69]	1.81	0.071	0.078
CAPE-42 Depressive Frequency	0.40	0.12	[0.16–0.63]	3.36	0.001*	0.005*
CAPE-42 Negative Distress	0.20	0.07	[0.05–0.36]	2.63	0.008*	0.014*
CAPE-42 Positive Distress	0.10	0.06	[-0.01–0.23]	1.72	0.080	0.080
CAPE-42 Depressive Distress	0.22	0.07	[0.07–0.36]	2.88	0.004*	0.008*
SIS-R Total Score	0.05	0.01	[0.02–0.07]	3.85	0.0001*	0.001*
SIS-R Positive Schizotypy	0.04	0.01	[0.01–0.07]	3.12	0.002*	0.0067*
SIS-R Negative Schizotypy	0.05	0.01	[0.02–0.09]	3.16	0.002*	0.005*

The results indicated a positive relationship between the CAPE-42 total score and several subscales, suggesting that a higher aggregated ERS significantly predicts elevated CAPE-42 total score, as well as higher depressive frequency, negative dimension, and depressive dimension distress scores. The results further demonstrated a positive association between the aggregated ERS and schizotypy, indicating that higher ERS levels are associated with elevated levels of both positive and negative schizotypy, as measured by the SIS-R scores. However, the aggregated ERS did not significantly predict CAPE-42 positive frequency subscale ($z=1.81$, $p= 0.0706$); CAPE-42 negative frequency subscale ($z= 1.85$, $p= 0.065$); CAPE-42 the positive dimension distress subscale ($z= 1.72$, $p= 0.08$).

3.3 The Relationship between Individual Environmental Risk Factors and Psychosis Proneness

In addition to examining the predictive value of the aggregated environmental risk score on psychosis proneness, the relationships between individual environmental risk factors and psychosis proneness were also investigated to provide a more nuanced understanding of their contributions (Table 3.5).

Table 3.5: Multilevel mixed-effects linear regression results showing associations between individual environmental risk factors and CAPE-42 and SIS-R subscales. SE = standard errors, CI = confidence intervals, (* $p < .05$)

Dependent Variable	Coef.	SE	95% CI	z-value	p-value	adj. p-value
Paternal Age (IV)						
CAPE-42 Total Score	-0.11	0.24	[-0.6, 0.36]	-0.47	0.636	0.72
CAPE-42 Negative Frequency	0.06	0.11	[-0.17, 0.29]	0.52	0.601	0.69
CAPE-42 Positive Frequency	-0.20	0.09	[-0.39, -0.01]	-2.08	0.038*	0.12
CAPE-42 Depressive Frequency	0.02	0.06	[-0.09, 0.14]	0.41	0.685	0.74
CAPE-42 Negative Dimension Distress	0.03	0.03	[-0.04, 0.10]	0.79	0.427	0.56
CAPE-42 Positive Dimension Distress	0.002	0.031	[-0.05, 0.06]	0.09	0.926	0.94
CAPE-42 Depressive Dimension Distress	0.04	0.03	[-0.02, 0.11]	1.23	0.218	0.37
SIS-R Total Score	-0.006	0.007	[-0.01, 0.007]	-0.86	0.389	0.55
SIS-R Positive Schizotypy	-0.006	0.007	[-0.02, 0.008]	-0.85	0.393	0.54
SIS-R Negative Schizotypy	-0.007	0.009	[-0.02, 0.01]	-0.85	0.398	0.54
Obstetric Complications (IV)						
CAPE-42 Total Score	2.39	2.40	[-2.31, 7.09]	1.00	0.319	0.503

Dependent Variable	Coef.	SE	95% CI	z-value	p-value	adj. p-value
CAPE-42 Negative Frequency	1.50	1.15	[-0.71, 3.82]	1.34	0.179	0.32
CAPE-42 Positive Frequency	-0.13	0.96	[-2.02, 1.75]	-0.14	0.89	0.93
CAPE-42 Depressive Frequency	0.92	0.61	[-0.28, 2.12]	1.50	0.135	0.27
CAPE-42 Negative Dimension Distress	0.25	0.39	[-0.52, 1.04]	0.65	0.515	0.63
CAPE-42 Positive Dimension Distress	-0.006	0.32	[-0.63, 0.62]	-0.02	0.984	0.98
CAPE-42 Depressive Dimension Distress	0.26	0.39	[-0.49, 1.03]	0.69	0.491	0.61
SIS-R Total Score	0.11	0.07	[-0.02, 0.25]	1.60	0.109	0.25
SIS-R Positive Schizotypy	0.07	0.07	[-0.07, 0.22]	0.97	0.331	0.50
SIS-R Negative Schizotypy	0.23	0.09	[0.05, 0.41]	2.60	0.009*	0.045*
Urbanicity (IV)						
CAPE-42 Total Score	-8.46	2.83	[-14.02, -2.91]	-2.99	0.003*	0.03*
CAPE-42 Negative Frequency	-3.60	1.27	[-6.36, -0.96]	-2.66	0.008*	0.048*
CAPE-42 Positive Frequency	-3.44	1.13	[-5.6, -1.2]	-3.04	0.002*	0.024*
CAPE-42 Depressive Frequency	-1.15	0.71	[-2.5, 0.24]	-1.62	0.105	0.26
CAPE-42 Negative Dimension Distress	-1.17	0.40	[-2.04, -0.31]	-2.66	0.008*	0.043*
CAPE-42 Positive Dimension Distress	-0.87	0.36	[-1.59, -0.16]	-2.41	0.016*	0.064
CAPE-42 Depressive Dimension Distress	-0.64	0.44	[-1.52, 0.22]	-1.46	0.143	0.27
SIS-R Total Score	-0.08	0.08	[-0.24, 0.07]	-1.04	0.3	0.48
SIS-R Positive Schizotypy	-0.12	0.08	[-0.29, 0.03]	-1.5	0.133	0.285
SIS-R Negative Schizotypy	-0.08	0.10	[-0.29, 0.12]	-0.76	0.445	0.56
Trauma (IV)						

Dependent Variable	Coef.	SE	95% CI	z-value	p-value	adj. p-value
CAPE-42 Total Score	6.04	2.31	[1.50, 10.50]	2.61	0.009*	0.041*
CAPE-42 Negative Frequency	1.81	1.13	[-0.39, 4.03]	1.61	0.108	0.25
CAPE-42 Positive Frequency	1.98	0.91	[0.18, 3.78]	2.16	0.031*	0.10
CAPE-42 Depressive Frequency	2.33	0.62	[1.10, 3.57]	3.72	0.0002*	0.004*
CAPE-42 Negative Dimension Distress	1.40	0.40	[0.60, 2.20]	3.43	0.001*	0.015*
CAPE-42 Positive Dimension Distress	0.82	0.32	[0.19, 1.46]	2.57	0.01*	0.042*
CAPE-42 Depressive Dimension Distress	1.12	0.40	[0.32, 1.91]	2.78	0.006*	0.04*
SIS-R Total Score	0.31	0.07	[0.17, 0.45]	4.40	0*	0*
SIS-R Positive Schizotypy	0.31	0.07	[0.16, 0.46]	4.12	0*	0*
SIS-R Negative Schizotypy	0.27	0.09	[0.08, 0.46]	2.82	0.005*	0.0375*
Cannabis (IV)						
CAPE-42 Total Score	-1.63	2.70	[-6.94, 3.66]	-0.60	0.545	0.60
CAPE-42 Negative Frequency	-0.15	1.31	[-2.72, 2.41]	-0.12	0.907	0.93
CAPE-42 Positive Frequency	-0.64	1.07	[-2.76, 1.46]	-0.60	0.550	0.64
CAPE-42 Depressive Frequency	-0.83	0.70	[-2.20, 0.50]	-1.17	0.240	0.40
CAPE-42 Negative Dimension Distress	-0.09	0.45	[-0.98, 0.80]	-0.21	0.837	0.89
CAPE-42 Positive Dimension Distress	-0.16	0.36	[-0.87, 0.54]	-0.46	0.649	0.72
CAPE-42 Depressive Dimension Distress	-0.34	0.40	[-1.21, 0.53]	-0.77	0.441	0.57
SIS-R Total Score	-0.18	0.08	[-0.34, -0.02]	-2.29	0.022*	0.08
SIS-R Positive Schizotypy	-0.15	0.08	[-0.32, 0.008]	-1.86	0.063	0.19
SIS-R Negative Schizotypy	-0.09	0.10	[-0.30, 0.10]	-0.88	0.376	0.55

3.3.1 Ethnic Minority and Migration History

In the sample, 170 participants (87.63 %) were of Turkish origin or had never immigrated, while 24 participants (12.37 %) were from other ethnic group or had an immigration history.

Ethnic minority or migration history did not significantly predict psychosis proneness measured by CAPE-42 total score ($z=1.69$, $p=0.092$). Ethnic minority also did not significantly predict positive frequency subscale ($z= 1.59$, $p= 0.111$), the negative frequency subscale ($z= 1.26$, $p= 0.209$), the depressive frequency subscale ($z= 1.42$, $p= 0.157$), the positive dimension distress score ($z= 1.63$, $p= 0.104$), the negative dimension distress score ($z= 0.95$, $p= 0.341$). However, ethnic minority or migration history significantly predicted the depressive dimension distress score of CAPE-42 ($z= 2.91$, $p= 0.004$). The results suggest that the presence of ethnic minority status or a migration history predicts increased levels of distress in the depressive domain of psychosis proneness. Ethnic minority did not statistically significantly predict SIS-R scores; SIS-R total score ($z= 1.85$, $p=0.064$), positive schizotypy ($z=1.47$, $p= 0.141$), negative schizotypy ($z= 1.71$, $p=0.088$).

3.3.2 Paternal Age

The mean paternal age, age of fathers when participants were born, was 31.67 years. Advanced paternal age was identified as a potential risk factor for the development of psychosis. Multilevel mixed effects linear regression analysis, with paternal age as the independent variable and psychosis proneness as the dependent variable, showed that paternal age did not predict psychosis proneness measured by CAPE-42 total score ($z= -0.47$, $p= 0.636$), negative frequency subscale of CAPE-42 ($z= 0.52$, $p= 0.601$), depressive frequency subscale of CAPE-42 ($z= 0.41$, $p= 0.685$), positive dimension distress score of CAPE-42 ($z=0.09$, $p=0.926$), negative dimension distress score of CAPE-42 ($z= 0.79$, $p= 0.427$), depressive dimension distress score ($z= 1.23$, $p= 0.218$). Paternal age also did not significantly

predict the SIS-R scores, SIS-R total score ($z=-0.86$, $p= 0.389$), Positive Schizotypy ($z= -0.85$, $p= 0.393$), Negative Schizotypy ($z= -0.85$, $p= 0.398$). On the other hand, paternal age significantly predicted positive frequency subscale of CAPE-42 ($z= -2.08$, $p= 0.038$). A negative association was observed between paternal age and the positive frequency subscale of CAPE-42, indicating that advanced paternal age is associated with lower scores of the positive frequencies of psychotic-like experiences.

3.3.3 Obstetric Complications

Among the 194 participants, the mothers of 109 participants (56.19 %) experienced obstetric complications during pregnancy or birth, while the mothers of 85 participants (43.81 %) had no complications. The existence of obstetric complications did not significantly predict psychosis proneness measured by CAPE-42 total score ($z= 1$, $p= 0.319$), positive frequency subscale of CAPE-42 ($z= -0.14$, $p= 0.89$), negative frequency subscale of CAPE-42 ($z= 1.34$, $p= 0.179$), depressive frequency subscale of CAPE-42 ($z= 1.5$, $p= 0.135$), positive dimension distress score of CAPE-42 ($z= -0.02$, $p= 0.984$), negative dimension distress score of CAPE-42 ($z= 0.65$, $p= 0.515$), depressive dimension distress score of CAPE-42 ($z= 0.69$, $p= 0.491$). Obstetric complications did not significantly predict the following SIS-R scores; SIS-R total score ($z= 1.6$, $p= 0.109$), positive schizotypy ($z= 0.97$, $p= 0.331$). On the other hand, obstetric complications significantly predicted negative schizotypy as measured by SIS-R ($z= 2.6$, $p= 0.009$). Thus, the results indicate that, in the current sample, the prevalence of obstetric complications predicted higher levels of negative schizotypy.

3.3.4 Urbanicity

139 participants (71.65 %) were born in urban areas defined as city or town, while 55 participants (28.35 %) were born in urban clusters or rural areas. Multi-level mixed effects linear regression showed that urbanicity significantly predicted psychosis proneness measured by CAPE-42 total score ($z= -2.99$, $p= 0.003$), the positive frequency subscale of CAPE-42 ($z= -3.04$, $p= 0.002$), the negative frequency subscale of CAPE-42 ($z= -2.66$, $p= 0.008$), the positive dimension distress

score of CAPE-42 ($z = -2.41$, $p = 0.016$), the negative dimension distress score of CAPE-42 ($z = -2.66$, $p = 0.008$). The result suggests that being born in rural areas of Turkey significantly predicts higher levels of total and positive and negative dimension scores of CAPE-42 to measure psychosis proneness. Urbanicity did not statistically significantly predict the following subscales: the depressive frequency subscale of CAPE-42 ($z = -1.62$, $p = 0.105$) and the depressive dimension distress score of CAPE-42 ($z = -1.46$, $p = 0.143$). The results suggest that urbanicity did not significantly predict the depressive dimension frequency or the distress associated with these psychotic-like experiences. Urbanicity also did not significantly predict SIS-R scores; SIS-R total score ($z = -1.04$, $p = 0.3$), positive schizotypy ($z = -1.5$, $p = 0.133$), negative schizotypy ($z = -0.76$, $p = 0.445$).

3.3.5 Childhood Trauma

Childhood trauma was defined as the presence of any trauma experienced at a severe level, whereas any reported exposure to trauma below this threshold was categorized as “no trauma”. In the sample, 51 participants (26.29 %) experienced severe level of any type of trauma (psychological, physical, sexual, physical neglect, psychological neglect, bullying), 143 participants (73.71 %) did not experience trauma. Multilevel mixed effects linear regression analysis showed that exposure to severe level of trauma significantly predicted higher levels of psychosis proneness measured by CAPE-42 total score ($z = 2.61$, $p = 0.009$), positive frequency subscale of CAPE-42 ($z = 2.16$, $p = 0.031$), depressive frequency subscale of CAPE-42 ($z = 3.72$, $p = 0.0002$), positive dimension distress score of CAPE-42 ($z = 2.57$, $p = 0.01$), negative dimension distress score of CAPE-42 ($z = 3.43$, $p = 0.001$), depressive dimension distress score of CAPE-42 ($z = 2.78$, $p = 0.006$). Trauma also significantly predicted psychosis proneness measured by SIS-R scores; SIS-R total score ($z = 4.4$, $p = 0.0000$), positive schizotypy ($z = 4.12$, $p = 0.0000$), negative schizotypy ($z = 2.82$, $p = 0.005$). Trauma did not significantly predict negative frequency subscale of CAPE-42 ($z = 1.61$, $p = 0.108$). The results indicate that exposure to childhood trauma is a significant and strong predictor of psychotic-like experiences and schizotypy, except for the negative frequency subscale.

3.3.6 Cannabis Use

47 participants (24.23 %) used cannabis little or a few times a year or a few times a month and above in their lifetime and 147 participants (75.77 %) never had any exposure to cannabis in their lifetime. Multilevel mixed effects linear regression result showed that using cannabis did not significantly predict psychosis proneness measured by CAPE-42 scores; total CAPE-42 score ($z = -0.6$, $p = 0.545$), positive frequency subscale of CAPE-42 ($z = -0.6$, $p = 0.55$), negative frequency subscale of CAPE-42 ($z = -0.12$, $p = 0.907$), depressive frequency subscale of CAPE-42 ($z = -1.17$, $p = 0.24$), positive dimension distress score of CAPE-42 ($z = -0.46$, $p = 0.649$), negative dimension distress score of CAPE-42 ($z = -0.21$, $p = 0.837$), depressive dimension distress score of CAPE-42 ($z = -0.77$, $p = 0.441$). Cannabis use only significantly predicted SIS-R total score ($z = -2.29$, $p = 0.022$), suggesting that usage of cannabis predicts lower levels of SIS-R total score. However, cannabis use did not significantly predict positive schizotypy ($z = -1.86$, $p = 0.063$), and negative schizotypy ($z = -0.88$, $p = 0.376$). These findings suggest that while cannabis use is associated with overall schizotypy, it does not appear to predict the specific dimensions of psychotic-like experiences as measured by the CAPE-42.

3.4 Schema about Self and Others Predicts Psychosis Proneness

The relationship between negative self-schema and psychosis proneness was explored by multilevel linear mixed effects regression model (Table 3.6). The results showed that negative self-schema significantly predicted psychosis proneness measured by Total CAPE-42 score ($z = 9.29$, $p < .001$), positive frequency subscale of CAPE-42 ($z = 5.67$, $p = 0.0000$), negative frequency subscale of CAPE-42 ($z = 7.02$, $p = 0.0000$), depressive frequency subscale of CAPE-42 ($z = 10.63$, $p = 0.0000$), positive dimension distress score of CAPE-42 ($z = 5.81$, $p = 0.0000$), negative dimension distress score of CAPE-42 ($z = 6.01$, $p = 0.0000$), depressive dimension distress score of CAPE-42 ($z = 7.11$, $p = 0.0000$). Negative Self-Schema also significantly predicted SIS-R scores; SIS-R total score ($z = 8.53$, $p = 0.0000$), positive schizotypy ($z = 7.77$, $p = 0.0000$), negative schizotypy ($z = 7.78$, $p = 0.0000$). The

results showed that increased levels of negative self-schema significantly predicted higher levels of psychosis proneness and schizotypy.

Table 3.6: Multilevel mixed-effects linear regression results showing associations between schema about self/others and CAPE-42 and SIS-R subscales. SE = standard errors, CI = confidence intervals, $*p < .05$

Dependent Variable	Coefficient	SE	95% CI	z-value	p-value	adj p-value
Negative Self-Schema						
CAPE-42 Total Score	1.60	0.17	[1.31, 2.01]	9.29	0.0010	0.0016
CAPE-42 Negative Frequency	0.65	0.09	[0.47, 0.84]	7.02	0.0000	0.0000
CAPE-42 Positive Frequency	0.40	0.07	[0.29, 0.59]	5.67	0.0000	0.0000
CAPE-42 Depressive Frequency	0.50	0.04	[0.41, 0.60]	10.63	0.0000	0.0000
CAPE-42 Negative Dimension Distress	0.21	0.03	[0.14, 0.28]	6.01	0.0000	0.0000
CAPE-42 Positive Dimension Distress	0.16	0.02	[0.10, 0.20]	5.81	0.0000	0.0000
CAPE-42 Depressive Dimension Distress	0.24	0.03	[0.17, 0.30]	7.11	0.0000	0.0000
SIS-R Total Score	0.04	0.005	[0.03, 0.06]	8.53	0.0000	0.0000
SIS-R Positive Schizotypy	0.04	0.006	[0.03, 0.06]	7.77	0.0000	0.0000
SIS-R Negative Schizotypy	0.06	0.008	[0.04, 0.07]	7.78	0.0000	0.0000
Negative Others-Schema						
CAPE-42 Total Score	1.32	0.19	[0.94, 1.70]	6.91	0.0010	0.0015
CAPE-42 Negative Frequency	0.46	0.09	[0.27, 0.65]	4.75	0.0000	0.0000
CAPE-42 Positive Frequency	0.46	0.07	[0.31, 0.61]	5.96	0.0000	0.0000

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Table 3.6 – continued from previous page

Dependent Variable	Coefficient	SE	95% CI	z-value	p-value	adj p-value
CAPE-42 Depressive Frequency	0.33	0.05	[0.23, 0.44]	6.42	0.0000	0.0000
CAPE-42 Negative Dimension Distress	0.13	0.03	[0.06, 0.20]	3.68	0.0002	0.0004
CAPE-42 Positive Dimension Distress	0.13	0.02	[0.07, 0.18]	4.65	0.0000	0.0000
CAPE-42 Depressive Dimension Distress	0.17	0.03	[0.10, 0.23]	4.94	0.0000	0.0000
SIS-R Total Score	0.02	0.006	[0.01, 0.04]	4.55	0.0000	0.0000
SIS-R Positive Schizotypy	0.02	0.006	[0.01, 0.03]	3.82	0.0001	0.0002
SIS-R Negative Schizotypy	0.04	0.008	[0.02, 0.05]	4.88	0.0000	0.0000
Positive Self-Schema						
CAPE-42 Total Score	-0.65	0.17	[-0.99, -0.31]	-3.81	0.0001	0.0002
CAPE-42 Negative Frequency	-0.31	0.08	[-0.47, -0.14]	-3.71	0.0002	0.0003
CAPE-42 Positive Frequency	-0.10	0.07	[-0.23, 0.03]	-1.43	0.1534	0.1615
CAPE-42 Depressive Frequency	-0.21	0.04	[-0.30, -0.11]	-4.45	0.0000	0.0000
CAPE-42 Negative Dimension Distress	-0.06	0.03	[-0.12, -0.001]	-2.02	0.0438*	0.0515
CAPE-42 Positive Dimension Distress	-0.04	0.02	[-0.09, -0.0007]	-1.99	0.0468*	0.0535
CAPE-42 Depressive Dimension Distress	-0.09	0.03	[-0.15, -0.03]	-2.97	0.0030	0.0043
SIS-R Total Score	-0.02	0.005	[-0.03, -0.01]	-4.90	0.0000	0.0000
SIS-R Positive Schizotypy	-0.02	0.005	[-0.03, -0.009]	-3.57	0.0004	0.0007

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Table 3.6 – continued from previous page

Dependent Variable	Coefficient	SE	95% CI	z-value	p-value	adj p-value
SIS-R Negative Schizotypy	-0.03	0.007	[-0.04, -0.01]	-4.65	0.0000	0.0000
Positive Others-Schema						
CAPE-42 Total Score	-0.58	0.23	[-1.04, -0.12]	-2.51	0.0120	0.0155
CAPE-42 Negative Frequency	-0.21	0.11	[-0.43, 0.009]	-1.88	0.0610	0.0678
CAPE-42 Positive Frequency	-0.23	0.09	[-0.41, -0.05]	-2.51	0.0121	0.0151
CAPE-42 Depressive Frequency	-0.13	0.06	[-0.26, -0.006]	-2.06	0.0394	0.0478
CAPE-42 Negative Dimension Distress	-0.04	0.04	[-0.13, 0.03]	-1.05	0.2935	0.3010
CAPE-42 Positive Dimension Distress	-0.03	0.03	[-0.09, 0.03]	-0.96	0.3358	0.3358
CAPE-42 Depressive Dimension Distress	-0.06	0.04	[-0.14, 0.01]	-1.52	0.1289	0.1394
SIS-R Total Score	-0.02	0.007	[-0.03, -0.01]	-3.39	0.0010	0.0015
SIS-R Positive Schizotypy	-0.02	0.008	[-0.03, -0.005]	-2.68	0.0074	0.0099
SIS-R Negative Schizotypy	-0.02	0.010	[-0.04, -0.009]	-2.88	0.0040	0.0055

The relationship between negative others-schema and psychosis proneness was further examined. The results showed that negative others-schema significantly predicted psychosis proneness measured by total CAPE-42 score ($z = 6.91$, $p < .001$), positive frequency subscale of CAPE-42 ($z = 5.96$, $p = 0.0000$), negative frequency subscale of CAPE-42 ($z = 4.75$, $p = 0.0000$), depressive frequency subscale of CAPE-42 ($z = 6.42$, $p = 0.0000$), positive dimension distress score of CAPE-42 ($z = 4.65$, $p = 0.0000$), negative dimension distress score of CAPE-42

($z = 3.68$, $p = 0.0002$), depressive dimension distress score of CAPE-42 ($z = 4.94$, $p = 0.0000$). Negative schema about others also significantly predicted SIS-R scores; SIS-R total score ($z = 4.55$, $p = 0.0000$), positive schizotypy ($z = 3.82$, $p = 0.0001$), negative schizotypy ($z = 4.88$, $p = 0.0000$). The findings revealed that increased levels of negative others-schema were significant predictors of increased psychosis proneness and schizotypy.

Positive sub-scores of Brief Core Schema Scale and Psychosis Proneness were also analyzed by mixed effects linear regression model. Positive Self-Schema significantly predicted psychosis proneness measured by total CAPE-42 score ($z = -3.81$, $p = 0.0001$), negative frequency subscale of CAPE-42 ($z = -3.71$, $p = 0.0002$), depressive frequency subscale of CAPE-42 ($z = -4.45$, $p = 0.0000$), positive dimension distress score of CAPE-42 ($z = -1.99$, $p = 0.0468$), negative dimension distress score of CAPE-42 ($z = -2.02$, $p = 0.0438$), depressive dimension distress score of CAPE-42 ($z = -2.97$, $p = 0.003$). Positive self-schema also significantly predicted SIS-R scores; SIS-R total score ($z = -4.9$, $p = 0.0000$), positive schizotypy ($z = -3.57$, $p = 0.0004$), negative schizotypy ($z = -4.65$, $p = 0.0000$). Positive self-schema did not significantly predict psychosis proneness measured by positive frequency subscale of CAPE-42 ($z = -1.43$, $p = 0.1534$). Findings showed that increased levels of positive self-schema significantly predicted decreased psychosis proneness and schizotypy.

Positive schema about others significantly predicted psychosis proneness measured by total CAPE-42 score ($z = -2.51$, $p = 0.012$), positive frequency subscale of CAPE-42 ($z = -2.51$, $p = 0.0121$), depressive frequency subscale of CAPE-42 ($z = -2.06$, $p = 0.0394$). However, positive schema about others did not significantly predict the following scores of CAPE-42: negative frequency subscale of CAPE-42 ($z = -1.88$, $p = 0.061$), positive dimension distress score of CAPE-42 ($z = -0.96$, $p = 0.3358$), negative dimension distress score of CAPE-42 ($z = -1.05$, $p = 0.2935$), depressive dimension distress score of CAPE-42 ($z = -1.52$, $p = 0.1289$). In addition, positive self-schema about others significantly predicted SIS-R scores; SIS-R total score ($z = -3.39$, $p = 0.001$), positive schizotypy ($z = -2.68$, $p = 0.0074$), negative schizotypy ($z = -2.88$, $p = 0.004$). The findings revealed that higher levels of positive others-schema significantly predicted reduced positive and depressive frequencies of psychotic-like experiences, as well as lower levels of schizotypy.

3.5 Negative Self-Schema Predicts VLPFC Activation during Working Memory

A slightly significant effect of negative self-schema on the left ventrolateral prefrontal cortex (VLPFC; p47r) ($z=2.01$, $p=0.044$) was found. VLPFC is known to be involved in language comprehension such as linguistically complex words [131] and in the cognitive control of memory such as controlled retrieval [132, 133].

3.6 Discussion and Conclusions

In this chapter, the aggregated environmental risk score, individual environmental risk factors for psychosis, and cognitive schemas about self and others were separately introduced into regression models to assess their power to predict psychosis proneness, as measured by the CAPE-42, and schizotypy, as measured by the SIS-R. Interpretation of the current results should be approached with caution, as the majority of existing literature centers on environmental risk factors and their association with schizophrenia rather than psychosis proneness or other related constructs. Notably, the sample in this thesis does not include individuals diagnosed with schizophrenia or any other psychosis-related disorders. Consequently, these results should be interpreted in the context of this limitation.

The current results suggest that increased aggregated ERS predicts increased psychotic-like experiences in different dimensions including depressive frequency, depressive and negative dimension distress and negative and positive schizotypy. On the other hand, aggregated ERS did not significantly predict positive and negative frequency and positive distress, suggesting that specific symptom dimensions within the psychosis-proneness spectrum may be differentially sensitive to environmental risk factors. These findings underscore the nuanced relationship between aggregated environmental risk and psychosis proneness, with certain symptom dimensions, such as depressive and negative symptoms, showing stronger associations with environmental risk. Further research could investigate underlying mechanisms linking aggregated environmental risk and specific psychosis proneness dimensions to clarify these differential associations and potential mediating factors.

Ethnic minority or migration status was found to significantly predict only the depressive dimension distress score of the CAPE-42. No significant associations were observed for the other subscales of the CAPE-42 or the SIS-R. The distress scores of the CAPE-42 measure the level of distress participants experience in response to the items on the positive, negative and depressive dimension. For instance, the items for the depressive dimension include: “Do you ever feel sad?”, “Do you ever feel pessimistic about everything?”, “Do you ever feel as if there is no future for you?”. Thus, ethnic minority status or migration status significantly predicts increased distress caused by the depressive items mentioned above. Previous studies found that ethnic minority leads to higher levels of psychotic-like experiences or schizotypy [134]. People with ethnic minority position may be exposed to increased social defeat and social stressors, thereby likely to lead to a higher risk to develop psychiatric conditions such as psychotic disorders [134, 135]. It should be noted that 24 participants in this sample had ethnic minority status or a migration history, which represents a small group and comprises only 12 families. It appears that the depressive dimension distress score of the CAPE-42 was particularly sensitive in capturing depressive experiences that were differentially expressed in the ethnic minority group in Türkiye compared to the other subscales. Furthermore, the ethnic minority group in Türkiye might more commonly report distress from experiencing depressive symptoms, whereas other symptoms, such as positive or negative symptoms, may be under-reported or less likely to be experienced. However, a sample size with larger ethnic minority group in Türkiye is required to confirm the validity of the current results. Although there is strong evidence for ethnic minority position or migration to have a stronger risk of developing psychosis-related disorders, the effect in the general population with psychotic-like experiences is not very clear. Furthermore, age and minority status are important factors while observing the effect of ethnic minority on psychotic-like experiences. For example, a previous study that conducted a meta-analysis showed that the risk existed for the adult population but not for children and adolescents, and that subgroups of ethnic minorities showed varying results [136]. Research on minority subgroups in Türkiye and their effect on psychosis proneness with a larger sample size is required. The current findings indicate that while ethnicity and migration history are not major predictors of general psychosis proneness or schizotypal traits, there is a specific vulnerability among ethnic minorities regarding depressive-related distress. This highlights the importance of considering culturally and socially specific factors, such as stressors

linked to minority status or migration, when assessing mental health outcomes. Further research could explore why depressive distress specifically shows this association.

Paternal age significantly predicted only the positive frequency subscale of the CAPE-42 score, showing that as paternal age increased, lower levels of positive frequency symptoms on the CAPE-42 were observed. Although paternal age at conception has been introduced as a risk factor [58], the current results did not show any significant predictions apart from the reversed relationship for the positive frequency subscale of the CAPE-42. This finding is not in line with previous research, and several reasons could explain this discrepancy. Initially, the mean paternal age of the current sample is 31.67 years. The reason behind this controversial finding could be the no prevalence of paternal age > 50 years in the current sample. Previous studies found a dose-response-like association between paternal age at conception and the risk for schizophrenia, showing that offspring of fathers aged 50 and older have approximately a 190 % greater risk of developing schizophrenia compared to those born to fathers aged 20 to 24 [58]. Secondly, the theory behind the high paternal age and increased risk for schizophrenia for the offspring is the possible mutations in sperm germ line [137]. However, in the current sample, the absence of fathers in the older age range prevents drawing firm conclusions about the expression of protective genetic factors in older fathers. Thirdly, sociocultural and environmental factors may play a role in this finding that older fathers may provide more resources and a stable environment for their offspring and mitigate other risk factors for psychosis. In fact, higher paternal age significantly predicted higher levels of socioeconomic status of the father ($z=3.12$, $p=0.002$). Fourthly, biological aging is another factor which could show differences to chronological age. Future research involving genetic, epigenetic and more detailed environmental factors is necessary to draw more firm conclusions.

Obstetric complications are well-known risk factors for an increased likelihood of developing schizophrenia later in life [138]. Although individual obstetric complications have demonstrated heterogeneous effects across studies, obstetric complications as a whole exhibit a modest yet consistent association with schizophrenia and other psychosis-related psychiatric conditions [14]. Meta analysis on obstetric complications found that people exposed to obstetric complications have twice as high risk to develop schizophrenia [139]. It was reported that obstetric complications disrupt neuronal development and cognitive abilities, ultimately

leading to a higher risk of developing schizophrenia later in life [140, 141]. However, obstetric complications alone may act as an additive factor, contributing to the risk of conversion to psychosis when combined with other risk factors [14, 33]. In the current sample, obstetric complications significantly predicted negative schizotypy, as measured by the SIS-R. No significant relationship was observed for the remaining subscales which measured psychosis proneness. Since the current study included twins, low birth weight was not included in the obstetric complications risk score due to its high prevalence in twin samples. Therefore, the lack of a relationship between obstetric complications and the scales of CAPE-42 and SIS-R, aside from negative schizotypy, could be explained by the exclusion of low birth weight from the analysis. In the current thesis, negative schizotypy was characterized by the mean scores of social isolation, introversion, hypersensitivity, and restricted affect. The results suggest that subjects exposed to obstetric complications are at a higher risk of experiencing negative schizotypy, including social isolation, introversion, hypersensitivity, and restricted affect, later in life.

One particularly intriguing and distinct finding of the current study regarding environmental risk scores for psychosis, in comparison to the existing literature, relates to the role of urbanicity. Most studies on urbanicity and its relationship with the risk of developing psychosis have originated in western countries, while very few have been conducted in Türkiye [46, 47]. Studies conducted in European and western countries have shown that urbanization is one of the well-established risk factors for psychosis [20, 21]. In contrast, the results of the current study suggest that being born in rural areas poses a greater risk for psychosis proneness compared to being born in an urban environment. All subscales of CAPE-42 besides the depressive frequency and depressive dimension distress scores had predicted that being born in the rural area actually significantly predicted higher levels of total, positive and negative dimension scores of psychosis proneness. The results also suggest that urbanicity did not show significant prediction power on depressive dimensions of psychosis proneness. In fact, Binbay et al. [47] found no association between urbanicity, defined as urban birth or current urban living, and higher rates of schizophrenia incidence in Türkiye. Earlier studies even reported higher incidences of schizophrenia in rural areas in Türkiye, although the difference between urban and rural areas was not significant [142].

Exposure to childhood trauma was one of the best predictors of psychosis. In the current study, except for the negative frequency subscale of the CAPE-42,

exposure to childhood trauma predicted all CAPE-42 and SIS-R scores. While earlier studies have identified childhood trauma as one of the strongest predictors of psychosis risk, the findings of the current study demonstrate that it is also a significant predictor of psychosis proneness. These findings collectively support the theory of psychosis as a continuum and highlight the presence of shared risk factors. In the current study, childhood trauma did not predict the frequency of negative symptoms, but it did predict the distress associated with experiencing these negative psychotic-like experiences. The negative symptoms frequency items measured a range of factors, including experiencing limited or no emotion, losing interest in others, lack of motivation, low energy, reduced engagement in daily activities, and neglecting personal hygiene. Childhood trauma is an umbrella term encompassing various types of trauma including physical, sexual, and psychological abuse. In the current study, all types of childhood trauma were combined and analyzed as a single entity. This approach allowed for capturing general exposure while avoiding overcomplication of statistical tests, as trauma was one of several risk factors examined. Consequently, the specific effects of individual types of childhood trauma on psychosis proneness were not investigated. However, the effects of each trauma type may have differing effects on the risk of psychosis [143]. For instance, psychological trauma itself diverges, as it may include forms ranging from verbal abuse to emotional neglect. Moreover, the co-occurrence of multiple trauma types can amplify their overall impact, leading to more severe psychopathology. A child's perception of the world begins to take shape within the family environment, where various forms of abuse, whether direct or indirect, play a critical role in shaping their understanding of themselves and the world around them. These experiences also impact neurobiological development, which can subsequently lead to a sense of insecurity and psychopathology including psychosis later in life [52, 144]. Therefore, each type of childhood trauma in fact should be examined separately to see their unique roles in shaping the child's future self and environment. Indeed, there are studies who included different types of childhood trauma to the aggregate risk score [33]. Future studies can examine the effects of different types of childhood trauma on psychosis proneness in the general population.

Cannabis use is one of the most widely used drugs and it is also one of the well-known risk factors of psychosis. Studies have shown varying results regarding cannabis use, with some identifying it as a causal factor in some cases and others demonstrating a two-fold increase in the risk of schizophrenia associated with a

history of cannabis use [145]. Nevertheless, most individuals who use cannabis do not necessarily develop a psychotic disorder [145]. In the current sample, cannabis use significantly predicted the SIS-R total score suggesting that usage of cannabis predicts lower levels of SIS-R total score. This finding suggests an inverse relationship between cannabis use and general schizotypy in the current sample. This finding contradicts previous studies and either may reflect that the current sample possesses unique characteristics or could be due to a chance. Cannabis use also did not significantly predict any of the CAPE-42 subscales, suggesting that the association between cannabis use and specific dimensions of psychotic-like experiences observed in other studies was not evident here. One potential reason for the lack of association observed between cannabis use and psychosis proneness could be the low frequency of use among participants. In our sample, individuals who reported only a few experimental instances of cannabis use were also categorized as users. The current results are not consistent with previous findings. Therefore, replication of the current results with larger sample size would be beneficial to have a firm conclusions.

Multilevel mixed-effects linear regression analysis provided valuable insights into how the aggregated risk score, individual risk factors, and schemas about the self and others predict psychosis proneness. We were only able to incorporate available data primarily consisting of environmental risk factors and schema types to predict psychosis proneness. However, genetic risk, which is commonly assessed through polygenic risk score for schizophrenia, was not included in the current study. Future research should incorporate genetic risk scores and gene environment interactions to provide a more comprehensive understanding of the predictors of psychosis proneness. Despite the significant predictions obtained through multilevel mixed-effects linear regression, the directionality of the relationships remains unclear. Therefore, to explore the directionality of these relationships, which is crucial for prevention purposes, a novel method called causal discovery analysis (CDA) was applied in the next chapter (Chapter 4).

Chapter 4

Causal Discovery Analysis Reveals Insights Into Psychosis Proneness, Brain Function, and Environmental Factors Among Young Individuals

The studies and results presented in this chapter are based on a publication by Sahin-Ilikoglu, T., Ma, S., Kummerfeld, E., Rawls, E., Tan H. Y. & Touloupoulou T. (2025). Causal discovery analysis reveals insights into psychosis proneness, brain function, and environmental factors among young individuals. *Psychiatry Research: Neuroimaging*, 351, 112015. doi:<https://doi.org/10.1016/j.psychresns.2025.112015> [1].

4.1 Sample Characteristics

Demographic, environmental and psychological variables are reported in Table 3.1, Table 3.2 and Table 3.3 in Chapter 3.

4.2 Causal Discovery Analysis

The GFCI algorithm was applied to develop a model for psychosis proneness score (PPS) incorporating variables across several domains: four sociodemographic , seven environmental , two psychological variables, including the psychosis proneness , three cognitive , four drug usage related variables, and a family history of psychosis , and 16 ROI based fMRI indices during the manipulation of information in working memory (Fig 2.2). The model output (PAG) of GFCI, including the effect sizes and statistical significance levels, is shown in Figure 4.1 and Figure 4.2.

The SEM demonstrated a good fit, with RMSEA= 0.052, Tucker-Lewis Index = 0.833. Figure 4.2 displays effect sizes adjacent to their respective arrows. All but four paths reached statistical significance at $p < .05$, with 39 of 57 being significant at $p < .01$ (Figure 4.2, Table 4.1). Unadjusted p-values were reported in the graph, in line with standard practice. Results from the Benjamini Hochberg procedure, presented in Table 4.1, show that 53 out of 57 paths remained significant at the $p < .05$ threshold after FDR correction. Notably, the correction did not change the overall significance pattern.

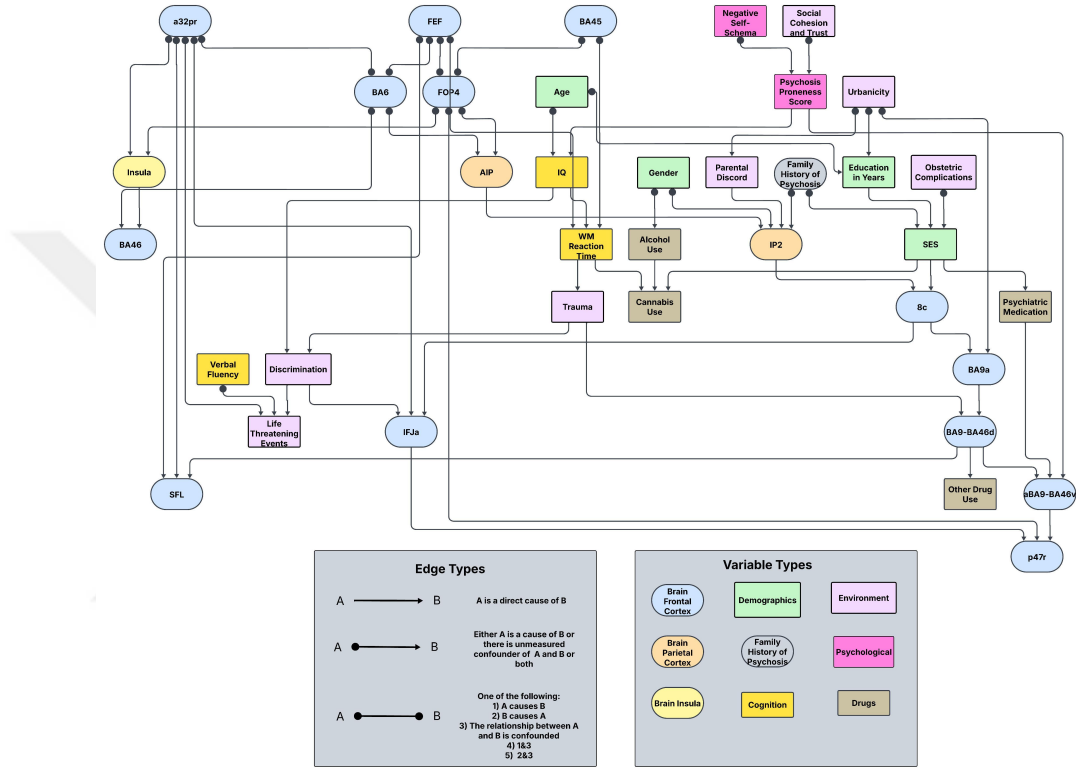


Figure 4.1: Causal Discovery Analysis for all variables and Manipulation phase of the Working Memory Paradigm. Causal Discovery Analysis was performed using GFCI for activations in ROIs when manipulating information during fMRI, environmental and psychological variables. (B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus; I.P.: Intraparietal Sulcus; a9-46v: frontal mid; FOP4: frontal operculum; IFJa: anterior inferior frontal gyrus; p47r: the orbital prefrontal cortex; a32pr: refers to a narrow strip of the anterior midcingulate cortex; FEF: frontal eye fields; SES: socioeconomic status; W.M.: working memory). Adapted from Sahin-Ilikoglu et al., 2025 [1].

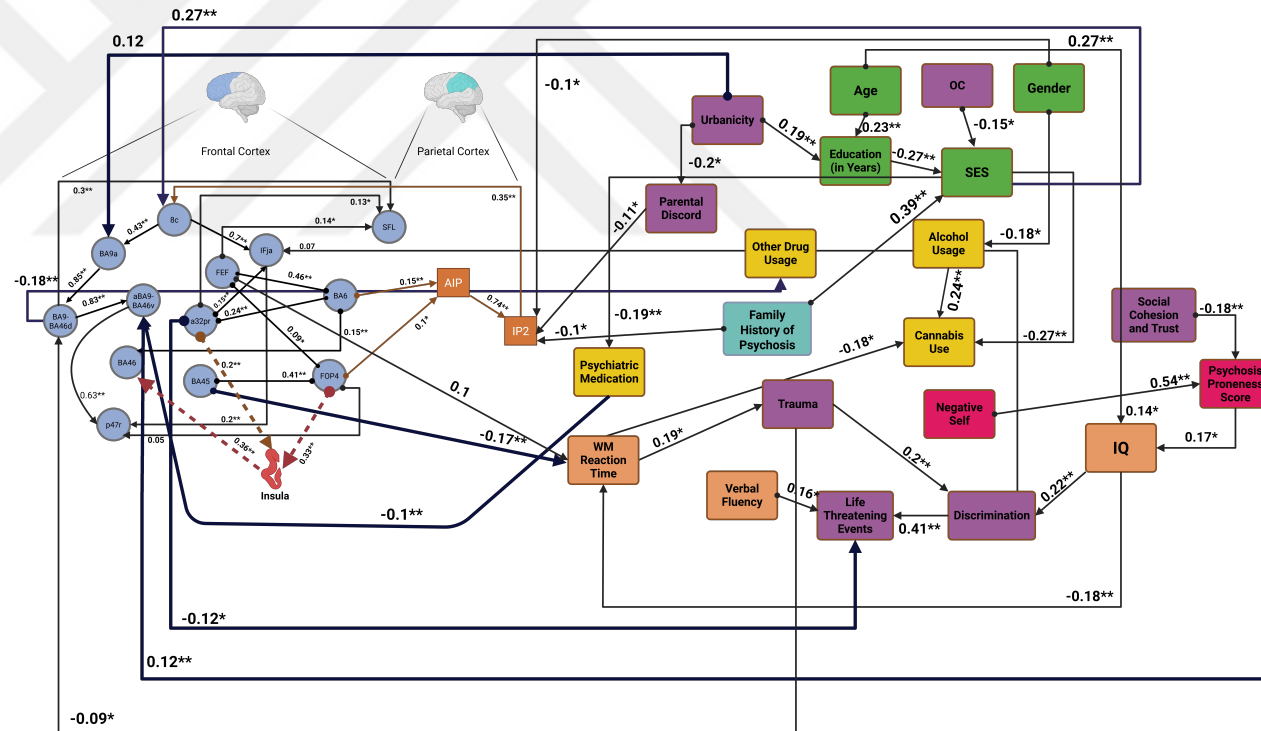


Figure 4.2: Complete Partial Ancestral Graph with Effect Sizes and p-value Information. Causal Discovery Analysis was conducted with GFCL, incorporating fMRI activation data from ROIs during information manipulation, along with environmental and psychological factors. (B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus; I.P.: Intraparietal Sulcus; a9-46v: frontal mid; FOP4: frontal operculum; IFJa: anterior inferior frontal gyrus; p47r: the orbital prefrontal cortex; a32pr: refers to a narrow strip of the anterior midcingulate cortex; FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory.)

** $p < 0.01$; * $p < 0.05$

(Created in BioRender. Sahin, T. (2025). <https://BioRender.com/gj42q12>)

Table 4.1: Effect Sizes of Variables Estimated via SEM for Relationships Suggested by PAG

lhs	op	rhs	est	se	z	p-value	CI Lower	CI Upper	Adj. p-value
p47r	~	BA9a-BA46v	0.62	0.05	12.21	0	0.52	0.73	0
IFJa	~	BA8c	0.69	0.04	15.02	0	0.6	0.78	0
BA9a-BA46v	~	BA9-BA46d	0.83	0.03	22.94	0	0.76	0.9	0
IP2	~	AIP	0.73	0.04	16.16	0	0.65	0.82	0
BA9-BA46d	~	BA9a	0.85	0.03	22.85	0	0.78	0.92	0
FEF	~~	BA6	0.46	0.06	7.01	2.25e-12	0.33	0.59	2.136e-11
Psychosis Proneness	~~	Negative Self	0.53	0.07	6.72	1.76e-11	0.38	0.69	1.43285e-10
FOP4	~~	BA45	0.41	0.06	6.68	2.33e-11	0.29	0.53	1.66036e-10
BA9a	~	BA8c	0.42	0.06	6.63	3.24e-11	0.3	0.55	2.05161e-10
Life Threatening Events	~	Discrimination	0.4	0.06	6.34	2.25e-10	0.28	0.53	1.28092e-09
Insula	~~	FOP4	0.33	0.05	5.89	3.66e-09	0.22	0.44	1.89562e-08
BA46	~	Insula	0.36	0.06	5.69	1.21e-08	0.23	0.49	5.74104e-08
SES	~~	Family History of Psychosis	0.39	0.07	5.49	3.81e-08	0.25	0.53	1.67067e-07
BA8c	~	IP2	0.35	0.06	5.46	4.55e-08	0.22	0.47	1.85113e-07

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lhs	op	rhs	est	se	z	p-value	CI Lower	CI Upper	Adj. p-value
BA6	~~	a32pr	0.23	0.04	4.8	1.55e-06	0.14	0.33	5.89062e-06
SFL	~	BA9-BA46d	0.29	0.06	4.71	2.41e-06	0.17	0.42	8.5834e-06
SES	~	Education in Years	-0.26	0.06	-4.46	8.17e-06	-0.38	-0.15	2.73836e-05
BA8c	~	SES	0.26	0.06	4.12	3.72e-05	0.14	0.39	0.0001
Cannabis Use	~	SES	-0.26	0.06	-3.98	6.62e-05	-0.4	-0.13	0.0001
p47r	~	IFJa	0.2	0.05	3.82	0.0001	0.09	0.3	0.0003
IFJa	~~	a32pr	0.15	0.04	3.71	0.0002	0.07	0.23	0.0005
Cannabis Use	~	Alcohol Usage	0.24	0.06	3.67	0.0002	0.11	0.37	0.0006
Insula	~~	a32pr	0.2	0.05	3.61	0.0002	0.09	0.31	0.0007
Education in Years	~~	Age	0.23	0.07	3.29	0.0009	0.09	0.37	0.002
BA46	~~	BA6	0.15	0.04	3.2	0.001	0.05	0.24	0.003
BA9a-BA46v	~	Psychosis Proneness	0.11	0.03	3.19	0.001	0.04	0.18	0.003
Discrimination	~	IQ	0.21	0.06	3.18	0.001	0.08	0.35	0.003
Discrimination	~	Trauma	0.2	0.06	2.99	0.002	0.07	0.33	0.005
Psychosis Proneness	~~	Social Cohesion and Trust	-0.17	0.06	-2.92	0.003	-0.29	-0.05	0.006

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lhs	op	rhs	est	se	z	p-value	CI Lower	CI Upper	Adj. p-value
AIP	~~	BA6	0.14	0.05	2.91	0.003	0.04	0.24	0.006
Working Memory RT	~~	BA45	-0.17	0.05	-2.85	0.004	-0.28	-0.05	0.007
Parental Discord	~~	Urbanicity	-0.2	0.07	-2.82	0.004	-0.33	-0.06	0.008
Cannabis Use	~	Working Memory RT	-0.18	0.06	-2.78	0.005	-0.31	-0.05	0.009
BA9a-BA46v	~	Psychiatric Medication	-0.1	0.03	-2.77	0.005	-0.17	-0.02	0.009
Education in Years	~~	Urbanicity	0.18	0.06	2.71	0.006	0.05	0.32	0.01
Trauma	~	Working Memory RT	0.18	0.06	2.71	0.006	0.05	0.32	0.01
Psychiatric Medication	~	SES	-0.19	0.07	-2.69	0.006	-0.33	-0.05	0.01
Working Memory RT	~	IQ	-0.18	0.06	-2.65	0.007	-0.31	-0.04	0.01
Other Drug Use	~	BA9-BA46d	-0.18	0.07	-2.59	0.009	-0.32	-0.04	0.01
SFL	~~	FEF	0.13	0.05	2.57	0.01	0.03	0.24	0.01
Alcohol Usage	~~	Gender	-0.18	0.07	-2.56	0.01	-0.32	-0.04	0.01
IQ	~	Psychosis Proneness	0.17	0.07	2.47	0.01	0.03	0.31	0.01
SES	~~	OC	-0.15	0.06	-2.47	0.01	-0.27	-0.03	0.01
IP2	~	Parental Discord	-0.11	0.04	-2.4	0.01	-0.19	-0.02	0.02

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lhs	op	rhs	est	se	z	p-value	CI Lower	CI Upper	Adj. p-value
SFL	~~	a32pr	0.13	0.05	2.39	0.01	0.02	0.24	0.02
Life Threatening Events	~~	Verbal Fluency	0.15	0.06	2.38	0.01	0.02	0.28	0.02
IP2	~~	Gender	-0.1	0.04	-2.36	0.01	-0.19	-0.01	0.02
FEF	~~	FOP4	0.08	0.03	2.34	0.01	0.01	0.16	0.02
BA9-BA46d	~	Trauma	-0.08	0.03	-2.34	0.01	-0.16	-0.01	0.02
IP2	~~	Family History of Psychosis	-0.09	0.04	-2.27	0.02	-0.17	-0.01	0.02
Life Threatening Events	~~	a32pr	-0.11	0.05	-2.18	0.02	-0.22	-0.01	0.03
AIP	~~	FOP4	0.1	0.04	2.13	0.03	0.008	0.19	0.03
IQ	~~	Age	0.13	0.06	2.02	0.04	0.004	0.27	0.04
BA9a	~~	Urbanicity	0.12	0.06	1.95	0.05	-4.84e-05	0.24	0.05
Working Memory RT	~~	FEF	0.1	0.05	1.93	0.05	-0.001	0.21	0.05
IFJa	~	Discrimination	0.07	0.04	1.54	0.12	-0.01	0.16	0.12
p47r	~~	FOP4	0.04	0.03	1.45	0.14	-0.01	0.11	0.14

(B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus; I.P.: Intraparietal Sulcus; a9-46v: frontal mid; FOP4:

frontal operculum; IFJa: anterior inferior frontal gyrus; p47r: the orbital prefrontal cortex; a32pr: refers to a narrow strip of the anterior midcingulate cortex; FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory; Op: operator; lhs: left-hand side; rhs: right-hand side; est: estimate; se: standard error; ci-lower and ci-upper: the lower and upper bounds of a 95% confidence interval around the point estimate)

4.3 Causal Model Results

The PAG presented in Figure 4.1 displayed multifaceted network connecting functional brain indices with other sets of variables. Some of these associations appeared to be direct, while others suggested more intricate paths, with the possibility of unmeasured latent factors. Such relationships, which may involve latent variable are referred to as “possibly confounded” relationships and require additional investigation.

4.3.1 The Partial Ancestral Graph (PAG) Suggests Possibly Causal Relationships Between Negative Self-Schema, Social Cohesion and Trust and Psychosis Proneness Score

A key observation emerging from the CDA was a positive and statistically significant possibly confounded link between negative self-schema and psychosis proneness score (PPS) ($ES = 0.54$, $p < 0.001$, resampling edge frequency (REF)= 12.76 %). Although this association may be influenced by an unmeasured confounding factor, the results suggest that greater levels of negative self-schema are related to increased levels of psychosis proneness score (PPS). Nevertheless, resampling with replacement analysis revealed that this possibly confounded edge demonstrated low stability across models, appearing in only 12.76 % of resampled graphs. Interestingly, unconfounded, direct edges between these variables were more frequently identified: a direct edge from negative self-schema to PPS was present in 32.02 % of resampled models, while a direct path in the opposite direction, from PPS to negative self-schema, was observed in 37.36 %. A lack of any connection between the two occurred in only 0.93 % of the samples (Table 4.2). To further explore the nature of these associations, we modeled the edges linked to PPS as direct causal effects, specifically examining the influence of Negative Self-Schema and Social Cohesion & Trust on PPS. The effect sizes were as follows: Negative Self-Schema PPS ($ES = 0.54$) and Social Cohesion & Trust PPS ($ES = -0.18$). These results were supported by consistent model fit indices, with RMSEA = 0.052 and TLI = 0.833 (Table A.3). In addition, we identified a negative association between social cohesion & trust and psychosis proneness

(ES= -0.18, $p=0.003$, REF = 9.28 %), showing that higher levels of sense of belonging and trust within the social environment are linked to lower levels of PPS. Similar to findings for negative self-schema, this association was potentially confounded, suggesting the influence of a latent common cause. Resampling analysis depicted low stability for this possibly confounded edge from social cohesion and trust to PPS (9.28 %). Direct association from social cohesion and trust to PPS were present in 20.42 % of resampled models, the reverse direction in 15.78 %, and no edge in 47.33 % (Table 4.2). Moreover, a relationship between psychosis proneness and IQ was found ($SE= 0.17, p < 0.05$, REF = 9.97 %). This result may imply that individuals with higher psychosis proneness may also show elevated IQ scores. However, the stability analysis indicated very low stability of this association, regardless of direction or confounding, with no edge observed in 80.05 % of samples (Table 4.2).

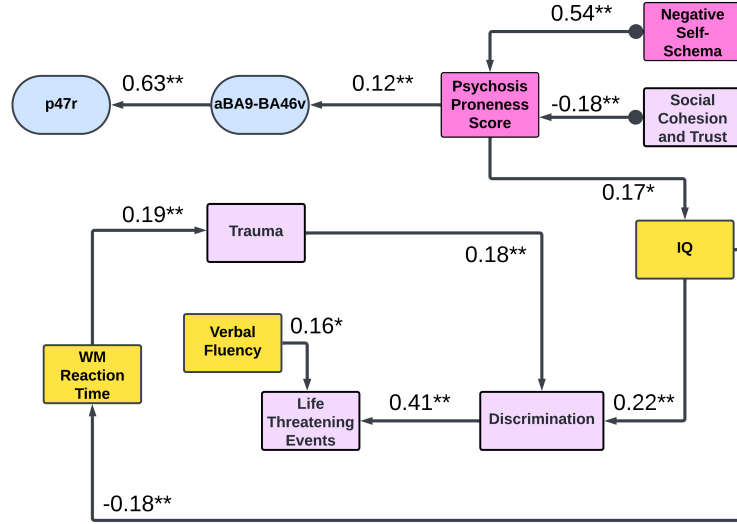


Figure 4.3: **Psychosis Proneness Subgraph.** GFCI returns a partial ancestral graph (PAG) depicting causal relationships between a set of variables, while assessing for unmeasured third variables in relationships (confounders). BA9: DLPFC; BA46: MPFC; P47r: Orbital Prefrontal Cortex. Adapted from Sahin-Ilikoglu et al., 2025 [1].

Since GFCI considers the possibility of latent variables, the presented graph shows some uncertainty about the possibility of the latent variables. Our main results suggest the possible confounded direct relationship between Negative Self-Schema to Psychosis Proneness Score and Social Cohesion & Trust and Psychosis Proneness Score. This possible confounded causal relationship ($\circ \rightarrow$) means the

following: either negative self-schema is the direct cause of psychosis proneness score, or there is a latent variable that is cause of negative self-schema and psychosis proneness score or both. This can mean three possible causal graphs that are not distinguishable from our data using the algorithms we used, i.e.

(A) *Negative self-schema* $\rightarrow$ *Psychosis Proneness Score*

(B) *Negative self-schema* $\leftrightarrow$ *Psychosis Proneness Score*

(C) *Negative self-schema* $\rightarrow$ *Psychosis Proneness Score* and *Negative self-schema* $\leftrightarrow$ *Psychosis Proneness Score*

Based solely on the statistical relationships within the data, the algorithm cannot ascertain whether a direct relationship exists between negative self-schema and psychosis proneness score. Without additional domain knowledge, we cannot definitively conclude the presence of a direct relationship.

4.3.2 Psychosis Proneness Score as a Causal Factor in Activation of the Dorsolateral Prefrontal Cortex

The analysis also revealed that greater psychosis proneness was directly linked to elevated activation in the BA9-BA46v, a region of the dorsolateral prefrontal cortex (DLPFC). This association was statistically significant (ES = 0.12, $p = 0.0013$), though it exhibited low stability across resampled models (REF = 8.58 %) between psychosis proneness and the functional neural correlates in the DLPFC region. The edge did not appear in the majority of resampled models (REF = 86.54 %; Table 4.2). In addition, aBA9-BA46v activation showed a significant positive influence on activation in p47r (ES = 0.63, $p < 0.001$, REF = 59.39 %), suggesting both direct and indirect influences of psychosis proneness on prefrontal brain activity.

The PAG revealed a possibly confounded, statistically significant association ($p < .01$) between activation in the midventrolateral prefrontal cortex (VLPFC;

approximately BA 45; inferior frontal gyrus pars triangularis) and working memory reaction time ($ES = -0.17$, $REF = 1.62\%$). This finding suggests that greater VLPFC activation is associated with faster responses during working memory task. Resampling with replacement analysis indicated that although the possibly confounded link appeared infrequently (1.62%), direct relationships were more common: VLPFC to WM reaction time occurred in 16.63% of resampled models, the reverse direction in 14.15% , and no link in 57.31% .

4.3.3 The Partial Ancestral Graph Suggests Causal Relationships Between Cognitive Variables and Other Variables

The graph revealed several additional associations involving cognitive variables. For instance, higher IQ appeared to be associated with reduced working memory reaction time ($ES = -0.18$, $p < 0.01$, $REF = 9.04\%$). However, the edge was unstable, missing in 76.1% of the resampled models. A statistically significant positive causal link was also found from working memory reaction time to trauma exposure ($ES = 0.19$, $p < 0.05$, $REF = 13.46\%$). Trauma, in turn, had a causal influence on discrimination ($ES = 0.2$, $p < 0.01$, $REF = 12.06\%$), which subsequently had influence on life-threatening events ($ES = 0.41$, $p < 0.01$, $REF = 35.5\%$). Additionally, possibly confounded associations were found between urban birth and parental discord severity ($ES = -0.2$, $p < 0.05$, $REF = 38.28\%$) and between higher verbal fluency and life-threatening events ($ES = 0.16$, $p < 0.05$, $REF = 1.86\%$).

4.3.4 The Partial Ancestral Graph Suggests Causal Relationships between fMRI Indexes and Other Variables

Several notable causal associations emerged between fMRI indices and other variables independent of the psychosis proneness score. Trauma was found to negatively influence activation in BA9-BA46d ($ES = -0.12$, $p < 0.05$, $REF = 4.4\%$) and parental discord showed a reversed association with intraparietal sulcus

(IP2) (ES= - 0.11, $p < 0.05$, REF = 12.76 %). A possibly confounded negative effect was found between a32pr activation and life-threatening events (ES = -0.12, $p < 0.05$, REF = 0.23 %). Furthermore, psychiatric medication use was associated with reduced DLPFC activation (ES= -0.1, $p < 0.01$, REF = 8.58 %). Activation in BA9-BA46d was negatively linked to non-cannabis drug use (ES = -0.18, $p < 0.01$, REF = 16.01 %), while higher parental socioeconomic status (SES) was positively associated with activation in 8c (ES = 0.27, $p < 0.001$, REF = 37.12 %). Additionally, possibly confounded associations were detected, including a negative relationship having a first-degree relative with psychosis and IP2 activation (ES = -0.1, $p < 0.05$, REF = 21.58 %), as well as between gender and IP2 (ES= -0.1, $p < 0.05$, REF = 32.02 %). A weak, statistically non-significant, possibly confounded link was observed between FEF activation and working memory reaction time (ES= 0.1, REF = 0.03 %). Similarly, urban birth showed a non-significant potentially confounded effect on BA9a activation (ES= 0.12, REF = 0.11 %).

Re-Sampling Analysis

Table 4.2: Resampling with Replacement Analysis for Main Results

Resampling with replacement analysis

Nodes		Proportion of 1,000 resamples with edge type						
Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
Negative Self	Psychosis Proneness Score	0.320	0.373	0.127	0.081	0.069	0.018	0.009
Psychosis Proneness Score	aBA9-BA46v	0.085	0.027	0.016	0.004	0	0	0.865
aBA9-BA46v	P47r	0.593	0.201	0.083	0.062	0.055	0.002	0
IQ	WM Reaction Time	0.090	0.109	0.009	0.023	0.007	0	0.761
IQ	Discrimination	0.185	0.127	0.025	0.018	0.004	0.004	0.633
WM Reaction Time	Trauma	0.134	0.160	0.048	0.051	0.027	0	0.577
BA45	WM Reaction Time	0.176	0.141	0.016	0.081	0.004	0.007	0.573
Trauma	Discrimination	0.120	0.183	0.037	0.018	0.016	0.002	0.621
Discrimination	Life Threatening Events	0.355	0.385	0.074	0.102	0.041	0.007	0.034
Alcohol Usage	Cannabis Use	0.278	0.257	0.058	0.020	0.018	0.004	0.361
Psychiatric Medication	aBA9-BA46v	0.085	0.076	0.023	0.011	0.004	0	0.798

Table 4.2: (continued)

Nodes		Proportion of 1,000 resamples with edge type						
Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
Education in Years	SES	0.29	0.239	0.060	0	0	0.020	0.389
Urbanicity	Education in Years	0	0	0.352	0	0	0.03	0.617
Urbanicity	BA9a	0.002	0	0.113	0	0	0	0.884
SES	8c	0.371	0	0.002	0	0	0.002	0.624
SES	Cannabis	0.394	0	0.018	0	0	0.097	0.489
Verbal Fluency	Life Threatening Events	0.092	0.051	0.018	0.011	0	0.002	0.823
BA9a	BA9-BA46d	0.306	0.454	0.139	0.053	0.044	0.002	0
FOP4	BA45	0.617	0.139	0.120	0.048	0.053	0.011	0.009
8c	IFja	0.566	0.194	0.125	0.041	0.051	0.020	0
BA9-BA46d	aBA9-BA46v	0.461	0.313	0.069	0.111	0.030	0.013	0
BA6	a32pr	0.454	0.190	0.102	0.048	0.048	0.018	0.136
AIP	IP2	0.461	0.308	0.125	0.065	0.020	0.018	0
BA6	FEF	0.410	0.313	0.102	0.081	0.085	0.007	0
Insula	BA46	0.331	0.227	0.051	0.027	0.039	0.002	0.320
FOP4	Insula	0.403	0.341	0.076	0.067	0.076	0.007	0.027
Family History of Psychosis	SES	0	0	0.826	0	0	0.030	0.143

Table 4.2: (continued)

Nodes		Proportion of 1,000 resamples with edge type						
Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
8c	BA9a	0.081	0.148	0.018	0.039	0.009	0.013	0.689
FEF	FOP4	0.120	0.109	0.023	0.027	0.011	0	0.707
IP2	8c	0.053	0.078	0.007	0.013	0.002	0	0.844
BA6	AIP	0.164	0.062	0.039	0.009	0.009	0.004	0.71
a32pr	IFJa	0.136	0.171	0.023	0.016	0.009	0.011	0.631
BA6	BA46	0.313	0.039	0.060	0.023	0.009	0.009	0.545
Psychosis Proneness Score	IQ	0.099	0.067	0.013	0.013	0.004	0	0.800
Age	IQ	0	0	0.208	0	0	0.002	0.788
BA9-BA46d	SFL	0.239	0.0881	0.023	0.020	0.007	0.007	0.614
FEF	SFL	0.334	0.0673	0.051	0.025	0.0232	0	0.498
Age	Education in Years	0	0	0.714	0	0	0.016	0.269
FOP4	AIP	0.083	0.051	0.030	0.023	0.004	0.011	0.795
FEF	Working Memory RT	0.092	0.046	0.032	0.023	0	0	0.805
IFJa	P47r	0.076	0.018	0.004	0	0.004	0	0.89
BA9-BA46d	Other Drug Usage	0.160	0.023	0.004	0.027	0	0	0.779
FOP4	p47r	0.15	0.09	0.041	0.018	0	0	0.679
OC	SES	0	0	0.2877	0	0	0	0.712

Table 4.2: (continued)

Nodes		Proportion of 1,000 resamples with edge type						
Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
a32pr	SFL	0.227	0.109	0.046	0.032	0.011	0.004	0.568
SC&T	Psychosis Proneness Score	0.204	0.157	0.092	0.046	0.018	0.007	0.47
SES	Psychiatric Medication	0.215	0	0.007	0	0	0.032	0.744
a32pr	LTE	0.081	0.071	0.002	0.018	0.002	0	0.823
Gender	Alcohol Usage	0	0	0.324	0	0	0.009	0.665
Gender	IP2	0.002	0	0.320	0	0	0.002	0.675
Trauma	BA9-BA46d	0.044	0.002	0.023	0.002	0	0	0.928
Discrimination	IFJa	0.062	0.030	0.007	0.004	0	0	0.895
WM Reaction Time	Cannabis	0.109	0.044	0.041	0.007	0.002	0	0.795
Parental Discord Severity	IP2	0.127	0	0.067	0	0	0	0.805
Urbanicity	Parental Discord Severity	0	0	0.382	0	0	0.030	0.587
a32pr	Insula	0.104	0.021	0.020	0.004	0	0	0.849
Family History of Psychosis	IP2	0.004	0	0.215	0	0	0	0.779

(B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus, I.P.: Intraparietal Sulcus; a9-46v: frontal mid, FOP4: frontal operculum, IFJa: anterior inferior frontal gyrus, p47r: the orbital prefrontal cortex, a32pr: refers to a narrow strip of the anterior midcingulate cortex, FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory)

4.3.5 Additional Partial Ancestral Graph with Negative Others Schema Included

In the main partial ancestral graph, CDA was executed with only including the negative self-schema subscale from the Brief Core Schema Scale. The reasoning behind was to not include several subscales from the same instrument as they may have highly connected. However, the difference between negative self and other schema is prominent and negative others schema might solve the possibly confounded relationship between the negative self-schema and psychosis proneness score. Therefore, causal discovery analysis was replicated by adding “Negative Others Schema” subscale from the Brief Core Schema Scale as negative others also indicated to have significant relationship with psychotic like experiences [129]. After incorporating “Negative Others schema” into the CDA, no edges were lost from the original Partial Ancestral Graph (PAG). However, the following new edges emerged:

Negative Others Schema $\rightarrow$ Trauma
Negative Others Schema $\rightarrow$ Negative Self-Schema
Education in Years $\rightarrow$ Negative Self-Schema
Age $o \rightarrow$ Negative Others Schema
Social Cohesion and Trust $o \rightarrow$ Negative Others Schema

Furthermore, the edge between the negative self-schema and psychosis proneness score became direct edge, indicating that in the suggested model, negative self-schema is a direct causal factor of psychosis proneness score. The revised PAG is shown in Figure 4.4 along with effect sizes and p-value information.

Figure 4.4 and Table 4.3 display the SEM-derived edge weights. The model indicated good fit, RMSEA= 0.049, Tucker-Lewis Index = 0.844. All but three paths are statistically significant at $p < .05$, with 43 out of 62 at reaching significance at $p < .01$ (Figure 4.4, Table 4.3). As standard, uncorrected p-values were used on graphs.

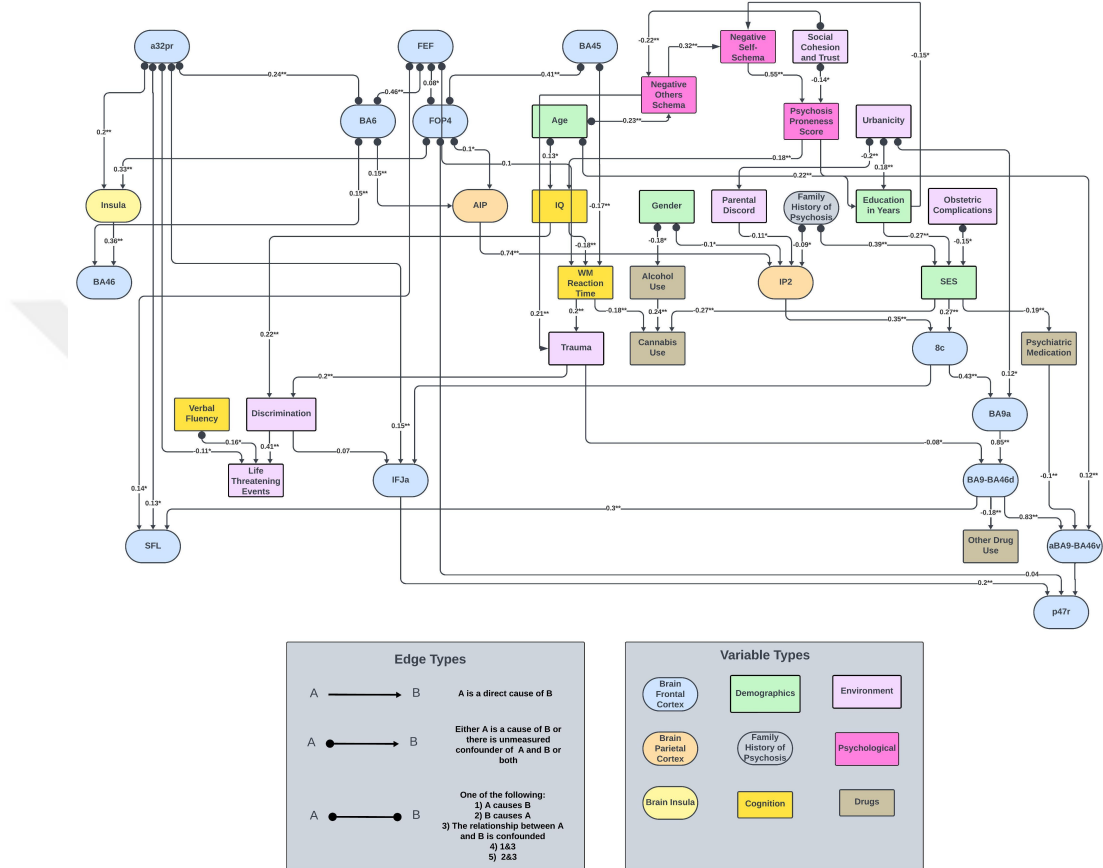


Figure 4.4: Causal Discovery Analysis including Negative Others Schema and Manipulation phase of the Working Memory Paradigm.

Causal Discovery Analysis was performed using GFCI for activations in ROIs when manipulating information during fMRI, environmental and psychological variables including the negative others schema. (B.A.:Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus, I.P.: Intraparietal Sulcus; a9-46v: frontal mid, FOP4: frontal operculum, IFJa: anterior inferior frontal gyrus, p47r: the orbital prefrontal cortex, a32pr: refers to a narrow strip of the anterior midcingulate cortex, FEF: frontal eye fields; SES: socioeconomic status; W.M.: working memory). Adapted from Sahin-Ilikoglu et al., 2025 [1].

Table 4.3: Effect Sizes Estimated via SEM for Relationships Suggested by the PAG Involving Negative Others

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper
p47r	~	BA9a-BA46v	0.62	0.05	12.29	0	0.52	0.73
IFJa	~	8c	0.69	0.04	15.02	0	0.6	0.78
Psychosis Proneness Score	~	Negative Self-Schema	0.55	0.05	9.34	0	0.43	0.66
BA9a-BA46v	~	BA9-BA46d	0.83	0.03	22.94	0	0.76	0.9
IP2	~	AIP	0.73	0.04	16.16	0	0.65	0.82
BA9-BA46d	~	BA9a	0.85	0.03	22.85	0	0.78	0.92
FEF	~~	BA6	0.46	0.06	7.01	2.25E-12	0.33	0.59
FOP4	~~	BA45	0.41	0.06	6.68	2.33E-11	0.29	0.53
BA9a	~	8c	0.42	0.06	6.63	3.23E-11	0.3	0.55
Life Threatening Events	~	Discrimination	0.4	0.06	6.34	2.21E-10	0.28	0.53
Insula	~~	FOP4	0.33	0.05	5.89	3.66E-09	0.22	0.44
BA46	~	Insula	0.36	0.06	5.69	1.21E-08	0.23	0.49
SES	~~	First Degree Family History of Psychosis	0.39	0.07	5.49	3.81E-08	0.25	0.53
8c	~	IP2	0.35	0.06	5.46	4.55E-08	0.22	0.47
Negative Self-Schema	~	Negative Others Schema	0.32	0.06	4.8	1.54E-06	0.19	0.45
BA6	~~	a32pr	0.23	0.04	4.8	1.55E-06	0.14	0.33
SFL	~	BA9-BA46d	0.29	0.06	4.71	2.41E-06	0.17	0.42
SES	~	Education in Years	-0.26	0.06	-4.45	8.2E-06	-0.38	-0.15
8c	~	SES	0.26	0.06	4.12	3.72E-05	0.14	0.39

Table 4.3: (continued)

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper
Cannabis Use	~	SES	-0.26	0.06	-3.98	6.62E-05	-0.4	-0.13
P47r	~	IFJa	0.2	0.05	3.82	0.0001	0.09	0.3
IFJa	~~	A32pr	0.15	0.04	3.71	0.0002	0.07	0.23
Cannabis Use	~	Alcohol Use	0.24	0.06	3.67	0.0002	0.11	0.37
Insula	~~	A32pr	0.2	0.05	3.61	0.0002	0.09	0.31
Negative Others Schema	~~	Age	0.22	0.06	3.29	0.0009	0.09	0.36
Education in Years	~~	Age	0.22	0.06	3.26	0.001	0.08	0.35
BA9a-BA46v	~	Psychosis Proneness Score	0.11	0.03	3.21	0.001	0.04	0.18
BA46	~~	BA6	0.15	0.04	3.2	0.001	0.05	0.24
Discrimination	~	IQ	0.21	0.06	3.18	0.001	0.08	0.35
Trauma	~	Negative Others Schema	0.21	0.06	3.13	0.001	0.08	0.34
Negative Others Schema	~~	Social Cohesion and Trust	-0.21	0.07	-3.12	0.001	-0.35	-0.08
Discrimination	~	Trauma	0.2	0.06	3.004	0.002	0.07	0.33
AIP	~~	BA6	0.14	0.05	2.91	0.003	0.04	0.24
Trauma	~	WM Reaction Time	0.19	0.06	2.9	0.003	0.06	0.33
WM Reaction Time	~~	BA45	-0.17	0.05	-2.85	0.004	-0.28	-0.05
Parental Discord	~~	Urbanicity	-0.2	0.07	-2.83	0.004	-0.33	-0.06
Cannabis Use	~	WM Reaction Time	-0.18	0.06	-2.78	0.005	-0.31	-0.05
BA9a-BA46v	~	Psychiatric Medication	-0.1	0.03	-2.77	0.005	-0.17	-0.02

Table 4.3: (continued)

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper
Education in Years	~~	Urbanicity	0.18	0.06	2.7	0.006	0.05	0.31
Psychiatric Medication	~	SES	-0.19	0.07	-2.69	0.006	-0.33	-0.05
WM Reaction Time	~	IQ	-0.18	0.06	-2.66	0.007	-0.31	-0.04
IQ	~	Psychosis Proneness Score	0.18	0.06	2.64	0.008	0.04	0.32
Other Drug Usage	~	BA9-BA46d	-0.18	0.07	-2.59	0.009	-0.32	-0.04
SFL	~~	FEF	0.13	0.05	2.57	0.01	0.03	0.24
Alcohol Use	~~	Gender	-0.18	0.07	-2.56	0.01	-0.32	-0.04
SES	~~	Obstetric Complications	-0.15	0.06	-2.47	0.01	-0.27	-0.03
Psychosis Proneness Score	~~	Social Cohesion and Trust	-0.14	0.05	-2.44	0.01	-0.25	-0.02
IP2	~	Parental Discord	-0.11	0.04	-2.4	0.01	-0.19	-0.02
SFL	~~	A32pr	0.13	0.05	2.39	0.01	0.02	0.24
Life Threatening Events	~~	Verbal Fluency	0.15	0.06	2.38	0.01	0.02	0.28
IP2	~~	Gender	-0.1	0.04	-2.36	0.01	-0.19	-0.01
BA9-BA46d	~	Trauma	-0.08	0.03	-2.35	0.01	-0.16	-0.01
FEF	~~	FOP4	0.08	0.03	2.34	0.01	0.01	0.16
Negative Self-Schema	~	Education in Years	-0.15	0.06	-2.33	0.01	-0.28	-0.02
IP2	~~	First Degree Family History of Psychosis	-0.09	0.04	-2.27	0.02	-0.17	-0.01
Life Threatening Events	~~	A32pr	-0.11	0.05	-2.18	0.02	-0.22	-0.01
AIP	~~	FOP4	0.1	0.04	2.13	0.03	0.008	0.19

Table 4.3: (continued)

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper
IQ	~~	Age	0.13	0.06	2.02	0.04	0.004	0.26
BA9a	~~	Urbanicity	0.12	0.06	1.96	0.04	0.0003	0.24
WM Reaction Time	~~	FEF	0.1	0.05	1.93	0.05	-0.001	0.21
IFJa	~	Discrimination	0.07	0.04	1.54	0.12	-0.01901	0.16
P47r	~~	FOP4	0.04	0.03	1.45	0.14	-0.01	0.11

8

Op: operator, lhs: left-hand side, rhs: right-hand side, es: estimate, se: standard error, ci-lower and ci-upper: the lower and upper bounds of a 95% confidence interval around the point estimate (B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus, I.P.: Intraparietal Sulcus; a9-46v: frontal mid, FOP4: frontal operculum, IFJa: anterior inferior frontal gyrus, p47r: the orbital prefrontal cortex, a32pr: refers to a narrow strip of the anterior midcingulate cortex, FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory)

4.4 Sensitivity Analysis

4.4.1 Alternative Variable Coding of Environmental Risk Factors

Since the level of effect of environmental risk factors on psychosis is still unknown, sensitivity analysis was conducted by coding environmental risk factors based on the odds ratios from the Maudsley Environmental Risk Score [2]. The following environmental risk factors: urbanicity, obstetric complications, cannabis use, childhood adversity, paternal age and ethnic minority were coded based on the Vassos et al. [2]. Briefly, urbanicity were divided into three categories; Urban center (1), Urban Cluster (0) and Rural (-1.5), obstetric complications score were calculated into two categories; no complications (0), complication with the largest OR score (Table A.1); Cannabis use were divided into three categories; no exposure (-1), little/moderate exposure (little or a few times a year) (0), and high exposure (a few times a month and above) (3); childhood trauma were divided into two categories; no childhood trauma (-1.5), existence of trauma (2.5), ethnic minority, native (0), others (2), paternal age; < 40 (0), 40-50 (0.5), > 50 (2). The remaining variables were coded in the same way as in the main analysis.

4.4.2 Structural Equation Modelling of the Sensitivity Analysis

Table 4.4: Effect Sizes Estimated via SEM for the Sensitivity Analysis

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper	Adj. p
p47r	~	BA9a-BA46v	0.62	0.05	12.21	0.0	0.52	0.73	0.0
IFJa	~	8c	0.69	0.04	15.03	0.0	0.6	0.78	0.0
BA9a-BA46v	~	BA9-BA46d	0.83	0.03	22.94	0.0	0.76	0.9	0.0
IP2	~	AIP	0.74	0.04	16.18	0.0	0.65	0.82	0.0
BA9-BA46d	~	BA9a	0.85	0.03	22.85	0.0	0.78	0.92	0.0
FEF	~~	BA6	0.46	0.06	7.018148	2.25e-12	0.334594	0.593894	2.06085e-11
Psychosis Proneness	~~	Negative Self	0.53	0.07	6.72	1.76e-11	0.38	0.69	1.38276e-10
FOP4	~~	BA45	0.41	0.06	6.68	2.33e-11	0.292521	0.53	1.60227e-10
BA9a	~	8c	0.43	0.06	6.64	2.94e-11	0.3	0.55	1.79709e-10
Life Threatening Events	~	Discrimination	0.4	0.06	6.34	2.25e-10	0.28	0.53	1.23598e-09
Insula	~~	FOP4	0.33	0.05	5.89	3.66e-09	0.22	0.44	1.82894e-08
BA46	~	Insula	0.36	0.06	5.69	1.21e-08	0.23	0.49	5.53913e-08
SES	~~	Family History of Psychosis	0.39	0.07	5.51	3.43e-08	0.25	0.53	1.45223e-07
8c	~	IP2	0.35	0.06	5.46	4.52e-08	0.22	0.47	1.77561e-07
BA6	~~	a32pr	0.23	0.04	4.8	1.55e-06	0.14	0.33	5.68427e-06
SFL	~	BA9-BA46d	0.29	0.06	4.71	2.4e-06	0.17	0.42	8.25255e-06
SES	~	Education in Years	-0.26	0.06	-4.39	1.11e-05	-0.38	-0.14	3.58641e-05

Table 4.4: (continued)

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper	Adj. p
8c	~	SES	0.26	0.06	4.12	3.71e-05	0.14	0.39	0.0001
p47r	~	IFJa	0.2	0.05	3.82	0.0001	0.09	0.3	0.0003
IFJa	~~	a32pr	0.15	0.04	3.71	0.0002	0.07	0.23	0.0005
Insula	~~	a32pr	0.2	0.05	3.61	0.0002	0.09	0.31	0.0007
Education in Years	~~	Age	0.23	0.07	3.31	0.0009	0.09	0.37	0.002
BA46	~~	BA6	0.15	0.04	3.2	0.001	0.05	0.24	0.003
BA9a-BA46v	~	Psychosis Proneness	0.11	0.03	3.19	0.001	0.04	0.18	0.003
Discrimination	~	IQ	0.21	0.06	3.18	0.001	0.08	0.35	0.003
Discrimination	~	Trauma	0.2	0.06	2.99	0.002	0.07	0.33	0.005
Psychosis Proneness	~~	Social Cohesion and Trust	-0.17	0.06	-2.92	0.003	-0.29	-0.058	0.007
AIP	~~	BA6	0.14	0.05	2.91	0.003	0.04	0.24	0.007
WM Reaction Time	~~	BA45	-0.17	0.05	-2.85	0.004	-0.28	-0.05	0.008
Parental Discord	~~	Urbanicity	-0.2	0.07	-2.84	0.004	-0.34	-0.06	0.008
BA9a-BA46v	~	Psychiatric Medication	-0.1	0.03	-2.77	0.005	-0.17	-0.02	0.009
Cannabis Use	~	Alcohol Usage	0.19	0.07	2.71	0.006	0.05	0.32	0.01
Trauma	~	WM Reaction Time	0.18	0.06	2.71	0.006	0.05	0.32	0.01
Psychiatric Medication	~	SES	-0.19	0.07	-2.69	0.006	-0.33	-0.05	0.01
Education in Years	~~	Urbanicity	0.18	0.06	2.68	0.007	0.04	0.31	0.01
WM Reaction Time	~	IQ	-0.18	0.06	-2.65	0.007	-0.31	-0.04	0.01

Table 4.4: (continued)

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper	Adj. p
Other Drug Usage	~	BA9-BA46d	-0.18	0.07	-2.59	0.009	-0.32	-0.04	0.01
SFL	~~	FEF	0.13	0.05	2.57	0.01	0.03	0.24	0.01
Alcohol Usage	~~	Gender	-0.18	0.07	-2.56	0.01	-0.32	-0.04	0.01
IQ	~	Psychosis Proneness	0.17	0.07	2.47	0.01	0.03	0.31	0.01
IP2	~	Parental Discord	-0.1	0.04	-2.4	0.01	-0.19	-0.02	0.02
SFL	~~	a32pr	0.13	0.05	2.39	0.01	0.02	0.24	0.02
Life Threatening Events	~~	Verbal Fluency	0.15	0.06	2.38	0.01	0.02	0.28	0.02
IP2	~~	Gender	-0.109	0.04	-2.36	0.01	-0.19	-0.01	0.02
SES	~~	OC	-0.14	0.06	-2.35	0.01	-0.26	-0.02	0.02
FEF	~~	FOP4	0.08	0.03	2.34	0.01	0.01	0.16	0.02
BA9-BA46d	~	Trauma	-0.08	0.03	-2.34	0.01	-0.16	-0.01	0.02
IP2	~~	Family History of Psychosis	-0.09	0.04	-2.33	0.01	-0.18	-0.01	0.02
Life Threatening Events	~~	a32pr	-0.11	0.05	-2.18	0.02	-0.22	-0.01	0.03
AIP	~~	FOP4	0.101	0.04	2.13	0.03	0.008	0.19	0.03
BA9a	~~	Urbanicity	0.12	0.06	2.04	0.04	0.005	0.25	0.04
IQ	~~	Age	0.13	0.06	2.02	0.04	0.004	0.27	0.04
WM Reaction Time	~~	FEF	0.1	0.05	1.93	0.05	-0.001	0.21	0.05
IFJa	~	Discrimination	0.07	0.04	1.54	0.12	-0.01	0.16	0.12

Table 4.4: (continued)

lhs	op	rhs	EST	SE	Z	p value	ci.lower	ci.upper	Adj. p
p47r	~~	FOP4	0.04	0.03	1.45	0.14	-0.01	0.11	0.14

Op: operator, lhs: left-hand side, rhs: right-hand side, es: estimate, se: standard error, ci-lower and ci-upper: the lower and upper bounds of a 95% confidence interval around the point estimate; B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus, I.P.: Intraparietal Sulcus; a9-46v: frontal mid, FOP4: frontal operculum, IFJa: anterior inferior frontal gyrus, p47r: the orbital prefrontal cortex, a32pr: refers to a narrow strip of the anterior midcingulate cortex, FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory

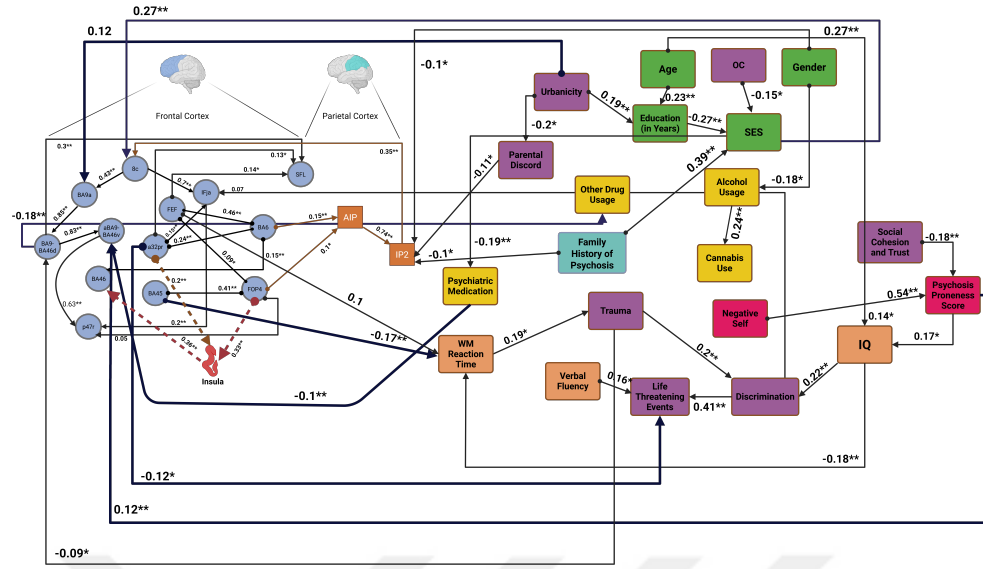


Figure 4.5: **Sensitivity Analysis: Causal Discovery of Environmental Risk Factors and the Working Memory Manipulation Phase.** Causal Discovery Analysis was performed using GFCI for activations in ROIs during the manipulation phase of working memory in fMRI. Variables included environmental risk factors from Vassos et al. (2020) [2], multidomain risks, and psychological variables. (B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus; I.P.: Intraparietal Sulcus; a9-46v: frontal mid; FOP4: frontal operculum; IFJa: anterior inferior frontal gyrus; p47r: orbital prefrontal cortex; a32pr: anterior midcingulate cortex; FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory). ** $p < 0.01$, * $p < 0.05$. (Created in BioRender. Sahin, T. (2025). <https://BioRender.com/jblr2km>)

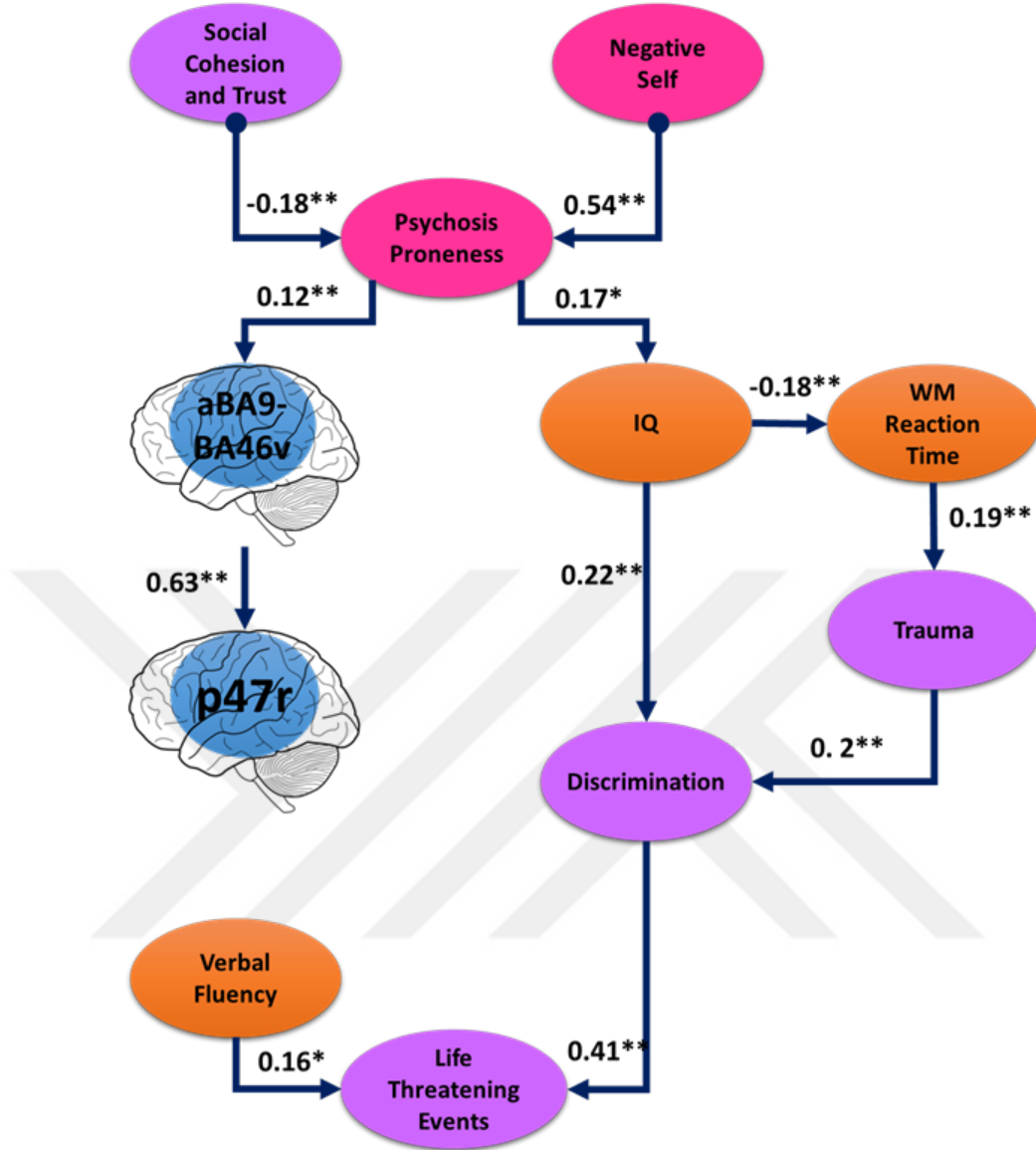


Figure 4.6: **Psychosis Proneness Subgraph of the Sensitivity Analysis.** GFCI returns a partial ancestral graph (PAG) depicting causal relationships between a set of variables, while assessing unmeasured third variables in relationships (confounders). (*BA9: dorsolateral prefrontal cortex (DLPFC)*; *BA46: medial prefrontal cortex (MPFC)*; *P47r: orbital prefrontal cortex.*) Adapted from Sahin-Ilikoglu et al., 2025 [1].

4.5 Results of the Sensitivity Analysis and SEM Comparison with the Main Results

The sensitivity analysis, which incorporated risk factors including cannabis, trauma, urbanicity, obstetric complications, paternal age, and ethnic minority based on the odds ratio from Vassos et al., 2020 [2], demonstrated that the primary findings remained unchanged. These findings continue to support the causal relationship between negative self-schema, SC&T and psychosis proneness, as well as the causal effect of psychosis proneness on aBA9-BA46v.

SEM results indicated no differences between the alternative model and the original model. The Tucker-Lewis Index (TLI) and Root Mean Square Error (RMSEA) of both models are provided in Table 4.5.

Table 4.5: Comparison of SEMs between the Main Model and Alternative Model

	Main Model	Alternative Model
Tucker-Lewis Index (TLI)	0.833	0.831
RMSEA	0.052	0.052

In comparison to the main model, in the alternative model only two edges were removed from the former PAG. The changed edges are provided in Table 4.6.

Table 4.6: Changed Edges in the Alternative Model

Node 1	Edge Type	Node 2
<i>Removed Edges</i>		
WM Reaction Time	→	Cannabis Use
SES	→	Cannabis Use

Additional analysis were conducted for the paths between Negative Self-Schema and psychosis proneness, social cohesion and trust and psychosis proneness by adding negative self-schema and social cohesion and trust as a direct edge

compared to possibly confounded edges. The effect sizes and general values of SEM did not change significantly (Table A.3). Rmsea value was 0.051 and tli was 0.83.

4.6 Discussion and Conclusions

In this chapter, a data-driven machine learning algorithm, CDA was employed to map causal relationships between psychosis proneness and multiple factors, involving self-schema, environmental and cognitive variables, and functional brain indices during working memory, a cognitive domain known to be disrupted in schizophrenia and among their healthy relatives.

In this chapter, the complex nature of psychosis proneness was explored, identifying its possible causal antecedents and consequences. Negative self-schema emerged as a key factor, showing a strong association with PPS (Figure 4.1, Figure 4.4, Table 4.1). The near absence of a “no edge” outcome in the stability analysis implies a reliable connection. However, the presence of all three edge types in the frequency distribution indicates ambiguity in causal direction and the influence of possible unobserved confounders. These findings suggest that negative self-schema may increase vulnerability to psychotic-like experiences, though reverse causation cannot be dismissed. Similar uncertainty applied to the relationship between low social cohesion and increased PPS, where confounding factors may play a role. On the neurobiological front, our analysis revealed a direct effect from PPS to DLPFC during working memory, although the edge showed low stability. This may represent neural compensation, given existing evidence of reduced prefrontal activation in individuals with psychosis. Together, these results the intricate interplay between psychological and neural factors in psychosis, offering valuable insights into future research and clinical strategies.

One of the main findings of this chapter is that negative self-schema is strongly associated with psychosis proneness. This result aligns with previous research indicating that individuals with psychosis, including those at elevated risk, often display maladaptive self-schema [82, 80, 83, 84], which often emerge early in life [146]. The current study builds upon this literature by examining individuals with psychosis proneness using a wide array of cognitive, environmental, and

neurobiological variables, alongside self-schema measures. Among the included variables, negative self-schema showed the strongest association with psychosis proneness, even exceeding other established risk factors such as trauma. However, this association’s directionality still remains uncertain. Resampling showed mixed results: a confounded edge, shown in the PAG, in 12.76 % of models, a direct edge from negative self-schema to PPS in 32.02 %, and the reverse in 37.36 %. Interestingly, the original model did not suggest a reverse direction, yet this was the most common in resampling, hinting at variability possibly due to differences in developmental stages within the sample, unmeasured confounders or limitations of self-report data. The consistent presence of this edge across resampled models suggests this relationship is meaningful. Further research is warranted to better understand its underlying nature. In schizophrenia, disruptions to self often manifest as depersonalization, derealization and disturbances in thought and perception related to one’s understanding of self and others, contributing to weakened sense of identity and social detachment [146, 147]. While the current study did not find aligned findings for early trauma as a predictor of psychosis proneness, it is worth noting that only 15 participants exceeded the 90th percentile threshold ($M = 96$; see Tables 3.1 and 3.3). This diverges from earlier findings showing that traumatic experiences can shape maladaptive beliefs about self and others [88, 89]. Nonetheless, our results emphasize the relevance of negative self-schema as a potential psychological contributor to psychosis proneness. Although unmeasured factors may influence this relationship, the findings suggest that individuals with a more negative self-image may be particularly vulnerable to psychosis-related symptoms.

Earlier research has demonstrated that social cohesion may buffer adolescents against the negative impact of stressful life events [148]. In another study, social cohesion and trust were linked to schizophrenia risk, though the pattern was U shaped [149]. Extending these insights, the current study identified a significant relationship between social cohesion and trust and psychosis proneness score, suggesting that diminished social cohesion and trust may contribute to elevated levels of psychosis proneness. This result further underscores the broader relevance of social cohesion, not only in clinical stages of illness but also in shaping vulnerability to psychotic-like experiences. As with negative self-schema, the connection between social cohesion and trust and psychosis proneness score was nuanced and somewhat unstable in resampling and may be influenced by unmeasured confounders. Notably, while urban birth did not directly predict PPS,

social cohesion and trust did, indicating that different environmental factors may contribute to psychosis vulnerability through separate mechanisms.

In this sample, a direct causal link was identified between PPS and activity in DLPFC, a brain region known to support executive functioning such as working memory [150, 151]. Although the observed effect ($ES = 0.12$) was relatively small, it aligns with previous research that has shown early neural changes in individuals who later develop psychosis [152], suggesting a possible cognitive underpinning of psychosis proneness. Despite this connection, the edge was not robust across resampled samples, appearing in only a minority of models, with no edge detected in high frequency. This suggests that the relationship may not be stable in all contexts and should be interpreted cautiously. Working memory impairments are consistently observed in schizophrenia [153] and among vulnerable individuals [154, 74, 155, 156]. Given the continuum model of psychosis, where frequent and distressing psychotic-like experiences may represent a milder expression of clinical symptoms, it is expected to observe PPS having a causal role in DLPFC during working memory task. Similar causal link between genetic risk for schizophrenia and brain function have been suggested in previous work [60].

Contrary to the commonly reported association between schizophrenia or first-episode psychosis and lower IQ levels [157, 158], our findings implied a possible positive relationship between PPS and IQ, suggesting that individuals with higher PPS may exhibit higher cognitive ability. While this may appear unexpected, it is not without precedent. Previous research have identified subgroups of individuals with schizophrenia who possess relatively elevated IQ scores and distinct clinical characteristics [159, 160]. Furthermore, high intellectual performance in adolescence has been associated with an increased likelihood of later bipolar disorder [161]. Additionally, some unaffected first-degree relatives, assumed to be obligate carriers due to familial schizophrenia, have also demonstrated higher IQs [162]. Nevertheless, due to the limited existing literature on this topic and the low edge stability found in our resampling analysis, this association remains uncertain and should be further explored in future research.

Previous research has demonstrated that atypical activation during working memory tasks involves both DLPFC and VLPFC [163]. A positively confounded relationship was observed between working memory reaction time and activation in VLPFC, a region known to be involved in controlled retrieval [133], as

well as and encoding and recognition processes [164]. The resulting model suggested no relationship between working memory reaction time and activation in the DLPFC. Furthermore, a possibly confounded association between the family history of psychosis and intraparietal sulcus (IP2) was found and supports the possible relationship between the familial risk and the reduced activation in IP2. Because molecular genetic data for schizophrenia, such as polygenic risk score, were not incorporated into the model, the possibly confounded relationship between working memory performance and VLPFC, and family history of psychosis and IP2 should be explored in future studies.

It is noteworthy that the only direct effect path from psychosis proneness score in our analysis led to DLPFC during the working memory task, with no corresponding effect on reaction time. While prefrontal and parietal regions are typically engaged during working memory, their activation does not necessarily align with reaction time performance in a straightforward manner [165]. Thus, this could help clarifying why DLPFC was not directly associated with performance speed. Previous findings have also suggested that as cognitive demand rises, DLPFC activation increases [165], possibly reflecting more complex cognitive mechanisms. The properties of working memory task used in this study might also have influenced this relationship. Prior work has shown that healthy participants activate the VLPFC (BA45), and engage subvocal rehearsal and phonological loop systems when processing and retaining information in working memory [166, 152]. Thus, the more evident direct association between VLPFC activity and reaction time may stem from these processes, whereas DLPFC may be more intricately linked to higher-order cognitive functions associated with psychosis proneness. Future studies should continue to examine how neural activation correlates with task performance in such contexts.

While some results from the data-driven analysis were anticipated such as the relationship between alcohol usage and cannabis or discrimination and life-threatening events, other findings especially those involving potentially confounded connections between variables unrelated to PPS were more complex. These include, for instance, a positive association between better verbal fluency and more experiences of life threatening events, increased reaction time in WM and existence of trauma, urban birth with less parental discord, lower activation in IP2 in females, increased age and increased level of IQ, reduction in a32pr and

more exposure to life threatening events. These relationships should be interpreted cautiously, and further research is required to validate these relationships.

Previous research has consistently shown a relationship between maltreatment and cognitive impairment [167, 168], yet the direction of this relationship remains ambiguous, whether trauma causes cognitive distortions or individuals with lower cognitive resources are more vulnerable to trauma. For instance, some research indicates that individuals with lower working memory capacity are more affected by emotional events during task performance [169]. Furthermore, findings in post-traumatic stress disorder research also suggest that lower IQ levels may exist prior to trauma exposure [170, 171], supporting the notion that individuals with reduced cognitive resources are more susceptible to environmental adversities such as trauma. In addition, cognitive decline might increase the likelihood of risk-taking behavior, possibly explaining findings like the association between increased WM reaction time and trauma exposure. Individuals with poorer cognitive abilities are also more prone to report negative self-experiences [172]. Since cognitive decline typically precedes psychotic symptoms [66], and trauma reports are elevated in individuals with psychosis [52, 53], these overlapping factors may contribute to complex pathways of risk. Although not always intuitive, the observed relationships may provide new explanations for these dynamics and help address existing gaps in the literature.

The lack of association between certain environmental risk factors such as trauma, cannabis, familial risk and PPS in this study may stem from two main factors. First, the relatively low levels of psychosis proneness within the sample could have reduced the likelihood of detecting meaningful links. Secondly, the study did not employ stratified recruitment procedures, such as pre-selecting cannabis users versus non-users, which led to fewer participants exposed to certain environmental risks. Since the analysis focused on mapping the overall directionality of multiple risk factors rather than isolating specific ones, direct associations may not have emerged. Moreover, participant generally exhibited subclinical symptoms, which did not meet the threshold for clinical diagnosis or treatment. Nonetheless, self-report tools were used, and such symptoms may still reflect meaningful psychological process with potential clinical implications. The lack of clinical-level symptom severity may partly explain the limited associations observed. While conventional power calculations are not suitable for CDA due to

the absence of traditional null hypothesis testing, recent simulations have demonstrated that CDA can detect meaningful effects with limited false positives even at the current sample size [173]. Nonetheless, the absence of known prevalence estimates for psychosis proneness constrains our ability to draw definite conclusions regarding environmental influences.

These results indicate that holding negative self-beliefs and perceiving a lack of social connectedness and trust may contribute to emergence of paranoid ideation and other unusual experiences, as reflected by the PPS. In turn, these psychological factors appear to influence specific neural activation patterns during working memory. The presence of reciprocal causal paths between PPS and neural activity suggests a complex interaction wherein cognitive processes and psychosis-like traits mutually influence one another. Additionally, the possible impact of weakened social cohesion and trust on PPS reinforces the role of the social context in shaping susceptibility psychotic experiences. The observed activation in the DLPFC associated with higher PPS may reflect neural correlates of psychosis vulnerability during cognitive tasks. Notably, the application of automated CDA tools such as GFCL, which have demonstrated strong performance in applied datasets [174] strengthens the reliability of these conclusions. This study advances the understanding of the psychological and neural interplay in psychosis and may help guide intervention strategies. Future studies could implement targeted strategies to improve self-concept and social integration and assess their effectiveness in reducing psychosis proneness.

4.7 Limitations and Strengths

While this study provides new insights into data-driven causal discovery of PPS in a non-clinical population, several limitations must be acknowledged when interpreting the findings. First, no clinical interviews were performed to validate whether participants' self-reported psychotic-like experiences were clinically meaningful. Secondly, genetic predisposition was not explicitly included in the causal modelling. Although previous studies estimate that aggregated genetic liability accounts for roughly 9.9 % of schizophrenia risk and 4.3 % of variance in general cognitive functioning [175, 176, 177], our model only included a proxy, first-degree family history of psychosis, which did not yield additional insight in

this context. Importantly, the GFCI algorithm permits the inclusion of latent variables, suggesting that indirect influences such as genetic or neurobiological factors may still be reflected in the PAG. In addition, prior research has highlighted that polygenic risk scores often show limited predictive value in general population studies [178]. Still, including polygenic risk score in future work may help clarify the possibly confounded associations between PPS, negative self-schema, and social cohesion and trust. Thirdly, the analysis was restricted to the left hemisphere, limiting the examination of neural activation relevant to language-based manipulation in working memory. Although the neuroimaging analysis focused on the left-hemisphere regions usually associated with language processing, comprehensive language assessments were not collected. Only, verbal fluency was assessed which may not adequately capture language related functions. This limits the interpretation of task-related activation in relation to specific linguistic processes. Fourth, the stability analysis showed inconsistencies with the original PAG, revealing low stability in some inferred relationships. For instance, the possibly confounded association between negative self-schema and PPS showed only modest stability. In contrast, direct edge from negative self-schema to PPS appeared in 32.02 % of resampled models, while the reverse direction occurred in 37.36 %. For social cohesion and trust, a direct path to PPS emerged in 16.26 % of resampled models, more frequently than the reverse or confounded edges. Drawing on expert judgment and existing literature, we hypothesized that both negative self-schema and social cohesion and trust are likely to exert a direct influence on PPS. This view was further supported by SEM results, where treating these edges as direct effects produced consistent effect sizes and model fit indices relative to the original model (Table A.3). Therefore, the detection of potential latent confounders by GFCI should be regarded as a methodological strength, allowing a nuanced view of variable interdependencies not easily captured through hypothesis-driven approaches. The complex interplay among variables likely contributed to the observed instability, and embracing this uncertainty enables more robust and reflective conclusions. Future studies with larger and more stratified samples can build on these findings to improve the reliability of causal inference. Lastly, while this study utilized a sample that included twins and siblings, it did not implement twin modelling due to sample size constraints and the study’s scope, which did not primarily focus on disentangling genetic versus environmental contributions. Future research may consider twin modelling approaches to more fully capture heritable and environmental

influences on psychosis proneness.

The strength of the present findings lies in their novel use of causal discovery analysis to investigate the mechanisms underlying psychosis proneness in a non-clinical sample of adolescents and young adults. While the results offer promising directions, they require validation through follow-up studies. Future research could involve testing interventions aimed at improving self-schema and social trust to observe whether these changes reduce psychosis proneness. These strategies may deepen our understanding of how self-perception and social factors influence vulnerability to psychosis.

4.8 Conclusion

To the best of our knowledge, this is the first study to utilize a data-driven causal discovery approach to model direct causal relationships among environmental risk factors, cognitive variables, negative self-schema, task-related fMRI activation and psychosis proneness. CDA allowed for identifying the most fitting structure through mathematical optimization. If validated, these findings underscore the importance of addressing self-perception and social connectedness early on, potentially preventing psychotic-like symptoms from emerging. These results suggest that internal experiences, such as negative self-schema and reduced social trust, may contribute more psychosis risk than external events like trauma. Furthermore, our results imply that psychosis proneness may already influence brain function, specifically in the DLPFC, even before clinical signs appear. These insights could inform more targeted prevention and intervention efforts.

Chapter 5

Causal Discovery Analysis to Find Pathways to Psychosis Proneness During Rest: rsfMRI

5.1 Introduction

Functional magnetic resonance imaging (fMRI) is commonly employed to assess brain activity both during cognitive tasks and in resting-state conditions. Aberrant functional activity and connectivity are often observed in disease states, and these neural deviations during psychosis are suggested to be present not only during active cognitive performance but also at rest, when the general integrity of the neural system is sustained [116, 179, 77].

Cognitive impairments in psychosis are known for impairments in working memory, social cognition and attention [180]. The dorsolateral prefrontal cortex (DLPFC) and parietal regions, key components of the frontoparietal network, have been implicated in working memory function during both active cognitive tasks [152] and resting-state brain activity [181]. Notably, frontoparietal activation might not be solely related to cognitive performance but may also reflect general internal processes independent of specific tasks [182]. Resting-state connectivity results suggest that cortical networks at rest indicate cognitive, motor, and sensory functions [181].

Research has predominantly reported decreased functional connectivity (FC) within the frontoparietal network in individuals with schizophrenia relative to healthy controls [183]. Other research has similarly reported reduced FC in the frontoparietal network [184]. In contrast, increased FC in frontoparietal networks has been related to worse working memory performance, independent of group (patient, healthy relatives, and controls) [185]. However, the relationship between FC in the general population, environmental risk factors for psychosis, and cognitive and demographic factors in relation to psychosis proneness has not been fully explored at once. Moreover, studies comparing both task-based performance and resting-state conditions are limited. Therefore, the final study of this thesis extends causal discovery analysis by incorporating network-level mean rsfMRI functional connectivity indices to complement the task-based fMRI findings presented in Chapter 4. This approach enables a comparison of neural patterns associated with psychosis proneness during cognitive task performance and resting state, aiming to determine whether such neural deviations occur independently of task performance.

5.2 Sample Characteristics

Sample characteristics are presented in Table 5.1.

Table 5.1: Sample Characteristics

Sample Characteristics	N=236	Min	Max
Demographic Variables			
Age, mean (SD)	19.68 (2.36)	14	24
Gender: Female, n (%)	90 (38.14%)		
Gender: Male, n (%)	146 (61.86%)		
Socioeconomic Status of Mother or Father			
Never worked or long-term unemployed	2 (0.85%)		
Routine work	12 (5.08%)		
Lower-level technical job	20 (8.47%)		
Lower-level service/sales/secretarial	16 (6.78%)		
Lower-level admin/technician	14 (5.93%)		
Self-employed	28 (11.86%)		
Small-medium business owner	14 (5.93%)		
Intermediate level	86 (36.44%)		
Middle-level manager	34 (14.41%)		
Senior manager	10 (4.24%)		
Years of Education, mean (SD)	13.78 (2.22)	8	18
Psychological Variables			
Psychosis Proneness, mean (SD)	74.19 (15.71)	42	122
Negative Self-Schema, mean (SD)	5.27 (4.68)	0	22
Environmental Variables			
Ethnic Minority: Turkish, n (%)	202 (85.59%)		
Ethnic Minority: Other, n (%)	34 (14.41%)		
Paternal Age < 40, n (%)	174 (89.69%)		
Paternal Age 40–50, n (%)	18 (9.28%)		

Sample Characteristics	N=236	Min	Max
Paternal Age > 50, n (%)	2 (1.03%)		
Paternal Age, mean (SD)	31.91 (5.51)	20	47
Obstetric Complications, mean (SD)	0.52 (0.98)	-0.5	2.5
No Exposure, n (%)	96 (40.68%)		
Exposed during pregnancy or birth, n (%)	140 (59.32%)		
Parental Discord: None, n (%)	87 (36.86%)		
Parental Discord: Some, n (%)	27 (11.44%)		
Parental Discord: Moderate, n (%)	49 (20.76%)		
Parental Discord: Marked, n (%)	52 (22.03%)		
Parental Discord: Violence, n (%)	21 (8.9%)		
Urban Birth: Urban center, n (%)	152 (72.38%)		
Urban Birth: Urban Cluster, n (%)	50 (23.81%)		
Urban Birth: Rural, n (%)	8 (3.81%)		
Childhood Trauma: Trauma, n (%)	61 (25.85%)		
Childhood Trauma: No Trauma, n (%)	175 (74.15%)		
Discrimination, mean (SD)	1.41 (1.59)	0	8
Life-threatening events (Last 12 months), mean (SD)	1.97 (1.9)	0	9
Social Cohesion and Trust, mean (SD)	30.73 (8.31)	10	55
Alcohol Usage > 12 drinks/year, n (%)	125 (52.97%)		
Alcohol Usage < 12 drinks/year, n (%)	111 (47.03%)		
Cannabis: No exposure, n (%)	179 (75.85%)		
Cannabis: Little/moderate, n (%)	37 (15.68%)		
Cannabis: High exposure, n (%)	20 (8.47%)		
Other Drug Use: Used, n (%)	21 (8.9%)		
Other Drug Use: Not used, n (%)	215 (91.1%)		
Psychiatric Medication: Used, n (%)	41 (17.37%)		
Psychiatric Medication: Not used, n (%)	195 (82.63%)		

Sample Characteristics	N=236	Min	Max
Family History of Psychosis: Yes, n (%)	14 (5.93%)		
Family History of Psychosis: No, n (%)	222 (94.07%)		
Cognitive Variables			
IQ, mean (SD)	101.91 (13.88)	70	154
Verbal Fluency, mean (SD)	13.41 (3.43)	4.25	24.5

5.3 Causal Discovery Analysis with rsfMRI Connectivity Indices

To model psychosis proneness, the GFCI was applied, incorporating variables sociodemographic (3), environmental (8), psychological, including the psychosis proneness (2), drug usage (4), family history of psychosis (1), and mean rsfMRI functional connectivity indices (6) at rest. The resulting PAG, including effect sizes and p-values, is illustrated in Figure 5.1.

Model fit statistics from the SEM demonstrated a good fit to the model, RMSEA= 0.038, Tucker-Lewis Index = 0.783. Edge weights are shown adjacent to their respective arrows in Figure 5.1. All but one edge were statistically significant at $p < .05$, with 23 out of 28 edges reaching significance at $p < .01$ (Figure 5.1, Table 5.2). Uncorrected p-values were used for the graphical representations.

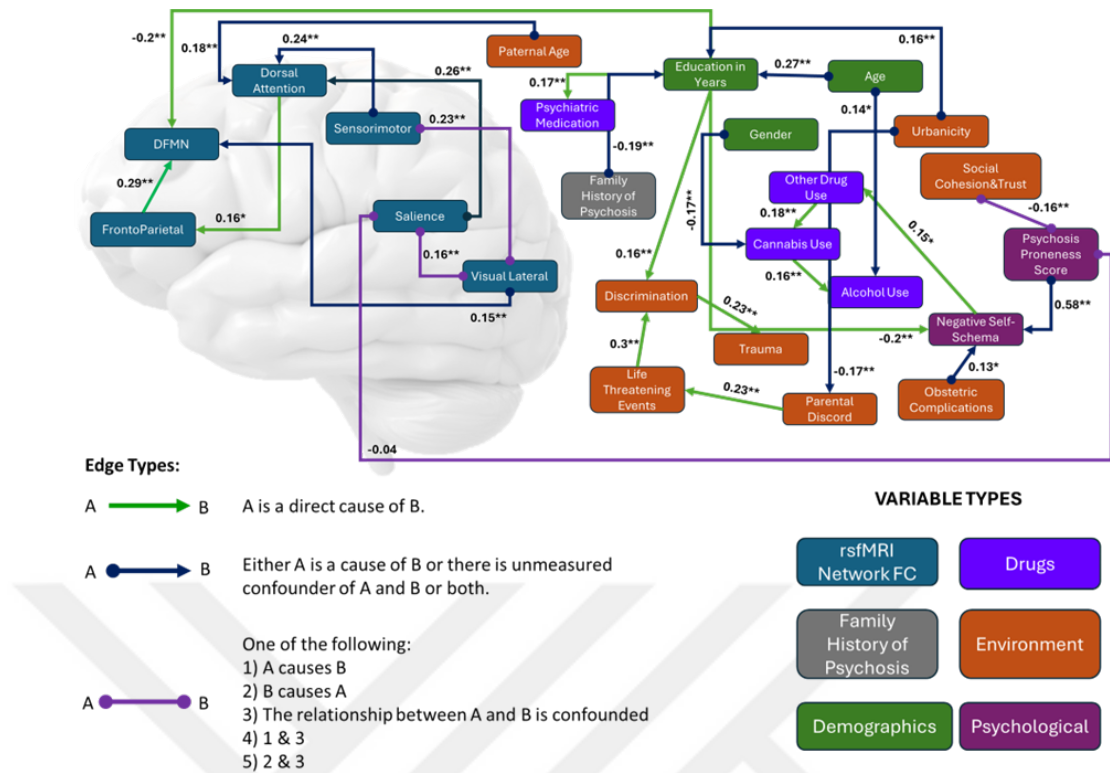


Figure 5.1: Partial Ancestral Graph depicting causal relationships among rsfMRI FC Indices and all variables.

The PAG displays estimated causal links among rsfMRI FC indices, environmental exposures, demographic and cognitive factors, and psychological variables. Causal Discovery Analysis was performed using GFCI for rsfMRI FC indexes, environmental and psychological variables. (FC: functional connectivity) (Brain illustration adapted with courtesy of <https://www.mindmedia.com>).

** $p < 0.01$; * $p < 0.5$

Table 5.2: SEM Results for the PAG Derived from rsfMRI FC Indices and Additional Factors

lhs	op	rhs	est	se	z	pvalue	ci.lower	ci.upper
DFMN	~	Fronto Parietal	0.29	0.06	4.8	1.13E-06	0.17	0.41
DFMN	~	Education in Years	-0.19	0.06	-3.26	0.001	-0.31	-0.07
Discrimination	~	Life Threatening Events	0.3	0.06	5.0	4.57E-07	0.18	0.42
Discrimination	~	Education in Years	0.16	0.06	2.66	0.007	0.04	0.28
Cannabis Use	~	Other Drug Usage	0.17	0.06	2.81	0.004	0.05	0.3
Fronto Parietal	~	Dorsal Attention	0.16	0.06	2.54	0.01	0.03	0.28
Alcohol use	~	Cannabis Use	0.16	0.06	2.59	0.009	0.04	0.28
Trauma	~	Discrimination	0.22	0.06	3.57	0.0003	0.1	0.35
Negative self-schema	~	Education in Years	-0.2	0.05	-3.91	9.04E-05	-0.3	-0.09
Psychiatric medication	~	Education in Years	0.16	0.06	2.64	0.008	0.04	0.29
Other Drug Usage	~	Negative self-schema	0.15	0.06	2.43	0.01	0.02	0.27
Life Threatening Events	~	Parental discord	0.22	0.06	3.58	0.0003	0.1	0.35
Dorsal Attention	~~	Salience	0.26	0.06	4.22	2.42E-05	0.14	0.38
Dorsal Attention	~~	Sensorimotor	0.24	0.06	4.01	6.02E-05	0.12	0.36
Dorsal Attention	~~	Paternal age	0.18	0.06	3.02	0.002	0.06	0.3
Visual Lateral	~~	Salience	0.15	0.05	2.65	0.007	0.04	0.27
DFMN	~~	Visual Lateral	0.15	0.05	2.58	0.009	0.03	0.26
Visual Lateral	~~	Sensorimotor	0.23	0.06	3.78	0.0001	0.11	0.35
Alcohol use	~~	Age	0.14	0.06	2.31	0.02	0.02	0.26

lhs	op	rhs	est	se	z	pvalue	ci.lower	ci.upper
Education in Years	~~	Age	0.26	0.06	4.16	3.14E-05	0.14	0.39
Education in Years	~~	Family History of Psychosis	-0.19	0.06	-3.09	0.001	-0.31	-0.07
Education in Years	~~	Urbanicity	0.16	0.06	2.64	0.008	0.04	0.28
Cannabis	~~	Gender	-0.16	0.06	-2.57	0.009	-0.29	-0.03
Negative self-schema	~~	OC	0.12	0.05	2.44	0.01	0.02	0.22
Negative self-schema	~~	Psychosis proneness	0.58	0.07	7.99	1.33E-15	0.43	0.72
Salience	~~	Psychosis proneness	-0.03	0.04	-0.83	0.4	-0.12	0.05
Social Cohesion & Trust	~~	Psychosis proneness	-0.15	0.05	-3.02	0.002	-0.25	-0.05
Parental discord	~~	Urbanicity	-0.16	0.06	-2.6	0.009	-0.29	-0.04

Op = operator, lhs: left-hand side, rhs: right-hand side, est: estimate, se: standard error, ci-lower and ci-upper: the lower and upper bounds of a 95% confidence interval around the point estimate. A negative estimate indicates an inverse relationship between the predictor (lhs) and the outcome (rhs); as the predictor increases, the outcome decreases.

GFCI excluded the following variables from the Partial Ancestral Graph (PAG): ethnic minority, IQ, socioeconomic status and verbal fluency.

The PAG revealed that psychosis proneness score had a significant, possibly confounded direct effect on negative self-schema ($ES = 0.58$, $p < 0.01$, $REF = 9.9\%$). This suggests that higher levels of psychosis proneness score may lead to higher levels of negative self-schema. However, the resampling with replacement findings indicated that the possibly confounded relationship between psychosis proneness score and negative self-schema had very low edge stability (9.9 %), while the proportion of resamples showing no edge was 0 % (Table A.5). Psychosis proneness score and Social Cohesion & Trust demonstrated a reversed and significant, possibly confounded relationship ($ES = -0.16$, $p < 0.01$, $REF = 3.5\%$). An inverse relationship was observed between social cohesion and trust and PPS indicating that higher cohesion and trust was associated with lower PPS, and vice versa. Yet, this connection showed limited stability in resampling analysis, with only 3.5 % edge presence and 35.14 % indicating no edge.

Additionally, it was observed that obstetric complications (OC) had a possibly confounded significant association with negative self-schema ($ES = 0.13$, $p < 0.05$, $REF = 0\%$), implying individuals with a history of obstetric complications may develop stronger negative self-schemas later in life. Yet, this link was not replicated in the resampled models, with an edge frequency of 0 %. A direct edge from OC to negative self-schema was observed in 22.43 % of the resamples, while no edge was observed in 77.57 % of the resamples.

No definite direct effect of psychosis proneness score on any resting-state FC indices was observed when causal discovery analysis was conducted. There was only a confounded relationship between psychosis proneness score and averaged salience network FC was observed, indicating several possible relationship types. It is possible that psychosis proneness score causes the mean Salience FC or conversely, that mean Salience FC causes psychosis proneness score. Alternatively, their relationship may be confounded by an unobserved factor. It is also possible that psychosis proneness score causes the mean Salience FC and that this relationship is confounded by an unobserved factor, or that the mean Salience FC causes psychosis proneness score and is likewise confounded by an unobserved factor. Structural equation modelling results showed that the confounded relationship between psychosis proneness and the mean salience network FC was not

statistically significant, and the effect size was very small ($ES = -0.04$, $REF = 0.75\%$). Resampling results indicated minimal stability for this edge type, with an 80 % frequency of no edge appearing between the nodes.

The PAG suggested several possible causal relationships. Years of education had a direct significant reversed effect on negative self-schema ($ES = -0.2$, $p < 0.01$, $REF = 32.34\%$). Negative self-schema had a significant direct causal link to the use of drugs other than cannabis ($ES = 0.15$, $p < 0.05$, $REF = 19.06\%$). The use of other drugs, in turn, had a significant direct causal effect on cannabis use ($ES = 0.18$, $p < 0.01$, $REF = 16.07\%$). Cannabis use then had a significant causal effect on alcohol use ($ES = 0.16$, $p < 0.01$, $REF = 14.39\%$). Age also had a possibly confounded significant relationship with alcohol use ($ES = 0.14$, $p < 0.05$, $REF = 46.36\%$), which is expected due to age regulations on alcohol consumption. Furthermore, gender had a possibly confounded relationship with cannabis use ($ES = -0.17$, $p < 0.01$, $REF = 39.63\%$), indicating that males had significantly higher levels of cannabis use compared to females.

Direct effects of environmental risk factors on psychosis proneness score were not observed. However, the PAG revealed various relationships among the environmental risk factors. Urbanicity had a possibly confounded direct effect on years of education ($ES = 0.16$, $p < 0.01$, $REF = 39.07\%$), suggesting a link between urban birth and increased educational attainment. Participants were primarily continuing their bachelor education, indicating that those born in urban areas might be more likely to enroll in graduate studies. Higher years of education had a direct significant effect on increased reporting of discrimination ($ES = 0.16$, $p < 0.01$, $REF = 22.99\%$). The PAG suggests that urbanicity had possibly confounded reversed effect on parental discord ($ES = -0.17$, $p < 0.01$, $REF = 44.86\%$). The result suggests that offspring born in urban regions reported less parental discord compared to those born in rural areas. Additionally, parental discord had significant direct effect on life-threatening events ($ES = 0.23$, $p < 0.01$, $REF = 37.95\%$). It suggests that offspring who report higher levels of parental discord in their household tend to experience more life-threatening events. Subsequently, life-threatening events had a direct effect on discrimination ($ES = 0.3$, $p < 0.01$, $REF = 44.86\%$), and discrimination had a direct effect on the experiencing trauma ($ES = 0.23$, $p < 0.01$, $REF = 29.16\%$).

Relationships between sociodemographic variables and other factors including

environmental, psychological, and resting-state functional connectivity indices were infrequently observed. However, years of education were found to have a significant direct effect on the mean DFMN FC ($ES = -0.20$, $p < 0.01$, $REF = 46.72\%$). Additionally, paternal age had a possibly confounded significant effect on the mean Dorsal Attention Network FC ($ES = 0.18$, $p < 0.01$, $REF = 47.1\%$). The result suggests that the increased age of father at conception increases the mean functional connectivity in the dorsal attention network during rest.

The direction of the relationship between negative self-schema and psychosis proneness is inherently complex and showed no definitive results. In Chapter 4, when task-based fMRI ROI indices and other variables were introduced to CDA, the results suggested that negative self-schema had a possibly confounded direct effect on psychosis proneness. However, when causal discovery analysis was applied using rsfMRI functional connectivity indices, the directionality appeared to be reversed, indicating that psychosis proneness had a possibly confounded effect on negative self-schema. One potential reason for these differing results could be the handling of prior knowledge introduced to the causal discovery analysis. Given the growing literature on the role of negative schema in psychosis [186, 187, 81], the tier structure in the knowledge box was revised: environmental risk factors and negative self-schema were assigned to tier 4, while psychosis proneness, resting-state FC indices, and psychiatric medication were placed in the final tier.

After reorganizing the knowledge arrangement, the directionality of the relationship between negative self-schema and psychosis proneness changed (Figure 5.2). The new generated PAG results indicated that negative self-schema has a direct effect on psychosis proneness ($ES = 0.6$, $p < 0.01$). In addition, social cohesion and trust exhibited a reversed direct causal effect on psychosis proneness ($ES = -0.16$, $p < 0.01$). Furthermore, the previously observed confounding association between psychosis proneness and the mean Salience Network functional connectivity was no longer present. The possibly confounded effects of years of education and obstetric complications on negative self-schema were also eliminated. In addition to the removed edges, new edges were introduced: years of education had a direct effect on psychosis proneness score ($ES = 0.17$, $p < 0.01$), trauma had a direct effect on both negative self-schema ($ES = 0.2$, $p < 0.01$) and Social Cohesion and Trust ($ES = -0.16$, $p < 0.05$). Lastly, obstetric complications had a possibly confounded direct effect on psychosis proneness score ($ES = -0.11$,

$p < 0.05$).

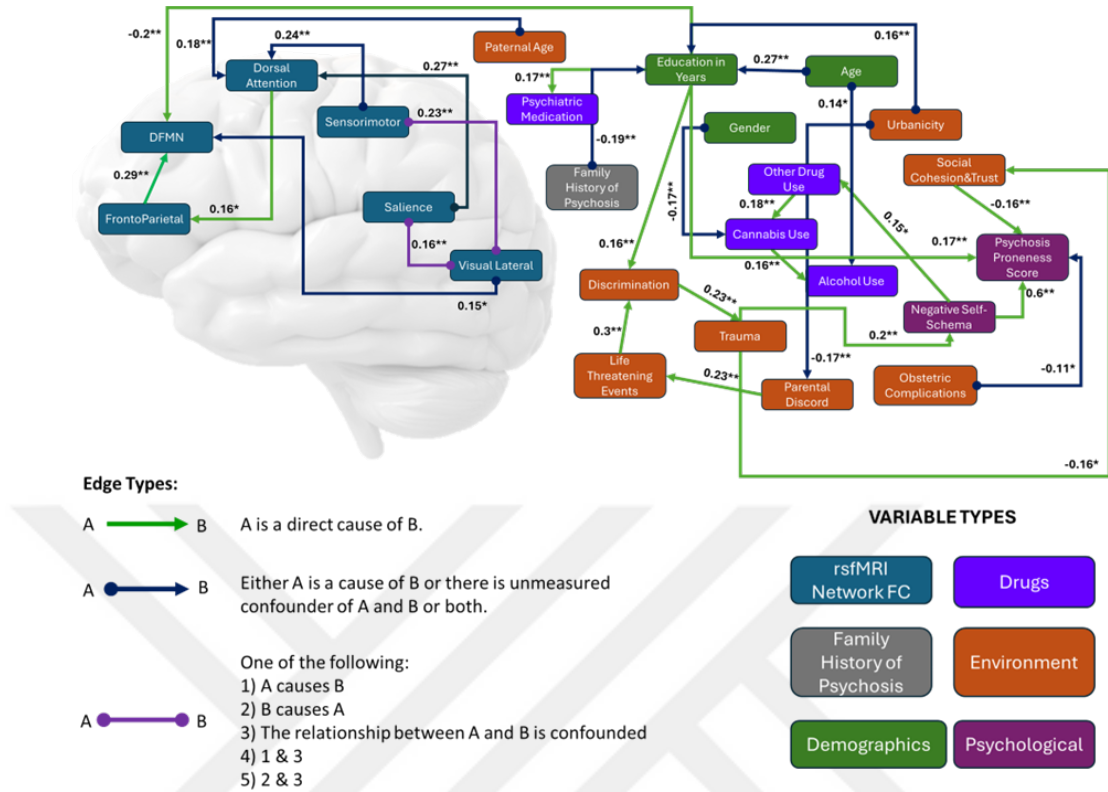


Figure 5.2: Causal Discovery Analysis with five levels of hierarchy for all variables and rsfMRI FC Indexes with Effect Sizes and p-value Information.

Causal Discovery Analysis was performed using GFCI for rsfMRI FC indexes, environmental and psychological variables. (FC: functional connectivity) (Brain illustration adapted with courtesy of <https://www.mindmedia.com>).

** $p < 0.01$; * $p < 0.5$

5.4 Exploring the Relationship Between Psychosis Proneness Score and Seed-based Resting-State Functional Connectivity

To further investigate the potential relationship between psychosis proneness score and seed-based resting state FC indices, causal discovery analysis was conducted using each ROI to ROI FC indices instead of network level mean indices used in previous analyses. The partial ancestral graph generated from individual functional connectivity indices revealed a direct causal effect of psychosis

proneness on functional connectivity between clusters with MNI coordinates $x = +0$, $y = -8$, $z = +4$ and the Right Dorsal Attention-Frontal Eye Fields (FEF). However, these individual functional connectivity indices were not controlled for family-relatedness. To address this limitation, a multilevel mixed-effects linear regression was conducted, controlling for family relatedness. This analysis confirmed that higher psychosis proneness significantly predicts stronger functional connectivity between MNI coordinates $x = +0$, $y = -8$, $z = +4$, which roughly corresponds to the thalamus (Figure A.1), and the Right Dorsal Attention-FEF ($z = 2.42$, $p = 0.016$).

5.5 Discussion

The PAG obtained from the causal discovery analysis conducted with sociodemographic, cognitive, environmental risk factors, psychological variables and mean resting-state functional connectivity indices suggest potentially informative relationships. In this sample, the results demonstrated during the brain at rest there was a possibly confounded relationship between psychosis proneness score and the mean Salience network functional connectivity, but the effect was very small with no statistical significance. The result suggests that in the current sample, when brain at rest, there was no effect of psychosis proneness score on the mean functional connectivity. It is important to note that only summary statistics for functional connectivity at rest were utilized. While mean functional connectivity values at the network level allow for interpretation of large-scale connectivity patterns, it may not capture more region-specific associations with psychosis proneness. Further validation analysis was performed using region to region functional connectivity indices. These individual connectivity indices reflect pairwise functional correlations between ROI time series. These results showed a causal effect of psychosis proneness score on the functional connectivity between the region roughly corresponding to thalamus and the right dorsal attention-FEF. These findings highlight a potential mechanistic relationship between psychosis proneness and specific neural circuits, particularly within the thalamocortical connectivity. The thalamus projects to cortical regions and dysconnectivity in these projections has been widely observed in psychosis spectrum disorders and such deviations have been linked to cognitive dysfunction and impaired attention [188, 189]. The dorsal attention network mainly consists of intraparietal sulcus

(IPS) and frontal eye fields (FEF) and it is primarily associated with goal directed attention, showing sustained activity when attention is actively maintained on a stimulus [190]. Studies have shown aberrant, typically reduced, thalamocortical connectivity in schizophrenia patients and prodromal stage of psychosis compared to healthy controls [191, 192]. In the current study, higher psychosis proneness score was associated with stronger resting-state functional connectivity between the thalamus and FEF. This increased connectivity may reflect a compensatory mechanism aimed at preserving maintaining attention in individuals with higher levels of psychosis proneness. While most earlier research has primarily concentrated on thalamic connectivity with the prefrontal cortex, one study also reported reduced amplitude of low frequency fluctuations in FEF and thalamus among patients compared to healthy controls [193]. Although earlier findings in clinical populations often showed reduced thalamocortical connectivity, the current study suggests that in non-clinical young individuals with elevated psychosis proneness, stronger functional connectivity within the dorsal attention network, specifically between the thalamus and FEF may emerge. The observed predictive relationship highlights the importance of examining the region-specific patterns of functional connectivity. This result may reflect the role of these neural regions in attention regulation and their susceptibility to cognitive disruptions associated with psychosis proneness. Further research could assess how these findings integrate with broader models of psychosis risk and symptomatology.

Negative self-schema is generally considered a risk factor for psychosis, however studies also suggest a bidirectional relationship between these two factors [129]. In the initial partial ancestral graph in this chapter (Figure 5.1), the possibly confounded effect of psychosis proneness score to negative self-schema was found. The following possibilities were present for this edge:

- (A) Psychosis proneness $\rightarrow$ Negative self-schema
- (B) Psychosis proneness $\leftrightarrow$ Negative self-schema
- (C) Psychosis proneness $\rightarrow$ Negative self-schema and Psychosis proneness $\leftrightarrow$ Negative self-schema

The results suggest that higher levels of psychosis proneness score may lead to an increase in negative self-schema, but the edge might also be bidirectional. To explore this edge further, the second PAG was generated by introducing a new

tier. In this configuration, it was assumed that negative self-schema precedes psychosis proneness. Under these assumptions, the resulting PAG (Figure 5.2) revealed negative self-schema as the direct cause of psychosis proneness score. The comparison of these two partial ancestral graphs underscores the importance of prior knowledge and temporal assumptions in causal discovery analysis. While the initial graph (Figure 5.1) reflects the possibility of confounded or bidirectionality, the second graph suggests that negative self-schema develops earlier and contributes causally to psychosis proneness. At first glance, the differences between the two PAGs arising from variations in tier configurations may seem like a limitation of the analysis. However, it highlights the importance of prior knowledge in guiding the application of causal discovery methods. Furthermore, causal discovery analysis can integrate domain knowledge, but the structure of the graph is still not predefined like structural equation modelling. These results in fact align with the exploratory aims of causal discovery analysis and acknowledge the complexity of real-world data. The current results did not establish a definitive directionality of the relationship, but it did confirm a strong association between negative self-schema and psychosis proneness, as resampling with replacement analysis shows 0 % for no edge frequency. More conclusive findings can be obtained through future research involving larger sample sizes with more at-risk populations and longitudinal designs.

In the first PAG, the results indicated a possibly confounded effect of obstetric complications on negative self-schema. On the other hand, the second PAG revealed a possibly confounded effect of obstetric complications on psychosis proneness score. While numerous studies have identified obstetric complications as a risk factor for psychosis, there is a lack of research exploring their relationship with negative self-schema [194, 139]. In the first PAG, negative self-schema is a collider that both obstetric complications and psychosis proneness score collide in negative self-schema. So, negative self-schema can have an effect on both psychosis proneness score and obstetric complications. It could be important to further investigate the effect of negative self-schema on both factors.

In the results of the first PAG, there was an undirected confounded relationship between social cohesion and trust and psychosis proneness score. On the other hand, in the second PAG, with the extra domain knowledge, social cohesion and trust was observed as a direct cause of psychosis proneness score. The well-being of an individual does not only come from the “self” and close surroundings like

family environments but also from the community individual lives in [195]. Social cohesion was defined with two important points: i) *the absence of a social conflict* encapsulating inequalities and polarizations in society, ii) *the presence of strong social bonds* [195]. The second PAG suggests that lower or absence of a social conflict and higher presence of social bonds causes reduced psychosis prone-ness. Thus, the results highlight the importance of social capital on individual well-being including psychosis. It is expected that in societies with lots of conflicts and less social bonds can have an increased impact on the psychopathology of individuals [196]. Supporting this, epidemiological studies have shown that populations exposed to armed conflict and violence exhibit a higher prevalence of mental health problems [197, 198]. Moreover, environmental factors such as urbanization and holding refugee position increases the risk of psychiatric disorders and sometimes of psychosis through the channels of social adversity, stress and isolation [199, 200]. Animal studies also confirm that repeated social defeat is a risk factor for attenuated behavior and depressive-like symptoms [201, 202]. These findings mirror the psychologically degrading effect of social stress observed in humans. In the current study, participants were mostly residents of the Ankara region and thus the results may be unique to location specific patterns of social dynamics. Future research involving different cities of Türkiye with different types of social capitals and its effect on psychotic-like experiences are warranted.

In the first graph, education in years had a direct reversed significant effect on negative self-schema while in the second graph this edge was lost, and education in years had direct positive effect on psychosis proneness score. These results suggest that more years spent in education may linked to lower levels of negative self-schema (1st PAG) or increased level of education may lead to increased level of psychosis proneness (2nd PAG). This shift in edge, likely reflects the effect of background knowledge on the resulting graph structure. Our participants were mostly university bachelor students and results from the 1st PAG may suggest that increased years in education can change the schema about self in a positive way as individuals can define themselves with a profession. On the other hand, 2nd PAG suggests that higher level of education comes with a risk of increased levels of psychotic-like experiences. The result is expected as the mean age of our sample is 19.68 as it coincides with the typical onset of psychosis and approximate enrollment to the university. It is crucial to note that higher level of education was shown to be correlated with better clinical, cognitive outcomes for the first episode psychosis patients compared to counterparts with lower education [203] and in our

study we only examined the psychotic-like experiences in the general population with critical periods of age in which higher levels of psychotic-like experiences are observed. To make a further interpretation, wider age recruitment is required. The results may weakly also suggest that university students are at higher risk as their environment and life changes drastically. So, University councils can take precautions such as increasing the social cohesion at the university to prevent further progression of psychotic-like experiences.

In both generated PAGs, negative self-schema was found to have an effect on increased usage of other drug use, which in turn impacted the increased use of cannabis. Subsequently, cannabis use influenced the increased use of alcohol. This indicates a directed pathway from negative self-schema to alcohol use. Therefore, interventions targeting negative self-schema have the potential to affect all intermediary factors along this pathway, ultimately influencing alcohol use.

The generated PAG suggests several possible causal relationships between mean resting-state FC indices and other factors. The reversed association between years spent in education and mean DFMN FC, as well as the positive link between paternal age and connectivity within the Dorsal Attention Network, highlights the complexity of these relationships. The relationship between more years spent in education and reduced mean DFMN FC may indicate the engagement of lesser degree of this network could be attributed to neural efficiency. Studies on parental age are mainly focused on the effects of advanced or teenage parental age on to offspring in terms of cognitive abilities, longevity and psychopathology [204, 205]. While several research have investigated how parental age relates to brain structure, volume and development [206, 207], yet there remains a lack of research on how it influences brain function and connectivity in offspring during adolescence and young adulthood, as studies focus on infancy, early childhood or morphology of the brain [206, 208]. The current findings indicate that increased parental age at conception is associated with greater functional connectivity within the dorsal attention network. The results may suggest that increased parental age may correlate with increased attentional process in the offspring. However, the literature on the dorsal attention network in schizophrenia presents conflicting evidence. While some studies suggest that the overactivation in the dorsal attention network is associated with the schizophrenia, others found less connectivity

in the dorsal attention network in schizophrenia patients [209, 192]. Future research is needed to explore the functional correlates of paternal age in the general population.

In both PAGs, urbanicity demonstrated a potentially confounded inverse effect on parental discord, suggesting that rural birth in Türkiye is linked to higher levels of parental conflict within households. This finding may reflect several underlying mechanisms. Initially, parents living in rural areas of Türkiye may have a lower socioeconomic status and educational backgrounds in comparison to those in urban areas. Lower socioeconomic status has been linked to financial stress and reduced availability of resources. These factors can contribute to increased household conflict. However, it is challenging to directly elaborate on the role of socioeconomic status, as socioeconomic status was excluded from the PAG generated by the GFCI algorithm. Further studies are required to better understand how parental socioeconomic status contributes to this pathway. Additionally, PAG suggested sequential pathway that parental discord had direct effect on life-threatening events and life-threatening events cause increased experiences of discrimination, which subsequently contributed to exposure to trauma. The chain of events highlights the interconnected nature of environmental stressors and their cumulative effect on mental well-being, as well as the increased vulnerability to experiencing additional environmental stressors.

In summary, CDA applied to mean resting-state FC indices and other variables uncovered intriguing relationships, providing insights into potential pathways linking psychosis proneness, other risk factors for psychosis, and their associations with resting-state FC indices in the general population. Initially, the association between negative self-schema and psychosis proneness score showed differing results in the first generated PAG and second generated PAG. In the first PAG, psychosis proneness score had a possibly confounded relationship to negative self-schema, whereas in the second PAG, the direction was reversed, with negative self-schema exerting a direct effect on psychosis proneness score. These conflicting findings are one of the limitations of the current study, as the direction of the relationship is yet to be discovered. Similarly, while there was a strong association between social cohesion and trust and psychosis proneness score, the directionality also differed between the two PAGs. Despite these ambiguities, both negative self-schema and social cohesion and trust were found

to have strong and significant relationships with psychosis proneness score. Future research utilizing longitudinal data is needed to resolve these uncertainties. Additionally, the PAG had no significant direct effects of psychosis proneness score on mean resting-state FC indices, indicating that psychosis proneness may not affect the mean resting-state functional connectivity. However, when CDA was applied to ROI-to-ROI resting-state connectivity indices, psychosis proneness score was found to have a direct effect on the functional connectivity between the region roughly corresponding to thalamus and the right FEF in dorsal attention network. These findings indicate that while mean connectivity indices may not capture the effects of psychosis proneness, individual connectivity indices could provide more detailed insights. Although the total number of individual connectivity indices poses challenges for graphical representation, they may offer a more precise understanding of the neural correlates of psychosis proneness.

Chapter 6

Overall Conclusions and Future Prospects

Risk factors for psychosis are among the most well-studied topics in the effort to understand debilitating disorders such as schizophrenia. Specifically, researchers have investigated the effects of environmental and genetic risk factors on the development of psychosis. Recently, the conceptualization of psychosis as a continuum has gained attention, as psychotic-like symptoms can also be experienced in the general population. There is a lack of studies extensively examining multiple risk factors for psychosis proneness in healthy Turkish adolescent and young adult population, employing both traditional methods such as regression and data-driven machine learning algorithm to both task-based and resting state fMRI data. This dissertation aimed to unravel the effects of psychological, cognitive and environmental risk factors on psychosis proneness and its neural correlates in the general population, focusing on adolescence and young adulthood. To this aim, various statistical approaches were employed. In Chapter 3 and Chapter 4 we used a dataset involving task-based fMRI ROIs and applied two different statistical methods. In Chapter 3, multilevel mixed effects linear regression was used to examine the effects of both individual and aggregate environmental risk factors, as well as schema variables on psychosis proneness. Chapter 3 also explored neural correlates of psychosis proneness during task-based fMRI. Next, in Chapter 4, we used a data-driven approach and investigated pathways to psychosis proneness and its neural correlates during task-based fMRI by introducing all relevant variables to GFCI algorithm to find best-fitting graph to our data.

Finally, in Chapter 5, we applied GFCI algorithm to the larger sample with resting-state functional connectivity indices to observe directional relationships between all variables to observe whether psychosis proneness is associated with any neural correlates when brain at rest.

In Chapter 3, a multilevel mixed effects linear regression analysis was performed to find predictive powers of both aggregated and individual environmental risk factors to psychosis proneness and schizotypy. The results revealed that aggregated ERS was a strong predictor of both constructs. Specifically, aggregated ERS significantly predicted depressive symptom frequency, the distress associated with depressive and negative symptoms, as well as positive and negative schizotypy. These results underscore the critical role of aggregated environmental risk factors in shaping vulnerability to psychosis and schizotypy. In fact, aggregated ERS were specifically able to capture the reactivity to psychotic-like experiences in negative and depressive dimensions, as reflected in higher distress levels. Aggregated ERS did not significantly predict frequency of positive, negative symptoms and distress associated with experiencing positive symptoms. These results may indicate that aggregated ERS may not be sensitive enough to predict certain symptoms dimensions, particularly those related to positive psychotic-like experiences. Furthermore, aggregated ERS was a strong predictor of schizotypy in all dimensions.

Considering the strong predictive power of the aggregated ERS, individual risk scores were also specifically investigated to determine whether they independently have significant predictive power for psychosis proneness and schizotypy. Initially, ethnic minority or migration history was found to significantly predict only the depressive dimension distress score of CAPE-42, indicating that being in a minority position can increase reactivity to depressive psychotic-like experiences. Our results also suggest that increased paternal age predicts a reduced frequency of positive psychotic-like experiences. This finding contradicts with the existing literature. However, it is important to highlight that the average paternal age was 31.67 years old, which is relatively young. It is important to evaluate the current results in the context of the region as younger fathers may provide fewer resources, including financial support, to their offspring. In fact, higher paternal age could be a protective factor against positive psychotic-like experiences. It is also worth noting that the current sample did not include father at at-risk ages (e.g., > 55 years), which may explain the absence of observed risk

effects associated with advanced paternal age. In Chapter 3, reporting obstetric complications significantly predicted higher levels of negative schizotypy, meaning higher levels of social isolation, introversion, hypersensitivity and restricted affect. This finding highlights the potential impact of abnormal embryonal or neonatal complications on neurodevelopment, which can lead to deviations in cognitive and social functioning and psychiatric disorders [210, 211]. Current findings on urbanicity showed results that differ from findings in western countries, with being born in rural areas of Türkiye predicting psychosis proneness, except in the depressive dimensions and schizotypy. These findings are important as they provide unique insights specific to Türkiye's general population in relation to psychosis proneness. Childhood trauma emerged as one of the strongest predictors of psychosis proneness across all dimensions except the negative frequency. Furthermore, exposure to trauma also predicted all schizotypy scores. In contrast to the existing literature, cannabis use was not found to be a significant predictor of psychosis proneness. Cannabis use only predicted SIS-R total score. This discrepancy may stem from the composition of the current sample, which included few heavy cannabis users. In summary, assessing the predictive power of individual risk factors has provided valuable insights into the specific dimensions of psychosis proneness and schizotypy they influence most effectively. To date, no comprehensive analysis has aimed to understand these mechanisms in such detail. Nonetheless, when compared to individual risk factors, the aggregated environmental risk score demonstrated greater predictive power, underscoring its value in capturing the cumulative impact of multiple risk factors on psychosis. However, it is important to note that the arrangement of the aggregated environmental risk score was based on data from western countries. For instance, in our sample, being born in a rural area emerged as a risk factor, in contrast to findings from western countries where urban areas are typically considered as a risk factor. Future studies are needed to develop and validate an adapted version of aggregated risk scores specific to Turkish population to enable more comprehensive and culturally relevant conclusions.

One of the important findings from Chapter 3 was that schema about self and others are strong predictors of psychosis proneness and schizotypy. The vast majority of literature on psychosis is mainly focused on the environmental and genetic risk factors and not enough research was conducted on how these factors shape the cognition of oneself or how cognitive processes impact the perception of environmental experiences in the general population. The findings showed that

negative self-schema is a stronger predictor of psychosis proneness and schizotypy than any of the environmental risk factors investigated. Negative self-schema and negative schema about others significantly predicted all dimensions of psychosis proneness and schizotypy. Positive self-schema predicted all dimensions of psychosis proneness except for the positive frequency subscale. Similarly, positive schema about others significantly predicted all frequency scores except for negative frequency and did not significantly predict dimension distress scores. However, positive schema about others significantly predicted all schizotypy scores. Results of this thesis demonstrated that negative self-schema is a robust predictor of psychosis proneness in the general population. Moreover, we found that higher negative self-schema is associated with increased activation in the VLPFC, a region implicated in emotion regulation. This finding is consistent with observations from a previous study that VLPFC activation in first-episode psychosis patients during working memory as a complementary to the reduced activation in DLPFC [152]. Our findings extend Tan et al.'s study by providing evidence that a similar mechanism may be observable in the general population and is related to individual differences in negative self-schema. This suggests that the compensatory role of VLPFC may not be exclusive to clinical populations but could represent neuromodulatory mechanism linking negative self-schema to psychosis proneness. VLPFC is also known to be involved in emotion regulation and activation in VLPFC is linked to activity in amygdala. Furthermore, higher activation in VLPFC is observed in patients with depression [212] so the relationship between higher negative self-schema and increased VLPFC activation could be explained by the disruptive emotional processes in the brain due to increased negative perception of the self. Given that psychosis proneness may arise from an accumulation of emotional, cognitive, and environmental stressors, the association between negative self-schema, VLPFC activation, and psychosis proneness provides a compelling pathway for understanding the early neural correlates of psychosis risk. Future research is needed to examine whether observed VLPFC activation is also compensatory to deviated DLPFC activation in individual with higher psychosis proneness. Additionally, animal models designed to mimic depression, combined with electrophysiological recordings from freely behaving animals, could provide valuable insights into the interplay between these two brain regions and their associations with depressive processes.

Despite the significant predictions obtained through multilevel mixed effects linear regression in Chapter 3, the direct causal pathways leading to psychosis

prone to psychosis, as well as whether psychosis proneness directly causes any neural activity, remain unresolved. To address this question, in Chapter 4, we applied Causal Discovery Analysis by using the GFCI algorithm to the same sample analyzed in Chapter 3, incorporating all sociodemographic, environmental, psychological variables and task-based fMRI activation indices during working memory. While in Chapter 3, we utilized a limited set of variables to predict psychosis proneness and its neural correlates through regression modelling, in Chapter 4, we expanded the scope by including all relevant and available data in our dataset. Unlike regression modelling, which is constrained to a smaller subset of variables, CDA allowed us to analyze the complete dataset simultaneously. Thus, these two chapters not only differ in their analytical approaches but also provide complementary insights into potential pathways leading to psychosis proneness. In Chapter 4, we used the GFCI algorithm to find causal graph also known as a partial ancestral graph (PAG) and used structural equation modelling (SEM) as a complementary approach to estimate effect sizes and assess the statistical significance of edges. We introduced all sociodemographic, environmental, psychological, and task-based fMRI ROI indices to explore pathways to psychosis proneness. The PAG suggested several paths and causal relationships between variables, with several key findings emerging. First, among all risk factors, negative self-schema has emerged as a possibly confounded cause of psychosis proneness. The result suggested that higher levels of negative self-schema possibly had a direct cause on higher level of psychosis proneness. Additionally, social cohesion and trust emerged as another possibly direct cause of psychosis proneness, suggesting that lower levels of social cohesion and trust possibly leads to higher levels of psychosis proneness. Furthermore, the analysis revealed a direct effect of psychosis proneness on DLPFC activation during working memory, suggesting that higher levels of psychosis proneness may drive increased activation in DLPFC. These results align with the idea that psychosis proneness may be shaped by negative self-schema and, in turn, influence neural activation during working memory. The causal relationships between brain function and psychosis proneness point to a complex interaction between cognitive control processes and the emergence of psychosis-related features. Additionally, the impact of a diminished sense of belonging and trust on psychosis proneness underscores the importance of social environmental factors in shaping vulnerability to psychosis. The positive relationship between psychosis proneness and activation in the DLPFC suggests a

potential neural basis for the manifestation of psychosis proneness during cognitive tasks. Despite the significant predictions obtained through multilevel mixed effect linear regression, using causal discovery analysis provided enhanced understanding of the causal directions between variables. CDA revealed that not all associations observed in Chapter 3 are causations. In fact, small percentages of association showed causation. For example, results obtained through multilevel mixed effects linear regression, in Chapter 3, revealed a strong association between trauma and psychosis proneness but CDA results revealed no direct effect of trauma to psychosis proneness. Overall, these scientifically derived relationships provided insight into the complex aspects of psychosis proneness and provide valuable insights into potential mechanisms underlying its development.

We further investigated whether the direct causal relationship between psychosis proneness and DLPFC activation observed during task-based fMRI could also be observed when the brain is at rest. To address this, in Chapter 5, we employed CDA on a dataset including resting-state mean connectivity indices. This dataset featured a larger sample compared to the one used in Chapter 4. Results indicated that psychosis proneness did not exhibit definitive causal relationship with mean resting-state FC indices. In the first PAG (Figure 5.1), there was only a non-directional association between psychosis proneness score and the mean Salience FC index. However, this relationship was neither statistically significant nor substantial in effect size. Furthermore, in the second PAG (Figure 5.2) generated using a different arrangement of prior knowledge, this association was no longer present. Considering the findings from Chapter 4 and Chapter 5, it can be initially concluded that psychosis proneness has a more pronounced effect on task-based activation compared to resting-state activity. However, it should be noted that rsfMRI dataset included a larger sample size, and as data-driven approach was employed, the results are inherently dependent on the input provided to the algorithm. Overall, task-based activity may be more sensitive to psychotic-like experiences than resting-state activity, as previous studies have demonstrated significant cognitive deviations in individuals with schizophrenia, not only during the state of the disease but also during their developmental progress prior to diagnosis. On the other hand, additional CDA with ROI-to-ROI resting-state FC indices without controlling for family relatedness was employed and results revealed that psychosis proneness directly affects functional connectivity between thalamus and the right FEF. The results indicate that increased psychosis proneness may directly cause increased FC in the dorsal attention network, a primarily

goal-directed network that has been shown to be disrupted both in individuals with schizophrenia and at-risk populations [213, 214]. These findings align with existing literature. Moreover, this result complemented the findings from Chapter 4, where psychosis proneness had a causal relationship with increased activation in DLPFC during working memory. In Chapter 4 and 5, there were conflicting results between PAGs regarding the direction of relationships between negative self-schema and psychosis proneness score, as well as between social cohesion and trust and psychosis proneness score. This disparity could be attributable to sample size differences and the inclusion of different fMRI indices. However, the resampling with replacement analysis showed similar results in comparison to the suggested PAGs. Although, the precise causal pathways remain uncertain between these nodes, the findings highlight a strong and significant association between them.

Taken together, the results obtained from task-based fMRI and rsfMRI, analyzed using two different statistical approaches to psychosis proneness and its neural correlates, point out that negative self-schema and social cohesion and trust could be potential causal factors of psychosis proneness. Additionally, psychosis proneness appears to influence task-related neural activations both during working memory performance and at rest. To conclude, whereas environmental influences linked to psychosis, including traumatic experiences, show strong associations with psychosis proneness, they do not necessarily indicate direct causation. The findings from this thesis emphasize the importance of targeting self-schema and social cohesion and trust to reduce the likelihood of psychotic-like symptoms in the non-clinical population. Moreover, the findings highlight the direct effects of psychosis proneness on task-related neural activations and functional connectivity in the general population, enabling additional insight into its neural mechanisms.

6.1 Limitations and Future Directions

Although this thesis presents new insights into psychosis proneness in non-clinical populations, the findings must be interpreted with caution due to several limitations. Firstly, no clinical interviews were conducted to separately assess whether the self-reported psychotic-like symptoms had diagnostic relevance. Secondly,

genetic predisposition was not directly integrated into the causal discovery analysis. While aggregated genetic liability accounts for approximately 9.9 % of the variance in schizophrenia risk and 4.3 % of the variance in general cognitive performance [175, 176, 177], this study relied on familial history of psychosis as a representation for genetic risk. However, this factor did not offer further explanatory power in the analysis. The GFCI algorithm utilized in Chapter 4 and Chapter 5 is capable of accommodating latent variables, unmeasured influences such as genetic predispositions and neurobiological factors, can still be incorporated in the output PAG. While genetic predisposition is recognized in schizophrenia research, its role appears more limited in non-clinical samples, where identifying robust genetic links has proven challenging [178]. Still, introducing PRS into analyses may clarify the complex interplay between negative self-schema, social cohesion and trust and PPS supporting the necessity of examining non-genetic contributors. Thirdly, restricting the analysis in Chapter 4 to the left hemisphere limited our investigation to the specific neural circuits involved in language-based processes within working memory. Fourth, the age range of participants spanned from adolescence to young adulthood. However, neuroimaging analyses were conducted using a standard adult MNI template without applying developmental normalization for participants younger than 18 years of age. Since these participants' brains structurally and functionally are still developing, the use of adult template may create anatomical inaccuracy and potentially influence localization. Fifth, the resampling analysis revealed limited stability for the PAGs and notable inconsistencies between the original PAGs and the resampled outcomes. For instance, in Chapter 4, the potentially confounded edge between negative self-schema and PPS showed low consistency across resamples. In contrast, the unconfounded edge from negative self-schema to PPS emerged in 32.02 % of the resampled models, whereas the reverse path appeared slightly more frequently, at 37.36 % (Table 4.2). Similarly, the direct, unconfounded effect of social cohesion&trust on PPS was present in 16.26 % of resamples, more often than either a confounded or reversed relationship. Depending on our hypothesis and previous research, we discuss that both negative self-schema and social cohesion&trust are probably to have a direct effect on PPS. To validate this interpretation, we conducted supplementary SEM incorporating these variables as direct predictors of PPS. The model fit indices, including RMSEA and TLI, along with the effect sizes, remained largely consistent with the original model (See Table A.3). Therefore, the presence of a possible latent factor should be seen not as a limitation but as

an asset of this data-driven method, providing insights beyond what expert judgment alone could deliver. The observed instability likely reflects the complexity and potential interactions among variables. Acknowledging uncertainty enables robust and contextually appropriate interpretations consistent with the aims of this thesis. Subsequent studies with larger and demographically focused cohorts may use these findings to improve the reliability and clarity of causal inferences. This study, which involved a twin and sibling sample, did not use twin modelling due to limited sample size and scope. Since the study did not prioritize genetic and environmental contributions, these factors were not directly analyzed. However, future research may consider applying twin designs to better understand the interplay between hereditary and environmental effects.

6.2 Conclusion

To best of our knowledge, this study is the first to apply both traditional regression method and a data-driven causal discovery analysis to examine risk factors and pathways to psychosis proneness by incorporating environmental risk factors, cognitive variables, schemas, working memory related brain activity and resting-state FC. Regression analysis found strong relationship between psychosis proneness and both aggregated environmental risk score and individual risk factors as well as schema about self and others. The applied method, CDA, complemented the previous analysis and found the most optimal model through algorithmic computation. If validated, these results highlight the potential benefit of early interventions aimed at modifying negative self-beliefs and addressing low levels of social cohesion and trust within the wider population, before such beliefs become deeply rooted and contribute to psychosis-like symptoms or eventual psychosis. This could prompt a shift in how vulnerability to psychosis is conceptualized, emphasizing the significance of internal psychological factors, such as self-perceptions and perceived social connectedness, over external exposures like trauma. In addition, the findings point to the possibility that psychosis proneness may already impact brain functioning, particularly within the DLPFC during working memory performance, even prior to the emergence of clinical symptoms. Furthermore, although the effect was not strong as task-based fMRI results, the functional connectivity in dorsal attention network and thalamus may also be

vulnerable to psychosis proneness when brain at rest. These results offer important understanding into the foundational processes of psychosis and may inform the development of more targeted and effective interventions and therapies.



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Appendix A

Supplementary Results

Table A.1: Rounded Ratios Calculated for Obstetric and Birth Complications

Risk Factor	Sub-categories	RR	Proportion	Weighted_RR	RRscaled	Scale 2	Rounded
Obstetric complications	No complications	1.00	0.49	1.08	0.91	−0.37	−0.50
	Preeclampsia	1.32	0.19		1.21	0.83	1.00
Obstetric complications	No complications	1.00	0.49	1.00	0.94	−0.26	−0.50
	Preterm placenta ablation	1.52	0.07		1.43	1.55	1.50
Obstetric complications	No complications	1.00	0.49	1.06	0.94	−0.25	−0.50
	Blood group intolerance	1.42	0.08		1.33	1.26	1.50
Obstetric complications	No complications	1.00	0.49	1.00	0.99	−0.01	0.00
	Rubella or syphilis	1.27	0.01		1.26	1.02	1.00
Obstetric complications	No complications	1.00	0.49	1.08	0.92	−0.35	−0.50
	Bleeding	1.54	0.09		1.41	1.51	1.50
Obstetric complications	No complications	1.00	0.49	1.01	0.98	−0.04	0.00
	Feverish infections	1.27	0.02		1.25	0.99	1.00
Birth complications	No complications	1.00	0.49	1.30	0.76	−1.17	−1.00
	Preterm rupture	1.86	0.27		1.42	1.52	1.50
Birth complications	No complications	1.00	0.49			0.00	0.00
	Preterm contractions		0.12				
Birth complications	No complications	1.00	0.49	1.14	0.87	−0.58	−0.50
	Preterm birth	1.35	0.34		1.18	0.72	0.50

Risk Factor	Sub-categories	RR	Proportion	Weighted_RR	RRscaled	Scale 2	Rounded
Birth complications	No complications	1.00	0.49	1.00	1.00	0.00	0.00
	Breech birth	1.00	0.05		1.00	0.00	0.00
Birth complications	No complications	1.00	0.49	1.04	0.95	−0.19	0.00
	Imminent asphyxia	1.93	0.03		1.84	2.60	2.50
Birth complications	No complications	1.00	0.49			0.00	0.00
	Infections		0.02				
Birth complications	No complications	1.00	0.49			0.00	0.00
	Birth Traumas		0.02				

Resampling with Replacement Analysis for Sensitivity Results

Table A.2: Resampling with Replacement Analysis for Sensitivity Results

Resampling with replacement analysis

Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
Negative Self	Psychosis Proneness Score	0.348	0.398	0.120	0.066	0.064	0.002	0
Psychosis Proneness Score	aBA9-BA46v	0.085	0.040	0.014	0.007	0	0	0.853
aBA9-BA46v	P47r	0.616	0.203	0.061	0.049	0.061	0.007	0
IQ	WM Reaction Time	0.161	0.104	0.009	0.040	0.009	0.004	0.670
IQ	Discrimination	0.206	0.137	0.019	0.021	0.009	0.004	0.601
WM Reaction Time	Trauma	0.106	0.213	0.030	0.085	0.014	0.007	0.542
BA45	WM Reaction Time	0.259	0.168	0.030	0.060	0.004	0.009	0.464
Trauma	Discrimination	0.082	0.213	0.042	0.023	0.011	0.002	0.623
Discrimination	Life Threatening Events	0.329	0.436	0.078	0.080	0.037	0.002	0.035
Alcohol Usage	Cannabis Use	0.232	0.120	0.052	0.037	0.011	0	0.545
Psychiatric Medication	aBA9-BA46v	0.123	0.090	0.026	0.011	0.002	0	0.746
Education in Years	SES	0.357	0.251	0.042	0	0	0.033	0.315
Urbanicity	Education in Years	0.002	0	0.317	0	0	0.049	0.630
Urbanicity	BA9a	0.007	0	0.068	0	0	0	0.924
SES	8c	0.402	0	0	0	0	0.009	0.587
Verbal Fluency	Life Threatening Events	0.078	0.064	0.0213	0.0071	0	0	0.829

Table A.2: (continued)

Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
BA9a	BA9-BA46d	0.274	0.462	0.139	0.068	0.042	0.011	0
FOP4	BA45	0.646	0.118	0.118	0.047	0.052	0.014	0.002
8c	IFja	0.590	0.193	0.120	0.045	0.045	0.023	0
BA9-BA46d	aBA9-BA46v	0.462	0.324	0.085	0.082	0.042	0.002	0
BA6	a32pr	0.445	0.187	0.101	0.045	0.052	0.023	0.144
AIP	IP2	0.412	0.272	0.149	0.087	0.052	0.026	0
BA6	FEF	0.424	0.277	0.085	0.087	0.106	0.016	0.002
Insula	BA46	0.360	0.187	0.075	0.019	0.037	0	0.319
FOP4	Insula	0.436	0.286	0.094	0.085	0.056	0.004	0.035
Family History of Psychosis	SES	0	0	0.829	0	0	0.016	0.154
8c	BA9a	0.099	0.135	0.037	0.052	0.014	0.014	0.646
FEF	FOP4	0.128	0.097	0.011	0.021	0.016	0.002	0.722
IP2	8c	0.047	0.090	0.009	0.009	0.009	0	0.834
BA6	AIP	0.154	0.087	0.023	0.009	0.011	0.004	0.708
a32pr	IFJa	0.142	0.208	0.016	0.035	0.007	0.030	0.559
BA6	BA46	0.286	0.052	0.061	0.009	0.019	0.009	0.561
Psychosis Proneness Score	IQ	0.082	0.106	0.016	0.007	0	0.002	0.784
Age	IQ	0	0	0.246	0	0	0.004	0.748
BA9-BA46d	SFL	0.218	0.078	0.021	0.030	0.007	0.002	0.642

Table A.2: (continued)

Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
FEF	SFL	0.298	0.064	0.064	0.028	0.023	0.004	0.516
Age	Education in Years	0.011	0	0.748	0	0	0.004	0.234
FOP4	AIP	0.106	0.068	0.016	0.014	0.007	0.002	0.784
FEF	Working Memory RT	0.104	0.052	0.042	0.026	0.004	0.002	0.767
IFJa	P47r	0.087	0.014	0.002	0	0	0	0.895
BA9-BA46d	Other Drug Usage	0.146	0.028	0.007	0.023	0.011	0	0.782
FOP4	p47r	0.163	0.090	0.040	0.007	0	0	0.699
OC	SES	0	0	0.319	0	0	0.002	0.677
a32pr	SFL	0.293	0.082	0.066	0.052	0.014	0.009	0.481
SC&T	Psychosis Proneness Score	0.189	0.154	0.099	0.030	0.030	0	0.495
SES	Psychiatric Medication	0.248	0	0.014	0	0	0.026	0.710
a32pr	LTE	0.085	0.087	0.014	0.026	0.009	0	0.777
Gender	Alcohol Usage	0	0	0.381	0	0	0.002	0.616
Gender	IP2	0	0	0.315	0	0	0	0.684
Trauma	BA9-BA46d	0.056	0.007	0.023	0	0	0	0.912
Discrimination	IFJa	0.061	0.056	0.014	0.011	0	0	0.855
Parental Discord Severity	IP2	0.135	0	0.099	0	0	0.002	0.763
Urbanicity	Parental Discord Severity	0.002	0	0.391	0	0	0.052	0.554
a32pr	Insula	0.092	0.045	0.014	0.004	0	0	0.843

Table A.2: (continued)

Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
Family History of Psychosis	IP2	0.002	0	0.182	0	0	0	0.815

(B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus, I.P.: Intraparietal Sulcus; a9-46v: frontal mid, FOP4: frontal operculum, IFJa: anterior inferior frontal gyrus, p47r: the orbital prefrontal cortex, a32pr: refers to a narrow strip of the anterior midcingulate cortex, FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory)

Additional Analysis for Edge Types for the Main Results

Table A.3: SEM Results for Negative Self-Schema and SC&T as Direct Edges to Psychosis Proneness

lhs	op	rhs	est	se	z	p-value	CI lower	CI upper
AIP	~~	FOP4	0.1	0.04	2.13	0.03	0.008	0.19
AIP	~~	BA6	0.14	0.05	2.91	0.003	0.04	0.24
Insula	~~	A32pr	0.2	0.05	3.61	0.0002	0.09	0.31
BA46	~	Insula	0.36	0.06	5.69	1.21E-08	0.23	0.49
BA46	~~	BA6	0.15	0.04	3.2	0.001	0.05	0.24
FEF	~~	BA6	0.46	0.06	7.01	2.25E-12	0.33	0.59
SFL	~	BA9-BA46d	0.29	0.06	4.71	2.41E-06	0.17	0.42
SFL	~~	FEF	0.13	0.05	2.57	0.01	0.03	0.24
SFL	~~	A32pr	0.13	0.05	2.39	0.01	0.02	0.24
FEF	~~	FOP4	0.08	0.03	2.34	0.01	0.01	0.16
Insula	~~	FOP4	0.33	0.05	5.89	3.66E-09	0.22	0.44
WM RT	~~	BA45	-0.17	0.05	-2.85	0.004	-0.28	-0.05
FOP4	~~	BA45	0.41	0.06	6.68	2.33E-11	0.29	0.53
P47r	~	IFJa	0.2	0.05	3.82	0.0001	0.09	0.3
P47r	~	BA9a-BA46v	0.62	0.05	12.21	0	0.52	0.73
P47r	~~	FOP4	0.04	0.03	1.45	0.14	-0.01	0.11
Other drug use	~	BA9-BA46d	-0.18	0.07	-2.59	0.009	-0.32	-0.04

Table A.3: (continued)

lhs	op	rhs	est	se	z	p-value	CI lower	CI upper
Discrimination	~	IQ	0.21	0.06	3.18	0.001	0.08	0.35
Discrimination	~	Trauma	0.2	0.06	2.99	0.002	0.07	0.33
IFJa	~	8c	0.69	0.04	15.02	0	0.6	0.78
IFJa	~	Discrimination	0.07	0.04	1.54	0.12	-0.01	0.16
IFJa	~~	A32pr	0.15	0.04	3.71	0.0002	0.07	0.23
BA6	~~	A32pr	0.23	0.04	4.8	1.55E-06	0.14	0.33
Life Threatening Events	~	Discrimination	0.4	0.06	6.34	2.25E-10	0.28	0.53
Life Threatening Events	~~	Verbal Fluency	0.15	0.06	2.38	0.016	0.02	0.28
Life Threatening Events	~~	A32pr	-0.11	0.05	-2.18	0.02	-0.22	-0.01
Cannabis Use	~	Alcohol Usage	0.24	0.06	3.67	0.0002	0.11	0.37
Cannabis Use	~	SES	-0.26	0.06	-3.98	6.62E-05	-0.4	-0.13
Cannabis Use	~	WM RT	-0.18	0.06	-2.78	0.005	-0.31	-0.05
Education in Years	~~	Urbanicity	0.18	0.06	2.71	0.006	0.05	0.32
SES	~	Education in Years	-0.26	0.06	-4.46	8.17E-06	-0.38	-0.15
Psychosis Proneness	~	Negative Self-Schema	0.53	0.05	9.2	0	0.42	0.65
Psychosis Proneness	~	SC&T	-0.17	0.05	-3.06	0.002	-0.29	-0.06
WM RT	~~	FEF	0.1	0.05	1.93	0.05	-0.001	0.21
WM RT	~	IQ	-0.18	0.06	-2.65	0.007	-0.31	-0.04
Trauma	~	WM RT	0.18	0.06	2.71	0.006	0.05	0.32

Table A.3: (continued)

lhs	op	rhs	est	se	z	p-value	CI lower	CI upper
8c	~	SES	0.26	0.06	4.12	3.72E-05	0.14	0.39
8c	~	IP2	0.35	0.06	5.46	4.55E-08	0.22	0.47
BA9a-BA46v	~	Psychosis Proneness	0.11	0.03	3.19	0.001	0.04	0.18
BA9a-BA46v	~	BA9-BA46d	0.83	0.03	22.94	0	0.76	0.9
BA9a-BA46v	~	Psychiatric Medication	-0.1	0.03	-2.77	0.005	-0.17	-0.02
BA9a	~	8c	0.42	0.06	6.63	3.24E-11	0.3	0.55
BA9a	~~	Urbanicity	0.12	0.06	1.95	0.05	-4.72E-05	0.24
IP2	~	AIP	0.73	0.04	16.16	0	0.65	0.82
IP2	~	Parental Discord	-0.11	0.04	-2.4	0.01	-0.19	-0.02
BA9-BA46d	~	BA9a	0.85	0.03	22.85	0	0.78	0.92
BA9-BA46d	~	Trauma	-0.08	0.03	-2.34	0.01	-0.16	-0.01
SES	~~	Family History of Psychosis	0.39	0.07	5.49	3.81E-08	0.25	0.53
Parental Discord	~~	Urbanicity	-0.2	0.07	-2.82	0.004	-0.33	-0.06
Education in Years	~~	Age	0.23	0.07	3.29	0.0009	0.09	0.37
Alcohol Usage	~~	Gender	-0.18	0.07	-2.56	0.01	-0.32	-0.04
SES	~~	OC	-0.15	0.06	-2.47	0.01	-0.27	-0.03
Psychiatric Medication	~	SES	-0.19	0.07	-2.69	0.006	-0.33	-0.05
IQ	~	Psychosis Proneness	0.17	0.07	2.47	0.01	0.03	0.31
IQ	~~	Age	0.13	0.06	2.02	0.04	0.004	0.27

Table A.3: (continued)

lhs	op	rhs	est	se	z	p-value	CI lower	CI upper
IP2	~~	Gender	-0.1	0.04	-2.36	0.01	-0.19	-0.01
IP2	~~	Family History of Psychosis	-0.09	0.04	-2.27	0.02	-0.17	-0.01

(B.A.: Brodmann; SFL: Superior frontal language area; AIP: anterior intraparietal sulcus, I.P.: Intraparietal Sulcus; a9-46v: frontal mid, FOP4: frontal operculum, IFJa: anterior inferior frontal gyrus, p47r: the orbital prefrontal cortex, a32pr: refers to a narrow strip of the anterior midcingulate cortex, FEF: frontal eye fields; O.C.: obstetric complications; SES: socioeconomic status; W.M.: working memory)

Table A4: RsfMRI FC Indices and Corresponding Coordinates

Table A.4: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Default Mode MPFC	DM-MPFC-1	cluster -2 +58 +2 rest_DefaultMode.MPFC
	DM-MPFC-2	cluster -46 +12 +16 rest_DefaultMode.MPFC
	DM-MPFC-3	cluster -52 -44 +44 rest_DefaultMode.MPFC
	DM-MPFC-4	cluster +48 -60 +28 rest_DefaultMode.MPFC
	DM-MPFC-5	cluster +52 -40 +42 rest_DefaultMode.MPFC
	DM-MPFC-6	cluster -46 -66 +30 rest_DefaultMode.MPFC
	DM-MPFC-7	cluster -52 -18 +46 rest_DefaultMode.MPFC
	DM-MPFC-8	cluster -50 -38 -2 rest_DefaultMode.MPFC
	DM-MPFC-9	cluster +26 -12 +28 rest_DefaultMode.MPFC
	DM-MPFC-10	cluster -14 -2 +16 rest_DefaultMode.MPFC
	DM-MPFC-11	cluster -14 -32 +22 rest_DefaultMode.MPFC
DefaultMode.LP left	DM-LP-L-1	cluster -36 -78 +38 rest_DefaultMode.LP 1
	DM-LP-L-2	cluster +2 +6 +64 rest_DefaultMode.LP 1
	DM-LP-L-3	cluster -22 +20 +50 rest_DefaultMode.LP 1
	DM-LP-L-4	cluster +24 +22 +46 rest_DefaultMode.LP 1

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
DefaultMode.LP right	DM-LP-L-5	cluster +56 -4 -16 rest_DefaultMode.LP l
	DM-LP-L-6	cluster -28 -84 +6 rest_DefaultMode.LP l
	DM-LP-L-7	cluster +30 +34 -12 rest_DefaultMode.LP l
	DM-LP-L-8	cluster +28 -76 +8 rest_DefaultMode.LP l
	DM-LP-L-9	cluster +2 +4 +28 rest_DefaultMode.LP l
	DM-LP-R-1	cluster +2 +6 +64 rest_DefaultMode.LP r
	DM-LP-R-2	cluster +46 -68 +30 rest_DefaultMode.LP r
	DM-LP-R-3	cluster +24 +26 +48 rest_DefaultMode.LP r
	DM-LP-R-4	cluster -24 +20 +50 rest_DefaultMode.LP r
	DM-LP-R-5	cluster -58 -12 -10 rest_DefaultMode.LP r
DefaultMode PCC	DM-LP-R-6	cluster +34 +36 -14 rest_DefaultMode.LP r
	DM-LP-R-7	cluster +4 +4 +28 rest_DefaultMode.LP r
	DM-PCC-1	cluster +2 -64 +50 rest_DefaultMode.PCC
	DM-PCC-2	cluster -48 +6 +12 rest_DefaultMode.PCC
	DM-PCC-3	cluster -22 +28 +40 rest_DefaultMode.PCC
	DM-PCC-4	cluster +56 -14 -16 rest_DefaultMode.PCC
	DM-PCC-5	cluster -56 -14 -12 rest_DefaultMode.PCC
	DM-PCC-6	cluster +30 -98 +12 rest_DefaultMode.PCC

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
SensoriMotor Lateral Left	DM-PCC-7	cluster -42 -44 +0 rest_DefaultMode.PCC
	SM-Lateral-L-1	cluster -56 -12 +34 rest_SensoriMotor.Lateral l
	SM-Lateral-L-2	cluster -2 -62 +66 rest_SensoriMotor.Lateral l
	SM-Lateral-L-3	cluster +0 +30 -12 rest_SensoriMotor.Lateral l
	SM-Lateral-L-4	cluster +48 -60 +2 rest_SensoriMotor.Lateral l
SensoriMotor Lateral Right	SM-Lateral-L-5	cluster +54 +32 -6 rest_SensoriMotor.Lateral l
	SM-Lateral-L-6	cluster +40 +40 +10 rest_SensoriMotor.Lateral l
	SM-Lateral-R-1	cluster +48 -12 +38 rest_SensoriMotor.Lateral r
	SM-Lateral-R-2	cluster -4 -70 +62 rest_SensoriMotor.Lateral r
	SM-Lateral-R-3	cluster +48 -60 +2 rest_SensoriMotor.Lateral r
	SM-Lateral-R-4	cluster -2 +30 -14 rest_SensoriMotor.Lateral r
	SM-Lateral-R-5	cluster +48 +36 -12 rest_SensoriMotor.Lateral r
	SM-Lateral-R-6	cluster +22 -64 +8 rest_SensoriMotor.Lateral r
	SM-Lateral-R-7	cluster +34 +24 -14 rest_SensoriMotor.Lateral r
	SM-Lateral-R-8	cluster +16 -74 +24 rest_SensoriMotor.Lateral r
	SM-Lateral-R-9	cluster +58 -30 -14 rest_SensoriMotor.Lateral r
	SM-Lateral-R-10	cluster -20 -64 +4 rest_SensoriMotor.Lateral r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
SensoriMotor Superior	SM-Lateral-R-11	cluster +0 -10 -2 rest_SensoriMotor.Lateral r
	SM-Superior-1	cluster -18 -36 +72 rest_SensoriMotor.Superior
	SM-Superior-2	cluster +4 +26 +66 rest_SensoriMotor.Superior
	SM-Superior-3	cluster -2 +44 -14 rest_SensoriMotor.Superior
	SM-Superior-4	cluster -48 -66 +6 rest_SensoriMotor.Superior
	SM-Superior-5	cluster +50 -62 +4 rest_SensoriMotor.Superior
	SM-Superior-6	cluster -4 -56 +22 rest_SensoriMotor.Superior
Visual Medial	SM-Superior-7	cluster +2 -56 -6 rest_SensoriMotor.Superior
	VisualMed-1	cluster +14 -82 +32 rest_Visual.Medial
	VisualMed-2	cluster -48 -40 +60 rest_Visual.Medial
	VisualMed-3	cluster -26 +62 +26 rest_Visual.Medial
	VisualMed-4	cluster +44 -4 +50 rest_Visual.Medial
	VisualMed-5	cluster -42 -8 +52 rest_Visual.Medial
	VisualMed-6	cluster +6 +4 +66 rest_Visual.Medial
	VisualMed-7	cluster +4 +24 +28 rest_Visual.Medial
	VisualMed-8	cluster +42 +2 +16 rest_Visual.Medial
	VisualMed-9	cluster +34 +8 +2 rest_Visual.Medial
	VisualMed-10	cluster +56 -52 -12 rest_Visual.Medial

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Visual Occipital	VisualMed-11	cluster +18 +60 -8 rest_Visual.Medial
	VisualMed-12	cluster +52 +16 -24 rest_Visual.Medial
	VisualOccip-1	cluster -26 -94 +18 rest_Visual.Occipital
	VisualOccip-2	cluster -26 +14 +66 rest_Visual.Occipital
	VisualOccip-3	cluster +40 -64 +38 rest_Visual.Occipital
	VisualOccip-4	cluster +44 -2 +52 rest_Visual.Occipital
	VisualOccip-5	cluster -44 -6 +52 rest_Visual.Occipital
	VisualOccip-6	cluster -42 -10 +2 rest_Visual.Occipital
	VisualOccip-7	cluster -6 +4 +68 rest_Visual.Occipital
	VisualOccip-8	cluster +54 +30 -4 rest_Visual.Occipital
Visual Lateral Left	VisualOccip-9	cluster +38 -16 +34 rest_Visual.Occipital
	VisualOccip-10	cluster +40 +2 +14 rest_Visual.Occipital
	VisualLat-L-1	cluster -24 -78 +26 rest_Visual.Lateral l
	VisualLat-L-2	cluster +22 -40 +14 rest_Visual.Lateral l
	VisualLat-L-3	cluster +44 -4 +50 rest_Visual.Lateral l
	VisualLat-L-4	cluster -40 -6 +52 rest_Visual.Lateral l
	VisualLat-L-5	cluster +14 +68 +26 rest_Visual.Lateral l
	VisualLat-L-6	cluster +42 +0 +16 rest_Visual.Lateral l
	VisualLat-L-7	cluster -12 -18 +40 rest_Visual.Lateral l

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Visual Lateral Right	VisualLat-L-8	cluster +14 -18 +40 rest_Visual.Lateral l
	VisualLat-L-9	cluster -22 +8 -6 rest_Visual.Lateral l
	VisualLat-L-10	cluster +54 +42 -10 rest_Visual.Lateral l
	VisualLat-R1	cluster +28 -78 +30 rest_Visual.Lateral r
	VisualLat-R2	cluster +20 -38 +16 rest_Visual.Lateral r
	VisualLat-R3	cluster +44 -2 +52 rest_Visual.Lateral r
	VisualLat-R4	cluster -36 -6 +48 rest_Visual.Lateral r
	VisualLat-R5	cluster -6 +70 +12 rest_Visual.Lateral r
	VisualLat-R6	cluster -12 -16 +40 rest_Visual.Lateral r
	VisualLat-R7	cluster +14 -18 +40 rest_Visual.Lateral r
Salience ACC	VisualLat-R8	cluster -58 +28 +14 rest_Visual.Lateral r
	VisualLat-R9	cluster +64 -30 -12 rest_Visual.Lateral r
	VisualLat-R10	cluster -52 +16 -24 rest_Visual.Lateral r
	Salience-ACC1	cluster +0 +22 +34 rest_Salience.ACC
	Salience-ACC2	cluster -40 -60 +30 rest_Salience.ACC
	Salience-ACC3	cluster -10 -68 +36 rest_Salience.ACC
	Salience-ACC4	cluster +0 +64 -16 rest_Salience.ACC
	Salience-ACC5	cluster +68 -34 -2 rest_Salience.ACC

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Salience AInsula Left	Salience-ACC6	cluster +24 -36 -4 rest_Salience.ACC
	Salience-ACC7	cluster +0 -2 -14 rest_Salience.ACC
	Salience-AInsula-L1	cluster -40 +12 +4 rest_Salience.AInsula l
	Salience-AInsula-L2	cluster +2 -56 +34 rest_Salience.AInsula l
	Salience-AInsula-L3	cluster +64 -6 -20 rest_Salience.AInsula l
	Salience-AInsula-L4	cluster -62 -14 -18 rest_Salience.AInsula l
	Salience-AInsula-L5	cluster -20 -70 +10 rest_Salience.AInsula l
	Salience-AInsula-L6	cluster -6 -4 -12 rest_Salience.AInsula l
	Salience-AInsula-L7	cluster +18 -70 +16 rest_Salience.AInsula l
	Salience-AInsula-L8	cluster +36 +38 -18 rest_Salience.AInsula l
	Salience-AInsula-L9	cluster +2 -98 +14 rest_Salience.AInsula l

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Salience AInsula Right	Salience-AInsula- R1	cluster +40 +12 +4 rest_Salience.AInsula r
	Salience-AInsula- R2	cluster -36 -66 +34 rest_Salience.AInsula r
	Salience-AInsula- R3	cluster -24 -98 +22 rest_Salience.AInsula r
	Salience-AInsula- R4	cluster +24 -96 +26 rest_Salience.AInsula r
	Salience-AInsula- R5	cluster +62 -6 -16 rest_Salience.AInsula r
	Salience-AInsula- R6	cluster -62 -14 -18 rest_Salience.AInsula r
	Salience-AInsula- R7	cluster -38 +56 -4 rest_Salience.AInsula r
	Salience-AInsula- R8	cluster +64 -40 -10 rest_Salience.AInsula r
	Salience-AInsula- R9	cluster +38 -24 +60 rest_Salience.AInsula r
	Salience-AInsula- R10	cluster +2 -56 +30 rest_Salience.AInsula r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Saliency RPFC Left	Saliency-RPFC-L1	cluster +36 -56 +30 rest_Saliency.RPFC l
	Saliency-RPFC-L2	cluster -32 +44 +28 rest_Saliency.RPFC l
	Saliency-RPFC-L3	cluster -58 -38 +32 rest_Saliency.RPFC l
	Saliency-RPFC-L4	cluster +64 -36 +34 rest_Saliency.RPFC l
	Saliency-RPFC-L5	cluster -50 +50 -6 rest_Saliency.RPFC l
Saliency RPFC Right	Saliency-RPFC-R1	cluster -36 -64 +34 rest_Saliency.RPFC r
	Saliency-RPFC-R2	cluster +30 +46 +28 rest_Saliency.RPFC r
	Saliency-RPFC-R3	cluster -34 +14 +10 rest_Saliency.RPFC r
	Saliency-RPFC-R4	cluster +58 -38 +36 rest_Saliency.RPFC r
	Saliency-RPFC-R5	cluster -64 -40 +42 rest_Saliency.RPFC r
	Saliency-RPFC-R6	cluster +36 +38 -14 rest_Saliency.RPFC r
	Saliency-RPFC-R7	cluster +56 +36 +20 rest_Saliency.RPFC r
	Saliency-RPFC-R8	cluster +70 -32 +4 rest_Saliency.RPFC r
	Saliency-RPFC-R9	cluster +62 +0 -18 rest_Saliency.RPFC r
	Saliency-RPFC-R10	cluster +0 -94 +0 rest_Saliency.RPFC r
	Saliency-RPFC-R11	cluster -12 -8 +0 rest_Saliency.RPFC r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
	Saliency-RPFC-R12	cluster -38 -8 +50 rest_Saliency.RPFC r
Saliency SMG Left	Saliency-SMG-L1	cluster -60 -38 +30 rest_Saliency.SMG l
	Saliency-SMG-L2	cluster -4 -52 +18 rest_Saliency.SMG l
	Saliency-SMG-L3	cluster +64 -36 +32 rest_Saliency.SMG l
	Saliency-SMG-L4	cluster +22 +34 +50 rest_Saliency.SMG l
	Saliency-SMG-L5	cluster +30 +48 +26 rest_Saliency.SMG l
	Saliency-SMG-L6	cluster +40 -2 +44 rest_Saliency.SMG l
	Saliency-SMG-L7	cluster +16 +48 -24 rest_Saliency.SMG l
	Saliency-SMG-L8	cluster +36 -70 +4 rest_Saliency.SMG l
	Saliency-SMG-L9	cluster +48 -80 +22 rest_Saliency.SMG l
	Saliency-SMG-L10	cluster +16 -68 +42 rest_Saliency.SMG l
Saliency SMG Right	Saliency-SMG-R1	cluster +60 -34 +30 rest_Saliency.SMG r
	Saliency-SMG-R2	cluster -36 -62 +38 rest_Saliency.SMG r
	Saliency-SMG-R3	cluster -62 -36 +32 rest_Saliency.SMG r
	Saliency-SMG-R4	cluster +36 -64 +46 rest_Saliency.SMG r
	Saliency-SMG-R5	cluster +4 -92 +28 rest_Saliency.SMG r
	Saliency-SMG-R6	cluster +28 +60 -14 rest_Saliency.SMG r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Dorsal Attention FEF Left	Salience-SMG-R7	cluster -38 -6 +50 rest_Salience.SMG r
	Salience-SMG-R8	cluster -10 +58 -22 rest_Salience.SMG r
	Salience-SMG-R9	cluster +32 +38 -10 rest_Salience.SMG r
	DorsalAtten-FEF-L1	cluster -28 -10 +64 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L2	cluster +4 -84 +44 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L3	cluster +50 -54 +54 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L4	cluster -26 +30 +28 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L5	cluster -48 -66 +6 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L6	cluster +50 -56 +2 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L7	cluster +16 -20 +14 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L8	cluster +6 +60 -10 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L9	cluster +4 +4 -6 rest_DorsalAttention.FEF l

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Dorsal Attention FEF Right	DorsalAtten-FEF-L10	cluster +32 -32 +6 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L11	cluster +20 +44 -16 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L12	cluster +28 +36 +32 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-L13	cluster +28 -54 -6 rest_DorsalAttention.FEF l
	DorsalAtten-FEF-R1	cluster +30 -8 +64 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R2	cluster +0 -22 +22 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R3	cluster +4 +26 +66 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R4	cluster -52 +36 +14 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R5	cluster +48 +24 +8 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R6	cluster +48 -66 +50 rest_DorsalAttention.FEF r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
	DorsalAtten-FEF-R7	cluster +50 -62 +6 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R8	cluster -48 -66 +6 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R9	cluster -16 -24 +4 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R10	cluster +30 +38 +34 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R11	cluster +44 +20 +56 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R12	cluster -44 +14 +56 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R13	cluster -4 -38 +80 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R14	cluster -66 -48 -4 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R15	cluster -16 +36 -26 rest_DorsalAttention.FEF r
	DorsalAtten-FEF-R16	cluster +34 -34 +6 rest_DorsalAttention.FEF r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
	DorsalAtten-FEF-R17	cluster +0 -8 +4 rest_DorsalAttention.FEF r
Dorsal Attention IPS Left	DorsalAtten-IPS-L1	cluster +6 +18 +70 rest_DorsalAttention.IPS l
	DorsalAtten-IPS-L2	cluster -40 -38 +46 rest_DorsalAttention.IPS l
	DorsalAtten-IPS-L3	cluster +50 +8 +26 rest_DorsalAttention.IPS l
	DorsalAtten-IPS-L4	cluster +52 +44 +16 rest_DorsalAttention.IPS l
	DorsalAtten-IPS-L5	cluster -50 -6 +56 rest_DorsalAttention.IPS l
	DorsalAtten-IPS-L6	cluster +18 -24 +8 rest_DorsalAttention.IPS l
	DorsalAtten-IPS-L7	cluster +24 +34 -14 rest_DorsalAttention.IPS l
	DorsalAtten-IPS-L8	cluster -42 +18 +56 rest_DorsalAttention.IPS l
Dorsal Attention IPS Right	DorsalAtten-IPS-R1	cluster +40 -36 +50 rest_DorsalAttention.IPS r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
	DorsalAtten-IPS-R2	cluster -2 +14 +70 rest_DorsalAttention.IPS r
	DorsalAtten-IPS-R3	cluster +34 +18 -14 rest_DorsalAttention.IPS r
	DorsalAtten-IPS-R4	cluster -48 +42 +22 rest_DorsalAttention.IPS r
	DorsalAtten-IPS-R5	cluster -16 -26 +6 rest_DorsalAttention.IPS r
	DorsalAtten-IPS-R6	cluster +52 -10 -16 rest_DorsalAttention.IPS r
	DorsalAtten-IPS-R7	cluster -48 -20 -10 rest_DorsalAttention.IPS r
	DorsalAtten-IPS-R8	cluster +52 -2 +56 rest_DorsalAttention.IPS r
	Fronto Parietal LPFC Left	
	FrontoPar-LPFC-L1	cluster +2 +58 +12 rest_FrontoParietal.LPFC l
	FrontoPar-LPFC-L2	cluster -42 +52 +2 rest_FrontoParietal.LPFC l
	FrontoPar-LPFC-L3	cluster +48 +38 +30 rest_FrontoParietal.LPFC l

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Fronto Parietal PPC Left	FrontoPar-LPFC-L4	cluster -50 -46 +48 rest_FrontoParietal.LPFC 1
	FrontoPar-LPFC-L5	cluster +56 -44 +54 rest_FrontoParietal.LPFC 1
	FrontoPar-LPFC-L6	cluster -62 -48 +0 rest_FrontoParietal.LPFC 1
	FrontoPar-LPFC-L7	cluster +70 -24 +8 rest_FrontoParietal.LPFC 1
	FrontoPar-LPFC-L8	cluster -4 -2 +28 rest_FrontoParietal.LPFC 1
	FrontoPar-LPFC-L9	cluster +14 +6 +16 rest_FrontoParietal.LPFC 1
	FrontoPar-LPFC-L10	cluster -2 -34 +38 rest_FrontoParietal.LPFC 1
	FrontoPar-PPC-L1	cluster -4 +12 +36 rest_FrontoParietal.PPC 1
	FrontoPar-PPC-L2	cluster -42 -62 +50 rest_FrontoParietal.PPC 1
	FrontoPar-PPC-L3	cluster -40 +18 +44 rest_FrontoParietal.PPC 1
	FrontoPar-PPC-L4	cluster +26 -20 +30 rest_FrontoParietal.PPC 1
	FrontoPar-PPC-L5	cluster -30 +18 -2 rest_FrontoParietal.PPC 1

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Fronto Parietal LPFC Right	FrontoPar-LPFC-R1	cluster -2 +60 +14 rest_FrontoParietal.LPFC r
	FrontoPar-LPFC-R2	cluster +42 +24 +46 rest_FrontoParietal.LPFC r
	FrontoPar-LPFC-R3	cluster +48 -50 +48 rest_FrontoParietal.LPFC r
	FrontoPar-LPFC-R4	cluster +4 -32 +42 rest_FrontoParietal.LPFC r
	FrontoPar-LPFC-R5	cluster +66 -26 -8 rest_FrontoParietal.LPFC r
	FrontoPar-LPFC-R6	cluster +8 -66 +48 rest_FrontoParietal.LPFC r
	FrontoPar-LPFC-R7	cluster -30 +18 -2 rest_FrontoParietal.LPFC r
	FrontoPar-LPFC-R8	cluster +58 +34 +4 rest_FrontoParietal.LPFC r
Fronto Parietal PPC Right	FrontoPar-PPC-R1	cluster -20 -54 +56 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R2	cluster +42 +20 +46 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R3	cluster +52 -50 +44 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R4	cluster -54 -56 +46 rest_FrontoParietal.PPC r

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
	FrontoPar-PPC-R5	cluster -44 +56 +4 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R6	cluster -24 -18 +38 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R7	cluster -66 -4 +28 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R8	cluster -60 +22 +12 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R9	cluster +58 +36 +6 rest_FrontoParietal.PPC r
	FrontoPar-PPC-R10	cluster +28 -20 +30 rest_FrontoParietal.PPC r
Language IFG Left	Language-IFG-L1	cluster +8 -44 +12 rest_Language.IFG l
	Language-IFG-L2	cluster -54 +22 +6 rest_Language.IFG l
	Language-IFG-L3	cluster -6 +20 +62 rest_Language.IFG l
	Language-IFG-L4	cluster +54 +26 +2 rest_Language.IFG l
	Language-IFG-L5	cluster +50 -30 +0 rest_Language.IFG l
	Language-IFG-L6	cluster +22 -94 +28 rest_Language.IFG l
	Language-IFG-L7	cluster +16 +8 +12 rest_Language.IFG l
	Language-IFG-L8	cluster -4 -14 +40 rest_Language.IFG l
	Language-IFG-L9	cluster +38 +2 +16 rest_Language.IFG l
	Language-IFG-L10	cluster -44 -8 -2 rest_Language.IFG l
	Language-IFG-L11	cluster -22 -24 -16 rest_Language.IFG l
	Language-IFG-L12	cluster +36 -6 -8 rest_Language.IFG l

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Language IFG Right	Language-IFG-R1	cluster -8 -46 +16 rest.Language.IFG r
	Language-IFG-R2	cluster +52 +28 +6 rest.Language.IFG r
	Language-IFG-R3	cluster +8 +14 +64 rest.Language.IFG r
	Language-IFG-R4	cluster -12 -98 +28 rest.Language.IFG r
	Language-IFG-R5	cluster +22 -94 +28 rest.Language.IFG r
	Language-IFG-R6	cluster -4 -16 +42 rest.Language.IFG r
	Language-IFG-R7	cluster -32 -4 +22 rest.Language.IFG r
	Language-IFG-R8	cluster -28 -22 +2 rest.Language.IFG r
	Language-IFG-R9	cluster +38 -2 +18 rest.Language.IFG r
	Language-IFG-R10	cluster +40 +40 +16 rest.Language.IFG r
Language pSTG Left	Language-pSTG-L1	cluster -56 -48 +24 rest.Language.pSTG l
	Language-pSTG-L2	cluster -18 +24 +6 rest.Language.pSTG l
	Language-pSTG-L3	cluster -8 +16 +62 rest.Language.pSTG l
	Language-pSTG-L4	cluster +40 -36 +46 rest.Language.pSTG l

Table continued: RsfMRI FC Indices and Corresponding Coordinates

Network Name	Short Name	Full Name / Coordinate
Language pSTG Right	Language-pSTG-L5	cluster +50 +4 +26 rest.Language.pSTG l
	Language-pSTG-R1	cluster +58 -46 +22 rest.Language.pSTG r
	Language-pSTG-R2	cluster -58 -50 +18 rest.Language.pSTG r
	Language-pSTG-R3	cluster +18 +26 +8 rest.Language.pSTG r
	Language-pSTG-R4	cluster +2 +20 +22 rest.Language.pSTG r
	Language-pSTG-R5	cluster -52 +6 +36 rest.Language.pSTG r
	Language-pSTG-R6	cluster +12 -26 +6 rest.Language.pSTG r
	Language-pSTG-R7	cluster -36 -4 +16 rest.Language.pSTG r

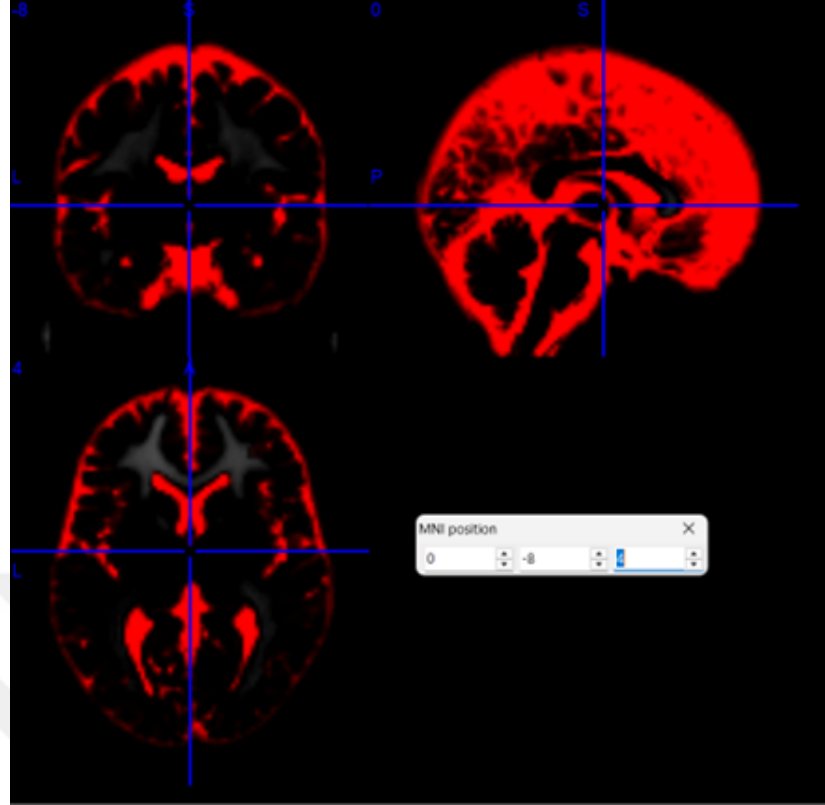


Figure A.1: **Supplementary Figure 1.** The anatomical location of MNI coordinates $x = +0$, $y = -8$, $z = +4$. Although the CompCor in the CONN toolbox was used to reduce cerebrospinal fluid (CSF)-related noise, the potential confounding influence of CSF on the observed resting state FC between this region and the right frontal eye fields (FEF) of the dorsal attention network was further evaluated. The CSF map derived from a participant overlaid onto MNI152 T1 anatomical template in MRIcron. At the $x = 0$, $y = -8$, $z = 4$ coordinates, the CSF mask did not show any signal intensity, suggesting that observed functional connectivity at this location is unlikely to be contaminated by CSF signal. In the image, CSF appears in red, while surrounding anatomical structures are displayed in grayscale.

Additional Analysis for Edge Types for the Main Results

Table A.5: Resampling with Replacement Analysis of rsfMRI Functional Connectivity Indices

Resampling with replacement analysis

Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
FrontoParietal	DFMN	0.452	0.211	0.149	0.071	0.052	0.001	0.061
Life Threatening Events	Discrimination	0.448	0.332	0.015	0.028	0.007	0.005	0.162
Education in Years	Discrimination	0.229	0.000	0.093	0.000	0.000	0.007	0.753
Other Drug Usage	Cannabis Use	0.160	0.224	0.095	0.080	0.018	0.020	0.400
Dorsal Attention	Fronto Parietal	0.125	0.065	0.005	0.026	0.005	0.001	0.770
Cannabis Use	Alcohol use	0.143	0.228	0.043	0.011	0.011	0.003	0.558
Discrimination	Trauma	0.291	0.196	0.028	0.046	0.009	0.007	0.420
Education in Years	Negative self-schema	0.323	0.000	0.005	0.000	0.000	0.020	0.605
Education in Years	Psychiatric medication	0.370	0.000	0.001	0.000	0.000	0.015	0.613
Negative self-schema	Other Drug Usage	0.190	0.022	0.018	0.028	0.009	0.000	0.730
Parental discord	Life Threatening Events	0.379	0.000	0.218	0.000	0.000	0.005	0.396
Salience	Dorsal Attention	0.386	0.254	0.160	0.039	0.018	0.009	0.130
Sensorimotor	Dorsal Attention	0.349	0.162	0.241	0.037	0.015	0.018	0.175
Paternal age	Dorsal Attention	0.001	0.000	0.471	0.000	0.000	0.007	0.519
Visual Lateral	Salience	0.114	0.304	0.035	0.106	0.015	0.003	0.420
Visual Lateral	DFMN	0.218	0.172	0.046	0.039	0.009	0.005	0.508

Table A.5: (continued)

Node 1	Node 2	$\rightarrow$	$\leftarrow$	$o \rightarrow$	$\leftarrow o$	$o-o$	$\leftrightarrow$	No Edge
Visual Lateral	Sensorimotor	0.200	0.340	0.074	0.222	0.054	0.005	0.102
Age	Alcohol use	0.001	0.000	0.463	0.000	0.000	0.009	0.525
Age	Education in Years	0.003	0.000	0.887	0.000	0.000	0.009	0.099
Family History of Psychosis	Education in Years	0.001	0.000	0.596	0.000	0.000	0.009	0.392
Urbanicity	Education in Years	0.001	0.000	0.390	0.000	0.000	0.005	0.601
Gender	Cannabis	0.001	0.000	0.396	0.000	0.000	0.000	0.601
OC	Negative self-schema	0.224	0.000	0.000	0.000	0.000	0.000	0.775
Psychosis proneness	Negative self-schema	0.415	0.284	0.099	0.117	0.035	0.048	0.000
Psychosis proneness	Salience	0.099	0.057	0.015	0.018	0.007	0.001	0.800
Social Cohesion & Trust	Psychosis proneness	0.115	0.375	0.072	0.044	0.035	0.003	0.351
Urbanicity	Parental discord	0.000	0.000	0.448	0.000	0.000	0.007	0.543
Education in Years	DFMN	0.467	0.000	0.000	0.000	0.000	0.022	0.510

OC: Obstetric Complications



Appendix B

Permission to Re-use Brain Figure



