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Cognitive Functioning in Schizophrenia: Characterising the Effects of Common Genetic Variation, Brain Structure, Inflammation, and Early Life Adversity

By

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A thesis submitted for the

Degree of Doctor of Philosophy (PhD) to the School of Psychology,

University of Galway, Ireland

Supervisors: Professor Gary Donohoe & Doctor Derek Morris

College of Arts, Social Sciences & Celtic Studies

Submitted: August 2023

TABLE OF CONTENTS

Statement of authorship

I declare that this thesis, which I submit for examination, is entirely my own work, except where otherwise stated by appropriate citations and acknowledgements. This thesis was carried out in accordance with the rules and regulations of the University of Galway and has not been submitted previously for any other academic award.

Signed: Date:

Emma Corley   17th August 2023

Statement of Contribution

The work from this thesis includes collaborative studies on psychosis involving multiple co-authors. Study 1 includes data from the Centre for Neuroimaging, Cognition and Genomics (NICOG) from patients with schizophrenia, schizoaffective disorder and bipolar disorder, and healthy controls. Data used for analysis in this thesis had been collected in multiple stages that contributed towards the Resource for Psychoses in Ireland. Genotyping of this sample was carried out by members of NICOG, Trinity College Dublin and Cognitive Genetics and Cognitive Therapy (CogGene). Participants' recruitment and acquisition of the MRI and clinical data for this project had been collected prior to the commencement of my PhD. Several researchers were involved in this collection, including Dr Dona Cosgrove, Dr Laurena Holleran, Dr Jessica Holland, Prof Aiden Corvin, Dr Derek Morris and Prof Gary Donohoe.

Studies 1 and 2, include data from the UK Biobank which was approved by the National Health Service (NHS) Research Ethics Service (reference 11/NW/0382). Access to the data was granted by the UK Biobank Access Committee (Project #23739). Myself and Dr Laura Fahey worked together to quality control the UK Biobank genotypic data. Analysis and write-up for this study was undertaken by myself with the support and input of my supervisors and from Dr Esther Walton.

For studies 3 and 4, data from the 'Immune Response & Social Cognition in Schizophrenia' ('iRelate') project was used. The iRelate project- which examines the impact of the environment, immune system and genetics on brain function and structure in schizophrenia- was funded by the European Research Council and awarded to Prof. Gary Donohoe in 2016. Participant recruitment of this data was ongoing from 2017-2019 and many individuals helped with this requirement, notably, Prof Gary Donohoe, Dr Derek Morris, Dr Brian Hallahan, Prof Colm McDonald, Dr Declan Mckernan, Dr Karolina Rokita, Dr Laura Costello, Dr David Mothersill & Dr Maria Dauvermann. The analyses carried out in manuscripts 3 and 4 were undertaken by the author. Saahithh Patlola assayed and quality controlled the inflammatory markers that were used as part of these studies. The author and Aodán Laighneah were both involved in inputting raw genotyping data and on genetic quality control checks. The supervisors and graduate research committee (GRC) advised and provided support in conducting this research.

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Publications Arising from this Thesis

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Chapter 3 Corley E, Fahey, L, Fitzgerald, J, et al. The impact of early adversity and education on genetic and brain morphological predictors of cognitive ability. *Genes, Brain and Behaviour*. 2023; 22(4):e12850. doi:10.1111/gbb.12850 .

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Chapter 5 Corley, E., Gleeson, C., Godfrey, E., Cowman, M., Patlola, S. R., Cannon, D. M., ... & Donohoe, G. (2024). Corpus callosum microstructural organization mediates the effects of physical neglect on social cognition in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *129*, 110875. doi.org/10.1016/j.pnpbp.2023.110875

Research Dissemination

Oral Presentations

    i.   Genetic and Inflammatory Effects on Childhood Trauma and Cognitive Function in Patients with Schizophrenia and Healthy Participants. **Genes, Brain and Behaviour 2023 conference- May 22-25th 2023- University of Galway, Ireland.**

    ii. Genetic and Inflammatory Effects on Childhood Trauma and Cognitive Function in Patients with Schizophrenia and Healthy Participants. **Schizophrenia International Research Society (SIRS) conference- 11-15th May 2023- Toronto, Canada.**

   iii. Genetics, Inflammation and Childhood Trauma: Effects on Cognition in Patients with

Schizophrenia and Healthy Participants. **Galway Neuroscience Centre Research Day- 2nd December 2022- Galway, Ireland.**

iv. Publishing: the perspective of a PhD student. **Annual School of Psychology Research Day- 2nd June 2022, University of Galway, Ireland.**

v. Microglial-Expressed Genetic Risk Variants, Cognitive Function and Brain Volume in Patients with Schizophrenia and Healthy Controls. **Schizophrenia International Research Society (SIRS) conference- 6-10th April 2022- Florence, Italy**.

vi. Schizophrenia International Research Society (SIRS) conference- 17th- 21st April 2021- Virtual meeting.

vii. Oral presentations were regularly presented at research group meetings. **NICOG and iRelate, at the University of Galway, Ireland.**

Poster Presentations

i. Genetic and Inflammatory Effects on Childhood Trauma and Cognitive Function in Patients with Schizophrenia and Healthy Participants. Irish Computational Biology & Genomics Conference- 4th-5th December- Galway, Ireland.

ii. Genetic and Inflammatory Effects on Childhood Trauma and Cognitive Function in Patients with Schizophrenia and Healthy Participants. **European College of Neuropsychopharmacology (ECNP) Neuroimaging Workshop- 16-19th March 2023- Nice, France.**

iii. The Impact of Early Life Adversity and Education on Genetic and Brain Morphological Predictors of Cognitive Ability. **WCPG- 13th-17th of September 2022- Florence, Italy.**

iv. Microglial-Expressed Genetic Risk Variants, Cognitive Function and Brain Volume in Patients with Schizophrenia and Healthy Controls. **Galway Neuroscience Centre (GNC) Research Day- 10th December 2021- University of Galway, Ireland.**

v. Microglial-Expressed Genetic Risk Variants, Cognitive Function and Brain Volume in Patients with Schizophrenia and Healthy Controls. **WCPG- 12th 14th October 2021- Virtual Meeting.**

vi. Microglial-Expressed Genetic Risk Variants, Cognitive Function and Brain Volume in Patients with Schizophrenia and Healthy Controls. **SIRS conference- 17th- 21st April 2021- Virtual meeting.**

vii. Microglial-Expressed Genetic Risk Variants, Cognitive Function and Brain Volume

in Patients with Schizophrenia and Healthy Controls. **GNC Research Day- 13th December 2019- University of Galway, Ireland.**

Conference Attendance

i.   The Brain Conference, 3rd-4th March 2022- Virtual Meeting.

ii. Eating Disorder Hope Conference- 25th February 2022- Virtual Meeting.

iii. YOULEAD 2nd Annual Youth Mental Health Conference- October 11th- 15th 2021, Virtual Meeting.

iv. The Brain Conference- 4th-5th March 2021- Virtual Meeting.

v.   Federation of European Neuroscience Societies- 9th-13th July 2020, Virtual Meeting.

vi. YOULEAD Annual Youth Mental Health Conference- October 5th-9th 2020- Royal College of Surgeons in Ireland (RCSI), Dublin.

Workshop Attendance

i.   European Congress of Neuropsychopharmacology Workshop for Early Career Scientists- 16th- 19th March 2023- Nice, France.

ii. Human Brain Anatomy Course- 11th-12th March 2023- King's College London.

iii. Communicating your research to the public- 31st March 2022.

iv. Developing Interdisciplinary Pathways Webinar- 8th February 2022.

v.   School of Psychology Statistics Workshop- A Beginner's Guide to Structural Equation Modelling- 21st February 2021- University of Galway, Ireland.

vi. Conducting Systematic Reviews- 25th August 2020- University of Galway, Ireland.

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ii. European Neuropsychopharmacology Early Career Scientist Award 2023.

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Thesis Abstract

Schizophrenia is a complex, highly polygenic neuropsychiatric disorder. Individuals with schizophrenia experience neurocognitive and social cognitive deficits that can impact their ability to work, live independently, and form relationships. These deficits are associated with several common genetic risk variants for schizophrenia and may be exacerbated by environmental factors such as childhood trauma. Increasing evidence suggests a role for the involvement of inflammation in mediating the genetic and environmental risk for schizophrenia. A current gap in knowledge is how such genetic, biological, and environmental factors combine and interact to explain variability in cognitive functioning in patients with schizophrenia. Investigating these neurobiological mechanisms as well as considering environmental effects that confer greater susceptibility to deficits in cognition is needed to clarify how best to target these deficits and to improve treatment development, implementation, and outcomes.

This thesis examines the relationship between genetics, early life adversity, and cognitive functioning in both individuals with schizophrenia and healthy participants. It also explores the role of immune and neural mechanisms behind these relationships. The four studies presented in this thesis demonstrate that exposure to early life adversity is associated with both social and neurocognitive functioning in patients with schizophrenia and healthy participants. Furthermore, the results show that proinflammatory cytokines and white matter microstructural organization mediate the association between early life adversity and cognitive ability. While the genetic liability for schizophrenia contributes to cognitive impairments in both patients and healthy controls, it has a modest effect. Overall, the findings from this thesis support the neurodevelopmental and immune hypotheses of schizophrenia and emphasise the need to target cognitive impairments and develop new strategies to mitigate the impact of adverse life experiences on brain structure in both clinical and nonclinical populations.

Thesis Overview

Chapter 1 begins with a general introduction to the clinical background and aetiology of schizophrenia, outlining its current definition, the disorder's impact on both society and affected individuals. Available treatment options are discussed. Following sections concentrate on the role of early life adversity on neurocognitive outcomes associated with schizophrenia. Further, the link between immune dysregulation and cognition in schizophrenia will be outlined.

The first empirical study arising from this body of work is described in **Chapter 2,** which explores the relationship between immune relevant schizophrenia risk genes, brain structure and cognitive functioning in patients and healthy participants. **Chapter 3** seeks to model the associations between genetic inheritance, environmental exposure, total grey matter volume and general cognitive ability in the UK Biobank sample. The third manuscript arising from this thesis is detailed in **Chapter 4** and builds upon previous studies to model genetic and inflammatory effects on early life adversity and later cognitive functioning in a case control sample. The fourth and final manuscript from this thesis is presented in **Chapter 5** and explores the potential mediating effects of inflammation and white matter microstructural differences on early life adversity and social cognition. In **Chapter 6** the findings from this thesis in the context of the overall literature are discussed and interpreted. Strengths and limitations of the thesis are addressed as well as directions for future research.

List of Abbreviations

ACC	Anterior Cingulate Cortex
ACE	Adverse Childhood Experiences
ACR	Anterior Corona Radiata
AD	Alzheimer's Disease
APOE	Apolipoprotein E
BBB	Blood Brain Barrier
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
C4	Complement Component 4
CANTAB	Cambridge Neuropsychological Test Automated Battery
CB	Cingulate Bundle
CBT	Cognitive Behavioural Therapy
CC	Corpus Callosum
CECE	Childhood Experience of Care and Abuse Questionnaire
CFI	Comparative Fit Index
CI	Confidence Interval
CNS	Central Nervous System
CNVs	Copy Number Variants
COX-2	Cyclooxygenase-2
CRP	C-Reactive Protein
CRT	Cognitive Remediation Therapy
CSMD1	CUB and Sushi Multiple Domains 1
CST	Cortico-Spinal Tract
CTQ	Childhood Trauma Questionnaire
CV	Coefficient of Variability
DDD	Daily Defined Dose
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DNA	Deoxyribonucleic Acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imagining
DUP	Duration of Untreated Psychosis
EIS	Early Intervention Service
ELA	Early Life Adversity

ELISA	Enzyme-Linked Immunosorbent Assay
ENIGMA	Enhancing NeuroImaging Genetics through Meta-Analysis
eQTL	Expression Quantitative Trait Locus
ERT	Emotion Recognition
FA	Fractional Anisotropy
FDR	False Discovery Rate
GC	Glucocorticoid
GM	Grey Matter
GO	Gene Ontology
GWAS	Genome-Wide Association Study
HLA	Human Leukocyte Antigen
HPA	Hypothalamic-Pituitary-Adrenal
HWE	Hardy Weinberg Equilibrium
ICA	Independent Component Analysis
ICD	International Statistical Classification of Disease and Related Health Problems
IFG	Inferior Frontal Gyrus
IFOF	Inferior Fronto-Occipital Fasciculus
IL-1β	Interleukin 1 Beta
IL-6	Interleukin 6
ILF	Inferior Longitudinal Fasciculus
INF-γ	Interferon Gamma
IPD	Imaging Derived Phenotypes
IQ	Intelligence Quotient
IRC	Irish Research Council
iRelate	Immune Response & Social Cognition in Schizophrenia
KB	Kilobase
KMO	Kaiser-Meyer-Olkin
LD	Linkage Disequilibrium
LMI	Logical Memory I
LMII	Logical Memory II
LNS	Letter Numbering Sequencing
MB	Megabase
MCCA	Multimodal Canonical Correlation Analysis
MFA	Minor Allele Frequency
MHC	Major Histocompatibility Complex
MR	Mendelian Randomisation

MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIS	National Incidence Study
NK	Natural Killer
NMDA	N-Methyl-D-Aspartate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OFC	Orbitofrontal Cortex
OR	Odds Ratio
PAL	Paired Associate Learning
PC	Principal Component
PCA	Principal Component Analysis
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PGC	Psychiatric Genomics Consortium
PGS	Polygenic Score
QC	Quality Control
RMET	Reading the Mind in the Eyes Task
RMSEA	Root Mean Square Error of Approximation
SANS	Scale for the Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms
SART	Sustained Attention to Response Test
SCID	Structured Clinical Interview for DSM
ScoRS	Schizophrenia Cognition Rating Scale
SD	Standard Deviation
SE	Standard Error
SEM	Structural Equation Modelling
SFI	Science Foundation Ireland
SLF	Superior Longitudinal Fasciculus
SNP	Single Nucleotide Polymorphism
SRMR	Standardised Root Mean Squared Residual
STG	Superior Temporal Gyrus
SWM	Spatial Working Memory
SZ	Schizophrenia
TBSS	Tract-Based Spatial Statistics
TEC	Traumatic Experiences Checklist
TFE	Turbo Field Echo

TIV	Total Intracranial Volume
TLI	Tucker-Lewis Index
TNF-α	Tumor Necrosis Factor Alpha
ToM	Theory of Mind
TrkB	Tropomyosin Receptor Kinase B
UF	Uncinate Fasciculus
URV	Ultra-Rare Coding Variant
VBM	Voxel-Based Morphometry
WAIS-III	Weschler Adult Intelligence Scale, Third Edition
WHO	World Health Organisation
WMS	Weschler Memory Scale
WTAR	Weschler Test of Adult Reading

List of Tables

Chapter 4

Chapter 5

List of Figures

Chapter 5

List of Appendices

Chapter 1: General Introduction

1. Schizophrenia

1.1. Clinical Overview

Schizophrenia is a severe neuropsychiatric disorder with typical onset in late adolescence or early adulthood. It is characterised by several clinical features, including psychotic symptoms-such as hallucinations, delusions, negative and disorganised symptoms, and cognitive dysfunctions (McCutcheon et al., 2021). Cognitive symptoms in particular, are important because, despite representing a significant predictor of daily functioning and quality of life, they are not substantially improved by available pharmacological treatments (Gebreegziabhere et al., 2022). The current understanding of the disorder is complex and multifactorial, with risk associated with multiple common and rare genetic variants and epigenetic, stochastic, and environmental factors. The interaction between genetic and environmental factors is widely believed to contribute to psychotic symptoms and impairments in cognition in individuals with schizophrenia.

According to the World Health Organization (WHO), more than 21 million people worldwide have a diagnosis of schizophrenia, affecting 0.5-1% of the general population (Saha et al., 2008). Schizophrenia is responsible for a significant health, social and economic burden, with the total expenditure in Ireland estimated at €460.6 million per annum in 2008 (Behan et al., 2008). Among mental health disorders, schizophrenia is considered one of the ten leading causes of years lived with disability across all age groups (World Health, 2022). The high cost of the disorder is due to its typical onset in early adulthood and the long-term impairments in social, cognitive, and occupational function. Further, it is associated with reduced life expectancy; individuals with the disorder have a mean life expectancy of about 15 years lower than the general population and a 5 to 10% lifetime risk of death by suicide (Olfson et al., 2021). It also represents one of the most stigmatised disorders in Ireland (Godfrey et al., 2023). According to the National Collaborating Centre for Mental (2014), approximately 30% of the total cost of schizophrenia treatment and public care can be attributed to direct costs. The remaining 70% comprises of indirect costs to society, such as benefit payments, informal care and private expenditures, criminal justice system services, and lost productivity due to unemployment or premature mortality among individuals with schizophrenia.

1.2.   Diagnostic Criteria for Schizophrenia

The clinical presentation of schizophrenia is highly heterogenous and can vary considerably between individuals and within individuals over time (Barnett et al., 2018). Formal symptoms are typically preceded by a prodromal phase characterised by subthreshold psychotic symptoms (George et al., 2017). To diagnose schizophrenia, at least two of the following symptoms must be present during a 1-month period: delusions (i.e., a firmly held belief that contradicts generally accepted reality, often persecutory or grandiose), hallucinations (i.e., perception of something not present, most frequently hearing voices that no one else hears), disorganised speech, eccentric or agitated behaviour, and negative symptoms (such as lack of drive, reduced motivation for social and productive activities, or reduced expression of emotion) (American Psychiatric Association, 2013).

The concept of schizophrenia has a long history. The systematic descriptions provided by German and Swiss phenomenologists Kraeplin and Bleuler in the late 19th century form the foundation of the current understanding of schizophrenia in which the disorder is associated with disability in multiple functional domains. Schizophrenia has high diagnostic sensitivity, with over 90% of diagnosed patients retaining their diagnosis after two and five years (George et al., 2017). However, debate exists around the validity of its construct as the disorder itself does not always present as a discrete entity and it has been proposed that psychotic symptoms should be studied according to a dimensional approach.

Currently, there are two classification systems used for establishing a diagnosis: the Diagnostic and Statistical Manual, 5th edition (DSM-V), published by the American Psychiatric Association (American Psychiatric Association, 2013), and the International Classification of Diseases, 11th edition (ICD) (WHO, 2022). Furthermore, the disorder is often conceptualised as having three distinct clinical stages: neurodevelopmental (premorbid), neuroplastic (prodromal, onset, and deteriorative) and neuroprogressive (deteriorative and chronic/residual) (Lieberman et al., 1997). The duration of psychotic symptoms before diagnosis and treatment, referred to as the duration of untreated psychosis (DUP), is approximately one year (Lieberman et al., 2001). In men, symptoms tend to manifest earlier than in women, which may also be associated with the severity of the illness (Aleman et al., 2003).

The DSM-V and ICD-11 classification systems provide guidelines that include other considerations necessary, such as the duration of symptoms and exclusions for other causes of symptoms including drug use and neurological disorders. They also provide diagnostic boundaries with other neuropsychiatric disorders, including mood and developmental disorders. Although not a formal part of DSM-V classification, cognitive impairments are increasingly recognised as a core feature of schizophrenia (Keefe et al., 2005), including deficits in neurocognitive domains and social cognitive ability. Currently, there are no formal biomarkers used to assist in diagnosing the condition. In addition to clinical symptom severity, cognitive symptoms remain one of the strongest predictors of functional status across several outcome domains and patient characteristics, including impaired occupational and academic performance, household integration, social functioning, participation in activities, and quality of life (See Green & Harvey, 2014 for review).

1.3. Treatment of Schizophrenia

1.3.1. Pharmacological Treatment

In terms of pharmacological treatment, second-generation (atypical) antipsychotics are commonly prescribed to help alleviate symptoms of schizophrenia and include the following: olanzapine, risperidone, aripiprazole, paliperidone, amisulpride, quetiapine, and ziprasidone. These are typically preferred over first-generation (typical) antipsychotics as they have a lower risk of extrapyramidal symptoms. Clozapine, although shown to be the most effective medication for treatment-resistant psychosis, is only prescribed following non-response to two other medications due to the risk of agranulocytosis associated with this drug (Patel et al., 2014). The efficacy of antipsychotic treatment for positive symptoms, relapse prevention and extending life expectancy is well-documented in several studies (Fountoulakis et al., 2020; Kane & Correll, 2022; Taipale et al., 2020). However, antipsychotics exert minimal effects on negative and cognitive symptoms and may even exacerbate these symptoms (Ballester & Frankel, 2017).

D_2 receptor antagonism in the brain is a common pharmacodynamic property of all antipsychotics, leading to the hypothesis that schizophrenia involves dysregulation of dopaminergic circuits. The 'dopamine hypothesis' of schizophrenia has undergone several revisions since it was first formulated by Arvid Carlsson and Margit Lindqvist (Brisch et al.,

2014; Carlsson & Lindqvist, 1963), positing that risk for schizophrenia stems from excess dopamine production and release in mesolimbic areas of the brain and decreased dopamine in the mesocortical projection to the dorsolateral prefrontal cortex (Pogarell et al., 2012). Research on the mechanism of action of antipsychotic medication has shown that at least 60-65% of striatal D_2 receptors must be occupied to alleviate positive symptoms in schizophrenia. At the same time, a further increase in D_2 blockade of over 77% has been shown to result in extrapyramidal symptoms and is not associated with improved antipsychotic efficacy (Patel et al., 2014). Initial antipsychotic treatment can successfully alleviate psychotic symptoms in most patients, with up to 76% achieving clinical remission within six months of their first episode (Kahn et al., 2018). However, two-thirds of patients continue to experience fluctuating phases of remission (residual phase) and relapse (active phase). Furthermore, only between 13.5% and 50% of patients achieve sustained clinical remission, or 'recovery', over longer periods (Jaaskelainen et al., 2013), and 30% of individuals with schizophrenia are resistant to antipsychotics (Lally & MacCabe, 2015).

In addition to dopamine, schizophrenia is believed to arise due to abnormalities in glutamatergic neurotransmission. Importantly, however, dopamine and glutamate are co-regulated; therefore, dopaminergic dysregulation may be a direct result of upstream glutamatergic abnormalities and reciprocally, it may worsen glutamatergic abnormalities (Buck et al., 2022). Research on humans and animals using *N*-methyl-d-aspartate (NMDA) receptor competitive antagonists, such as ketamine, suggests that schizophrenia-related symptoms may be caused by a reduction in the normal activity of the NMDA receptors, particularly negative and cognitive symptoms.

1.3.2. Psychosocial Interventions

Although pharmacological treatments can alleviate psychotic symptoms in people with schizophrenia, these drugs typically do not significantly improve social, cognitive, and occupational functioning. Additional benefits can be found from psychosocial interventions that address a wide range of an individual's health needs, such as symptom severity, relapse, treatment adherence and overall functioning. Psychosocial interventions include but are not limited to cognitive behavioural therapy (CBT), cognitive remediation therapy (CRT), behavioural family interventions and supported education and employment. CBT is a structured and standardised approach that helps patients manage their psychotic experiences by examining and re-evaluating their thoughts and perceptions. CRT is a behavioural training intervention

designed to improve cognitive impairments in schizophrenia (Bowie et al., 2020). Meta-analyses report moderate effect sizes for reducing psychotic symptoms following psychological intervention (Bighelli et al., 2018; Wykes et al., 2008). Cognitive remediation is the most effective treatment modality for addressing cognitive impairments, although overall effect sizes for CRT on cognitive functioning are small (Solmi et al., 2023).

Early Intervention Services (EIS) aim to detect and treat psychotic symptoms at an early stage of illness to prevent associated behavioural and psychosocial problems using a multi-component model of care. Common features of EIS include prescribing and monitoring of antipsychotic medication, provision of psychosocial and behavioural treatments, small patient-to-staff ratios, and 1-3 years duration (O'Connell et al., 2021). Recent meta-analytic findings demonstrate that EIS are an effective resource in providing treatment for addressing psychotic symptoms and highlight the importance of early intervention for individuals with schizophrenia. To further improve treatment outcomes in schizophrenia, a major focus of current research is to better understand the causal factors contributing to poor social and occupational outcomes. In this context, understanding the biological mechanisms leading to poorer cognitive impairment as a leading predictor of poorer functioning remains a key research challenge.

1.4.   Cognition in Schizophrenia

Cognitive deficits have been described as a core component of schizophrenia since the earliest descriptions of the disorder by Kraeplin as 'dementia praecox' and include deficits in neurocognitive and social cognitive domains. In schizophrenia, cognitive impairments are heritable and aggregate among unaffected relatives, including parents and siblings (Zhang et al., 2018). Almost 80% of individuals with schizophrenia fall short of their predicted cognitive function based on premorbid intelligence and parental education levels (McCleery & Nuechterlein, 2019; Tripathi et al., 2018). The effect sizes associated with cognitive impairments range from moderate to large, and on average, individuals with schizophrenia perform between one and two standard deviations below that of healthy controls across most cognitive measures (Keefe et al., 2011). Both in chronic states of illness and during the first episode of psychosis, impairments are observable in processing speed, verbal learning and memory, visuospatial learning, and memory, working memory, attention, reasoning and problem-solving (Green et al., 2019). All of these domains, when assessed reliably, demonstrate observable differences between patients and healthy comparison groups that remain evident

when outcomes are assessed longitudinally (Green et al., 2004). In patients with schizophrenia, cognitive symptoms (both neurocognitive and social cognitive domains) are distinct from positive and negative symptoms (Chang et al., 2020a; Moura et al., 2022).

While several comprehensive reviews have shown that most neurocognitive and social cognitive domains in schizophrenia are affected (Mesholam-Gately et al., 2009), the most severe impairments are typically found in episodic memory (Heinrichs & Zakzanis, 1998) executive functioning (Reichenberg & Harvey, 2007), general cognitive ability (Kalkstein et al., 2010) and working memory (Forbes et al., 2009). In addition, impairments in processing speed have been widely reported in schizophrenia research (Palmer et al., 2009) but are likely a result of deficits in other domains that rely heavily on the rapid and efficient information processing (Kalkstein et al., 2010). Deficits in social cognition, including mentalising and emotion processing, have been demonstrated in individuals with schizophrenia (Bora et al., 2009; Gica et al., 2019; Gold et al., 2012). These impairments are consistently associated with functional outcomes such as employment status, independent living, social skills, and interpersonal relationships (Shamsi et al., 2011). They have also been linked to adverse environmental effects such as inflammation and childhood trauma (Shannon et al., 2011). A more thorough summary of the domains of general cognitive ability, episodic and working memory, and social cognitive domains are discussed below, which are of primary interest to this thesis.

1.4.1. General Cognitive Ability

General cognitive ability is a broad term relating to global intellectual quotient (IQ) or 'g'- which underlies multiple specific abilities, including verbal, spatial, numerical, and mechanical skills (Spearman, 1904). In research settings, one of the most used tests of intelligence is the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1997a). Version 3 (WAIS-III), established in 1997, comprises of 14 subtests designed to measure different intelligence domains, including performance IQ, verbal IQ, and full-scale IQ (FSIQ). These are standardised according to age-related norms. In clinical and research settings, these tests can be time-consuming, and short forms of this measure have been validated, including those suitable for individuals with schizophrenia (Blyler et al., 2000). Other commonly used measures of global intelligence include composite scores of subtests from assessment batteries that measure multiple cognitive domains. Individuals with schizophrenia are estimated to have a premorbid

IQ deficit of approximately half a standard deviation (SD), and by the first episode this impairment increases to 1 SD (Jonas et al., 2022).

1.4.2. Episodic Memory

Episodic memory, defined as memory for objects and events related to a specific space and time, is an aspect of cognition which has consistently been shown to be impaired in schizophrenia (Imamoglu et al., 2022; Kwok et al., 2021). Such impairments in episodic memory are found even when accounting for factors such as antipsychotic medication, duration of illness, and severity of symptoms (Guo et al., 2019). Episodic memory can be measured via recall and recognition paradigms designed to assess long-term encoding, storage, and retrieval of event representations. For this thesis, two subtests from the WAIS-III were used to measure episodic memory functioning: Logical Memory Task (I and II) and two subtests from the Wechsler Memory Scale third edition (WMS- III) (Wechsler, 1997b)- the Faces Task (I and II).

1.4.3. Working Memory

Working memory deficits are evident early in the course of schizophrenia (Fusar-Poli et al., 2012). Working memory refers to a limited-capacity system for the storage of information and the ability to mentally manipulate information over short periods. It is strongly related to executive functioning, and several models of working memory have been proposed in the literature (Baddeley & Hitch, 1974; Cowan, 1999; Engle et al., 1999). Meta-analytical work suggests that working memory deficits are associated with schizophrenia and are not solely attributed to IQ deficits (Forbes et al., 2009). Two widely used measures of working memory included in this thesis are the spatial working memory (SWM) task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge-Cognition, 2015) and the Letter-Number Sequencing (LNS) task from the WSM-III.

1.5. Social Cognition in Schizophrenia

In addition to neurocognitive impairments, social cognitive deficits are a central feature of schizophrenia (Cowman et al., 2023; Grant et al., 2017). Social cognition is a complex concept that involves the ability to create representations of relationships between oneself and others and can be used flexibly to guide social behaviour (Adolphs, 2001; Green et al., 2008). It is considered a multidimensional construct encompassing several key domains, such as theory of

mind/mentalising, emotion processing, social perception, and attributional style/bias (Pinkham et al., 2014). In studies investigating first-episode psychosis and clinical or genetic risk, social cognitive impairments are apparent even in the prodromal phase of the disorder (Pinkham et al., 2014). Recent work has demonstrated the importance of social cognition in terms of functional outcomes in patients, including interpersonal relationships, employment and independent living, which account for a proportion of variance beyond that explained by neurocognitive measures (Pinkham & Penn, 2006). In a recent review, social cognitive deficits accounted for roughly 20% of the variance explained in psychosocial function (Cowman et al., 2021). In case-control studies, the largest impairments have been observed for emotion processing (d=0.89), theory of mind (d=0.96), and social perception (d=1.04) (Vaskinn & Horan, 2020).

1.5.1. Emotion Processing and Recognition

Emotion processing or recognition is considered a key factor in social dysfunction and has been studied extensively in schizophrenia. It refers to the capacity to interpret the emotions of others (Ekman, 1993) and is an essential component of proper communication and social functioning (Pinkham et al., 2014). Deficits in facial emotion recognition are a well-replicated finding in schizophrenia, detected at psychosis onset with the same severity observable at more advanced stages of the illness, particularly for negative emotions (Gao et al., 2021). Several meta-analyses have reported large effect sizes for impairments in emotion perception (Hoekert et al., 2007; Kohler et al., 2010). Measures of emotion recognition typically involve rating emotions displayed in pictures of facial expressions or voices. Participants are then asked to identify these emotions. The Emotion Recognition Task (ERT) is a commonly used method for assessing emotion recognition in schizophrenia, as well as in other psychiatric disorders and non-clinical populations. The ERT is part of the CANTAB (Robbins et al., 1994) and is known for its ease of administration, feasibility, and tolerability.

1.5.2. Theory of Mind

Impairments in theory of mind (ToM), also known as 'mental state attribution', 'intentional stance', 'mentalising', and 'reflexive awareness', have been documented in patients with schizophrenia (Brüne, 2005). ToM refers to the ability to infer the mental and emotional states of others from social cues like body language, facial expressions, and indirect language, as well as contextual information. Impairments in ToM can significantly hinder interpersonal

communication, as seen in autism spectrum disorder (Aguillon-Hernandez et al., 2016; Fernandes et al., 2018). Multiple studies have found a connection between poor ToM performance and worse functional outcomes in individuals with schizophrenia (Dimopoulou et al., 2017; Javed & Charles, 2018; McCleery et al., 2014; Mondragón-Maya et al., 2017), with two studies suggesting that poor ToM could act as a mediator between non-social cognitive deficits and functional outcome (Dimopoulou et al., 2017; Javed & Charles, 2018). In data from 50 studies assessing ToM (n= 1,760), Savla et al., (2013) reported a large effect size in patients with schizophrenia compared to healthy participants.

The Reading the Mind in the Eyes Task (RMET), also known as the 'Eyes Task' and the Hinting Task, are frequently used to measure ToM in schizophrenia research. Both tasks are used in this thesis. The Eyes Task was originally developed for autism research by Baron-Cohen and colleagues (Baron-Cohen et al., 2001; Baron-Cohen et al., 1997), but it has since been widely used to assess ToM in other neuropsychiatric disorders, including schizophrenia. This task measures the ability to infer the mental states of others by observing their expressions around the eyes (Guariglia et al., 2015). The Hinting Task, developed by Corcoran et al., (1995), assesses the ability to infer the intentions of various characters from short descriptions of social interactions.

1.6.   Onset and Course of Cognitive Impairments

First-episode psychosis patients, including antipsychotic naïve individuals, demonstrate cognitive impairments comparable to those in more chronic stages of the disorder (Zhang et al., 2018). Deficits are also observed, albeit in attenuated form, before the emergence of psychotic symptoms and in those at high risk of psychosis (Lam et al., 2018). Evidence from longitudinal research suggests that, in most cases, individuals with schizophrenia experience long-term stability in cognitive impairment (Allott et al., 2020; Thompson et al., 2013). A few studies have, however, reported a decline in cognitive functioning over time (Irani et al., 2011; Zanelli et al., 2022) or improvement (Bora & Murray, 2014). These discrepancies may be consonant with normal as opposed to accelerated ageing. It is also likely that a small subset of patients experience progressive deterioration of cognitive functioning later in life. Overall, the findings support the contention that schizophrenia is, at least in part, a neurodevelopmental disorder and that cognitive impairment is an important endophenotype in schizophrenia.

1.7.   Brain Structural Alterations and Cognitive Impairment

A significant amount of research has been carried out to understand the neural basis of cognitive impairment in schizophrenia using various neuroimaging methods. The overall results suggest that individuals with greater impairment in cognitive functioning, including social cognition exhibit more significant alterations in whole-brain grey and white matter (Antonova et al., 2004; Fujiwara et al., 2015; Kelly et al., 2018; Khalil et al., 2022). Regionally, the most consistently observed findings are reduced grey matter volume in the medial temporal, superior temporal, and prefrontal areas (Duan et al., 2021; Herold et al., 2013; Peterson et al., 2023). These regions are critically involved in episodic memory, processing of auditory information and working memory, respectively. Grey matter alterations in schizophrenia are partly hereditary, as demonstrated by twin and genome-wide association studies (GWASs) and are sensitive to the effects of early environmental factors, including early life adversity (Lim et al., 2014). In terms of social cognition, emotion facial recognition is thought to be primarily associated with the fusiform gyrus, amygdala, superior temporal gyrus (STG), prefrontal cortex (PFC) and anterior cingulate cortex (ACC) (Fujiwara et al., 2015; Kelly et al., 2018; King et al., 2021). The medial PFC and the STG have been shown to play critical roles in social perception and knowledge (Pelphrey & Carter, 2008). Animal and post-mortem studies have demonstrated that cortical grey matter reduction is likely a result of reduced dendritic complexity and synaptic density integration (Bennett, 2011; Berdenis van Berlekom et al., 2020; Howes & Onwordi, 2023; Sellgren et al., 2019).

In addition, schizophrenia is considered a disorder of disrupted neural connectivity, in which impaired efficient communication between brain regions contributes to the associated symptoms and changes in cognition. In this regard, white matter, which forms structural connections between regions, has been shown to be altered in schizophrenia. Diffusion tensor imaging (DTI) is a non-invasive MRI technique used to measure *in vivo* water molecule diffusion to provide information on the integrity of myelinated axon pathways in white matter. While several tensor metrics exist, fractional anisotropy (FA) is a popular scalar metric derived from DTI, which uses the three-dimensional motion of water to estimate the homogeneity of diffusion in tissue. Similar to grey matter changes, reductions in FA have been found in both chronic and first-episodic patients as well as in unmedicated individuals with schizophrenia (Amodio et al., 2018; Meng et al., 2019; Yang et al., 2020; Zhang et al., 2016), suggesting that they are not secondary to later progression of the disorder or to treatment effects.

In the largest international study by the ENIGMA consortium in over 4,000 individuals with schizophrenia, widespread reductions in FA were found across the majority of commissural, projection and association white matter tracts, including the superior longitudinal fasciculus (SLF), cingulate bundle (CB), uncinate fasciculus (UF), corpus callosum (CC) and inferior longitudinal fasciculus (ILF) and anterior corona radiata (ACR) (Kelly et al., 2018). The largest of these effects were observed for global white matter, the ACR and the CC. Many of these tracts serve as long connection fibres supporting inter-regional communication, and their disruption is implicated in cognitive functioning. Indeed, reduced FA in these white matter tracts is associated with impairments in general cognitive ability (Holleran et al., 2020) and memory functioning (Karlsgodt et al., 2008). Significant correlations between FA measures and social cognitive ability in patients with schizophrenia have also been observed, particularly in the CB, the SLF and CC (Burke et al., 2022; Calarco et al., 2023; Hegde et al., 2020; Koshiyama et al., 2018). FA reductions have been found in chronic and first-episodic patients with schizophrenia (Amodio et al., 2018; Meng et al., 2019; Yang et al., 2020; Zhang et al., 2016).

1.8. The Aetiology of Cognitive Impairment in Schizophrenia

The finding that cognitive deficits and structural brain alterations are present at the time of the first episode of psychosis and in individuals at high risk for the disorder suggests that there may be pre-existing neural differences that leave at risk-individuals more vulnerable to later insults (i.e., prenatal disruptions, genetics) and that observed changes may be due to disruptions in developmental processes early in life. Indeed, the current consensus is that the aetiology of schizophrenia and cognitive deficits is multifactorial, resulting from a combination of genetic and environmental factors. These factors are thought to contribute to developmentally mediated changes in neuroplasticity and brain connectivity, which form the basis of several hypotheses of aberrant neural activity contributing to the manifestation of associated cognitive symptoms (McCutcheon et al., 2019). However, a current gap in knowledge is how these factors combine and interact to explain variability in cognitive functioning in patients with schizophrenia. Investigating these neurobiological mechanisms, as well as considering environmental effects that confer greater susceptibility to deficits in cognition, is needed to clarify how best to target these deficits and to improve treatment development, implementation, and outcomes. The following sections of the thesis provide an overview of the current state-of-the-art research on the genetic and environmental underpinnings of cognition, which has seen significant progress

in understanding these at an individual level over the past decade. Further, given the renewed interest in investigating inflammatory alterations in schizophrenia and its relevance to cognition and environmental stress, the immune hypothesis of schizophrenia will be discussed.

1.8.1. Common Genetic Variation and Cognition

There is evidence that common genetic variation and rare DNA sequence variants contribute to genetic susceptibility to cognitive impairments in schizophrenia. Twin and family studies have consistently shown that there is a significant genetic component to schizophrenia, with heritability estimated at around 80% (Sullivan et al., 2003). The disorder is, however, highly polygenic, with multiple common variants contributing, each of small effect (median odds ratio (OR) < 1.05) (Trubetskoy et al., 2022). In the most recent and largest GWAS of schizophrenia, which included 76,755 individuals with schizophrenia and 243,649 healthy participants, 287 loci (minor allele frequency (MAF) >1%) were identified (Trubetskoy et al., 2022).

Genetic risk for schizophrenia can be summarised at the individual level by polygenic scores (PGSs). These scores provide a cumulative estimate of common genetic risk for the disorder based on the number of risk alleles an individual carries, weighted by the odds ratio of risk associated with each allele. Currently, PGSs predict approximately 24% of the variance in schizophrenia liability (Trubetskoy et al., 2022). In genetic studies, general cognitive ability is often used to index cognitive performance because it is a valid construct with high heritability. It also allows for the combination of unrelated cognitive tests to increase sample size and statistical power. However, studies have also shown that there are substantial and independent genetic effects on specific cognitive domains, such as episodic memory and executive function (Gui et al., 2022). It is estimated that a third of the genetic risk for schizophrenia may be mediated by influences on cognition (Toulopoulou et al., 2019). These risk variants are implicated in several known biological processes, including synaptic function, synaptogenesis, and other aspects of neuronal and glial function as well as within the major histocompatibility complex (MHC) region.

1.8.2. Rare and De-Novo Mutations and Cognition

Genetic liability for schizophrenia also includes rarer genetic variants that involve the deletion or duplication of sections of DNA- copy-number variants (CNVs) and ultra-rare coding variants

(URVs). These variants are only found in 2 to 3% of people with schizophrenia but carry much larger effects on individual risk (OR= 2-60) (Singh et al., 2022). Many CNVs affect genes implicated in neurodevelopment, and some evidence suggests that increased CNV burden is associated with reduced cognitive functioning (McCutcheon et al., 2020). However, it is noteworthy that while many common and rare genetic variants have been implicated in schizophrenia, casual variants are located mainly in non-coding regions of the genome, making it difficult to identify underlying genes and derive clear functional insights.

1.8.3. Gene sets Implicated in Cognition

Different methodological approaches, including the use of biological labels such as gene ontologies, regulome approaches, and gene co-expression, have provided some perspectives on how genetic risk translates into the neurobiology of cognitive impairments in schizophrenia. These methodological approaches typically group genes based on (1) known functions (e.g., synaptic release genes, transcription factors, immune genes), (2) gene-centred pathways (e.g., C4, TrKB, AKT, BDNF, or DISC1 signalling), (3) disease pathophysiology (e.g., ApoE), (4) cell specificity (e.g., oligodendrocytes, microglia), (5) substrate activity (e.g., receptor tyrosine kinases), and (6) chromosomal location (22q11-13 genes). For variants that have known biological effects, these tend to overlap with genes related to cognitive ability, including genes involved in synaptic function, long-term potentiation, glutamate and dopamine neurotransmission, as well as voltage-gated calcium channel genes (Koch et al., 2020; Lam et al., 2019). A snapshot of some of the genetic architecture of schizophrenia is shown graphically in Figure 1.1 below.
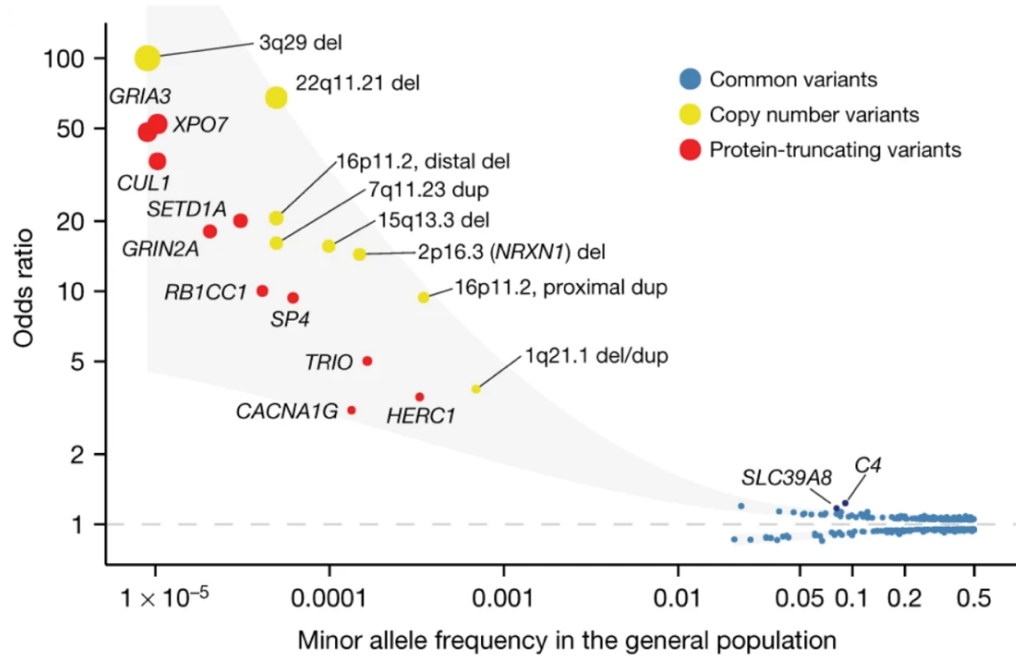
Figure 1.1. Genetic architecture of schizophrenia

The genetic architecture underlying schizophrenia which includes thousands of common genetic variants of small effect (blue), CNVs (yellow) and URVs of large effect (red). Taken from (Singh et al., 2022).

1.8.4. Environment Risk Factors

Schizophrenia is estimated to have a heritability of around 32-36% by the psychiatric genetics consortium (PGC) study and other GWASs, which is much lower than the estimates from family studies (Purcell et al., 2009; Skene et al., 2018; Wray & Visscher, 2010). One explanation for the 'missing' heritability is that genes involved have not been identified by GWASs, because their effect sizes are too small or because they are extremely rare (Owen & Williams, 2021). On the other hand, it is also plausible that GWASs inadequately measure environmental factors that are known to be relevant to the risk of schizophrenia and impairments in cognition. Clinical and epidemiological research has implicated numerous environmental factors for impairments in cognitive functioning that interact with genetic predisposition during prenatal and postnatal stages of development.

Prenatal and early life factors, including prenatal viral and maternal infections, stress during pregnancy and perinatal obstetric complications such as hypoxia, were among the first environmental factors found to be associated with schizophrenia later in life (Rethelyi et al., 2013; Triplett et al., 2022). Numerous other studies have demonstrated a link between urban

upbringing migration, substance misuse, childhood trauma, parental loss or separation and the development of schizophrenia (Pedersen et al., 2022; Stilo & Murray, 2019). There is increasing evidence that certain risk factors for schizophrenia have a combined or additive effect on schizophrenia beyond the associated risk of each factor alone. This 'double hit' theory of schizophrenia suggests that a combination of genetic susceptibility coupled with environmental insults, including stress and childhood trauma, can lead to the onset of symptoms in individuals with the disorder (Guerrin et al., 2021). Currently, it is hypothesised that several hits, including genetic, biological, and environmental risk factors interact in a complex manner during key periods of development to contribute to cognitive deficits. Importantly, however, these effects can have a pleiotropic effect in that they are associated with multiple psychiatric conditions that may not be specific to psychosis but to a more general disruption of neurodevelopment. Unravelling how these interactions produce neurobiological changes leading to deficits in cognition remains a major challenge in the area.

1.9.   Early Life Adversity

Early life adversity (ELA) involves exposure to events perceived as a threat to one's physical or emotional well-being, which exceeds a child's ability to cope and self-regulate, resulting in prolonged periods of physiological hyperarousal (Pechtel & Pizzagalli, 2011). Globally, the prevalence of ELA is estimated to occur between 25% and 40% of the population (Saunders & Adams, 2014; Xie et al., 2018). The term ELA refers to various types of adversity, including emotional and physical abuse, sexual abuse, and emotional and physical neglect that have occurred before 18 years of age (Read et al., 2001). In broader terms, ELA may also include the loss of a parent or a caregiver, separation or divorce of a parent or caregiver, and natural disasters (De Bellis & Zisk, 2014). ELA is a significant predictor of mental and physical health conditions (Danese & J Lewis, 2017). Further, it is considered a transdiagnostic risk factor for almost all common mental health conditions, including, major depressive disorder (Mandelli et al., 2015), bipolar disorder (Aas et al., 2016; Quide et al., 2021; Quidé et al., 2020), borderline personality disorder (Baptista et al., 2023), and psychosis (Popovic et al., 2019). A full description of each of the trauma subtypes used in this thesis are detailed in Table 1.1, which is based on the Fourth National Incidence Study (NIS-4) (Sedlak et al., 2010).

In relation to schizophrenia more specifically, exposure to ELA conveys a threefold increased risk of psychosis, suggesting a strong link between these adverse events and schizophrenia onset

(Varese et al., 2012). It has also been demonstrated that compared to the general population, a history of ELA is more prevalent among individuals with a schizophrenia spectrum or affective disorder (including bipolar and major depression with psychotic features) (Larsson et al., 2013a). The association between ELA as a risk factor for the development of schizophrenia is further underscored by research documenting the adverse effects of ELA on poorer outcomes, such as increased symptom severity (Dokuz et al., 2022), cardiovascular disease (Scott-Storey et al., 2019), depressive symptoms (Kelly et al., 2016), poorer treatment response (Kilian et al., 2020), educational attainment (Sideli et al., 2022), global functioning (Appiah-Kusi et al., 2017) and cognitive impairments (Aas et al., 2014; Rokita et al., 2021). In patients with a high risk for psychosis, a history of ELA was associated with greater positive and negative symptom severity, depressive symptoms, and lower levels of global functioning (Appiah-Kusi et al., 2017). In a recent study investigating the prevalence of ELA in psychiatric outpatients, physical neglect and emotional neglect were the two most reported types of types among those with schizophrenia (Devi et al., 2019).

Table 1.1. Fourth National Incidence Study criteria for childhood trauma subtypes

Trauma Subtype	Definition
Sexual Abuse	Any sexual act with a minor, including sexual penetration, molestation with genital contact, attempted sexual abuse with physical contact, child prostitution or pornography and exposure to sexually explicit material or voyeurism.
Physical abuse	Hitting a child with hands or an object, kicking, punching, throwing, deliberately dropping, shaking, grabbing, dragging, pushing, or pulling, or otherwise causing actual or threatened physical harm.
Physical Neglect	The refusal of custody or the deliberate failure to provide or seek needed care, supervision, nutrition, clothing, shelter, and personal hygiene or other disregard of a child's physical needs and safety.
Emotional Abuse	Verbal assaults or other abuse, threats, terrorization, administration of unprescribed substances or close confinement.
Emotional Neglect	Inadequate nurturing and affection, deliberate failure to provide or seek needed care for emotional-behavioural problems, allowing substance abuse or maladaptive behaviour, overprotectiveness, inappropriately advanced expectations, inadequate structure and exposure to maladaptive behaviours and environments or domestic violence.

Taken from Sedlak et al., (2010)

1.9.1. Tools for Examining Early Life Adversity

There are several tools available to examine ELA. One such tool is the Adverse Childhood Experiences (ACE) study questionnaire designed by Felitti et al., (1998), which divides traumatic experiences into three subtypes: abuse (physical, sexual, emotional), neglect (physical, emotional), and household dysfunction (domestic violence towards a parent, substance abuse or other mental illness and problematic separation/divorce). Another common measure includes the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997), which is used as the primary measure of ELA in this thesis. The CTQ consists of 28 items with five types of childhood trauma assessed: sexual abuse, physical abuse, emotional abuse, physical neglect, and emotional neglect. Each subscale has five statements, and three additional statements are included to identify participants who may minimise abuse. Although both the CTQ and ACE questionnaires have demonstrated good reliability and validity in clinical and non-clinical populations (Kim et al., 2013; Paivio & Cramer, 2004; Dudeck et al., 2015), investigating childhood trauma presents several challenges, particularly since experiences of ELA are evaluated retrospectively (Frissa et al., 2016). This is a critical issue to consider, as individuals with schizophrenia frequently experience symptoms that may affect their attention and ability to recall autobiographical memories. However, studies examining the temporal stability of these measures in individuals with schizophrenia over time have found high test-retest reliability and internal consistency of the CTQ in this population (Kim et al., (2013). Further, work has found moderate correlations between retrospective and prospective recall of ELA, with both measures explaining a similar amount of variation in adverse life outcomes (Reuben et al., 2016).

1.9.2. Early Life Adversity and Cognition in Schizophrenia

Individuals who have experienced ELA and those diagnosed with schizophrenia exhibit greater deficits in cognitive functioning. A recent meta-analysis of 3,315 individuals with psychosis demonstrated a significant negative relationship between overall cognition and ELA (r= -0.055, 95% CI -0.09, -0.02) (Vargas et al., 2019). Exposure to ELA impacts negatively upon several cognitive domains, such as working memory (Vargas et al., 2019), executive functioning, episodic memory (Carrilho et al., 2019; Kasznia et al., 2021; Shannon et al., 2011) and general cognition (Wells et al., 2020). Multiple prospective cohort studies have shown that reverse causation is unlikely to account for this association (Arseneault et al., 2011; Horwitz et al.,

2001; Kelleher et al., 2013). Consequently, there is a great need to understand the precise biological mechanism(s) underpinning the effects of ELA on the brain and how this may confer an increased risk of developing cognitive impairments in schizophrenia.

One of the first studies to examine the association between different types of childhood adversities and cognitive domains found that physical neglect was the strongest predictor of cognition in patients with psychosis (Aas et al., 2012). Numerous studies since support a link between physical neglect and reduced neurocognitive functioning (De-Nardin et al., 2022; Lakkireddy et al., 2022; Li et al., 2017; Morkved et al., 2020; Ucok et al., 2015; Vaskinn, Engelstad, et al., 2021) as well as social cognition (King et al., 2021; Vaskinn, Melle, et al., 2021) (See table 1.2). While the most consistently reported association between childhood trauma and cognition is for physical neglect, some studies have also found sexual abuse (Aas et al., 2012; De-Nardin et al., 2022) and emotional neglect (Kincaid et al., 2018) to be significant predictors of cognitive deficits. Further, in a review paper which examined general versus specific events of childhood trauma on cognitive function, general cognitive ability and memory functioning were the domains most consistently associated with increased exposure to ELA, particularly in terms of physical trauma (neglect and abuse) (Dauvermann & Donohoe, 2019). Key studies that followed since the publication of this paper are detailed in Table 1.2. In a later review examining social cognitive functioning, emotional and physical abuse, as well as neglect were found to be significant predictors of ToM and emotion recognition (Rokita et al., 2018).

Various subtypes of trauma may have distinct impacts on cognition. One theory suggests that childhood abuse and neglect have different effects on brain development; that childhood abuse (emotional, physical and sexual) is associated with an affective pathway, while neglect (physical and emotional) is connected to a cognitive pathway (Van Dam et al., 2015; van Os et al., 2017). The affective pathway relates to an increased sensitivity to stress or altered emotional reactivity to daily stress characterised by more pronounced positive and affective symptoms, while the cognitive pathway reflects more general neurodevelopmental impairments, with greater deficits in cognitive functioning (Kilian et al., 2017). As neglect involves a failure of caregivers to meet basic emotional and physical needs, including nutrition and proper medical care during illness, and is often linked to other forms of abuse, it has been speculated that the adverse neurocognitive consequences could be more extensive than for other forms of abuse (Wells et al., 2020).

Table 1.2. Summary of recent studies examining specific subtypes of ELA and cognitive performance in patients with schizophrenia

Study	*n*	Age (M, SD)	ELA Measure	Cognition	Main Findings
Vaskinn, Engelstad, et al., (2021)	26	38.2 (7.3)	CTQ	Neurocognition, Social Cognition	Physical neglect associated with theory of mind after controlling for IQ.
Vaskinn, Melle, et al., (2021)	68	29.4 (8.1)	CTQ	Social Cognition	Physical neglect strongest predictor of theory of mind.
De-Nardin et al., (2022)	105	24.3 (9.7)	CTQ	Neurocognition	Physical neglect, emotional abuse, physical abuse, and sexual abuse correlated with SCoRS.
Morkved et al., (2020)	78	29.84 (12.37)	CTQ	Neurocognition	Physical neglect associated with attention and working memory.
Pignon et al., (2019)	294	32.1 (9.8)	CTQ	Level of insight)	Physical neglect associated with poor insight.
Lakkireddy et al., (2022)	324*	39.58 (14.64)	ACE- IQ	Neurocognition, Social Cognition	Physical neglect associated with neurocognition. Interaction between sexual abuse and familial risk on neurocognition.
King et al., (2021)	104	42 (10.95)	CTQ	Neurocognition, Social Cognition	Physical neglect correlated with both neurocognitive and social cognitive domains.
Kincaid et al., (2018)	66	45 (11.4)	TEC	Social cognition	Emotional neglect predicted impairments in ToM.
Wang et al., (2022a)	63	27.5 (6.8)	CTQ	Neurocognition	Emotional Neglect and sexual abuse negatively correlated with cognitive function

Kilian et al., (2018)	56	23.8 (6.2)	CTQ	Neurocognition, Social Cognition	Emotional and physical neglect were significant predictors of the variance in verbal learning, social cognition and general cognitive ability.
Kasznia et al., (2021)	127	31.1 (13.8)	CECA.Q	Neurocognition	Early life adversity (total score) was associated with memory and general cognitive ability
Velikonja et al., (2019)	225	38.6 (11.5)	CTQ	Neurocognition	Severity of childhood trauma exposure was associated with working memory, verbal learning and memory and visual learning and memory.
Kim et al., (2019)	27	42.48 (11.86)	CTQ	Neurocognition	Emotional neglect significantly predicted social functioning
Senner et al., (2023)	215	42.9 (12)	CTQ	Neurocognition	Physical neglect and abuse were associated with impaired neurocognitive performance

* Patients include schizophrenia, bipolar disorder, obsessive-compulsive disorder and alcohol use disorder

Note. CTQ= Childhood Trauma Questionnaire, ACE-IQ = Adverse Childhood Experiences- International Questionnaire, TEC= Traumatic Experiences Checklist, ToM= Theory of Mind, ScoRS= Schizophrenia Cognition Rating Scale. CECA.Q= The Childhood Experience of Care and Abuse Questionnaire

1.9.3. Early Life Adversity and Genetic Contributions

The heritable component of ELA is not immutable and is thought to be expressed through gene-environment relationships. These correlations can be passive, where parental genes affect family environments that are then passed down to their children, or they can be active, where children's genes shape their behaviours (e.g., risk-taking behaviours). In addition, evocative gene-environment correlations may increase this risk (Sallis et al., 2021). In a recent GWAS meta-analysis of childhood trauma, 14 independent genetic loci were identified, many of which were enriched for regulatory chromatin markers in brain tissue and genes expressed in excitatory neurons (Warrier et al., 2021). In the same study, Mendelian Randomization (MR) analyses found a bidirectional causal effect on schizophrenia, suggesting both passive and active gene-environment correlation effects. Similarly, Sallis et al., (2021) found a positive association between schizophrenia PGSs and exposure to trauma in children and adolescents using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Norwegian Mother, Father and Child Cohort Study (MoBa). More recently, Marchi et al., (2022) found that childhood trauma mediated an association between schizophrenia PGS and psychotic symptoms, while Aas et al., (2021) found that the strongest interactions between ELA and genetic risk for schizophrenia were for physical abuse and neglect. However, other studies have failed to observe such an interaction effect (Lemvigh et al., 2023; Trotta et al., 2016).

1.9.4. Neurobiological Effects of Early Life Adversity

Although adverse environmental factors are consequential for cognitive function at all stages of the life course, early life or childhood adversity is particularly important as it is a time when the nervous system is highly sensitive to the effects of stress. Early and middle childhood brain development is characterised by enhanced plasticity, neurogenesis, synaptic growth, and organisation of neural circuits, and thus any disruptions to these developmental processes can affect a wide range of cognitive abilities (Stevens et al., 2018). The underlying biological mechanisms linking ELA to that of increased risk of psychosis and cognitive impairments of the disorder are postulated to, in part, involve altered hypothalamic-pituitary-adrenal (HPA) axis and immune functioning, which under stressful circumstances, responds by increasing the production of cortisol and other glucocorticoids (GCs) by the adrenal glands. Activation of the HPA axis has also been linked to an increase in levels of proinflammatory cytokines such as IFNγ, IL-1β, IL-6 and TNF-α and neuroimmune signalling (Diaz-Chávez et al., 2020; Lumertz

et al., 2022), which is discussed further below. Finally, psychological mechanisms, including cognitive schemas, emotional self-regulation, experience of social defeat, disrupted attachment styles, and dissociative mechanisms, may further exacerbate this risk (Misiak et al., 2017). This increased stress reactivity may represent both an expressed genetic liability and an acquired vulnerability due to exposure to ELA. Ultimately, cognitive and biological pathway disruptions can have long-lasting consequences on the structure and function of the brain (De Bellis & Zisk, 2014; Hanson et al., 2015; Teissier et al., 2020) and contribute to behavioural changes such as neurocognitive and social deficits (Fan et al., 2022; Michel et al., 2022; Rokita et al., 2020).

1.9.5. Brain Structural Alterations and Early Life Adversity

Substantial evidence demonstrates that exposure to ELA is associated with brain structural alternations. Previous reviews and meta-analyses have reported structural changes, particularly in the hippocampus, amygdala, regions of the PFC such as the ACC, the orbitofrontal cortex (OFC), the IFG, and the dorsolateral prefrontal cortex (DLPFC) (Holz et al., 2020; Mothersill & Donohoe, 2016; Paquola et al., 2016; Teicher et al., 2016). These areas of the brain are broadly implicated in socio-affective functioning, general cognitive ability and memory functioning, and executive control (Pollok et al., 2022). Beyond this converging research, the results of individual studies demonstrate that adversity-related changes are apparent widely throughout the brain, with total grey matter reductions, decreased cortical thickness and volume loss evident (Cancel et al., 2019; Teicher et al., 2016).

While the association between trauma exposure and grey matter abnormalities in schizophrenia has received considerable attention, the study of white matter connections and more general structural connectivity patterns is primarily overlooked in patients with schizophrenia. Work to date, however, suggests that exposure to ELA may be associated with widespread reductions in FA, with a predilection for the CC and cortico-limbic tracts (Oestreich et al., 2017; Poletti et al., 2015). Two studies in first-episode psychosis patients (Asmal et al., 2019; Poletti et al., 2015) found that those who had experienced ELA had reduced FA in several regions of the brain, including the CC, SLF, ILF, inferior fronto-occipital fasciculus (IFOF) and the forceps major. Further evidence for lower FA in schizophrenia comes from Molina et al., (2018), who examined physical neglect as a subtype of ELA and demonstrated an inverse relationship between a history of physical neglect and lower FA in white matter connections between the left-superior-medial prefrontal cortex and the left hippocampus in patients with schizophrenia.

As demonstrated by animal studies, prolonged exposure to stress can affect the typical development of white matter by altering axonal and dendritic growth and glial cells necessary for myelination (Jauregui-Huerta et al., 2010). More work is needed to elucidate the mechanisms by which ELA might impact upon brain structural abnormalities in schizophrenia.

1.10. Immune Dysregulation in Schizophrenia

One likely mechanism by which ELA can impact on brain structure and, subsequently, cognitive impairments is through inflammatory processes. The link between the immune system and schizophrenia was postulated more than a century ago but has recently become an area of increasing interest due to advances in clinical, molecular, and genetic research (Saether et al., 2021). One of the first lines of evidence linking schizophrenia to that of immune system alterations was from epidemiological studies showing an increased prevalence of autoimmune conditions in schizophrenia, including psoriasis, celiac disease, interstitial cystitis, Sjogren's syndrome and thyrotoxicosis (Benros & Mortensen, 2020). In an early systematic review by Khandaker et al., (2012), childhood infections were observed to increase the risk of schizophrenia by an odds ratio of ~1.7. Previous reviews have summarised key lines of evidence associating schizophrenia to changes in various immune processes; (see Khandaker & Dantzer, 2016; Upthegrove & Khandaker, 2020), however the remaining section of this thesis will focus on the evidence relating immune genetic loci and peripheral cytokine levels to their association on ELA and cognitive impairments in schizophrenia.

1.10.1. Immune-Relevant Genetic Loci and Cognition

Genetic studies support evidence for a role in altered immune function in schizophrenia. This is largely driven by the finding that single nucleotide polymorphisms (SNPs) in the MHC region on chromosome 6 remains the top-ranking locus implicated in the disorder (overall OR: 1.2, p= 1.205×10^{-39}) (Trubetskoy et al., 2022). The MHC region encodes several proteins that regulate innate and adaptive immune response through antigen presentation, inflammatory regulation, microglial activation and the complement system, and the impact of this region in several immune-mediated disorders has been well established (Misra et al., 2018). Relevant immune genes in the MHC region include human leukocyte antigen (HLA) genes, tumour necrosis factor genes (TNF, LTA, LTB), as well as complement component genes (BF, C2, C4A, C4B). However, the MHC region also contains many genes that serve other biological functions

besides immunity, and the high linkage disequilibrium (LD) in this region makes it difficult to statistically associate any single variant in the region. Notwithstanding, fine mapping of associations derived from GWASs has emerged for the immune gene, C4, as a susceptibility gene in schizophrenia, albeit of small effect (Sekar et al., 2016). C4 is a member of the classical complement cascade, part of the innate immune system and is involved in synaptic reorganisation during development. In addition, evidence from animal studies has demonstrated that over-expression of C4A is associated with excessive synaptic pruning in the brain, likely contributing to behavioural changes and cognitive impairments (Yilmaz et al., 2021)

The structure of the C4 gene comprises an intronic transposable element and copy number variation. It has a variable tandem array of one to three isotypes denoted as short or long forms. In the study by Sekar et al., (2016), more tandem repeats predicted increased expression of the C4A isotype in post-mortem brain tissue in patients with schizophrenia. Similarly, Rey et al., (2020) and Purves-Tyson et al., (2020) found over-expression of C4A in multiple brain regions in patients with schizophrenia compared to healthy controls. C4A gene expression has also been implicated in both structural brain alterations and cognitive symptoms of schizophrenia. In work by Donohoe et al., (2018) and Hatzimanolis et al., (2022), genetically predicted higher C4 expression was associated with reduced memory function and reduced cortical activation. Moreover, work in our group has shown that these cognitive and cortical associations appear to broadly generalise to genetic risk variants in the complement pathway and to neurodevelopment (Holland et al., 2019; Holland, Cosgrove, et al., 2020).

Interestingly, genetic loci of CUB and Sushi Multiple Domains 1 (CSMD1)- which encodes a protein inhibitor of the C4 gene- have also been associated with memory functioning in patients with schizophrenia and healthy controls (Donohoe et al., 2013; Hatzimanolis et al., 2022; Ortega-Alonso et al., 2017). The link between risk for schizophrenia and immune function, however, is not only limited to MHC genes or genes implicated in the complement system. As reviewed by Pouget (2018), almost 40 non-MHC genes implicated in immunity were linked to the risk of schizophrenia, including 28 genes highly expressed within B and T lymphocytes, and 11 which encode proteins targeted in immunomodulatory drugs. Additional studies have reported associations between increased risk of schizophrenia and the rs1143634 SNP in the gene encoding IL-1β (Hudson & Miller, 2018), as well as the rs1800629 mutation in the gene encoding TNF-α (Kadasah et al., 2017; Suchanek-Raif et al., 2018). Taken together the results

of these studies provide evidence implicating aberrant inflammatory response in impairments in cognition in patients with schizophrenia.

1.10.2. Inflammatory Markers and Schizophrenia

In addition to genetic research, evidence linking dysfunctional inflammatory processes to the disorder comes from studies examining peripheral biomarkers of inflammation in the blood and cerebrospinal fluid of individuals with schizophrenia. Altered levels of pro- and anti-inflammatory immune markers have been observed in patients during acute relapses and first presentations of schizophrenia (Goldsmith et al., 2016; Halstead et al., 2023; Miller et al., 2009; Miller & Goldsmith, 2019). Inflammatory markers, which include cytokines and chemokines, are signalling proteins that coordinate innate (e.g., monocytes/macrophages) and adaptive (e.g., B- and T-lymphocytes) immunity. In the central nervous system (CNS), the production and release of inflammatory markers are closely related to microglial activity, which are the primary resident macrophages of the brain. Microglia have several roles, such as clearing tissue debris and damaged cells, myelin development and protecting against pathogens (Kettenmann et al., 2011). They also play an essential role in synaptic removal and pruning in the developing brain in both prenatal and postnatal life (Paolicelli et al., 2011; Thion & Garel, 2017). While direct evidence for the involvement of microglia in schizophrenia is derived through post-mortem and *in vivo* positron emission tomography (PET) studies (see Marques et al., (2019) for review), interpretation of microglial activation is typically inferred from peripheral levels of inflammatory markers.

Several meta-analyses have confirmed that schizophrenia is associated with disruption of the cytokine milieu and the propensity to produce proinflammatory markers (Khandaker et al., 2015). While there is some heterogeneity in the literature regarding the extent to which proinflammatory markers associate with schizophrenia, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) are the most commonly investigated inflammatory markers in psychosis research because they are easy to detect in plasma. Across multiple studies, higher levels of IL-6, TNF-α and CRP have consistently been shown in first-episode psychosis patients and chronically ill patients (Baumeister et al., 2016; Fernandes et al., 2016; Halstead et al., 2023). Further, in a meta-analysis of over 70 studies, Miller & Goldsmith (2019) found that CRP and IL-6, among others, were correlated with total psychopathology and

negative symptoms. Similar findings have also been observed by Momtazmanesh et al., (2019) and Dahan et al., (2018).

1.10.3. Inflammatory Markers and Cognition

Importantly and of relevance to this thesis, elevated levels of proinflammatory cytokines have been implicated in cognitive impairments in patients with first-episode psychosis and chronic schizophrenia (Dawidowski et al., 2021; Kogan et al., 2018; Misiak et al., 2021; Patlola et al., 2023). In a recent review led by our group, higher levels of IL-6, IL-1B, TNF-α and CRP were significantly associated with measures of cognitive functioning (Patlola et al., 2023). While multiple domains were implicated in this study, the most consistent associations were observed for memory processes and executive functions. It is interesting to speculate about why memory function is associated with immune processes and the aforementioned immune genetic loci– whether this simply reflects the size of deficit related to schizophrenia or an aspect of cognition sensitive to either immune function or factors related to immune function (e.g., ELA). In relation to the latter, inflammatory markers, including IL-1B, IL-6 and TNF-α, are strongly expressed in the hippocampus and widely throughout the brain and are therefore well placed to modulate memory (Donzis & Tronson, 2014). Another area of cognition which may be altered by inflammation is social cognition and may reflect stress-induced neuroinflammation within the neural circuitry responsible for regulating social cognitive processes. Due to insufficient studies in the literature, Patlola et al., (2023) did not include social cognitive domains. However, some evidence suggests that emotion recognition and ToM ability are associated with levels of IL-6 (King et al., 2021; King et al., 2023) and IL-12 (Ospina et al., 2022).

1.10.4. Early Life Adversity and Inflammation

There appears to be a cumulative effect of risk factors associated with schizophrenia and immune dysregulation on several outcomes, including cognitive functioning. Recent work has focused their interest on the interaction between ELA and neurobiological factors in order to provide broader insights into altered inflammation leading to cognitive impairments in schizophrenia. Several clinical studies have shown that inflammatory markers, such as IL-6, TNF-α and CRP, are particularly elevated in patients who experienced ELA, including physical or sexual abuse, emotional abuse, or neglect in childhood (King et al., 2021; Quidé et al., 2020; Rokita et al., 2020). Among the first researchers to investigate this link, Dennison et al., (2012)

demonstrated elevated levels of IL-6 and TNF-α in patients with schizophrenia exposed to ELA compared to healthy controls. More recently, Quidé et al., (2020) reported increased levels of IL-6, TNF-α and CRP in patients with psychosis who had experienced ELA. Aas et al., (2017) found that childhood trauma in patients was particularly sensitive to the effects of CRP, which has also been supported by meta-analytical work (Baumeister et al., 2016). Furthermore, higher levels of CRP were correlated with the severity of ELA in a large sample of individuals with mixed diagnoses of schizophrenia and bipolar disorder (Aas et al., 2017). Indeed, across multiple cohorts, ELA has been associated with elevated levels of peripheral cytokines, irrespective of diagnosis (Holland et al., 2019, Khandaker, et al., 2020; Khandaker et al., 2018). As such, it has been speculated by some that inflammation might represent a common underlying mechanism of cognitive impairment more broadly rather than diagnosis per se. Supporting this view, Davis et al., (2019) found that IL-6 and depressive mood symptoms mediated an association between ELA and cognitive functioning in a middle-aged sample.

1.10.5. Early Life Adversity, Inflammation and Cognition

Notwithstanding, since individuals with schizophrenia- in addition to having greater exposure to ELA- also exhibit alterations in the HPA axis (Bradley & Dinan, 2010), inflammation as well as cognitive deficits and brain structural abnormalities, it is of particular interest to examine the link between ELA and underlying biological processes to cognitive functioning in psychosis. In genetically vulnerable individuals, ELA may impact upon immune functioning to prime microglia, leading to overactivation, aberrant synaptic pruning, neurogenesis, and white matter abnormalities (Monji et al., 2009). Neuroinflammation can therefore result in structural and functional impairments (Sankowski et al., 2015) which, in turn, have been associated with cognitive impairments (Saether et al., 2021) (see Figure 1.2).

To this end, recent work from our group on the 'Immune Response and Social Cognition' (iRelate) project led by Prof. Gary Donohoe illustrates the importance of modelling these associations in the context of cognitive functioning. For example, Rokita et al., (2018) has shown that social cognitive abilities, primarily ToM and emotion recognition, are altered in patients with schizophrenia exposed to high levels of ELA. Further, across all types of adversity, physical neglect was associated with more negative effects on social cognitive abilities (Rokita et al., 2018). Extending this work, structural grey matter volumes of the ACC and functional connectivity of the default mode network (DMN) were found to mediate the association

between physical neglect and social cognitive abilities (Dauvermann et al., 2021; Mothersill & Donohoe, 2016; Rokita et al., 2020). Most recently, work carried out by the iRelate group has demonstrated that the relationship between ELA and cognition is mediated by higher levels of IL-6 and reduced connectivity of the DMN (King et al., 2021; King et al., 2023).

1.11. Outstanding Gaps in the Literature

Genetic, neurobiological, and environmental risk factors for schizophrenia individually show small-to-moderate effects. None appear necessary nor sufficient, and all are shared with other disorders (Dean & Murray, 2005). The temporal delay between most environmental exposures and the onset of schizophrenia provides support for the conceptualisation of schizophrenia as a neurodevelopmental disorder. It is widely believed that environmental exposures alone do not generate the clinical phenotype. Instead, cognitive impairments likely emerge due to a combination of genetic risk and environmental exposure(s), the latter perhaps in a critical period of neurodevelopmental vulnerability (Davis et al., 2016). The past few years have seen significant progress in identifying individual factors (genetic, biological, and environmental) that contribute to these effects, including results from GWASs, gene set analysis, neuroimaging research and clinical and epidemiological work. However, despite these significant advances, work remains in an early stage of modelling how these genetic factors interact with environmental factors to accurately account for variation in general cognitive ability.

Biological mechanisms by which ELA impacts brain structure and cognition may be at least partly associated with immune dysfunction. Evidence of immune involvement is supported by GWASs identifying immune-related genotypes and findings of altered levels of inflammatory markers in individuals with schizophrenia. Nevertheless, several questions remain. First, in terms of genetic risk, the classical pathway of the complement system has been implicated in the observed cognitive deficits in schizophrenia (Holland et al., 2019); however, far less is known about whether genetic variation relevant to immunity more broadly contributes also to this risk. One obvious avenue to explore is the impact of microglia because these cells have known roles in neuronal survival, synaptic pruning and plasticity and neurogenesis (Nettis et al., 2020). Altered microglia function has been hypothesised to influence various aspects of brain physiology and cognitive function relevant to schizophrenia leading to structural and functional changes in the brain that predispose individuals to psychiatric disorders (Howes & McCutcheon, 2017). Whether genetic variation in these cells contributes to the risk of

schizophrenia and neurodevelopment is an area unexplored. Moreover, it is of interest to examine to what extent individuals with schizophrenia also have a genetic vulnerability toward immune alterations and/or neurodevelopment that may add to or interact with the effects of adversity and cognitive impairments.

On a separate but converging point, studies to date that have characterised the relationship between genetic risk, environment and cognitive symptoms have typically focused on pre-specified genes. For example, Aas et al., (2012) found that individuals carrying the short allele of the 5-HTTLPR gene and had been exposed to ELA exhibited lower cognitive functioning compared to other groups. Similarly, individuals carrying Met allele of the Val66Met polymorphism in the BDNF gene and who experienced high levels of ELA showed more pronounced cognitive impairments, as well as having smaller hippocampal volume and larger ventricles (Aas et al., 2013). To the author's knowledge, only one study (Sideli et al., 2023) has investigated the role of genetic liability for psychosis using a cumulative genetic risk score (i.e., PGS) to the association between ELA and cognition, which reported nonsignificant results. As such, the role of cumulative genetic risk on the association between ELA and cognitive functioning remains unclear. This is particularly important as the risk for schizophrenia is constituted by numerous common genetic variants of only a very small individual effect.

Further, questions remain regarding the association between ELA and inflammation on cognitive functioning. While work strongly indicates a role of memory functioning with influences from genetic factors, whether these associations extend to other neuro/social cognitive processes is not yet known. In addition, evidence for changes in peripheral cytokines in schizophrenia has been fraught with substantial heterogeneity. Several potential explanations exist for these discrepancies, including small sample sizes, differences in genetic liability, samples assayed, and several confounding factors (i.e., BMI, smoking, medication effects). Another reason could be that previous studies have focused on individual markers, neglecting the complex interaction between different inflammatory and immune-related signalling. Indeed, several lines of research from animal, imaging, and peripheral and cerebrospinal fluid studies support crosstalk and interconnectedness between these inflammatory markers and the impact of these on the CNS (Guzmán et al., 2010).

For example, IL-6 is a proinflammatory cytokine produced by macrophages, monocytes and microglia and has close functional relationships with TNF-α and CRP. Specifically, elevated levels of IL-6 disrupt the integrity of the blood-brain barrier (BBB), resulting in an influx of peripheral cytokines (i.e., CRP and TNF-α) to exacerbate microglial-mediated processes as well as stimulate neuroendocrine release. CRP is an acute-phase protein that is primarily synthesised by hepatocytes in the liver, whose production is regulated by proinflammatory cytokines, specifically IL-6 and, to a lesser extent, IL-1B and TNF-α (Sproston & Ashworth, 2018). Additionally, CRP contributes to systemic inflammation by inducing the release of other inflammatory markers and stimulating the activity of natural killer (NK) and macrophage cells (Diaz-Salazar et al., 2020). Overproduction and stimulation of TNF-α and IL-6 have been linked to neurogenesis, neuronal cell death, and innate and adaptive immunity. Despite this evidence demonstrating biological interconnectedness between these inflammatory markers, no study to date has examined the influence of these inflammatory markers on cognition concomitantly in patients with schizophrenia who have been exposed to ELA.

The intricacy of inflammatory signalling presents several issues in understanding the roles and mechanisms of cytokines in neural and cognitive functioning. Given the complexity of inflammatory marker signalling in the brain, it is possible that shifting the focus from individual markers to a combined approach will be a constructive way to understand the impact of inflammatory signalling on memory and cognitive function. Finally, it is worth noting that while progress has been made in identifying biological mechanisms underlying the association between ELA, inflammation, and cognition (i.e., functional connectivity of the DMN; King et al., 2023) the study of white matter connections, has been largely overlooked. As such, it remains to be investigated whether these associations with cognition reflect changes in structural connectivity within white matter tracts on which cognitive processes are known to depend on (Fields, 2008).

Identifying the impact of early life adverse experiences on immune system regulation, the contribution of genetic risk variants involved, and subsequent clinical outcomes such as cognitive functioning may help to elucidate new insights into the biological basis of cognitive symptoms involved in schizophrenia and neurodevelopmental processes. Further, unravelling the complex interactions among these factors may help identify promising new targets for

improving cognitive functioning in patients with schizophrenia, which currently fail to ameliorate these cognitive impairments and have little efficacy on functioning.
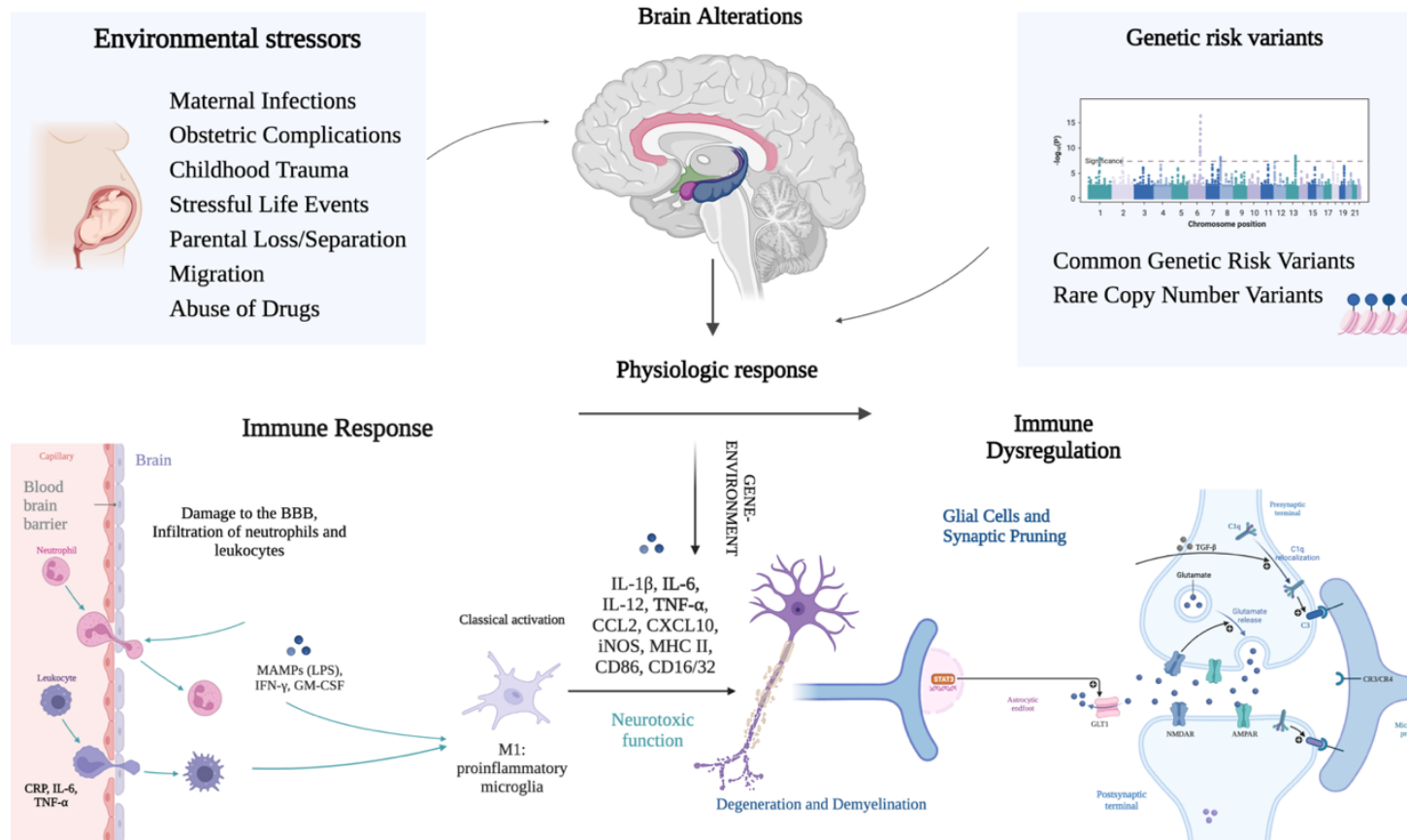
Figure 1.2. Relationship between inflammation and cognitive functioning in schizophrenia

Genetic vulnerability to schizophrenia and environmental stressors may result in a heightened immune response leading to a disruption of the permeability of the blood-brain barrier and elevated levels of proinflammatory markers. Microglia may become primed to later external stressors and over time this can disrupt glial cell functioning, synaptic pruning, and demyelination

1.12. Thesis Aims and Outline

The main objective of this thesis is to explore the contribution of and interaction between early life adversity and different biological factors including genetics, inflammation and brain structure that influence cognitive functioning in patients with schizophrenia and healthy controls. Considering the importance of cognitive impairment and immune changes in schizophrenia, as well as the potential role of the immune system in cognitive dysfunction, it becomes crucial to investigate the relationship between cognitive and immune variables in schizophrenia. The specific aims and objectives of each study included in this thesis are summarised below:

Manuscript 1 (Chapter 2). This study aims to investigate the effect of a microglial genetic score on that of cognitive performance and total grey matter in a sample of patients with schizophrenia and healthy participants.

Manuscript 2 (Chapter 3). Study 2 study uses structural equation modelling to better understand the associations between genetic inheritance, environmental exposure, total grey matter volume and general cognitive ability in a UK Biobank sample. Specifically, this study explores whether ELA and education moderate the association between genetics, brain structure and cognition.

Manuscript 3 (Chapter 4). This study seeks to build on earlier work by modelling the association between genetic and inflammatory effects on early life adversity and cognitive functioning in both patients with schizophrenia and healthy participants.

Manuscript 4 (Chapter 5). This study aims to address the importance of white matter microstructural to the relationship between ELA, inflammation, and cognitive functioning in patients with schizophrenia.

Chapter 2: Microglial-Expressed Genetic Risk Variants, Cognitive function and Brain Volume in Patients with Schizophrenia and Healthy Controls

Microglial-Expressed Genetic Risk Variants, Cognitive function and Brain Volume in Patients with Schizophrenia and Healthy Controls

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Abstract

Changes in immune function are associated with variance in cognitive functioning in schizophrenia. Given that microglia are the primary innate immune cells in the brain, we examined whether schizophrenia risk associated microglial genes (measured via polygenic score analysis) explained variation in cognition in patients with schizophrenia and controls ($n=$ 1,238) and tested whether grey matter mediated this association. We further sought to replicate these associations in an independent sample of UK Biobank participants ($n = 134,827$). We then compared the strength of these microglial associations to that of neuronal and astroglial (i.e., other brain-expressed genes) polygenic scores and used MAGMA to test for enrichment of these gene sets with schizophrenia risk. Increased microglial schizophrenia polygenic risk was associated with significantly lower performance across several measures of cognitive functioning in both samples; associations which were then found to be mediated via total grey matter volume in the UK Biobank. Unlike neuronal genes which did show evidence of enrichment, the microglial gene set was not significantly enriched for schizophrenia, suggesting that the relevance of microglia may be for neurodevelopmental processes related more generally to cognition. Further, the microglial polygenic score was associated with performance on a range of cognitive measures in a manner comparable to the neuronal schizophrenia polygenic score, with fewer cognitive associations observed for the astroglial score. In conclusion, our study supports the growing evidence of the importance of immune processes to understanding cognition and brain structure in both patients and in the healthy population.

2.1. Introduction

Schizophrenia (SZ) is a complex neuropsychiatric disorder in which impairments in cognitive function strongly predict level of disability. Although the aetiology of SZ remains only partly understood, liability is genetically mediated with complex environmental interactions involved. Genome-wide association studies (GWASs) have demonstrated that the immune system may be involved in these interactions, mainly due to the strong association of genetic variants in the major histocompatibility complex (MHC) region (Pardinas et al., 2018; Ripke et al., 2014). In humans, the MHC region encodes ~230 genes, and is associated with immune function. In particular, variation of the complement component 4 (C4) gene has been associated with SZ risk (Sekar et al., 2016); we recently demonstrated that genetically predicted higher C4 expression was associated with both reduced memory function and reduced cortical activation (Donohoe et al., 2018). We have further shown that these cognitive and cortical associations appear to generalise to genetic risk variants in the complement pathway more broadly (Holland et al., 2019; Holland, Cosgrove, et al., 2020). Complement protein expression has also been linked with increased risk of transition from high-risk state to psychosis (Mongan et al., 2020).

In addition to evidence associating the complement pathway to SZ risk and cognition, microglia - the resident macrophages of the brain - have been linked to SZ pathophysiology and cognition. These cells have several functions including, but not limited to, phagocytosing apoptotic cells, synaptic pruning, modulating neurogenesis and regulating synapse plasticity (Ormel et al., 2020; Salter & Stevens, 2017). Given these roles, altered microglia function has been hypothesised to influence a variety of aspects of brain physiology and cognitive function relevant to SZ (Howes & McCutcheon, 2017). This is supported by findings of elevated peripheral cytokines such as IL-6, IL-1β, TNF-α and C-reactive protein in patients (Lesh et al., 2018; Wu et al., 2019), which have in turn been linked to reductions in grey matter volume and with poorer cognitive performance (Fillman et al., 2016). In addition, post-mortem and *in vivo* neuroimaging studies have reported aberrant microglial activation in SZ, particularly in the hippocampal area, a region synonymous with memory function and dysfunction (Doorduin et al., 2009; Hill et al., 2021; Petrasch-Parwez et al., 2020; Trepanier et al., 2016). However, whether microglial perturbations are genetically mediated by structural brain measures has not yet been established.

Given the link between the immune system and cognition, we sought to investigate the effects of a microglial genetic score on that of cognitive performance and total grey matter (GM) in a sample (n = 1,238) of patients with SZ and healthy participants (discovery sample). In addition to considering any issues of multiple testing, our rationale for selecting this global metric of brain structure was based on this region being robustly associated with cognitive ability. Further, to offset any potential issues of power, we replicated these associations in a large independent sample of UK Biobank participants (n =134,827). We hypothesised that participants carrying a higher SZ polygenic burden would demonstrate poorer performance on measures of cognitive ability and that lower total GM volume would mediate this relationship. We further hypothesised that microglial genes would be enriched for SZ risk and that microglial PGSs would demonstrate an association with cognitive ability in a manner comparable to other brain-relevant genetic variants previously implicated in SZ, cognition and/or immunity (i.e., neurons, astroglia). Such investigations into genetic and structural imaging correlates of cognition may help elucidate a potential mechanism by which immune genes contribute to the cognitive deficits observed in SZ.

2.1. Materials and Methods

2.2.1. Irish Discovery Sample

A total of 1,238 Irish SZ patients and healthy participants (489 females, 740 males) aged 18-72 (M= 41.15, SD= 12.84) were included in this study for whom neuropsychological data and genome-wide data were available. These comprised of *n*= 908 clinically stable patients with either (a) a diagnosis of SZ and schizoaffective disorder (SZA) (*n*= 676) and a broader category of psychosis cases diagnosed with either 1) bipolar disorder with psychotic features, 2) major depressive disorder with psychotic features, 3) delusional disorder and 4) psychosis not otherwise specified (*n*= 232). To ascertain diagnosis, patients were administered the Structural Clinical Interview for the DSM-IV (Spitzer et al., 1992). Healthy participants (*n*= 330) were recruited from the general population through local media advertisements and online. They were aged between 18-65 years and had no history of major mental health issues, intellectual disability or acquired brain injury. Further information on this sample has been detailed elsewhere (Cosgrove et al., 2018; Donohoe et al., 2018; Holland, Cosgrove, et al., 2020). All assessments carried out were in accordance with the relevant ethics committees' approval from each participating site (Appendix A) and informed written consent was obtained prior to the study (Appendix B). Participants undergoing structural MRI were also screened for MRI safety criteria (Appendix C).

2.2.2. Cognitive Assessment

Cognitive functioning was examined across three domains including general cognitive ability, working memory and episodic memory. General cognitive functioning was measured using selected subtests from the Wechsler Adult Intelligence Scale, third edition (WAIS-III) (Wechsler, 1997a) and the Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001). Working memory was assessed using the Letter Number Sequencing (LNS) task from the Wechsler Memory Scale, third edition (WMS-III) (Wechsler, 1997b), and the Spatial Working Memory (SWM) task from the Cambridge Automated Neuropsychological Test Battery (CANTAB) (Robbins et al., 1994). Episodic memory was examined using the logical memory subtests and the faces subtests (immediate and delayed conditions) from the WMS-III, as well as the paired associations learning task (PAL; stages completed and total errors) from the CANTAB. To reduce multiple testing burden, an unrotated principal component analysis was

performed for the available episodic memory tests and explained 72% of variance in memory scores.

2.2.3. Structural MRI

A subset of participants (47 patients, 66 healthy participants) underwent structural MRI. MR images were obtained on a Philips Intera Achieva 3T MR system, with whole brain imaging consisting of T1-weighted images (180 slices-duration 6 minutes) using a turbo field echo (TFE) gradient pulse sequence, with a slice thickness of 0.9 mm and a 230 x 230 field of view. Detailed procedures for the image volumetric analysis have been described elsewhere (Cosgrove et al., 2018). Briefly, cortical reconstruction, parcellation and segmentation of the T1 images were processed using FreeSurfer (v6.0) (Fischl et al., 2002). Processed images underwent motion correction, intensity normalisation, transformation to Talairach space and skull stripping. Whole-hemisphere measures were visually inspected and statistically evaluated for outliers following standardised ENIGMA protocols (http://enigma.ini.usc.edu/protocols/imaging-protocols).

2.2.4. Genetic Data

Genotype data was obtained from DNA extracted from saliva or whole blood samples. Complete GWAS data was available on all samples. Participants for this study had been genotyped with either an Affymetrix 6.0 chip as part of the Wellcome Trust Case Control Consortium 2 (Strange et al., 2012) or on the Illumina HumanCoreExome chip. Imputation of these datasets was performed using 1000 Genomes Phase I data and IMPUTE2 (Howie et al., 2009) to yield approximately 10 million single nucleotide polymorphisms (SNPs) genome-wide per sample. Only SNPs that passed quality control filtering were imputed using the 1000 Genomes reference panel.

2.2.4.1. Brain Expressed Gene Sets

To explore the impact of SZ risk alleles linked to microglia, we restricted our SZ-PGS and gene set analysis to loci expressed within microglial cells. This microglial list (*n*= 294) was based on recent transcriptome work by Saunders et al., (2018) which used Drop-seq to profile single-cell RNA expression in 690,000 cells and 565 cell types from the adult mouse brain, accessible through the online software *DropViz* (http://dropviz.org/). For this, we selected genes that

demonstrated greater than two-fold increased expression within microglial cells. Mouse gene IDs were converted to human gene IDs using BioMart.

To compare these microglial genes with other brain-relevant genes, we generated two additional gene sets from genes expressed within neuronal ($n= 375$) and astroglial ($n= 286$) cells; again, based on genes showing greater than two-fold increased expression. The rationale for choosing these other gene sets is as follows: 1) cognitive functioning is mainly dependent on the expression of neuronal genes and 2) astroglial cells represent the other cell type that is most consistently associated with neuroinflammatory processes (see Supplementary Tables 2.1-2.3 for details of these gene sets). As a complementary analysis, gene ontology (GO) enrichment of biological processes, cellular components and molecular functions was performed using the software FUMA (Watanabe et al., 2017) to test if processes associated with specific cell type functions were uniquely enriched within each gene set. As shown in Figure 2.1, this analysis confirmed that the microglial, neuronal and astroglial gene sets were good representatives of each cell type's specific functioning. A schematic overview of the steps taken for generating these gene sets is shown in Supplementary Figure 2.1, along with the subsequent analytical procedures.
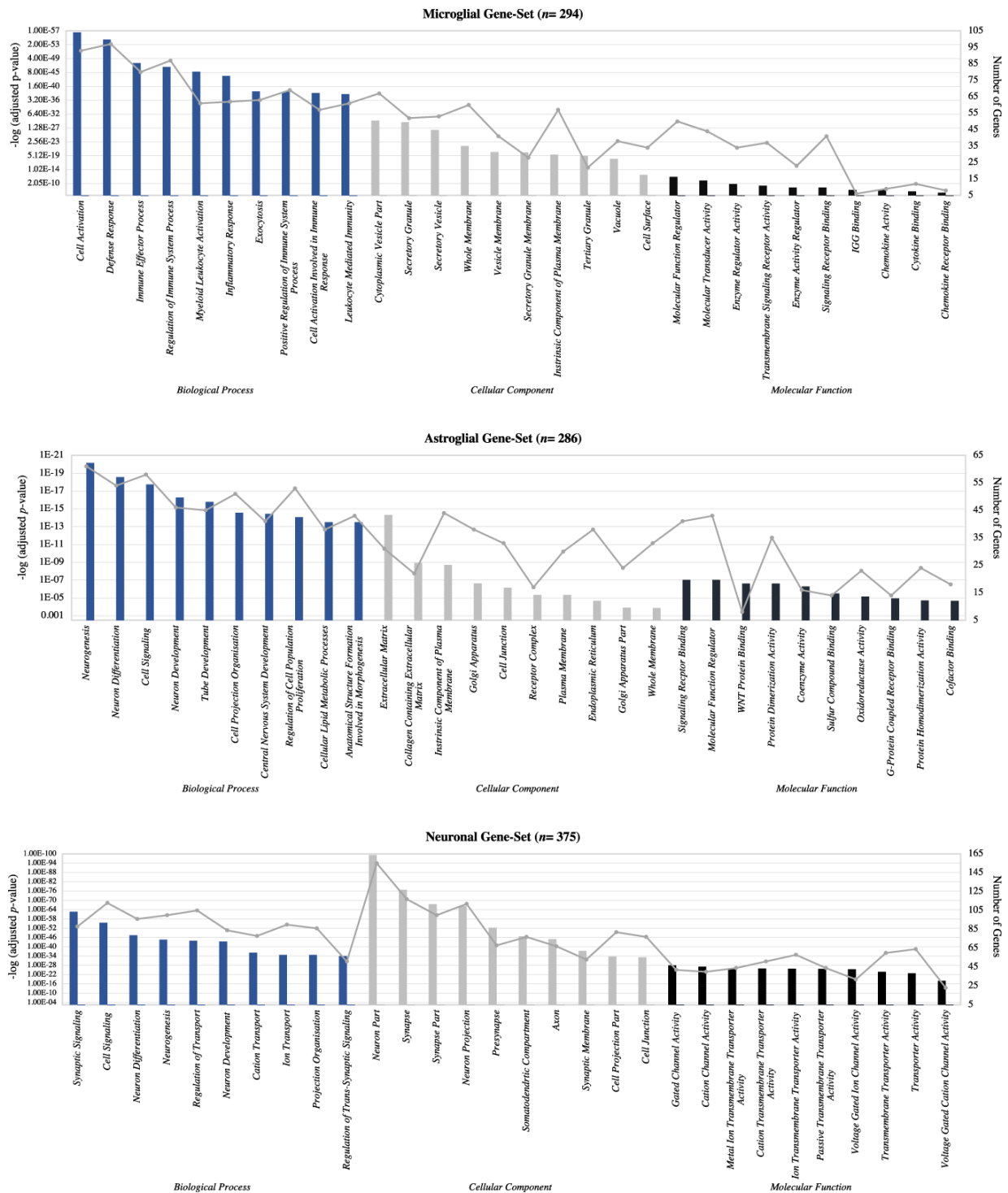
Figure 2.1. Gene ontology enrichment analysis

GO enrichment analysis for the top 10 biological processes, cellular components and molecular functions of the microglial, neuronal and astroglial gene sets. The analyses indicated that these gene sets accurately represent the specific functions of each cell type. The line plot displays the numbers of differentially expressed genes in each specific function. The bar plot displays the adjusted p-values (FDR (false discovery rate) <0.05).

2.2.4.2. Polygenic Score (PGS) Calculation

SZ-PGSs were calculated based on the results from the SZ GWAS meta-analysis conducted on 40,675 cases and 64,643 controls of European ancestry (Pardinas et al., 2018). For each of the gene sets, we identified SNPs within our genes of interest and captured SNPs within and outside the gene's coding region by specifying a symmetrical annotation window of $\pm$ 20Kb. Genotype data for SNPs in these gene set regions were extracted for our Irish samples from their full GWAS data. PLINK 1.9 software was used to perform quality control (QC) on the data (Purcell et al., 2007) whereby SNPs were excluded if minor allele frequency (MAF) <0.1%, SNP missingness < 2%, and Hardy-Weinberg equilibrium (HWE) < p 10-6. An effect-size weighted SZ-PGS for the microglia, neurons and astroglia variants were then computed for each individual based on a threshold of p <0.05 using PRSice2 software (Choi & O'Reilly, 2019). A p-value threshold of 0.05 was chosen since this has shown to maximally capture polygenic risk across a large number of independent samples (Ripke et al., 2014). Variants within the MHC (chr6:25 Mb–35 Mb) were removed from the genotype data due to high linkage disequilibrium in this region.

2.2.4.3. Gene Enrichment Analysis

For our gene set analyses, we used MAGMA v1.06 (de Leeuw et al., 2015) to test if the microglial, neuronal and astroglial gene sets were enriched for genes associated with SZ risk. Briefly, enrichment analyses consisted of the following steps: (1) an annotation step to map SNPs onto genes; (2) a gene analysis step to identify gene p-values using the most recent SZ GWAS summary statistics; and (3) a gene-level analysis to test whether these gene cell types showed enrichment for SZ.

2.2.5. Statistical Analysis

To estimate microglial SZ-PGS effects on cognitive performance, multiple regression analyses were carried out using IBM SPSS Statistics Version 26.0 (IBM Corp, Armonk, NY, 2017), with cognitive test scores as the dependent variable. The significance threshold was set at p <0.016 to correct for the three domains of cognitive function (α = 0.05/3 = 0.016). To examine if total GM volume mediated the association between PGS and cognitive performance we used model 4 from the PROCESS v3.5 macro (Hayes, 2017). A bootstrapping method was applied to assess the indirect effects based on 10,000 bootstrapped samples using 95% bias-corrected confidence intervals. Microglial SZ-PGS associations were then compared to neuronal and astroglial SZ-

PGSs by deriving a Z score based on the statistical significance of the associations found and their effect size (standardised beta value). We did so to determine whether SZ-associated SNPs within microglial genes showed a stronger effect on cognitive performance than other selected brain-expressed genes. Throughout, all analyses were corrected for age and sex, and intracranial volume was controlled for in our imaging analysis.

2.2.6. UK Biobank Replication Sample

To examine whether the results for SZ-PGS predicting cognition in patients and controls were comparable with results in a population-based sample, we tested these SZ-PGS associations in an independent dataset of UK Biobank participants ($n=$ 134,827). The analytic methods followed those of the main case-control analysis using the discovery Irish sample (cognitive measures: fluid intelligence score, numerical memory score, symbol-digit substitution score and general cognitive ability (constructed using a PCA of the three available cognitive tests). UK Biobank analyses were conducted under project number 23739 and approved by the National Health Service Research Ethics Service (reference 11/NW/0382). For imaging, genotyping, quality control, and imputation details, see Supplementary Information (section 2.6).

2.3. Results

2.3.1. Participant Characteristics of the Irish Discovery and UK Biobank

Participant characteristics of the discovery sample, including clinical, demographic, and cognitive information are presented in Supplementary Table 2.4 (see Supplementary Table 2.5 for UK Biobank participant details). Pearson's product-moment correlation coefficients were first carried out to test an association between the SZ-PGSs and covariates of no interest. Results indicated no association between the SZ-PGSs and age, sex, or years in education in either sample. Further, in our discovery sample of patients, no associations between the SZ-PGSs, severity of symptoms or medication dosage (as measured in terms of chlorpromazine equivalents) were found.

2.3.2. Association between Microglial SZ-Polygenic Scores and Cognition

For the regression analyses, which included the full discovery sample, microglial SZ-PGS significantly predicted variation in performance IQ (F change= 7.727, R^2 *change*= 0.009, Std beta= -0.096, p= 0.006), full-scale IQ (F change= 6.618, R^2 *change*= 0.008, Std beta= -0.089, p= 0.010) and episodic memory (F change= 13.703; R^2 change= 0.018, Std beta= -0.135, p <0.001) as well as nominal associations with verbal IQ and the LNS task (Table 2.1). The observed direction of effect was that greater microglial SZ-PGS was associated with a decrease in cognitive performance.

The most markedly significant domain was found for episodic memory, and when the sample was subdivided into patients and controls, this association remained significant in cases (F change= 4.842, R^2 *change*= 0.009, Std beta= -0.096, p= 0.028) and trended toward significance in controls (F change= 3.68, R^2 *change*= 0.024, Std beta= -0.154, p= 0.057). In a post hoc analysis of narrow psychosis patients (SZ and SZA patients only), the association between the microglial PGS and episodic memory was in the same direction (F change= 1.217, R^2 *change*= 0.003, Std beta= -0.055) but was nonsignificant (p= 0.271). All other cognitive measures though, did not show any significant association with PGS at either nominal or corrected significance level when grouped accordingly. Details of these group comparisons are reported in Supplementary Table 2.6.

Table 2.1. Regression analysis of polygenic scores and cognitive performance across gene sets in the discovery and UK Biobank sample

	Microglia				Neurons				Astroglia			
	β	R^2 Change	F Change[1]	p	β	R^2 Change	F Change	p	β	R^2 Change	F Change	p
Discovery Sample												
Full-Scale IQ	-0.089	0.008	6.62	0.010	-0.124	0.015	13.17	<0.001	-0.038	0.001	1.05	0.306
Performance IQ	-0.096	0.009	7.73	0.006	-0.116	0.013	11.61	0.001	-0.058	0.003	2.46	0.117
Verbal IQ	-0.070	0.005	4.78	0.029	-0.101	0.010	10.38	0.001	-0.024	0.001	0.44	0.507
WTAR	-0.047	0.002	1.84	0.176	-0.095	0.009	7.56	0.006	0.000	0.001	0.01	0.909
LNS	-0.075	0.006	5.47	0.020	-0.023	0.001	0.52	0.472	-0.078	0.006	4.37	0.037
Spatial WM	-0.058	0.003	2.37	0.124	-0.073	0.005	3.81	0.051	-0.032	0.001	0.63	0.427
Episodic Memory	-0.135	0.018	13.70	<0.001	-0.104	0.011	8.17	0.004	-0.087	0.008	4.95	0.027
UKB Replication												
Fluid Intelligence	-0.013	0.00018	21.08	<0.001	-0.016	0.000263	30.73	<0.001	-0.013	0.00016	19.44	<0.001
Numerical Memory	-0.003	0.00001	0.405	0.525	0.002	0.000002	0.098	0.755	-0.002	0.000006	0.24	0.627
Symbol-Digit	-0.019	0.00036	19.05	<0.001	-0.012	0.000400	21.26	<0.001	-0.015	0.00021	11.22	0.001
General Cognition	-0.013	0.00016	5.45	0.020	-0.013	0.000143	4.77	0.029	-0.009	0.00009	2.98	0.084

Abbreviations: WTAR, Wechsler Test of Adult Reading; LNS, Letter-Number Sequencing, Spatial WM, Spatial working memory

[1] The F value represents the result of the test where the null hypothesis is that the regression coefficients are equal to zero. A significant F change demonstrates that the variables added significantly improve the model prediction

2.3.2. Association between Microglia, Cognition and GM Volume

Given the significant association with microglial SZ-PGS and episodic memory, we sought to investigate whether a possible interaction existed between microglia and brain structure, as indexed by total GM volume. For this, no significant interaction effect between the microglial SZ-PGS and GM volume for episodic memory was observed in the sample. The standardised indirect effect was 0.0572 and the 95% bias corrected CIs were -0.0237 to 0.193 (Figure 2.2). However, the total number of participants with complete genetic and MRI overlap for this memory test was small (n= 47) and the non-significance of this association could reflect the limited power of the sample.

2.3.3. Comparison of Microglia, Neuronal and Astroglial SZ-PGS

When comparing the effect size estimates of the different SZ-PGSs, the difference in magnitude between the microglial, neuronal and astroglial SZ-PGSs with cognitive ability was not statistically significant (Table 2.2). However, the association between neuronal SZ-PGS and cognitive ability was comparable to the microglial SZ-PGS, which significantly predicted variation across multiple measures of cognition (R^2 Change range= 0.009 to 0.015, Std beta range= -0.095 to -0.124). By comparison, only nominal significant weak associations were observed between astroglial SZ-PGS and two cognitive measures - episodic memory (Std beta= -0.087, p= 0.027) and the LNS task (Std beta= -0.078, p= 0.037) (Table 2.2). For the mediation analysis, GM volume did not mediate the association between these SZ-PGSs and episodic memory (Figure 2.2).

(a)

Indirect effect (ab)
β = 0.06 [-0.02, 0.19]

β = 0.14, p = 0.241 a

Total GM Volume

β = 0.41, p = 0.020

b

Microglial PGS

c

β = -0.12, p = 0.388

Episodic Memory

(b)

Indirect effect (ab)
β = 0.05 [-0.59, 0.26]

β = 0.12, p = 0.322 a

Total GM Volume

β = 0.44, p = 0.010

b

Neuronal PGS

c

β = -0.28, p = 0.036

Episodic Memory

(c)

Indirect effect (ab)
β = 0.03 [-0.09, 0.18]

β = 0.05, p = 0.734 a

Total GM Volume

β = 0.50, p = 0.015

b

Astroglial PGS

c

β = -0.15, p = 0.355

Episodic Memory

Figure 2.2. Mediation results of polygenic score associations in the discovery sample

Values are standardised estimates; dashed paths are non-significant. Indirect estimates are reported (a*b). (a) The effect of microglial polygenic score on episodic memory as mediated via grey matter volume; (b) The effect of neuronal polygenic score on episodic memory as mediated via grey matter volume; (c) The effect of astroglial polygenic score on episodic memory as mediated via grey matter volume.

2.3.4. UK Biobank Replication Sample

For the regression analyses which included UK Biobank participants, microglial SZ-PGS significantly predicted variation in fluid intelligence (F change= 21.084, R^2 *change*= 0.0002, Std beta= -0.013, p <0.001) and the symbol digit substitution test (F change= 19.047, R^2 *change*= 0.0004, Std beta= -0.019, p= <0.001) but not numerical memory (F change= 0.405, R^2 *change*= 0.00001, Std beta= -0.003, p= 0.525) (Table 2.1). After performing an unrotated principal component of these cognitive tests, this combined general cognitive ability factor was significantly associated with microglial SZ-PGS (F change= 5.451, R^2 *change*= 0.0002, Std beta= -0.013, p= 0.020). The direction of these effects was the same as those observed for our discovery sample (i.e., increased SZ-PGS was associated with lower cognitive ability). The neuronal and astrocyte SZ-PGSs also significantly predicted variation in cognitive performance (Table 2.1), although again the association between astroglial SZ-PGS and cognitive function was weaker than for the other two gene sets.

To examine whether these associations were mediated via GM volume, we selected general cognitive ability, rather than memory performance given the non-significant SZ-PGSs associations with this test. Here, we found that total GM volume partially mediated the relationship between the microglial SZ-PGS and general cognitive ability. As shown in Figure 2.3, the standardised regression coefficient for GM volume and cognitive ability and for microglial SZ-PGS and cognitive ability were both significant. The standardised indirect effect was -0.0042 (95% CI based on based on 10,000 samples: -0.0081 to -0.0005). In contrast, GM volume did not significantly mediate the SZ-PGS cognitive association for either neuronal (std beta= 0.0026, 95% CIs [-.0012, 0.0065], p= 0.285) or astroglial (std beta= 0.0010, 95% CIs [-.0027, 0.0047], p= 0.528) expressed genes (Figure 2.3). Consistent with the results from the discovery sample, effect size estimates for the SZ-PGS associations with measures of cognitive functioning were not statistically different across gene sets (Table 2.2).

Table 2.2. Cognitive comparison of the microglia, neuronal and astroglial polygenic scores

	Microglia vs Neurons		Neurons vs Astroglia		Microglia vs Astroglia	
	Z-Score	p-Value	Z-Score	p-Value	Z-Score	p-Value
Discovery Sample						
Full-Scale IQ	0.69	0.490	1.63	0.103	0.96	0.337
Performance IQ	0.40	0.689	1.11	0.267	0.72	0.472
Verbal IQ	0.67	0.503	1.54	0.124	0.91	0.363
WTAR	0.96	0.337	-1.83	0.067	-0.59	0.374
LNS	1.12	0.268	1.09	0.276	0.06	0.952
Spatial WM	0.281	0.790	0.75	0.453	0.47	0.638
Episodic Memory	0.56	0.576	0.30	0.764	0.84	0.401
UKB Replication						
Fluid Intelligence	0.72	0.472	0.72	0.472	0	1
Numerical Memory	-0.71	0.478	-0.57	0.569	0.14	0.889
Symbol-Digit	1.03	0.303	0.44	0.660	0.59	0.555
General Cognition	0	1	0.49	0.624	0.49	0.624

Abbreviations: WTAR, Wechsler Test of Adult Reading; LNS, Letter-Number Sequencing, Spatial WM, Spatial working memory

2.3.5. Enrichment Analysis

We tested for enrichment of microglial, neuronal and astroglial gene sets with risk of SZ, controlling for number of SNPs in each set. For this analysis, genotype information was available for 203 microglial genes, 350 neuronal genes and 262 astroglial genes after excluding missing/incomplete SNP data. Here, we found that the microglial gene set was not significantly enriched for genes associated with SZ risk (std beta= -0.0087, SE= 0.0773 p= 0.860). Similarly,

no enrichment was observed for the astroglial gene set (std beta= 0.004, SE= 0.0662, *p*= 0.268). By comparison, the neuronal gene set showed enrichment for SZ risk (std beta= -0.0285, SE= 0.058, *p*= 0.0002).
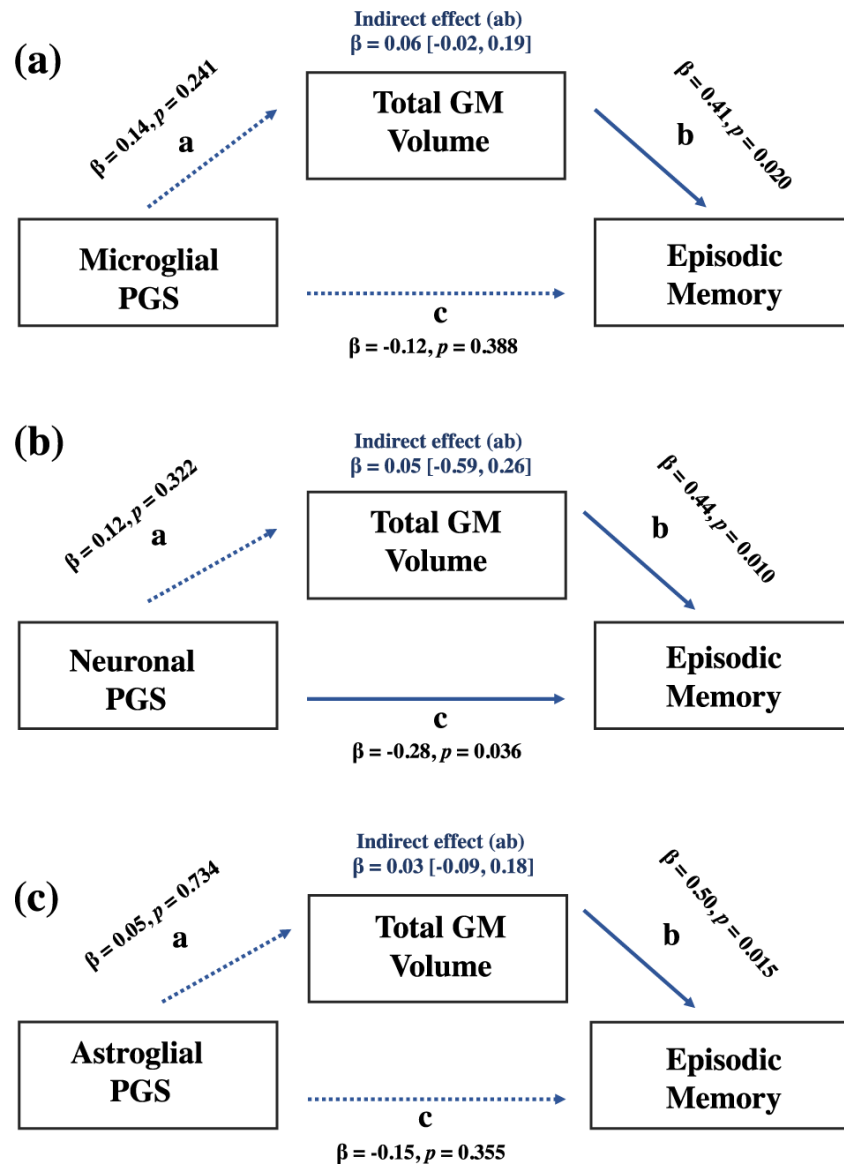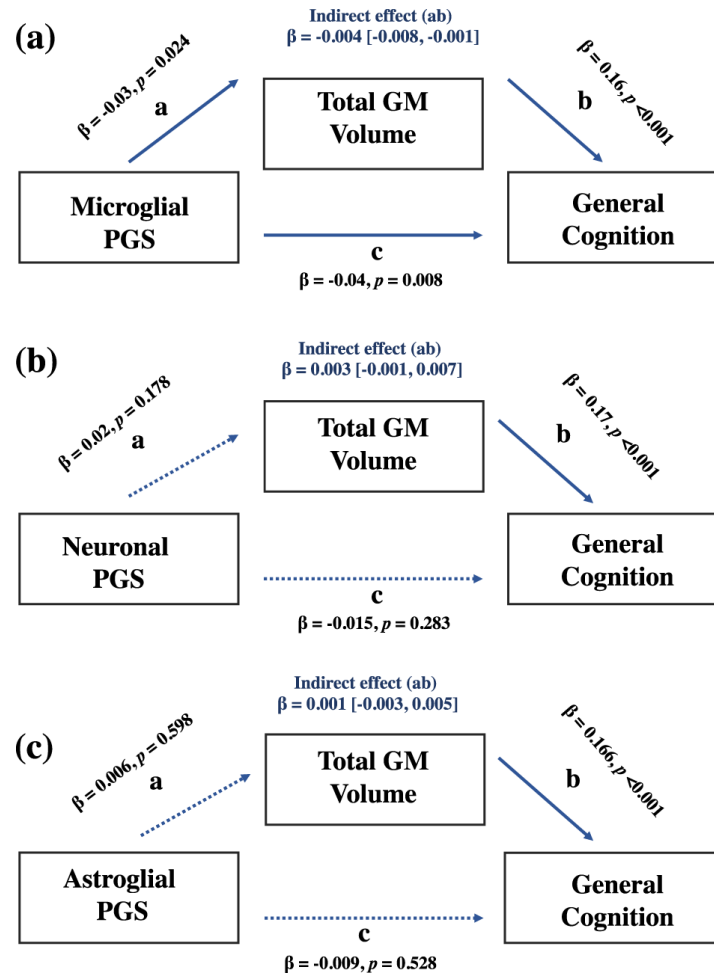

Figure 2.3. Mediation results of polygenic score associations in the UK Biobank sample.

Values are standardised estimates; dashed paths are non-significant. Indirect estimates are reported (a*b). (a) The effect of microglial polygenic score on general cognitive ability as mediated via grey matter volume; (b) The effect of neuronal polygenic score on general cognitive ability as mediated via grey matter volume; (c) The effect of astroglial polygenic score on general cognitive as mediated via grey matter volume.

2.4. Discussion

In this study we sought to characterise the effects of microglial-expressed genetic variants on cognitive functioning and brain structure in a sample of patients with SZ and healthy participants. To our knowledge this is the first genetic study to associate variation in a microglial-expressed gene set to cognitive performance. Consistent with previous studies showing a link between complement genes and cognition carried out by us (Donohoe et al., 2018; Donohoe et al., 2013; Holland et al., 2019; Holland, Cosgrove, et al., 2020) and others (Athanasiu et al., 2017; Zhang et al., 2017), we found that a microglial SZ-PGS predicted variation on multiple cognitive measures, with the strongest association observed for memory function. In our replication sample, we further found evidence that total grey matter volume mediated the association between microglial SZ-PGS and cognitive ability. Remarkably, while the effect size estimates between the different PGSs and cognition did not differ significantly, the microglial SZ-PGS predicted cognitive functioning to a comparable extent as found for the neuronal SZ-PGS. This suggests that, in addition to neuronal genes, microglial-expressed common genetic variation may also have relevance to cognitive functioning, both in patients and in healthy participants, and to understanding brain structural development related to cognition.

2.4.1. Polygenic Score Analysis of the Microglial Gene set

In the regression analysis of the discovery sample, increased microglial SZ-PGS was associated with lower scores on several cognitive measures (performance IQ, full-scale IQ and episodic memory). While these associations were observed for a range of neurocognitive functions, episodic memory was the cognitive domain most strongly associated with the microglial SZ-PGS. These findings are highly consistent with previous studies documenting an association between immune genetic risk variants and memory performance in patients. As noted above, we have previously demonstrated an association between CSMD1 (a gene implicated in complement function) and memory (Donohoe et al., 2013) in patients with SZ, and further shown that genetically predicted C4 RNA expression correlates with episodic memory performance (Donohoe et al., 2018). Among the cognitive impairments associated with SZ, memory function deficits are

consistently among the largest observed (Ranganath et al., 2008). It is interesting to speculate about why memory function is associated with immune-related genetic variation – whether this simply reflects the size of deficit associated with schizophrenia, or an aspect of cognition sensitive to either immune function or factors related to immune function (e.g., stress). While association data by its nature prevents us from drawing any causal influences, it is noteworthy that the association observed was not specific to patients, but rather observed across the entire sample, suggesting that this association may not be illness specific.

In addition to SZ, microglial abnormalities have also been found to influence memory performance in several different cohorts, including in patients with Alzheimer's Disease (AD) (Zou et al., 2020). Interestingly, in AD, microglial overactivation has been found to co-occur with structural changes in the brain and with memory deficits (Malpetti et al., 2020). Although few studies have directly examined the relationship between microglial pathology and brain structure in SZ, these findings are noteworthy here, as they suggest that brain structure and cognitive processes may be linked to microglial abnormalities. Interestingly, despite the absence of a direct relationship between microglia and brain structure, our study found that GM volume mediated the association between microglial PGS and general cognitive ability. At a genetic level, this suggests that microglia may indirectly associate with structural brain changes. However, this mediation effect was only observed in the UK Biobank sample, possibly reflecting a false positive finding, or a lack of power in the smaller discovery sample. Confirming these results will require testing in large longitudinal datasets consisting of genetic, cognitive, and imaging data.

2.4.2. Comparison of the Microglial, Neuronal and Astroglial PGS

When examining other gene cell types expressed in the brain, we found that the neuronal SZ-PGS was, as expected, also significantly associated with measures of cognitive performance. Indeed, neuronal susceptibility variants have consistently been implicated in SZ and in the cognitive symptoms of the disorder (e.g., Hertzberg et al., 2015; Lips et al., 2012). In our study, we found that the neuronal SZ-PGS showed effects on cognitive performance that were not specific to any

one aspect of cognition. This may suggest that neuronal expressed genes have a more general impact on cognitive functions in SZ, unlike microglial genes, which show a more substantial influence on memory processes. By contrast, the astroglial SZ-PGS only predicted variation in memory performance at a nominal level, explaining considerably less variance on this aspect of cognition compared to the microglial and neuronal SZ-PGSs. Finally, unlike neuronal genes, our microglial gene set did not show evidence of enrichment for SZ risk. This, together with the significant associations of the microglial PGS analysis, may indicate that the relevance of microglial-expressed genetic variation is for neurodevelopmental processes related more generally to cognition, rather than to illness risk per se.

2.4.3. Strengths and Limitations

Strengths of our study include a novel investigation of the relationship between microglial genetic variants and cognition, the relatively large size of our case/control sample, and replication of these findings in a larger cohort. At the same time, the impact of the microglial SZ-PGS on cognition was small (0.8-1.8% of the variance explained). Although modest, this is consistent with prior research demonstrating that associations between common variants and SZ risk and cognition are of small effect. Additionally, the total number of individuals with complete genetic, cognitive and MRI data in our discovery sample was small, limiting our ability to infer an effect of GM volume on microglia and cognition, particularly in the patient group. Further, the microglial gene set was derived from mouse brain data- the caveat being the non-identity of genetic variation and brain morphology to humans (e.g., immune-relevant genes such as C4A, C4B and SIGEC-11 are not present in mice but they are in humans (Konishi et al., 2017; Sekar et al., 2016). We also acknowledge that although genes were selected based on their expression levels within certain cell types, many genes may have alternative roles in immune and non-immune functions. However, our enrichment analysis for GO biological processes and molecular functions supports that these gene sets are, to a large extent good representatives of the cell type's specific functioning (Figure 2.1). A final limitation is that our SZ-PGSs were derived using relatively common SNPs (MAF > 0.01) and did not include rare SNPs identified via exome-based studies. However, SNPs with lower frequencies are unlikely to greatly affect the group-wide findings reported here.

2.5. Conclusion

In conclusion, our findings provide evidence that increased microglial polygenic risk is associated with decreased cognitive performance in both patients with SZ and healthy controls. We further highlight that variation in GM volume may mediate the observed association between the microglial PGS and cognition, supporting evidence of immune processes being associated with variation in brain structure. We also highlight, both the non-illness specificity of the findings and the absence of microglial enrichment for SZ risk and interpret this to reflect the relevance of microglial-expressed genetic variation is for neurodevelopmental processes related more generally to cognition. This is also consistent with the finding that the strength of association between the microglial and neuronal PGSs did not differ significantly but rather demonstrated comparable associations across the various cognitive tests.

Notwithstanding, future studies with larger SZ samples will be required to clarify whether illness-specific effects exist between microglia, cognition, and brain structure. Further, giving the growing evidence that not just genetic but also environmental factors (e.g., childhood adversity) are associated with immune function and cognition in SZ (Baumeister et al., 2016; Rokita et al., 2018; Rokita et al., 2020) modelling the interaction between immune-related genetic variants and environmental factors will be an important avenue for future research. Finally, modelling the association between microglial function and cognition in animal studies will be necessary for eliciting the neural basis of the association reported here.

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Author contributions

Conceptualisation: EC, LH, DWM, GD; Methodology: EC, LH, LF, DWM GD; Formal analysis: EC, GD; Investigation: EC, LH, LF, LC, DWM, GD; Writing - original draft preparation: EC, GD; Writing - review and editing: EC, LH, LF, AC, DWM, GD; Funding acquisition: EC, GD; Resources: GD, AC; Project administration: DWM, GD. All authors contributed to and approved the final version of the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

2.6. Supplementary Information

UK Biobank Sample

Descriptive Statistics of UK Biobank Sample

A total of 134,827 UK Biobank participants (71,843 females, 62,984 males) aged 40-73 years (M= 56.38, SD.= 7.69) had cognitive and genome-wide data available.

UK Biobank Cognitive Measures

The three cognitive tests used in the present study were fluid intelligence (UK Biobank Field ID: 20016), symbol-digit substitution (UK Biobank Field ID: 20159) and numerical memory (UK Biobank Field ID: 20240). The fluid intelligence test consisted of a series of 13 items assessing verbal and arithmetical deduction (Cronbach α reliability= 0.62)[1]. The symbol-digit test, which is similar in format to the Symbol Digit Modalities Test[2] involved matching symbols to single-digit integers. The score was based on the number of correct symbol-digit matches made in 60 seconds. For the numerical memory test participants were shown a two-digit number which they had to recall after a short pause. Numbers increased by one until the participant made an error or until they reached the maximum number of 12 digits. As a measure of general cognitive ability, scores of these three cognitive tests were entered into an unrotated principal component analysis. This intelligence factor explained 51% of variance in intelligence scores.

UK Biobank Structural MRI Data

MRI data were collected in a single Siemens Skyra 3T scanner with a standard 32-channel head coil located at UK Biobank's recruitment centre. T1-weighted MPRAGE data was acquired in the sagittal plane using a three-dimensional magnetization-prepared rapid gradient-echo sequence at a resolution of 1 x 1 x 1 mm, with a 208 x 256 x 256 field of view. Global and regional brain IPDs were extracted using FMRIB's Automated Segmentation Tool (FAST)[3]. A global brain imaging-derived phenotype of total grey matter volume (UK Biobank field ID: 25006) was used.

Participants with severe and visual normalisation problems were removed by the UK Biobank. Further details of the brain imaging protocols have been published elsewhere[4].

Genotype Data

Genotyping was performed using the Affymetrix UK BiLEVE Axiom array (807,411 probes) on 50,000 individuals, and the Affymetrix UK Biobank Axiom R array (820,967 probes) on the rest of the sample. The two arrays have over 95% common content. Before the release of the genetic data, quality control (QC) measures were applied and details of these steps can be found in Bycroft et al.,[5]. Building on these QC metrics, we excluded SNPs on the basis of SNP missingness > 0.02, minor allele frequency (MAF) <0.01, Hardy–Weinberg equilibrium (HWE) $\leqslant 1 \times 10^{-6}$, imputation quality score <0.9 and differing allele frequency between the two arrays. PLINK 1.9 software was used to perform quality control (QC) on the data[6]. Individuals were also removed based on non-European ancestry, relatedness, discordant sex information, high heterozygosity/missingness, chromosomal aneuploidies and retracted consent. Following the QC steps described above, 64,478 SNPs were included for analysis.

Supplementary Table 2.1. | List of microglial expressed genes, including their chromosome and base pair locations (± 20 KB)

Gene	Chromosome	Start	Stop	Gene	Chromosome	Start	Stop
ABCA9	17	66950773	67078442	ITPR2	12	26468285	27006131
ADAM17	2	9609392	9715917	KCNK6	19	38790484	38839654
ADAP2	17	29228698	29306340	LAIR1	19	54845235	54902241
ADGRE1	19	6867560	6960464	LAPTM5	1	31185315	31250683
ADORA3	1	112005970	112126602	LAT2	7	73604087	73664164
ADRB2	5	148186156	148274628	LCP1	13	46680058	46776459
AIF1	6	31562969	31604798	LCP2	5	169655088	169744822
AIM2	1	159008790	159066685	LGALS13	19	40073169	40118114
ALOX5AP	13	31267615	31358565	LGALS14	19	40174946	40220088
ANG	14	21132336	21182345	LGALS16	19	40126558	40171287
APBB1IP	10	26707253	26876732	LGALS3BP	17	76947335	76996061
ARHGAP17	16	24910710	25046695	LHFPL2	5	77761038	77964648
ARHGAP30	1	160996731	161059760	LIMD2	17	61753249	61798527
ARHGDIB	12	15074949	15134562	LIPA	10	90953326	91031660
ATF3	1	212718676	212814119	LPAR6	13	48965181	49038840
B4GALT1	9	33090636	33187356	LPCAT2	16	55522913	55640582
BANK1	4	102691764	103015969	LRRC3	21	45855393	45898739
BASP1	5	17196932	17296954	LSP1	11	1854200	1933493
BIN2	12	51654822	51738446	LST1	6	31533956	31576686
BLNK	10	97931455	98051333	LTC4S	5	179199263	179243616
BLVRB	19	40933691	40991725	LY86	6	6568934	6675216
BMP2K	4	79677532	79857519	LYL1	19	13188002	13233974
BST2	19	17482238	17536458	LYN	8	56772386	56945006
C15orf39	15	75471219	75524510	LYVE1	11	10558712	10610365
C1QA	1	22943118	22986175	LYZ	12	69722134	69768013
C1QB	1	22959682	23008130	MAF	16	79607745	79654622
C1QC	1	22949969	22994603	MAFB	20	39294488	39337880
C3AR1	12	8190919	8238955	MAN1C1	1	25923959	26131258
C4A	6	31929834	31990457	MAN2B1	19	12737322	12797591
C4B	6	31962572	32023195	MLXIPL	7	72987524	73058903
C5AR1	19	47793104	47845327	MMP9	20	44617547	44665200
CCDC88B	11	64087690	64145006	MNDA	1	158781168	158839270
CCL15	17	34303476	34349084	MPEG1	11	58955983	59000494
CCL18	17	34371643	34418841	MRC1	10	18078332	18220091
CCL23	17	34320096	34365005	MS4A6A	11	59919080	59972139
CCL24	7	75420766	75472674	MS4A6E	11	60082355	60128441
CCL3	17	34395602	34437506	MS4A7	11	60125949	60183427
CCL3L1	17	34603842	34645730	MYLIP	6	16109277	16168479
CCL4	17	34411220	34453014	MYO1F	19	8565674	8662331
CCL4L2	17	34518468	34560275	NAGPA	16	5054845	5103942

CCL8	17	32626066	32668421	NCF1	7	74168309	74223720
CCR5	3	46391633	46437697	NCF2	1	183504697	183580056
CD14	5	139991313	140033286	NCKAP1L	12	54871495	54956899
CD163	12	7603412	7676414	NRROS	3	196346656	196408875
CD180	5	66457205	66512617	OLFML3	1	114502030	114544875
CD300A	17	72442509	72500937	P2RX7	12	121550622	121644439
CD300LD	17	72556111	72608370	P2RY12	3	151034631	151122600
CD302	2	160605139	160675115	P2RY13	3	151024096	151067337
CD33	19	51708335	51763274	P2RY6	11	72955550	73029670
CD36	7	80211504	80328593	PAG1	8	81860045	82044303
CD37	19	49818632	49863863	PALD1	10	72218564	72348206
CD52	1	26624411	26667014	PDE3B	11	14645191	14913605
CD53	1	111393821	111462558	PF4	4	74826542	74867841
CD68	17	7462805	7505429	PIK3CG	7	106485723	106567592
CD74	5	149761200	149812543	PLA2G15	16	68259240	68314965
CD84	1	160490884	160569306	PLEK	2	68572322	68644585
CD86	3	121754209	121859990	PLEKHO1	1	150102170	150151825
CEBPA	19	33770840	33813430	PLOD3	7	100829258	100881011
CFH	1	196601008	196736634	PLXNB2	22	50693408	50766062
CFP	X	47463612	47509704	PNP	14	20917538	20966165
CLEC10A	17	6957856	7003626	PPCDC	15	75295927	75363067
CLEC4A	12	8256228	8311203	PPFIA4	1	202975649	203067864
CLEC4C	12	7860235	7922069	PPP1R18	6	30624166	30675672
CLEC4M	19	7808035	7854491	PRCP	11	82515409	82632733
CLEC5A	7	141607157	141666783	PRKCD	3	53175223	53246733
CLEC6A	12	8588591	8650926	PROS1	3	93571881	93712934
CMTM6	3	32502804	32564403	PSMB8	6	32788494	32832712
COL27A1	9	116898231	117092975	PTAFR	1	28453677	28540447
CPA3	3	148563043	148634874	PTGS1	9	125112809	125177982
CRYBB1	22	26975362	27033991	PTPN18	2	131093580	131152982
CSF1R	5	149412854	149512935	PTPN6	12	7035740	7090479
CSF3R	1	36911644	36968915	PTPRC	1	198588098	198746605
CTC1	17	8108139	8171413	PYCARD	16	31192807	31234097
CTSC	11	88006760	88090941	RAB3IL1	11	61644706	61733747
CTSH	15	79194092	79257436	RAC2	22	37601301	37660339
CTSS	1	150682672	150758433	RASAL3	19	15542435	15595382
CX3CR1	3	39284985	39343226	RCSD1	1	167579474	167697933
CYBA	16	88689697	88737492	RGS10	10	121239339	121322222
CYBB	X	37619266	37692718	RGS19	20	62684534	62731356
CYSLTR1	X	77506965	77603193	RGS9	17	63113456	63243821
CYTH4	22	37658495	37731389	RNASE4	14	21132259	21188761
DAB2	5	39351776	39445335	RNASEL	1	182522769	182578420
DHRS3	1	12607939	12697820	RNASET2	6	167322992	167390077
DNASE2	19	12966025	13012409	RPS6KA1	1	26836249	26921520
DOCK2	5	169044251	169530386	RUNX1	21	36140098	36441595

Gene	Chr	Start	End	Gene	Chr	Start	End
DOCK8	9	194865	485259	SALL1	16	51149886	51205183
DSE	6	116581231	116782422	SALL3	18	76720275	76779770
EDEM1	3	5209359	5281650	SAMSN1	21	15837549	15975723
ELK3	12	96568207	96681606	SELPLG	12	108995671	109047735
EMP3	19	48808629	48853810	SEMA4D	9	91955706	92132906
ENTPD1	10	97451536	97657023	SFT2D2	1	168175255	168232088
F11R	1	160945001	161011133	SH2B3	12	111823720	111909427
F13A1	6	6124311	6340924	SIGLEC6	19	52000951	52055110
FAM111A	11	58890219	58942512	SIPA1	11	65385578	65438391
FCER1G	1	161165087	161209038	SLA	8	134028973	134135604
FCGR1A	1	149734232	149784074	SLC11A1	2	219226752	219281617
FCGR1B	1	120906128	120955944	SLC15A3	11	60684555	60739257
FCGR2A	1	161455205	161509360	SLC16A6	17	66243167	66307405
FCGR2B	1	161612905	161668444	SLC29A3	10	73059010	73143147
FCGR2C	1	161531129	161591010	SLC2A5	1	9077005	9151763
FCRL2	1	157695523	157767119	SLC7A8	14	23574504	23672869
FCRL3	1	157626271	157690775	SLC9A9	3	142964063	143587373
FERMT3	11	63954152	64011363	SLCO2B1	11	74842032	74937445
FES	15	91407665	91459006	SLFN12	17	33718079	33780302
FGD2	6	36953423	37016845	SLFN12L	17	33781942	33834758
FLI1	11	128536430	128703162	SLFN13	17	33742115	33795856
FMNL1	17	43279192	43344685	SMAGP	12	51619133	51684202
FMNL3	12	50011724	50121197	SNX18	5	53793589	53862416
FOLR2	11	71907819	71952994	SPI1	11	47356409	47420127
GAL3ST4	7	99736865	99786373	STAB1	3	52509354	52578512
GBP3	1	89452360	89508556	STARD8	X	67847511	67965684
GCNT1	9	79014752	79142332	STK17B	2	196978307	197056336
GMFG	19	39798999	39846726	SULT1A1	16	28596908	28654907
GMIP	19	19720285	19774457	SUSD3	9	95800989	95867420
GNA15	19	3116191	3183766	SYNGR2	17	76144632	76189009
GNGT2	17	47263596	47307936	TAC1	7	97341271	97389784
GOLM1	9	88609018	88735116	TBXAS1	7	139458047	139740125
GPR183	13	99926789	99979749	TCIRG1	11	67786462	67838366
GPR34	X	41528221	41576530	TCN2	22	30983070	31043047
GPSM3	6	32138543	32183300	TGFBI	5	135344584	135419507
GPX3	5	150379999	150428554	TGFBR1	9	101847412	101936474
GRAP	17	18903969	18970336	TGFBR2	3	30627994	30755634
GRAPL	17	19010782	19082148	TIFAB	5	134764558	134808089
GSDMD	8	144615383	144665232	TLR7	X	12865202	12928480
GUSB	7	65405671	65467301	TM6SF1	15	83756301	83826111
HACD4	9	20983620	21051635	TMEM106A	17	41343865	41392061
HAVCR2	5	156492843	156556248	TMEM119	12	108963622	109011894
HCK	20	30619991	30709659	TMEM173	5	138835113	138882343

Gene				Gene			
HCLS1	3	121330246	121399791	TMEM176A	7	150477854	150522208
HHEX	10	94429681	94475408	TMEM37	2	120167501	120216096
HK2	2	75039782	75140481	TMEM86A	11	18700351	18746332
HLA-DQB1	6	32607241	32654466	TNFAIP8	5	118584418	118750294
HLA-DQB2	6	32703837	32751330	TNFAIP8L2	1	151109095	151152731
HPGD	4	175391328	175464049	TNFRSF1A	12	6417923	6471283
HPGDS	4	95199707	95284027	TREM2	6	41106244	41150924
IFI27L2	14	94574118	94615957	TRIM5	11	5656740	5726339
IFI30	19	18264590	18308934	TSPAN14	10	82194038	82302394
IGF1	12	102769645	102895563	TXNIP	1	145418438	145462635
IGFBP4	17	38579676	38633982	TYROBP	19	36375303	36419211
IL10RA	11	117837106	117892198	UNC93B1	11	67738575	67791593
IL10RB	21	34618665	34689539	VASP	19	45990688	46050247
IL16	15	81454941	81625104	VAV1	19	6752679	6877377
IL21R	16	27393483	27483363	WAS	X	48522186	48569818
IL6R	1	154357669	154461926	ZFHX3	16	72796784	73112534
IRF5	7	128557976	128610089	ZFP36	19	39877487	39920052
IRF8	16	85912774	85976212				
ITGAM	16	31251288	31364213				
ITGB2	21	46285864	46368753				
ITGB5	3	124460795	124626500				

Supplementary Table 2.2. | List of Neuronal Expressed Genes, including their Chromosome and Base Pair Locations (± 20 KB)

Gene	Chromosome	Start	Stop	Gene	Chromosome	Start	Stop
AAK1	2	69668532	69921481	MAPK10	4	86916276	87535284
ABHD8	19	17382940	17441045	MAPK8	10	49494698	49667403
ACHE	7	100467615	100514594	MAPK8IP2	22	51019114	51072409
ADAM23	2	207288263	207505851	MATK	19	3757971	3822127
ADARB1	21	46473768	46666478	MCTP1	5	94019446	94640279
ADARB2	10	1208073	1799670	MEGF11	15	66167417	66578222
ADCY1	7	45593739	45782715	MEIS2	15	37161406	37413504
ADCYAP1	18	884944	932173	MTUS2	13	29578748	30097892
ADD2	2	70814750	71015357	MYT1L	2	1772885	2355032
AMIGO2	12	47449490	47493734	NALCN	13	101686130	102088843
ANKRD34B	5	79832574	79886307	NAP1L2	X	72412135	72454684
ANO1	11	69904408	70055634	NAT8L	4	2041239	2090816
ARHGAP20	11	110427766	110603912	NCS1	9	132914857	133019583

ARHGAP44	17	12672856	12914960	NDNF	4	121936768	122014176
ARHGEF17	11	72999334	73100136	NEFH	22	29856219	29907379
ARHGEF4	2	131574489	131824836	NETO2	16	47091614	47197908
ARL4C	2	235381685	235425697	NEUROD1	2	182517815	182565603
ARX	X	25001811	25054065	NGFR	17	47552655	47612379
ASIC4	2	220358892	220423494	NME7	1	169081769	169357205
ATCAY	19	3859862	3948077	NMNAT2	1	183197372	183407737
ATP1A3	19	42450734	42521649	NOS1AP	1	162019564	162373321
ATP2B2	3	10345707	10769716	NPPA	1	11885766	11928402
ATP6V1G2	6	31479694	31522076	NPTX1	17	78420948	78471643
B3GALT2	1	193128175	193175784	NPTXR	22	39194457	39259987
B4GALT6	18	29182210	29285799	NPY	7	24303782	24351484
BAIAP3	16	1363602	1419439	NR4A2	2	157160944	157218860
BCL11B	14	99615624	99757861	NRGN	11	124589742	124637106
BCL2L15	1	114400790	114450169	NRIP3	11	8982123	9045596
BEND6	6	56799773	56912140	NRSN2	20	307426	360304
BEX1	X	102297579	102339168	NTRK1	1	156765432	156871642
BEX2	X	102544274	102585974	NXPH1	7	8453585	8812593
BTBD11	12	107692190	108073419	NXPH3	17	47633220	47681189
C11orf87	11	109272846	109319840	OGFOD1	16	56465402	56533012
C1QTNF4	11	47591216	47636211	PDE11A	2	178467980	178993066
CABP1	12	121058355	121125127	PDE1A	2	182984763	183407919
CACNA1A	19	13297256	13754804	PDE1B	12	54923134	54993023
CACNA1B	9	140752241	141039076	PDYN	20	1939403	1994732
CACNA1E	1	181362238	181797219	PGM2L1	11	74021363	74129518
CACNA1G	17	48618429	48724835	PHYHIP	8	22057222	22109854
CACNA2D1	7	81555760	82093114	PKIA	8	79408374	79537502
CACNA2D2	3	50380233	50561675	PLCXD2	3	111373523	111585294
CACNB3	12	49187577	49242724	PLD5	1	242226288	242707998
CADM3	1	159121399	159193103	PLEKHA6	1	204167979	204366793
CADPS2	7	121938481	122546813	PLK5	19	1504073	1555455
CALB2	16	71372616	71444341	PLXNA4	7	131788091	132353447
CALN1	7	71224476	71932136	PMCH	12	102570237	102611623
CALY	10	135118927	135170475	PNCK	X	152915185	152974465
CAMK1D	10	12371481	12897545	PNOC	8	28154503	28220872
CAMK2A	5	149579054	149689854	PODXL2	3	127328024	127411652
CAMK2B	7	44236749	44394176	POU2F2	19	42570263	42720737
CAMK2N2	3	183957001	183999251	POU4F1	13	79152497	79197673
CARTPT	5	70994990	71036875	POU6F2	7	38997598	39552694
CBLN2	18	70183915	70325756	PPP1R1B	17	37762993	37812879
CD44	11	35140417	35273949	PRKAR1B	7	568834	787287
CDK5R1	17	30793637	30838274	PROX1	1	214136524	214234595
CDS1	4	85484132	85592491	PRRT2	16	29803177	29847201
CHAT	10	50797141	50921925	PRUNE2	9	79206292	79541003
CHD5	1	6141853	6260183	PSD	10	104142376	104201296

CHGA	14	93369425	93421638	PTPN5	11	18729475	18834268
CHGB	20	5872076	5926007	PTPRT	20	40681392	41838610
CHL1	3	218279	471090	PVALB	22	37176728	37235523
CHRM2	7	136533416	136725002	RAB3C	5	57858048	58175213
CHRNA3	15	78865394	78933637	RALYL	8	85075022	85854079
CHRNB4	15	78896461	79040096	RAPH1	2	204239068	204420133
CIB2	15	78376948	78443886	RASGEF1A	10	43669983	43782367
CKMT1A	15	43965084	44011420	RASGRF1	15	79232289	79403115
CKMT1B	15	43865252	43917099	RBFOX1	16	6049095	7783340
CLEC2L	7	139188602	139249730	RBFOX3	17	77065427	77532230
CLIP4	2	29300571	29432509	RBMS3	3	29302473	30071886
CLSTN3	12	7262294	7331541	REEP2	5	137754706	137802658
CNR1	6	88829583	88896078	RELN	7	103092231	103649963
CNTNAP1	17	40814631	40871832	RESP18	2	220172131	220217899
CNTNAP2	7	145793453	148138090	RGS17	6	153305594	153472384
CORO2A	9	100863257	100974922	RGS8	1	182595239	182673711
CPLX1	4	758745	839986	RIMS1	6	72576406	73132845
CPLX3	15	75098888	75144141	RIMS3	1	41066351	41151329
CRH	8	67068620	67110960	RIT2	18	40303192	40715657
CRMP1	4	5729811	5914785	RNF157	17	74118534	74256454
CX3CL1	16	57386370	57438960	ROBO2	3	75935846	77719115
CXXC4	4	105369469	105436058	ROBO3	11	124715282	124771366
CYGB	17	74503438	74567257	RPH3A	12	112988184	113356686
CYTIP	2	158251131	158365473	RPRM	2	154313852	154355322
DACH1	13	71992098	72461330	RSPO3	6	127419749	127538910
DCAF12L2	X	125278337	125320080	RUSC1	1	155270687	155320905
DGKK	X	50088408	50233737	RYR2	1	237185505	238017288
DGKQ	4	932675	1000683	SACS	13	23882965	24027841
DIRAS1	19	2694565	2741416	SAMD14	17	48167404	48227246
DISP2	15	40630436	40683257	SCG2	2	224441658	224487221
DLG4	17	7073209	7143021	SCN1A	2	166825670	167004523
DLK1	14	101172042	101221539	SCN1B	19	35501588	35551352
DLX1	2	172929468	172974405	SCN2B	11	118012666	118067388
DLX6	7	96614860	96660351	SCN3A	2	165924032	166080577
DMTN	8	21886506	21960038	SCN8A	12	51964050	52226648
DMXL2	15	51719908	51935030	SCN9A	2	167031695	167252503
DNAJC27	2	25146505	25214963	SCRT1	8	145367965	145411184
DNM1	9	130945658	131037527	SCUBE1	22	43573289	43759394
DPP6	7	153564182	154705995	SEMA3E	7	82973222	83298326
DSCAM	21	41362926	42239065	SEMA6B	19	4522600	4579820
DYNC1I1	7	95381866	95759634	SERPINI1	3	167433031	167563356
DYNC2H1	11	102960160	103370591	SH3BGR	21	40797781	40907433
DZANK1	20	18344011	18467925	SH3BP1	22	38010661	38082939
ECEL1	2	233324537	233372538	SIPA1L1	14	71767166	72227946
EEF1A2	20	62099366	62150505	SIX3	2	45148902	45193216

EGFR	7	55066714	55344313	SLC10A4	4	48465360	48511213
ELAVL2	9	23670102	23846335	SLC12A5	20	44630356	44708784
ELFN1	7	1707755	1807590	SLC17A6	11	22339643	22421049
ELMOD1	11	107441817	107557505	SLC17A8	12	100730857	100835837
ENO2	12	7002909	7052861	SLC18A3	10	50798347	50840765
ERBB4	2	212220446	213423565	SLC24A3	20	19173290	19723581
ERC2	3	55522336	56522391	SLC32A1	20	37333105	37378015
EVL	14	100417786	100630573	SLC35D3	6	137223402	137266777
FAM155A	13	107800883	108539083	SLC4A10	2	162260843	162861792
FAT2	5	150863654	150968505	SLC4A3	2	220472049	220526702
FIBCD1	9	133757825	133834673	SLC4A8	12	51765101	51922980
FOXP2	7	113706382	114353827	SLC5A7	2	108582979	108650450
FXYD6	11	117687693	117768201	SLC6A17	1	110673108	110764824
FZD1	7	90873783	90918123	SLC7A14	3	170157372	170323863
GABRA1	5	161254197	161346975	SLIT2	4	20234883	20642184
GABRB3	15	26768693	27204686	SLITRK4	X	142690596	142743596
GABRG2	5	161474546	161602542	SNAP91	6	84242599	84439410
GAD1	2	171649723	171737661	SNCB	5	176027085	176077530
GAD2	10	26485236	26613487	SNPH	20	1226960	1309972
GADD45A	1	68130744	68174021	SOX11	2	5812799	5861516
GATA3	10	8075567	8137161	SPHKAP	2	228824666	229066361
GLRA1	5	151182074	151324403	SPTB	14	65193002	65366601
GNAL	18	11668955	11905684	SPTBN4	19	40952148	41102370
GNAZ	22	23392540	23487224	SRRM3	7	75811216	75936605
GNG2	14	52272913	52466060	SST	3	187366694	187408187
GNG8	19	47117333	47157942	SSTR2	17	71141151	71187185
GPR151	5	145872666	145915753	ST8SIA3	18	54998044	55058962
GPR162	12	6910711	6959136	STEAP2	7	89776904	89887451
GPR26	10	125405871	125474123	STX1B	16	30980577	31041949
GPRASP2	X	101947104	101993607	SULT4A1	22	44200389	44278398
GRIK1	21	30889254	31332351	SUSD4	1	223374161	223557544
GRIN1	9	140012842	140083207	SYN1	X	47411303	47499252
GRIN2A	16	9832376	10296611	SYN2	3	12025876	12252900
GRIN2B	12	13673165	14153053	SYNGR3	16	2019661	2064276
GRIN2C	17	72818162	72877627	SYNPR	3	63193991	63622597
GRM1	6	146328782	146778734	SYP	X	49024269	49076718
HAP1	17	39853994	39910896	SYT13	11	45241852	45327870
HAPLN4	19	19346450	19393605	SYT2	1	202539724	202699545
HECW1	7	43132198	43625600	SYT4	18	40827843	40877615
HOPX	4	57494155	57568065	SYT6	1	114611913	114716541
HPCA	1	33331595	33384042	TAC3	12	57383784	57442667
HS3ST4	16	25683347	26169009	TACR1	2	75253590	75446826
HS6ST2	X	131740044	132115423	TBC1D24	16	2505147	2575735
HSPA12A	1	118410705	118522086	TCEAL3	X	102842379	102904618
HTR2C	X	113798551	114164624	TCEAL5	X	102508619	102551800

HTR3A	11	113825603	113881035	TCEAL6	X	101375448	101417942
IGHM	14	106300349	106342323	TENM1	X	123489753	124117666
IPCEF1	6	154455631	154697926	TENM2	5	166691804	167711162
IQSEC3	12	96765	248460	TENM3	4	183045140	183744177
IRX1	5	3576168	3621517	TEX15	8	30669060	30768122
IRX2	5	2725959	2772969	THY1	11	119268090	119315695
ISL1	5	50658921	50710564	TMEM130	7	98455800	98520083
KCNAB2	1	6031526	6181253	TMEM132E	17	32887768	32986337
KCNC1	11	17736359	17824602	TMEM163	2	135193330	135496570
KCNC3	19	50795194	50856772	TMEM179	14	104921015	105091984
KCNG4	16	84235823	84293356	TMEM59L	19	18698240	18751849
KCNIP1	5	169760491	170183636	TMEM91	19	41836816	41909988
KCNJ12	17	21259509	21343179	TRBC1	7	142532587	142574261
KCNK2	1	215159118	215430436	TRBC2	7	142541934	142583641
KCNK3	2	26895619	26976288	TRO	X	54926895	54977864
KCNMA1	10	78609359	79418353	TSPAN18	11	44728015	44973972
KCNQ2	20	62017542	62123993	UBE2QL1	5	6428736	6515022
KCTD8	4	44155926	44470824	UFSP1	7	100466346	100507339
KIFC2	8	145671426	145719585	UGCG	9	114639046	114717649
KIT	4	55504085	55626881	UNC13A	19	17692137	17819401
KLC2	11	66004765	66055331	UNC80	2	210616717	210884024
KLHDC8B	3	49189044	49233917	UNCX	7	1252543	1296954
KLHL1	13	70254726	70702591	USP29	19	57610506	57663294
L1CAM	X	153106969	153194677	VAMP1	12	6551403	6600153
LGI2	4	24980469	25052501	VAT1L	16	77802427	78034004
LHX1	17	35274084	35321917	VAV2	9	136607016	136877726
LHX6	9	124944856	125011905	VGF	7	100785790	100828874
LHX8	1	75574119	75647218	VIP	6	153051933	153100900
LINGO1	15	77885369	78133242	VSNL1	2	17700393	17858285
LMTK3	19	48968528	49036446	VSTM2L	20	36511499	36593752
LONRF2	2	100869753	100959195	WDR6	3	49024495	49073386
LRFN5	14	42056773	42393752	WIF1	12	65424406	65535346
LRRC3B	3	26644297	26772267	WNT5A	3	55479743	55543973
LRRC55	11	56929221	56979191	YPEL4	11	57392560	57437417
LRRTM3	10	68665764	68879588	ZCCHC12	X	117937753	117980931
LY6H	8	144219331	144262128	ZCCHC18	X	103336822	103380533
LYNX1	8	143825752	143879640	ZDBF2	2	207119387	207199148
LYPD1	2	133382426	133449152	ZFHX2	14	23970066	24045401
MADD	11	47270712	47371582	ZNF23	16	71461500	71516998
MAPK10	4	86916276	87535284	ZNF536	19	30699197	31224445
MAPK8	10	49494698	49667403				
MAPK8IP2	22	51019114	51072409				
MATK	19	3757971	3822127				
MCTP1	5	94019446	94640279				

Supplementary Table 2.3. | List of astroglial expressed genes, including their chromosome and base pair locations (± 20 KB)

Gene Name	Chromosome	Start	Stop	Gene Name	Chromosome	Start	Stop
A2M	12	9200260	9288825	LHX2	9	126743949	126815580
ABCD2	12	39923835	40033553	LIX1	5	96407574	96498576
ABHD3	18	19210858	19304766	LPAR4	X	77983206	78032591
ABHD4	14	23047146	23101265	LRIG1	3	66409221	66571687
ABI3BP	3	100448000	100732359	LRRC2	3	46536913	46641589
ACAA2	18	47289869	47360330	LUZP2	11	24498516	25124150
ACAD8	11	134103389	134155749	LXN	3	158343611	158410482
ACOT1	14	73983818	74030498	MAOB	X	43605858	43761693
ACOT11	1	54987930	55124865	MAPK4	18	48066448	48278194
ACOT2	14	74014324	74062357	MARCKSL1	1	32779433	32821980
ACSBG1	15	78439810	78558030	MBOAT2	2	8972820	9163942
ACSS1	20	24966868	25059616	MDK	11	46382306	46425375
ADAMTS1	21	28188066	28237728	MERTK	2	112636056	112807138
ADHFE1	8	67322420	67403836	METRN	16	745115	789655
ADRA2A	10	112816790	112860658	MGST1	12	16480076	16782193
AGT	1	230818269	230870043	MLC1	22	50477820	50544331
ALDH1A1	9	75495578	75715358	MMP14	14	23285766	23338236
ALDH1L1	3	125802412	125936837	MOB3B	9	27305207	27549779
ALDH6A1	14	74503553	74571196	MPV17L2	19	18283992	18327758
APLN	X	128759240	128808933	MSI1	12	120759133	120826983
APPL2	12	105547074	105650016	MSX2	5	174131536	174177896
AQP4	18	24412002	24465782	MYBPC1	12	101942131	102099796
ARHGEF26	3	153818792	153995616	MYOC	1	171584557	171641823
ATP13A4	3	193099866	193330900	NAAA	4	76811809	76882204
AXL	19	41705108	41787671	NCAN	19	19302782	19383042
BMPR1B	4	95659119	96099599	NFE2L2	2	178072323	178277425
BOK	2	242478136	242533546	NKAIN4	20	61852136	61924046
BTBD17	17	72332555	72378085	NOTCH1	9	139368896	139460314
BTD	3	15622848	15707329	NPAS3	14	33384139	34293382
C16orf74	16	85703690	85804735	NPY	7	24303782	24351484
C1orf198	1	230952865	231025335	NR2E1	6	108467262	108530013
C4A	6	31920194	31980852	NRARP	9	140174083	140216703
C4B	6	32006249	32046275	NUPR1	16	28528606	28570495
C4orf19	4	37435563	37645117	OAF	11	120061475	120121041
CABLES1	18	20694528	20860431	OMG	17	29579031	29644557
CACNG5	17	64811235	64901603	PACRG	6	163128164	163756524
CBR3	21	37487210	37538864	PAPSS2	10	89399370	89527462
CBS	21	44453301	44517053	PAQR6	1	156193206	156237881
CCDC24	1	44437031	44482200	PAQR7	1	26167701	26217744
CD302	2	160605364	160674753	PAX3	2	223044607	223183715

CD38	4	15759898	15874953	PBXIP1	1	154896552	154948599
CD70	19	6563194	6624114	PCDH10	4	134050470	134149356
CDC42EP1	22	37936454	37985412	PCDH17	13	58185944	58323445
CDC42EP4	17	71259763	71328314	PDLIM4	5	131573364	131629147
CHRDL1	X	109897084	110059286	PDPN	1	13889960	13964452
CIB1	15	90753207	90797279	PHGDH	1	120182421	120306838
CLDN10	13	96065858	96252013	PHKG1	7	56128440	56180689
CNTFR	9	34531430	34610121	PIGS	17	26860401	26918890
CPNE2	16	57106449	57201878	PLCD4	2	219452488	219521907
CPQ	8	97637455	98181882	PLCE1	10	95733746	96112580
CSDC2	22	41936767	41993745	PLEKHO2	15	65114088	65180206
CSGALNACT1	8	19241672	19635540	PLXNB1	3	48425261	48491594
CTHRC1	8	104363743	104415225	PMP22	17	15113095	15188643
CTSO	4	156825270	156895063	POU3F2	6	99262580	99306660
CTXN3	5	126964736	127014322	POU3F3	2	105451969	105496929
CXCL14	5	134886373	134934969	POU3F4	X	82743269	82784775
CYP2D6	22	42502501	42546908	PPP1R1B	17	37762993	37812879
CYP2J2	1	60338980	60412462	PPP1R3C	10	93368199	93412811
CYP4F2	19	15968833	16028930	PPP1R3G	6	5065720	5107455
DAO	12	109232708	109314819	PRELP	1	203424956	203480480
DBX2	12	45388455	45464882	PREX1	20	47220790	47464420
DDAH1	1	85764164	86063933	PREX2	8	68844353	69169265
DECR1	8	90993633	91084320	PROCA1	17	27010215	27058872
DIO2	14	80643873	80874100	PRODH	22	18880294	18944066
DKK3	11	11964653	12051316	PRRX1	1	170611869	170728560
DMRTA2	1	50863222	50909172	PSD2	5	139155406	139244051
DPY19L3	19	32876449	32996801	PSPH	7	56058744	56139297
DUSP6	12	89721009	89767048	PYGM	11	64493861	64547769
EFHD1	2	233450767	233567491	RAB31	18	9688162	9882548
EFNB2	13	107122079	107207462	RAB34	17	27021299	27065447
EGFR	7	55066714	55344313	RAPGEF3	12	48108455	48184823
ELOVL2	6	10960992	11064547	RARRES2	7	150015408	150058763
EMID1	22	29581840	29675586	RASL11A	13	27824464	27867827
EMP2	16	10602279	10694555	RBP1	3	139216276	139278671
EMX2	10	119281955	119329056	RDH5	12	56094151	56138489
ENHO	9	34501038	34543039	RFTN2	2	198412948	198560769
ENTPD2	9	139922550	139968497	RFX4	12	106956685	107176581
EPHX2	8	27328296	27423081	RGMA	15	93566636	93652433
ETNPPL	4	109643196	109704210	RGS20	8	54744368	54891863
EVA1A	2	75676428	75816848	RHOC	1	113223728	113270056
EZR	6	159166773	159260444	RHOJ	14	63650832	63779937
F3	1	94974781	95027356	RLBP1	15	89733100	89784982
FABP7	6	123080620	123125219	RNASET2	6	167322992	167390679
FAM20A	17	66511254	66617530	RORB	9	77092281	77328093
FGFR2	10	123217848	123377972	S100A6	1	153487075	153528720

FGFR3	4	1775034	1830599	SASH1	6	148573440	148893186
FGFRL1	4	983724	1040685	SCARA3	8	27471385	27554293
FJX1	11	35619735	35662419	SCRG1	4	174285852	174347531
FOXB1	15	60276421	60373929	SELENBP1	1	151316778	151365209
FSCN1	7	5612439	5666286	SFRP1	8	41099481	41187016
FXYD7	19	35614154	35665204	SFRP5	10	99506508	99551709
FZD1	7	90873783	90918123	SHISA9	16	12975477	13354272
FZD10	12	130627004	130670285	SLC12A4	16	67957377	68023504
FZD2	17	42614925	42656907	SLC13A3	20	45166463	45324714
GABRA4	4	46900917	47016424	SLC14A1	18	43284092	43352485
GABRG1	4	46017786	46146098	SLC15A2	3	121592936	121682949
GAS1	9	89539279	89582104	SLC1A4	2	65195611	65270999
GDF10	10	48405815	48458976	SLC25A18	22	18023139	18093760
GFAP	17	42962376	43014305	SLC27A1	19	17559578	17636977
GJB6	13	20776110	20826534	SLC30A10	1	219838769	220151989
GJC3	7	99500892	99547243	SLC39A12	10	17973891	18105286
GLDC	9	6512464	6665650	SLC6A11	3	10837885	11002419
GLI3	7	41980548	42297469	SLC7A10	19	33679570	33736756
GNB4	3	179096990	179189378	SLC7A11	4	139065251	139183503
GNG12	1	68147149	68319150	SLC7A2	8	17334597	17448082
GNG5	1	84944008	84992248	SLC9A3R1	17	72724791	72785492
GPC5	13	92030929	93539490	SLCO4A1	20	61253797	61337137
GPC6	13	93859095	95079655	SLITRK2	X	144879350	144927360
GPLD1	6	24404793	24515433	SMOX	20	4081627	4188394
GRIN2C	17	72818162	72877627	SMPD2	6	109741966	109785122
GSTK1	7	142921186	142987947	SMPDL3A	6	123090315	123150865
HADH	4	108890870	108976331	SNTA1	20	31975761	32051698
HAPLN1	5	82913624	83037432	SOAT1	1	179242925	179347815
HDAC8	X	71529366	71812953	SOD3	4	24771534	24822464
HES1	3	193833934	193876521	SOX1	13	112701913	112746020
HES5	1	2440184	2481684	SOX2	3	181409714	181452221
HHATL	3	42714155	42764319	SOX21	13	95341886	95384389
HK2	2	75041108	75140486	SOX5	12	23662440	24123966
HOPX	4	57494155	57568065	SREBF1	17	17693713	17760325
HSD11B1	1	209839510	209928295	SRGAP1	12	64218073	64561613
HSPB8	12	119596447	119678936	ST3GAL4	11	126205535	126330239
ID4	6	19817617	19860915	ST3GAL6	3	98431080	98560045
IGDCC4	15	65653802	65735410	STK32A	5	146594526	146787415
IGSF1	X	130387480	130553677	SYT10	12	33507173	33612754
IGSF11	3	118599404	118884915	TEAD1	11	12675969	12986298
IKBIP	12	98987183	99058891	THRSP	11	77754907	77799397
IL18	11	111993974	112054840	TIMP4	3	12174551	12220851
IRX5	16	54944774	54988397	TLCD1	17	27031366	27074953
ITGB8	7	20350325	20475377	TLR3	4	186970306	187029223
ITIH3	3	52808784	52863025	TMEM176A	7	150477491	150522208

JAM2	21	26991584	27109874	TMEM176B	7	150468373	150518448
KCNJ16	17	68029570	68151749	TNC	9	117762806	117900536
KCNN2	5	113676642	113852337	TOM1L1	17	52956748	53059310
KCTD5	16	2712476	2779031	TRIB2	2	12837015	12902860
KLF15	3	126041478	126096285	TRIL	7	28972974	29017934
KLF3	4	38645817	38722663	TRPM3	9	73123979	74081820
KLHL13	X	117011776	117271303	TSPAN15	10	71191229	71287425
LAPTM4B	8	98767285	98885241	TST	22	37386900	37435681
LBH	2	30434397	30566596	TUBB2B	6	3204495	3251964
LCAT	16	67953653	67998034	VCAM1	1	101165298	101224601
LFNG	7	2532163	2588811	WNT7A	3	13837755	13941618
LGI4	19	35595417	35653355	WNT7B	22	46296242	46393009
LGR6	1	202143029	202308909	ZFYVE21	14	104162067	104220005

Supplementary Table 2.4. | Participant characteristics of the Irish discovery sample

	Whole Sample	Patient Group	Control Group
n	1,238	908	330
Age, mean (SD)	41.15 (12.84)	43.02 (12.42)	35.87 (12.64)
Gender (Male %)	59.77%	65.7%	44.4%
Education, years mean (SD)	-	12.67(2.54)	-
Chlorpromazine Equivalents mean (SD)	-	461.54 (457.62)	-
SAPS, mean (SD)	-	19.64 (19.19)	-
SANS, mean (SD)	-	23.39 (19.86)	-
Full-scale IQ, mean (SD)	100.87 (22.29)	92.03 (19.16)	119.91 (15.65)
Verbal IQ, mean (SD)	99.14 (22.27)	92.04 (19.99)	118.52 (15.82)
Performance IQ, mean (SD)	99.58 (18.38)	91.11 (19.31)	117.89 (19.17)
WTAR, mean (SD)	98.53 (18.38)	93.72 (18.75)	109.79 (10.68)
LNS, mean (SD)	8.97 (3.99)	7.74 (3.44)	12.45 (3.31)
Spatial WM, mean (SD)	-.2063 (1.500)	-.4063 (1.57)	.3197 (1.19)
Episodic Memory, mean (SD)	.000 (1.000)	-.3804(.8585)	1.011 (.4454)

Abbreviations: SAPS, scale for the assessment of positive symptoms; SANS, scale for the assessment of negative symptoms; WTAR, Wechsler test of adult reading, LNS, letter-number sequencing, WM, working memory

Supplementary Table 2.5. | Participant characteristics of the UK Biobank sample

Variable	Mean (SD)	*n*
Age	56.38 (7.69)	134,827
Gender (F:M)	71,843: 62,984	134,827
Fluid Intelligence Score	5.99 (2.15)	134,827
Numerical Memory Score	6.93 (1.48)	42,104
Symbol Digit Score	19.78 (5.04)	44,813
Microglial-SZ Polygenic Score	-7.807e-3 (5.313e-4)	134,827
Neuronal-SZ Polygenic Score	-7.206e-3 (2.654e-4)	134,827
Astroglial-SZ Polygenic Score	-5.637e-3 (3.562e-4)	134,827
Grey Matter Volume (mm^3)	616724.65 (55577.21)	13,311

Supplementary Table 2.6 | Association between schizophrenia microglial polygenic score and cognitive performance in the discovery sample

	Whole Group				Psychosis Patients				Healthy Controls			
	F Change	*R²* Change	β	*p*	*F* Change	*R²* Change	β	*p*	*F* Change	*R²* Change	β	*p*
FSIQ	6.62	0.008	-0.089	0.010	1.56	0.003	-0.052	0.213	0.09	0.00001	0.022	0.764
Perf IQ	7.73	0.009	-0.096	0.006	3.09	0.005	-0.072	0.080	0.46	0.002	0.050	0.499
Verbal IQ	4.78	0.005	-0.070	0.029	0.82	0.001	-0.033	0.367	0.50	0.003	0.052	0.481
WTAR	1.84	0.002	-0.047	0.176	0.04	0.0001	-0.008	0.845	0.43	0.002	-0.048	0.376
LNS	5.47	0.006	-0.075	0.020	3.20	0.004	-0.067	0.074	2.80	0.014	0.120	0.096
Spatial WM	2.37	0.003	-0.058	0.124	0.88	0.002	-0.040	0.358	1.51	0.010	0.098	0.222
Episodic Memory	13.70	0.018	-0.135	<.001	4.84	0.009	-0.096	0.028	3.68	0.024	-0.154	0.057

Abbreviations: FSIQ, full scale IQ; PERF IQ, performance IQ, WTAR, Wechsler test of adult reading, LNS, letter-number sequencing, WM, working memory

Supplementary Figure 2.1. | Genetic analysis pipeline
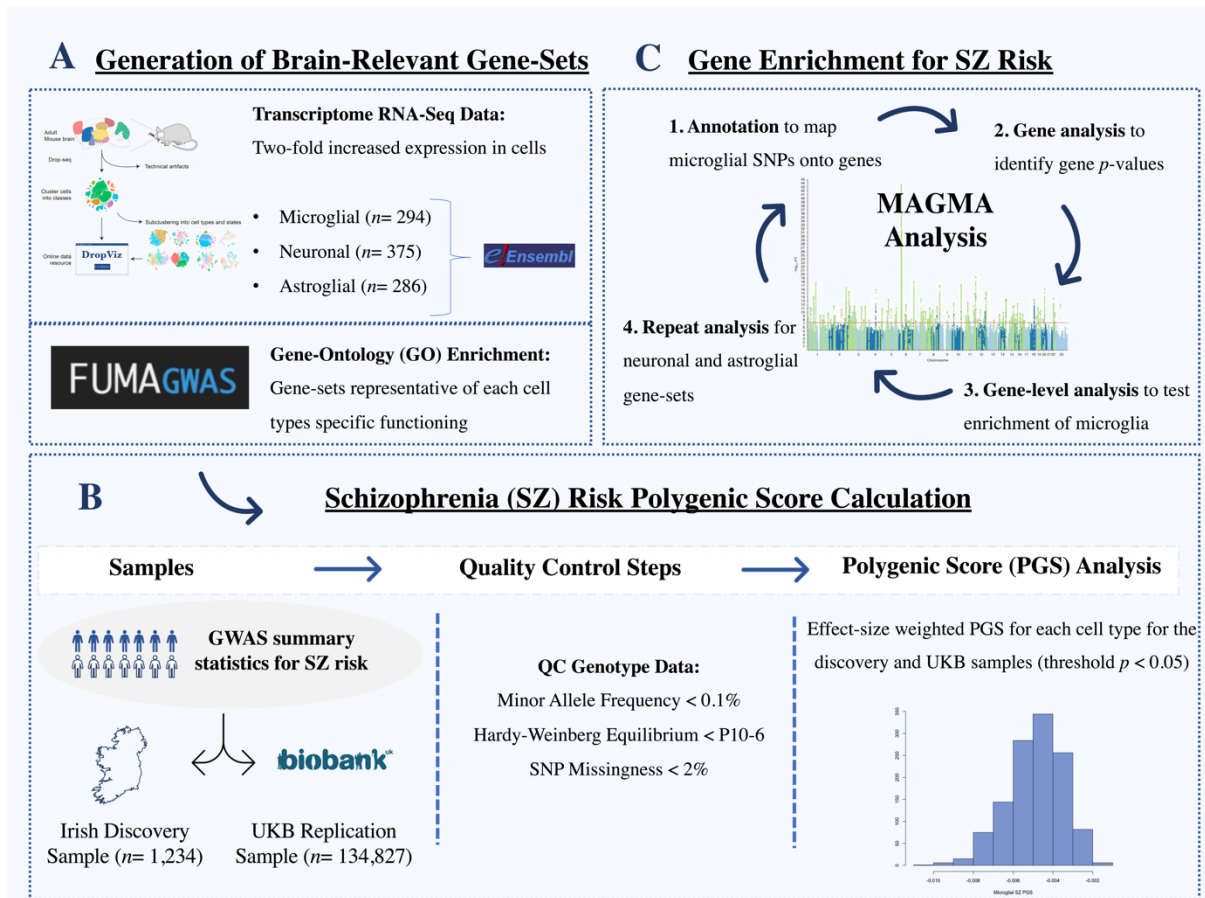
Schematic overview of the steps taken for the genetic analysis. (A) Generation of the microglial, neuronal and astroglial gene sets with subsequent gene-ontology enrichment analysis; (B) Polygenic score calculation of the Irish Discovery sample and the UK Biobank samples. Genotype data was quality controlled and a polygenic score (based on a threshold of $p < 0.05$) was calculated for each of the gene sets in both samples; (C) Gene enrichment analysis performed for the microglial, neuronal and astroglial gene sets to test for enrichment of these genes with risk for schizophrenia.

Supplementary References

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Chapter 3: The Impact of Early Adversity and Education on Genetic and Brain Morphological Predictors of Cognitive Ability

The Impact of Early Adversity and Education on Genetic and Brain Morphological Predictors of Cognitive Ability

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Abstract

Cognitive ability is a strong predictor of occupational achievement, quality of life and physical health. While variation in cognition is strongly heritable and has been robustly associated with early environment and brain morphology, little is known about how these factors combine and interact to explain this variation in cognition. To address this, we modelled the relationship between common genetic variation, grey matter volume, early life adversity and education and cognitive ability in a UK Biobank sample of $n=$ 5,237 individuals using structural equation modelling. We tested the hypotheses that total grey matter volume would mediate the association between genetic variation and cognitive ability, and that early life adversity and educational attainment would moderate this relationship. Common genetic variation, grey matter volume, and early life adversity were each significant predictors in the model, explaining ~15% of variation in cognitive ability. Contrary to our hypothesis, grey matter volume did not mediate the relation between genetic variation and cognition performance. Neither did early life adversity or educational attainment moderate this relation, although educational attainment was observed to moderate the relationship between grey matter volume and cognitive performance. We interpret these findings in terms of the modest explanatory value of currently estimated polygenic scores accounting for variation in cognitive performance (~5%), making potential mediating and moderating variables difficult to confirm.

3.1.   Introduction

Cognitive ability is a strong predictor of mental and physical health, as well as mortality (Deary et al., 2022). In the last decade, knowledge about how biological and environmental factors influence cognition has grown rapidly. This includes knowledge about the contribution of genetic variation and environmental factors, as well as the impact of both on brain morphological differences associated with cognition. In particular, the recent availability of large-scale data, including the UK Biobank, has propelled exciting developments in the area. Despite the significant advances in our understanding of the genetics of cognition, brain structure and environment, we remain at an early stage of modelling how these factors combine and interact. Addressing this gap in knowledge is critical because maintaining cognitive ability in the general population is important for reducing disability across the lifespan. In addition, a substantial body of literature suggests that variability in cognitive functioning can be explained by modifiable risk factors, including that of early life stress and educational attainment (Zaninotto et al., 2018).

At a genetic level, twin and family studies have confirmed the heritability of cognitive ability, accounting for about 50% of the total variance in cognition. The contribution of genetics to explaining variation in cognitive ability increases during childhood and adolescence and remains high throughout adulthood (Briley & Tucker-Drob, 2021; Plomin & von Stumm, 2018). Results from genome-wide association studies (GWASs) have demonstrated that cognition is highly polygenic, with hundreds of genetic loci of small effect (Plomin & von Stumm, 2018), and that these loci cluster in genes involved in regulating brain-specific gene expression (Deary et al., 2022). While these effects are small and difficult to detect, the use of polygenic scores (PGSs) has made it possible to model the cumulative effects of individual genetic variants and facilitate detection of gene-environment interactions associated with cognition. In the largest study to date (Savage et al., 2018), an intelligence based PGS was found to explain up to 5.2% of the variability in intelligence.

A positive association between cognition and brain size has also been robustly identified by multiple studies (Cox et al., 2019; Lee et al., 2019; Ritchie et al., 2015), with both phenotypes

sharing a common genetic origin (Grasby, 2021; Jansen et al., 2022). Indeed, Jansen and colleagues identified an overlap of 67 genes between both traits with a genetic correlation of 0.23, and the association between genetic variants and cognition has been observed to be partly mediated by grey matter (GM) volume (Jansen et al., 2022). In a recent study by (Cox et al., 2019) examining differences in global and regional measures of grey and white matter volume, the strongest contribution to the variance explained in cognitive ability was found for total GMV.

It is widely hypothesised that genetic variation and brain volume both interact with environmental factors to explain variation in cognitive ability (D'Amico et al., 2022; Lett et al., 2020). Early life adversity (ELA), including abuse, neglect, witnessing domestic or other violence, and chronic poverty (Holland, Cosgrove, et al., 2020; Smith & Pollak, 2020), has received a great deal of attention in the literature. Exposure to ELA during periods of heightened plasticity may alter developmental trajectories via structural neurobiological mechanisms that in turn, increase the risk of cognitive impairments in adulthood (Wade et al., 2022). Indeed, in both clinical and non-clinical samples, ELA has been found to be associated with variability in brain structure, including reductions in total GM volume (Lim et al., 2018; Rokita et al., 2020), and across limbic and prefrontal regions (Popovic et al., 2019; Price et al., 2021; Teicher et al., 2016), several large prospective and retrospective studies have documented an association between ELA and poorer cognitive outcomes in adulthood (Loman et al., 2010; McDermott et al., 2012; Smith & Pollak, 2020; Wolf & Suntheimer, 2019; Zeytinoglu et al., 2022). Further, in a recent moderated mediation study by (Wang et al., 2021) GM volume was found to mediate the association between an intelligence based PGS and cognitive function; this relationship was in turn moderated via ELA, based on data from the Adolescent Brain Cognitive Development study.

In addition to detrimental environmental factors that may moderate the association between genetic variation and cognition, the potential for mitigating factors to buffer the relationship between adverse early experiences and cognitive ability in adulthood, is also poorly understood. In particular, greater years in education has been observed to have positive effects on both cognitive and general health outcomes in individuals exposed to early adverse experiences (Boller et al., 2017; Ding & He, 2021; Greenfield & Moorman, 2018; Khambati et al., 2018).

Consequently, the relationship between educational experience and cognitive ability may be causally bi-directional (Davies et al., 2019; Peng & Kievit, 2020). Confirming this, however, is made difficult by other genetic and environment factors that likely confound the relationship, including ELA, making it important to model these factors together as potential moderators in the relationship between genetic variation and cognition. Furthermore, understanding how ELA is associated with neurobiological mechanisms underlying cognitive ability and whether these effects can be targeted, for example, via educational attainment, has the potential to inform interventions for individuals exposed to ELA.

The purpose of the present cross-sectional study was to examine the moderating role of ELA to the association between genetic variation, total GM volume and cognitive ability using the UK Biobank. For this moderated mediation analysis, we used structural equation modelling (SEM) and generated a latent factor of cognitive ability that was representative of cognitive domains of reasoning, processing speed, working memory and executive function. We hypothesised that the mediating effects of total GM volume to the association between genetic variation and cognitive ability would vary depending on the severity of ELA experienced. Genetic variation was indexed using a PGS of Verbal-Numeric Reasoning (VNR), derived from a GWAS we carried out using a non-overlapping sample of 89,748 UK Biobank participants. Finally, we tested the hypothesis that greater educational attainment would at least in part, moderate the effects of ELA on the association between total GM volume, genetic variability, and cognitive ability.

3.2. Materials and Methods

3.2.1. Participants

The current study used data from the UK Biobank; a large epidemiological cohort study of middle and older age individuals recruited between 2006 and 2010 in the United Kingdom. The study was approved by the National Health Service (NHS) Research Ethics Service (reference 11/NW/0382) and our access to the data was granted by the UK Biobank Access Committee (Project #23739). The total n of UK Biobank participants with cognitive and genetic information available was 115,482. This sample was spilt into an adequately powered discovery GWAS sample of 89,748 and a sample of 16,383 used to inform the PGS calculation. The total complete target sample with all available data included n= 5,237; age= 38-72 years; 2,711 females, 2,562 males. The discovery sample subset (n= 89,748) of participants were used to carry-out the VNR GWAS. Selection of the sample and further details of this breakdown are provided in Supplementary Figure 3.1.

Table 3.1. Descriptive characteristics of the UK Biobank sample

	N (%)	Mean (SD)	Range
Age (Years)	16, 383 (100%)	56.44 (7.82)	38-72
Education (No college/College)	16, 371 (100%)	1,742: 3,530	-
Sex (F:M)	16,383 (100%)	2,711: 2,562	-
Verbal-Numerical Reasoning	16, 383 (100%)	6.76 (2.03)	0-13
Symbol-Digit	9,741 (59%)	20.2 (5.04)	0-41
Numerical Memory	9,963 (61%)	6.90 (1.39)	0-12
Trails Making Test Part B	8,708 (53%)	64.70 (18.73)	20.56-746.53
Grey Matter Volume (mm^3)	5,273 (32%)	616142 (55476.34)	445943-616142
IQ Polygenic Score (Z score)	16,383 (100%)	1.52e-17 (1)	-4.30-3.97
Early Life Adversity	15,437 (94%)	1.5 (2.073)	0-16

Note. Means, standard deviations (SD) and ranges reported, except for frequencies are given for educational attainment and sex.

3.2.1. Cognitive Measures

Cognitive tests were administered online on the same day as the MRI scan. As a measure of cognitive ability, we selected four cognitive tests: VNR, Symbol-Digit Substitution, Numerical Memory and Trail Making Part B, to maximally capture important domains of cognitive ability including reasoning, processing speed, working memory and executive function. From this we constructed a latent variable of cognitive ability as previous work has shown improvement when combining these tests into a latent variable (Cox et al., 2019; de la Fuente et al., 2021; Hepsomali & Groeger, 2021; Newby et al., 2021).

The Verbal-Numerical reasoning test involved a series of 13 items assessing verbal and arithmetical deduction (Cronbach α reliability= 0.62) (Hagenaars et al., 2017). The symbol-digit test, which is similar in format to the symbol digit modalities test (Smith, 1973), involved matching symbols to single-digit integers and is a well validated measure of processing speed. The score was based on the number of correct symbol-digit matches made in 60 seconds. For the numerical memory test- a measure of working memory- participants were shown a two-digit number which they had to recall after a short pause. Numbers increased by one until the participant made an error or until they reached the maximum number of 12 digits. In the trail-making test part B, participants were presented with the numbers 1-13 and the letters A-L arranged pseudo-randomly on the screen. They were instructed to alternate between touching the numbers in numeric order and letters in alphabetical order (i.e., 1-A-2-B-3-C). As detailed by Salthouse (2011) and Cox et al., (2019), part B of the Trail-Making test includes both elements of speed and executive functioning. Full details on the content and administration of each test have been published elsewhere (Fawns-Ritchie & Deary, 2020).

3.2.2. Education

As a measure of education, UK Biobank participants were asked which of the following qualifications applied to them (with the option of selecting more than one), 1) college or university degree; 2) A levels or AS levels or equivalent; 3) O levels or GCSE or equivalent; 4) CSEs or equivalent; 5) NVQ or HND or HNC or equivalent; 6) Other professional qualifications, for

example, nursing, teaching/none of the above; 7) prefer not to answer. Following the approach described by (Rietveld et al., 2013) we created a binary variable for education to index whether participants had obtained a college or university-level degree.

3.2.3. Early Life Adversity

Childhood adversity items were based on the short version of the Childhood Trauma Questionnaire Short Form (CTQ-SF) (Glaesmer et al., 2013). The CTQ-SF is a self-report questionnaire measuring physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect. Items that were included in the analysis consisted of the following: 'When I was growing up…' '…I felt loved' (Loved as a Child): '…people in my family hit me so hard that it left me with bruises or marks' (Physical Abuse); '…I felt that someone in my family hated me' (Hated as a Child); '…someone molested me (sexually)' (Sexual Abuse) and 'There was someone to take me to the doctor if I needed it' (Physical Neglect). All questions were rated on a Likert 5-point scale: never true, rarely true, sometimes true, often, very often true. Additionally, there was the option: 'prefer not to answer', which was recoded as a missing value. Scores ranged from 0-20, with higher values representing more frequent adversity events. Given the non-normality of these scores, ELA was log transformed. Distribution and frequency of these scores are detailed in Supplementary Figure 3.2.

3.2.4. MRI Acquisition and Analysis

MRI data were collected in a single Siemens Skyra 3 T scanner with a standard 32-channel hear coil located at UK Biobank's recruitment centre. T1-weighted MPRAGE data was acquired in the sagittal plane using a three-dimensional magnetization-prepared rapid gradient-echo sequence at a resolution of 1 x 1 x 1 mm, with a 208 x 256 x 256 field of view. Global and regional brain imaging-derived phenotypes (IDPs) were processed by the UK Biobank team and made available to approved researchers. Full details of the brain imaging protocols, and quality control (QC) measures have been made available (Alfaro-Almagro et al., 2018). For our study, we used a global brain IDP of total GM volume, which had been extracted using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001). Scans of individuals with severe and visual normalization

problems were excluded by the UK Biobank through manual inspection (as noted in Alfaro-Almagro et al., 2018).

3.2.5. Genome-Wide Association Analysis of Cognitive Ability

We performed a GWAS of intelligence using the VNR test from the UK Biobank (discovery sample n= 89,748). We chose to conduct our own GWAS primarily to avoid sample overlap in the PGS analysis. The VNR test rather than all four available tests was chosen to maximise the number of participants. However, in agreement with previous authors (e.g., Hagenaars et al., 2017) we acknowledge that basing our GWAS on the VNR test, in isolation, is a limitation of the study. Cognitive tests available in the UK Biobank are restricted, in that not all participants had completed the same number of tests. For comparison, data on all four tests were available for only 36,383 participants which would not be sufficiently powered to calculate genome-wide summary data for a PGS of cognitive ability. Notwithstanding, when we examined the degree of correlation between our GWAS beta values to that of previously published GWAS of intelligence (Sniekers et al., 2017) we found a strong positive correlation between these values.

Genotype data was collected and imputed by the UK Biobank team. Full details of these along with imputation procedures are available in a publication (Bycroft et al., 2018). In addition to the QC steps performed by the UK Biobank, we removed SNPs on the basis of SNP missingness > 0.02, Hardy–Weinberg equilibrium < $1 \times 10\text{-}6$ and imputation quality score <0.9. Further, multi-allelic SNPs were removed as well as SNPs differing in allele frequencies across the genotyping arrays (UK BiLEVE, UK Biobank axiom arrays). The sample was restricted to those of European ancestry which were identified using principal component analysis (PCA) and 1000 genomes Project (1KGP) data. The multi-mean of the top ten PCs for 1KGP samples of European ancestry (identified via CEU code) was calculated and participants with a Mahalanobis distance < 6 SD from this multi-mean were considered to be of European descent. Samples were also removed based on the following: relatedness, discordant sex info, high heterozygosity/missingness, chromosomal aneuploidies or retracted consent. Following QC, a total of 7,829,832 variants and 89,748 individuals (41,895 males and 47,853 females) were included. We used a linear regression

model in the discovery sample to test for genetic association with intelligence using PLINK 2 (https://www.cog-genomics.org/plink/2.0/). For the analysis, age, gender, genotyping array, UK Biobank assessment centre, socioeconomic status (as assessed by the Townsend Deprivation Index) and the top 10 principal components of genetic population structure were entered in the linear regression.

3.2.6. Polygenic Score Calculation

We performed a PGS analysis based on our GWAS of VNR (herein referred to as IQ-PGS) using PRSice-2 (Euesden et al., 2015). To avoid potential bias induced by sample overlap, we generated these scores in an independent sample of 16,383 UK Biobank participants (not included in our GWAS) for whom cognitive, genomic and adversity measures were available. SNPs in high linkage disequilibrium were clumped according to PRSice-2 guidelines. Following this a total of 604,290 variants were included for analysis. An effect-size weighted PGS was then computed for each individual based on a threshold of $p <0.05$ with the total number of variants used to inform the PGS being 37,052. While previous studies have used multiple PGS thresholds, we chose a p-value of 0.05 as this has been shown to maximally capture polygenic risk across a large number of independent samples (Ripke et al., 2014). Additionally, we have previously observed this threshold to be the most informative (Cosgrove et al., 2017).

3.2.7. Statistical Analysis

SEM calculations were performed in R (version 4.1.2) using the Lavaan package (Rosseel, 2012). To improve convergence, before conducting the SEM analyses, the neural, genetic, and cognitive measures were standardised. Missing data were assumed to be missing at random and analyses were conducted using Full Information Maximum Likelihood (FIML) estimation. Model fits were assessed with the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), the Root Mean Square Error of Approximation (RMSEA) and the Standardised Root Mean Square Residual (SRMR). The following conventional cut-off values were used to determine acceptable model fit: CFI > 0.90, TLI > 0.90, RMSEA < 0.06 and SRMR < 0.06 (Rosseel, 2012).

We first assessed the mediating role of total GM volume to the association between IQ-PGS and cognitive ability. Cognitive ability was defined as a latent construct using the four cognitive tests (see Section 3.2.2). We further examined whether this association was better captured by the cognitive latent variable or the Verbal-Numerical Numerical Reasoning test alone. We next evaluated whether ELA would moderate (a) the association between IQ-PGS and cognitive ability, (b) the association between total GM volume and cognitive ability and/or (c) the mediation effect. Finally, we investigated whether the structural model differed across educational groups. See figure 3.1 for a schematic overview of the models.
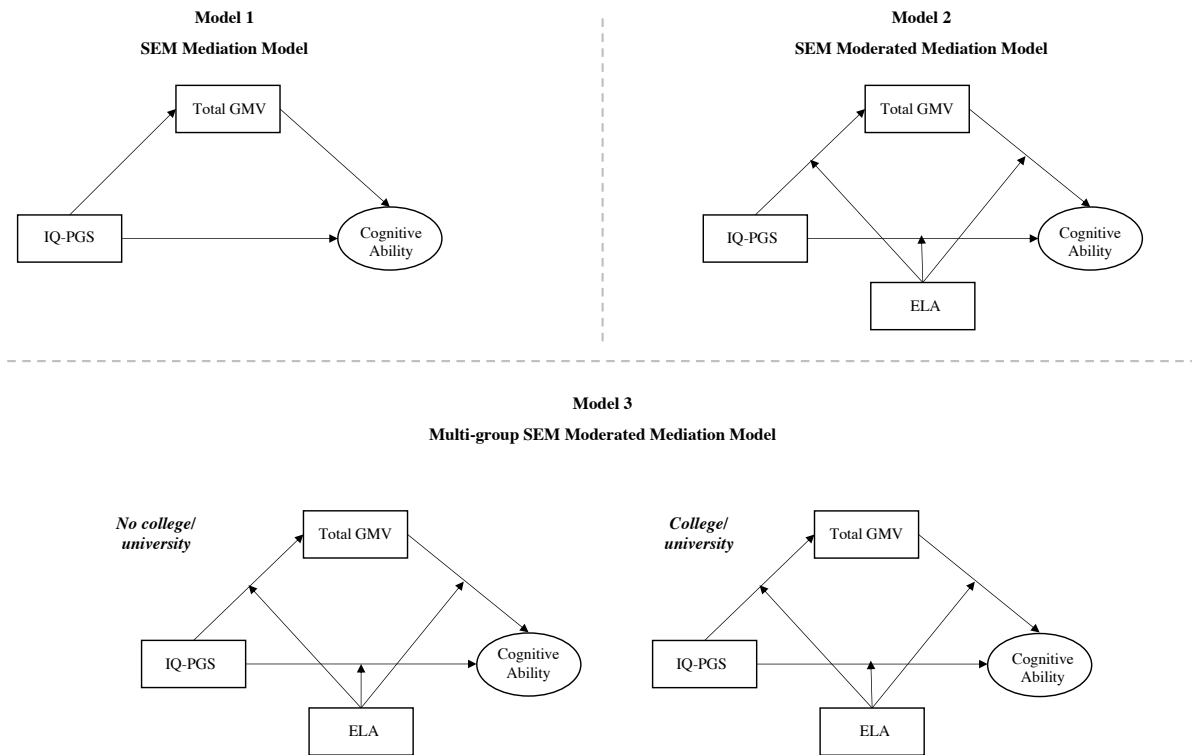
Figure 3.1. Schematic overview of the SEM models tested

Model one (mediation model) examines the mediation effect of total GM volume on the relationship between IQ-PGS and cognitive ability. Model 2 (moderated mediation) examines the moderating role of ELA on IQ-PGS, total GM volume and cognitive ability (direct and indirect pathways). Model 3 (multi-group SEM model) examines these associations across different educational groups: individuals without (group one) and with a college/university degree or higher (group two).

The moderating effect of education (college/university degree vs no college/university degree) was carried out using a multi-group SEM, which allowed for the estimation of measurement invariance (factor loadings and path coefficients) across the two groups. Given the sensitivity of the $\Delta\chi2$ to sample sizes, differences to reject invariance across specifications were based on the following indices and values only: ΔCFI ≤ 0.01 and ΔRMSEA ≤ 0.015 for both factor loadings and intercepts and ΔSRMR ≤ 0.03 for factor loadings and $\leq .01$ for intercepts (Chen, 2007; Cheung & Rensvold, 2002). Throughout models tested, we corrected for age, sex and total intracranial volume (TIV).

3.3. Results

3.3.1. Is the Association between IQ-PGS and Cognition Mediated by GM volume?

Testing our first hypothesis, which examined the mediating role of total GM volume on the association between IQ-PGS and cognitive ability, we found that the data had two fit indices (TLI and SRMR) outside our pre-registered criteria (CFI = 0.913; TLI = 0.864; RMSEA = 0.045, SRMR= 0.069). Modification indices (>10) suggested the inclusion of residual correlations between (1) Verbal-Numerical Reasoning and Numerical Memory, (2) Verbal-Numerical Reasoning and Trails-Making Part B and (3) Trails-Making Part B and Numerical Memory. Following the addition of these residual correlations, the data fit the model well (CFI = 0.994; TLI = 0.982; RMSEA = 0.016, SRMR= 0.032).

In this model which covaried for the effects of age, sex and TIV, the percentage of variance explained by the IQ-PGS and total GM volume on the latent variable of cognitive ability was 14%. By comparison, the percentage of variance explained in the model when the latent variable of cognitive ability was replaced with the VNR test alone was 7%. All associations with cognitive ability were in the expected positive direction, with the largest association being observed for total GM volume (β = 0.327, SE= 0.006, p <0.001) followed by IQ-PGS (β = 0.181, SE= 0.006, p < 0.001). However, the association between the IQ-PGS and total GM volume was nonsignificant (β = 0.032, SE= 0.020, p = 0.100), and the relationship between IQ-PGS and cognitive ability was not mediated by total GM volume (*indirect effect* β = 0.023, 95% CIs= -0.002; 0.023, SE= 0.006, p = 0.096). IQ-PGS accounted for 3% of the variance explained in cognition ability. Results of these associations are shown in Figure 3.2.
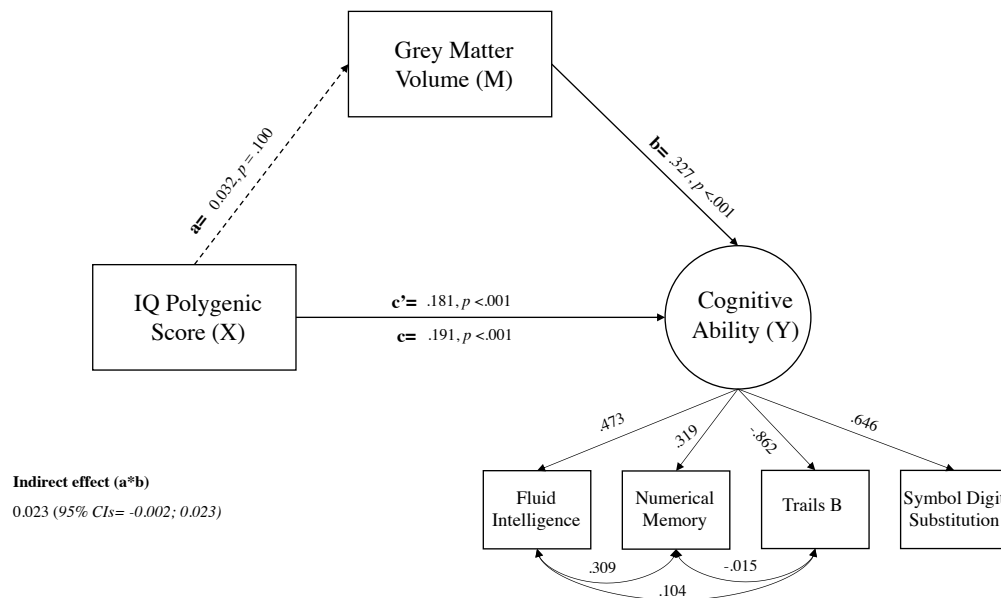
Figure 3.2. SEM mediation model

The association between the IQ based polygenic score on cognitive ability as mediated via total GM volume. X refers to the predictor variable (IQ-PGS), M the mediator variable (total GM volume) and Y the outcome variable (cognitive ability). Values are standardised beta estimates. Age, sex, and total intracranial volume were corrected for. Significant paths are denoted by solid lines and non-significant paths are dotted lines.

3.3.2. Does ELA Moderate the Effect of IQ-PGS and/or Total GM volume on Cognition?

Next, we sought to determine whether any differences in structural relationships were influenced by exposure to ELA. Age, sex and TIV were included as covariates of no interest. The results of this model fit the data well (CFI = 0.987; TLI = 0.974; RMSEA = 0.013, SRMR= 0.029), and in total, explained 15% of the variance in cognitive ability. As in the previous model, the direct effects of IQ-PGS and total GM volume on cognitive ability were both significant (Figure 3.3). In addition, a direct negative association was found between ELA and GM volume (β = -0.062, SE= 0.010 p < 0.001) and between ELA and cognitive ability (β = -0.077, SE= 0.006, p < 0.001).

Contrary to our hypothesis, ELA was not a significant moderator in this moderated mediation model (*indirect effect* β = -0.003, 95% CIs= -0.021; 0.014, SE= 0.009, *p* = 0.714).
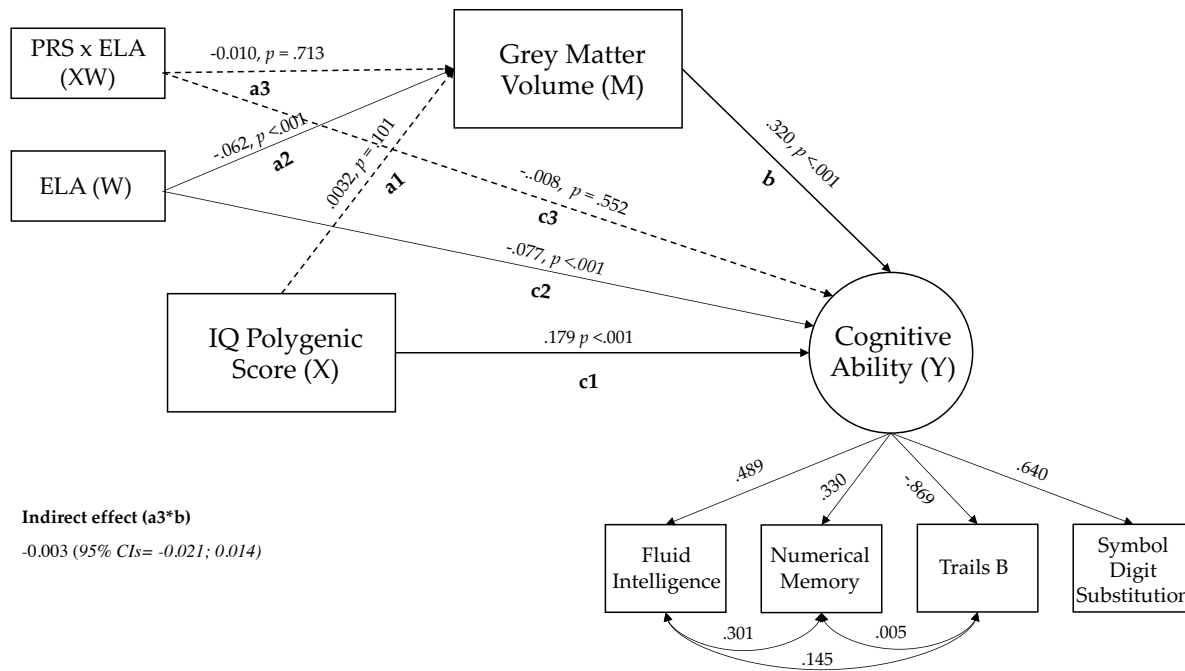
Figure 3.3. SEM moderated mediation model

The moderating effect of early life adversity on the IQ based polygenic score on cognitive ability as mediated via total GM volume. X refers to the predictor variable (IQ-PGS), M the mediator variable (total GM volume), W the moderator variable (ELA) and Y the outcome variable (cognitive ability). Values are standardised beta estimates. Age, sex and total intracranial volume were corrected for. Significant paths are denoted by solid lines and non-significant paths are dotted lines.

3.3.3. Does Education Moderate the Effects of ELA on Cognitive Ability, either Directly or via its Effects on IQ-PGS and/or Total GM volume?

Our final model examined whether education moderated the effects of adversity on cognitive ability through its association with IQ-PGS and/or total GM volume. Here, the model fit the data well (CFI= 0.967, TLI= 0.949, RMSEA= 0.018, SRMR= 0.034), and the variance explained in cognitive ability was comparable to those with (14.3%) and without (13.5%) a college/university degree. Before testing for group differences, we tested for measurement invariance across the educational groups by (1) constraining the loadings (metric invariance) and (2) the loadings and intercepts (scalar invariance) to equality (tested with ANOVA, Table 3.2). In all model's, acceptable fit indices were observed, and we found that metric and scalar invariance were held across groups. Thus, any observed differences in structural relations were not due to differences or errors in measurement and we proceeded to the multigroup analysis using our baseline model.

Table 3.2. Multigroup SEM model: Testing for measurement invariance across the different educational groups

	Δχ2 (*p*-value)*	df	ΔCFI	ΔTLI	ΔRMSEA	ΔSRMR
Configural model			-	-	-	-
Equal loadings	179.53 (< 0.001)	3	0.002	0.001	0	0
Equal loadings & intercepts	977.03 (< 0.001)	4	0.009	0.007	0.001	0.006

*We report chi-square χ2 difference for transparency purposes only due to the sensitivity of the Δχ2 to sample size.

As shown in Table 3.3, IQ-PGS and total GM volume were directly associated with cognitive ability, while the relationship between IQ-PGS and GM volume was nonsignificant in both groups. A significant moderating effect of ELA on the association between grey matter volume and cognitive ability was observed in the group who had been to college/university (*indirect effect* β = 0.015, 95% CIs= -0.022; -0.008, SE= 0.004, *p* <0.001). However, there was no evidence of a moderated mediation effect of ELA on the association between total GM volume, IQ-PGS and cognitive ability in either group (see Table 3.3).

Table 3.3. Standardised coefficients of moderated mediation model across the educational groups

	No College/ University				College/ University			
	β	SE	*p*	95% CIs	β	SE	*p*	95% CIs
PGS → GM (a1)	0.029	0.024	0.220	-0.018, 0.076	0.010	0.034	0.764	-0.057, 0.077
GM → IQ (b1)	0.304	0.016	< 0.001	0.273, 0.336	0.331	0.023	< 0.001	0.286, 0.376
PGS x ELA → GM (a2)	-0.013	0.038	0.730	-0.088, 0.061	-0.011	0.043	0.807	-0.095, 0.074
ELA → GM (a3)	-0.049	0.012	< 0.001	-0.072, -0.027	-0.016	0.017	0.337	-0.049, 0.017
ELA → IQ (c3)	-0.032	0.006	< 0.001	-0.043, -0.020	-0.016	0.009	0.062	-0.034, 0.001
PGS X ELA → IQ (c2)	-0.009	0.017	0.597	-0.043, 0.025	0.008	0.024	0.752	-0.039, 0.054
ELA X GM → IQ (b2)	-0.005	0.006	0.338	-0.016, 0.006	-0.015	0.004	<0.001	-0.022, -0.008
PGS → IQ (c1)	0.179	0.015	< 0.001	0.150, 0.207	0.143	0.021	< 0.001	0.101, 0.185
PGS → ELA → GM → IQ (a2*b1)	-0.003	0.014	0.807	-0.031, 0.025	-0.004	0.012	0.730	-0.077, 0.019

Note. PGS: polygenic score. GM: grey matter volume. IQ: Intelligence. ELA: early life adversity

3.4.   Discussion

Based on rich multivariate data from 5,273 individuals from UK Biobank, our study sought to model the complex relationship between genetic variation, GM volume, ELA and education on cognitive ability. Consistent with previous studies, we found that genetic variation, as measured by IQ polygenic score and total GM volume were each independently predictive of cognitive ability. We did not find evidence that GM volume mediated the association between genetic variation and cognitive performance. We further found that ELA was also significantly associated with cognitive performance, but that neither ELA nor years in education moderated the relationship between genetic variation and cognition, either directly or indirectly via GM volume.

3.4.1.   Brain Morphology and the Relationship between IQ-PGS and Cognition

Previous studies have found that structural brain metrics are positively associated with cognition (Ritchie et al., 2020), and that both share a common genetic basis (Grasby, 2021; Jansen et al., 2022; Lett et al., 2020). In our study, we focused on total GM volume given its consistent, albeit modest, association (~0.15-0.35) with cognition, and because cognitive ability is likely to involve multiple brain areas rather than one specific region (Cox et al., 2019; Deary et al., 2022). In line with previous studies, IQ-PGS and total GM volume were both predictive of cognitive ability. However, total GM volume was not a significant mediator of the relationship between IQ-PGS and cognitive ability either alone or when moderated by environmental variables.

One interpretation of these findings is that although significant direct associations were observed between cognitive performance and both genetic variation (as measured by the IQ-PGS) and GM volume, the modest amount of variation in cognitive performance explained by genetic variation may have limited our power to detect a mediating effect of brain volume. Despite the sample size (> 5,000 individuals) available for the analysis, a more sensitive measure of brain structure and/or volume may have been required to identify its mediating role. Alternatively, while cognitive variation and GM volume were associated, the underlying genetic variation shared between these phenotypes may be insufficient to confirm GM volume as a significant mediator of the relationship between an IQ polygenic score and cognitive variation.

3.4.2. Environmental Exposure as a Moderator of the Genetic and Brain-Related Underpinnings of Cognitive Ability

In addition to the associations observed between cognitive performance and polygenic variation and brain volume, exposure to adversity experienced in early life was also significantly associated with cognitive performance. Consistent with previous studies from our group and others, greater exposure to ELA was associated with lower cognitive performance. Contrary to our hypothesis however, ELA was not observed to moderate the relationship between polygenic variance and cognitive performance either directly or indirectly via moderated mediation of brain volume. Educational experience was also not observed to be a significant moderator in the relationship between polygenic variation and cognition, although it was observed to moderate the relationship between GM volume and cognitive performance.

Previous studies from our group and others have found evidence of association between ELA, structural variation in GM volume and cognitive functioning in both clinical and non-clinical samples (Begemann et al., 2023; Goltermann et al., 2021; Lim et al., 2018; Rokita et al., 2020). The present study differed from these previous studies by testing whether exposure to ELA represented a potential moderator of genetic effects rather than as an independent variable in its own right. For example, in the Rokita et al., (2020) clinical study, ELA was included as the main predictor of cognitive variation in the model, the effects of which were then observed to be mediated by GM volume. For the present study in which genetic variation was the main predictor variable, the relatively small variation in cognitive variation explained by IQ-PGSs coupled with the limited genetic overlap between GM volume and cognition may have obscured the moderating effects of childhood adversity. Although this issue might be mitigated by a larger sample size, a more parsimonious conclusion is the explanatory power of the model tested was limited. If true, future studies may benefit from testing alternative models, for example, testing whether polygenic variation might moderate the effects of early environmental exposure to cognitive performance, either directly, or as mediated by a measure of brain volume.

3.4.3. Strengths and Limitations

The cross-sectional design of this study prevents us from drawing any firm conclusions about causality. Indeed, for the models tested here, one could equally speculate about whether individuals with lower cognitive ability and/or socioeconomic status are at greater risk for exposure to ELA, and it will be important for future studies to examine these associations longitudinally. Another potential limitation is that ELA was measured using retrospective self-reports. However, it is noteworthy that retrospective reports of ELA are shown to correlate moderately well with prospective measures and demonstrate comparable effects on negative life outcomes (Reuben et al., 2016). Future studies will benefit from the inclusion of a prospective assessment of ELA, as well as considering the developmental timing and frequency of trauma exposure, which may mediate the effects on cognitive functioning (Danese et al., 2017). We did not examine other environmental risk factors (e.g., low birth weight and family income) nor did we include regional specific brain MRI volumes, which may also contribute to variation in cognitive ability. As such, future research should implement a fully data driven approach to include such factors.

Other potential limitations include validity and reliability of the cognitive tests used here, which were brief and administered unsupervised. Notwithstanding, a recent study by Fawns-Ritchie & Deary (2020), demonstrated that these cognitive tests correlated well with validated standard tests and had a moderate to high test-retest reliability. We further attempted to overcome this limitation by generating a latent variable of cognition comprising of several important domains of cognitive functioning. However, we note that basing our GWAS on the VNR in isolation, may not have been the most informative approach to characterise genetic variation involved in cognitive functioning. Large scale GWASs that comprehensively measure cognition- and exclude sample overlap of the UK Biobank- are therefore needed to identify the retrospective contribution of these factors. Finally, it is notable that the highest loadings on the cognitive ability factor was for the Symbol-Digit test and the Trails-Making test part B; both of which measure executive functioning. Executive function is a worthwhile domain to consider in relation to adversity as it is recognised as an important protective factor for individuals exposed to ELA, promoting better stress and

emotion regulation as well cognitive functioning (Lund et al., 2022). Finally, while we controlled for the effects of age, the UK Biobank sample is restricted to middle and older age adults which potentially limits the generalizability of the results.

Our investigation of the relationship between IQ-PGS, ELA, education and brain morphology on cognition has important strengths, including the large sample size and the inclusion of imaging and genetic data. Further, the SEM approach taken to characterise these associations expands on prior research, which has mostly used simpler regression approaches to analyse the complex relationships between biological and environmental predictors of cognition. The main advantages of SEM are that (1) it considers measurement error among variables, (2) it allows testing complex patterns of relationships and hypotheses simultaneously, (3) it evaluates constructs that cannot be directly measured, (4) allows for residual correlations among variables that may have multicollinearity issues and (5) it can test invariance of effects across different groups. Further, this multivariate technique allowed us to test both direct and indirect effects in an overall model.

3.5.   Conclusions

This study sought to model the relationship between polygenic variation, environmental exposure, brain volume and cognitive performance in a large non-clinical sample. While polygenic variation, early adversity and brain volume were each observed to be independently associated with cognitive performance, the hypothesised moderated mediation model was not supported. Given the modest explanatory value of currently estimated polygenic scores, we conclude that future studies modelling the relationship between these variables may benefit from consideration of polygenic variation as itself a moderator of other (e.g., environmental) factors rather than as a predictor variable which is itself moderated.

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Author Contributions

Author contributions; Conceptualization: EC, GD, DWM, LH; Methodology: EC, GD, LF, JF; Formal analysis: EC, GD; Investigation: EC, GD, LF, JF, EW, LH, DWM; Writing - original draft preparation: EC, GD; Writing - review and editing: EC, GD, LF, JF, EW, LH, DWM; Funding acquisition: GD; Resources: GD, DWM; Project administration: GD, DWM. All authors contributed to and approved the final version of the final version of the manuscript.

Competing interests

The authors declare no competing interests.

3.6.   Supplementary Information

Supplementary Figure 3.1. | Analytical N of the UK Biobank sample

Genotype data was quality controlled to remove samples based on non-European ancestry, relatedness, discordant sex information, high heterozygosity and missingness, chromosomal aneuploidies and those who retracted consent. Single nucleotide polymorphisms (SNPs) were removed based on: minor allele frequency (MAF) <0.01, SNP missingness > 0.02, Hardy-Weinberg equilibrium (HWE) $\leqslant$ 1 x 10^{-6} and imputation score <.0.9. Following this, 115,482 participants had cognitive and genetic data and of those, 89,784 samples (discovery samples) were used for our initial GWAS of cognitive ability. Results from this GWAS was then carried forward to generate a polygenic score for the remaining sample of 16,383 UK Biobank participants (target sample). These individuals were selected as they had environmental (early life adversity), education, genetic and at least one measure of cognitive data available. The total N available for participants with data on all measures available was 5,237.
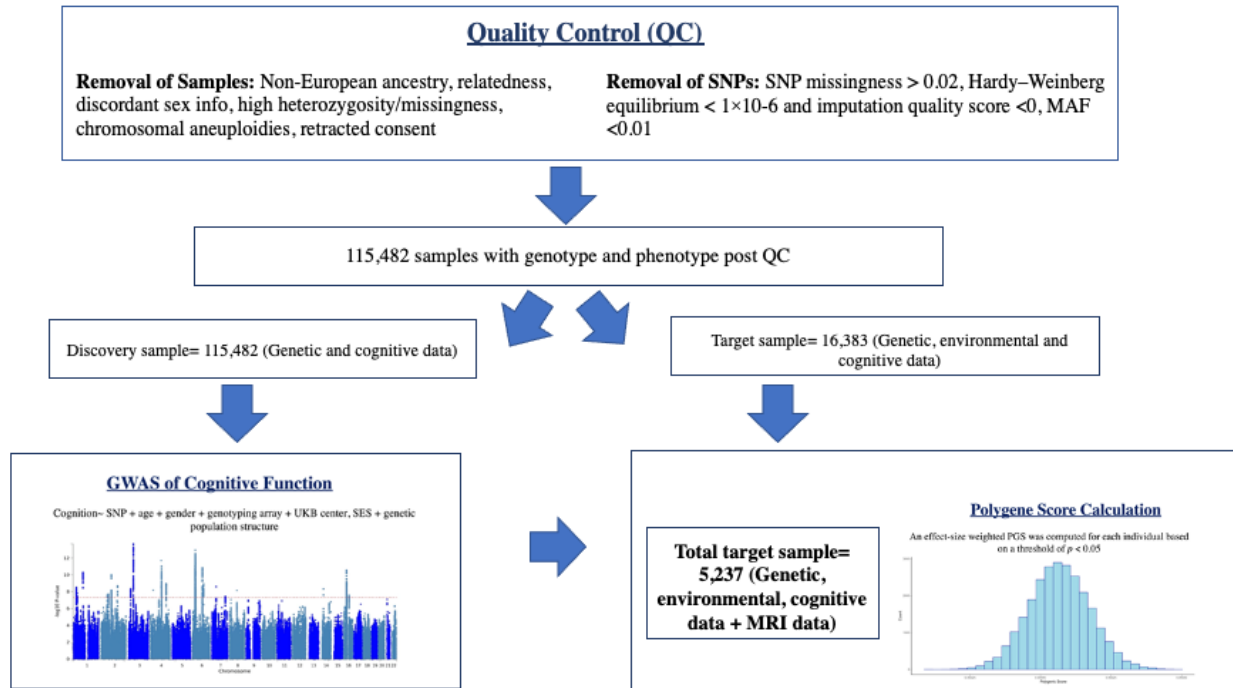
Supplementary Figure 3.2. | Graphs depicting distribution of early life adversity in the UK

Biobank sample
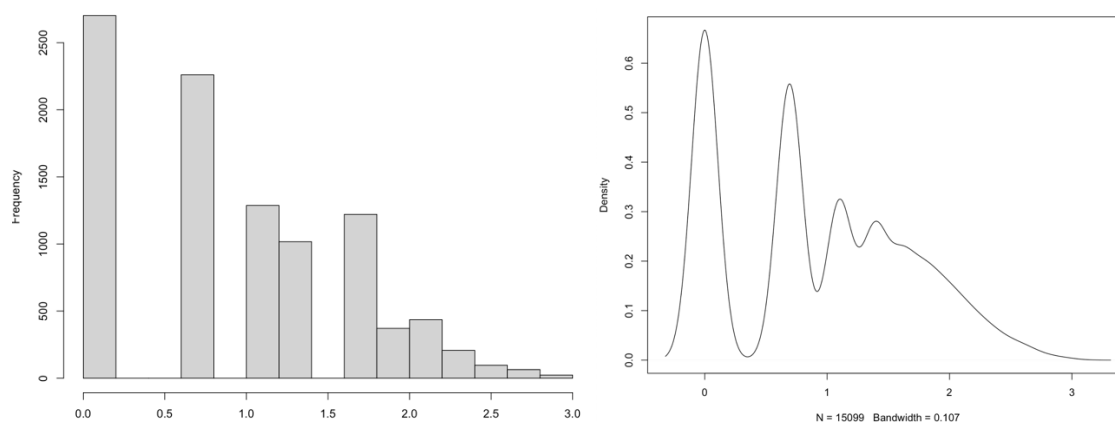
Supplementary Figure 3.3. | Manhattan plot of genome-wide association study of verbal-

numerical reasoning in the UK Biobank (n= 115,482)
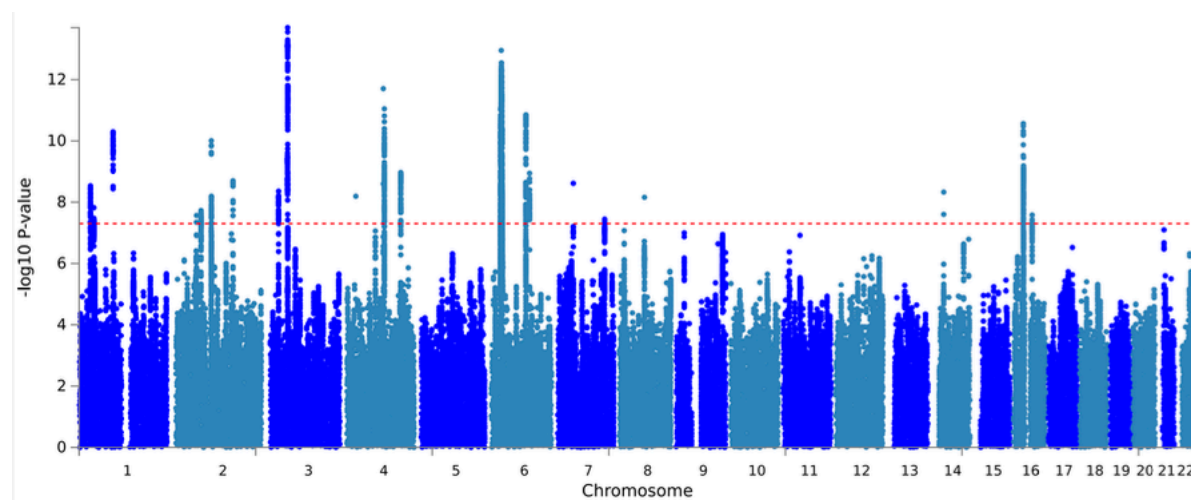
The y-axis shows the -log10 transformed P-values of each SNP from the GWAS. The x-axis shows the base pair position along the

chromosomes. The dotted read line shows the Bonferroni corrected P-value (P<5.0E-8).

Supplementary Figure 3.4. | Functional consequences of SNPs on genes
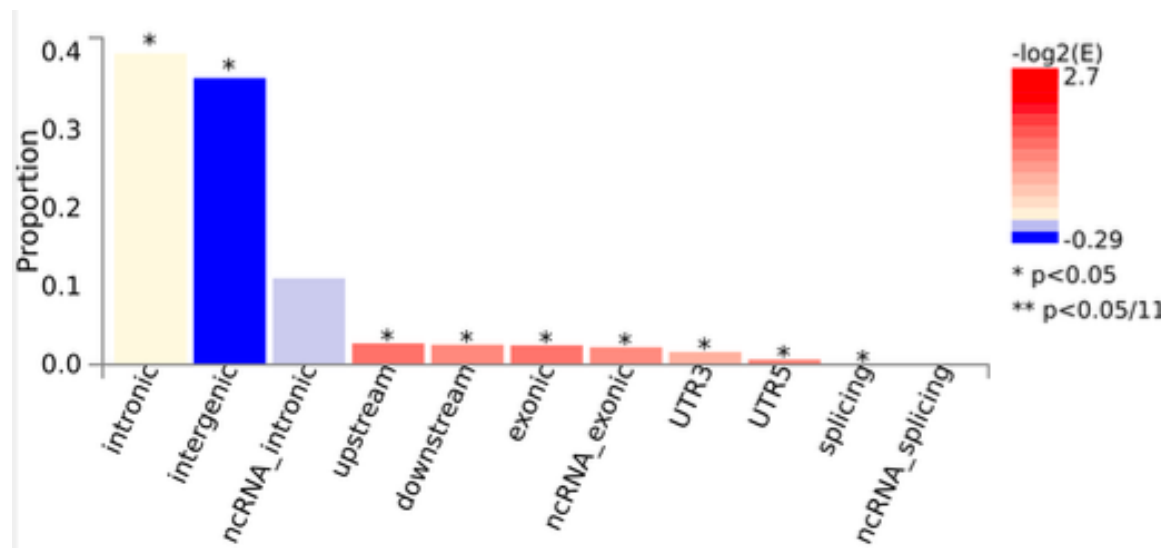
This histogram displays the proportion of SNPs (all SNPs in LD of Ind. sig. SNPs) which have corresponding functional annotation

assigned in FUMA. Bars are coloured by log2 (enrichment) relative to all SNPs in the reference panel.

Supplementary Table 3.1. | Significant genomic loci associated with verbal numerical reasoning

and their independent significant SNPs

Locus	rsID	chr	pos	p	start	end	SNPs
1	rs10914453	1	32075036	2.93E-09	32064903	32140733	95
2	rs12028010	1	41764471	1.51E-08	41750648	41850182	168
3	rs6678734	1	96176563	5.06E-11	96169760	96221653	37
4	rs59992825	2	58755062	2.71E-08	57771606	58764938	17
5	rs7605066	2	71529331	1.86E-08	71525698	71678520	85
6	rs34795510	2	100608840	9.84E-11	100516638	100967511	111
7	rs2358016	2	162007430	1.99E-09	161991197	162092640	11
8	rs1606173	3	24072710	4.39E-09	23963183	24079795	54
9	rs141072066	3	49783181	2.02E-14	49385417	50209053	417
10	rs34811474	4	25408838	6.39E-09	25408838	25408838	1
11	rs13107325	4	103188709	1.97E-12	102926923	103198082	7
12	rs57692580	4	106214476	8.96E-12	106048360	106379808	315
13	rs2278304	4	152593409	1.07E-09	152280333	152752413	155
14	rs7775835	6	28678357	1.11E-13	25884519	29607101	1041
15	rs4458695	6	98528404	1.41E-11	98316558	98591622	145
16	rs9384679	6	108864419	1.13E-09	108861264	109005588	41
17	rs3735478	7	44800176	2.42E-09	44768421	44804225	9
18	rs6954712	7	133618853	3.58E-08	133322697	133727497	115
19	rs13259607	8	71352047	6.93E-09	71138299	71352148	4
20	rs7146202	14	33303517	4.68E-09	33293122	33309357	40
21	rs3986619	16	28341631	2.73E-11	28336882	28895130	266
22	rs113137339	16	53524670	2.62E-08	53429180	53538157	44

Chapter 4: Genetic and Inflammatory Effects on Childhood Trauma and Cognitive Functioning in Patients with Schizophrenia and Healthy Participants

Genetic and Inflammatory Effects on Childhood Trauma and Cognitive Functioning in Patients with Schizophrenia and Healthy Participants

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Abstract

Recent studies have reported a negative association between exposure to childhood trauma, including physical neglect, and cognitive functioning in patients with schizophrenia. Childhood trauma has been found to influence immune functioning, which may contribute to the risk of schizophrenia and cognitive symptoms of the disorder. In this study, we aimed to test the hypothesis that physical neglect is associated with cognitive ability and that this association is mediated by a combined latent measure of inflammatory response and moderated by higher genetic risk for schizophrenia. The study included 279 Irish participants, comprising 102 patients and 177 healthy participants. Structural equation modelling was used to perform mediation and moderation analyses. Inflammatory response was measured via basal plasma levels of IL-6, TNF-α, and CRP, and cognitive performance was assessed across three domains: full-scale IQ, logical memory, and the emotion recognition task. Genetic variation for schizophrenia was estimated using a genome-wide polygenic score based on genome-wide association study summary statistics. The results showed that inflammatory response mediated the association between physical neglect and all measures of cognitive functioning and explained considerably more variance than any of the inflammatory markers alone. Furthermore, genetic risk for schizophrenia was observed to moderate the direct pathway between physical neglect and measures of non-social cognitive functioning in both patient and healthy participants. However, genetic risk did not moderate the mediated pathway associated with inflammatory response. Therefore, we conclude that the mediating role of inflammatory response and the moderating role of higher genetic risk may independently influence the association between adverse early life experiences and cognitive function in patients and healthy participants.

4.1.   Introduction

4.1.1. Childhood Trauma and Cognitive Impairments in Schizophrenia

Schizophrenia (SZ) is a complex neuropsychiatric disorder characterised by both clinical symptoms and cognitive impairments. Understanding these cognitive impairments is important as they represent significant predictors of occupational, social and economic functioning in patients with SZ (Green et al., 2019). At an environmental level, both cross-sectional and longitudinal studies report a negative association between exposure to early life adversity (ELA) and cognitive functioning, as measured by impairments in general cognitive ability, attention memory processes, executive function and social cognition (Bucker et al., 2013; Dauvermann & Donohoe, 2019; Holland, Cosgrove, et al., 2020; Poletti et al., 2017; Rokita et al., 2021; Schalinski et al., 2018; Smith & Pollak, 2020). Childhood trauma is reported at a much higher level in samples of individuals affected with SZ than in the general population and is associated with an increased odds ratio for schizophrenia of ~2.8 (Larsson et al., 2013b; Varese et al., 2012). Although several studies have reported an association between risk for SZ and general and specific types of childhood trauma (e.g., neglect and abuse), exposure to physical neglect, defined as failure of caregivers to provide a child's basic physical needs, has consistently found to be associated with cognitive impairments in SZ (Aas et al., 2012; Dauvermann & Donohoe, 2019; King et al., 2021; Rokita et al., 2018; Rokita et al., 2020). Further, in recent work by (Morkved et al., 2020) and others (De-Nardin et al., 2022; Lakkireddy et al., 2022; Ucok et al., 2015; Vaskinn, Engelstad, et al., 2021), variance in cognitive ability in patients with SZ has been found to vary across subtypes of childhood trauma, with the strongest impairments in cognition being observed for individuals that have been exposed to childhood physical neglect.

4.1.2. Childhood Trauma, Cognition, and Immune Response

A change in immune response is hypothesised as one potential mechanism by which childhood trauma may negatively impact both SZ risk and cognitive function. This hypothesis is supported by evidence that immune processes are capable of modulating brain development and neurotransmission, leading to excessive synaptic pruning, glial priming, apoptosis and modulation

of the hypothalamus-pituitary-adrenal (HPA) Axis (Baumeister et al., 2016; Eckstrand et al., 2019; Mondelli & Vernon, 2019). Evidence of aberrant immune response comes from numerous reviews (Miller et al., 2014; Rodrigues-Amorim et al., 2018) and longitudinal studies (Patlola et al., 2023) documenting an association between elevated levels of peripheral inflammatory markers, childhood trauma and increased risk of SZ.

In terms of psychosis, associations between a chronic proinflammatory state and SZ have been widely reported (Chase et al., 2016; Upthegrove & Khandaker, 2020), with elevated cytokine concentrations typically associated with increased psychotic symptom severity (Goldsmith et al., 2016). Most importantly, proinflammatory markers, including interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) have been found to be particularly elevated in SZ patients who have experienced childhood trauma (Baumeister et al., 2016; Dennison et al., 2013; Di Nicola et al., 2013; Mondelli & Vernon, 2019; Rokita et al., 2020). The importance of these inflammatory markers in the context of risk for SZ has also been supported in a recent systematic review by (Halstead et al., 2023). Further, in studies by our group and others (Davis et al., 2019), elevated levels of IL-6 have consistently been shown to mediate the association between childhood trauma and cognitive performance, particularly social cognition. However, whether this mediating effect is specific to IL-6 or extends more broadly to other inflammatory markers such as CRP and TNF-α is not yet known. Further, as these and other cytokines function collectively, with levels of each being reciprocally determined, it could be argued that these cytokines should be analysed together as a combined measure rather than in isolation. In support of this, several lines of research from animal, imaging, and peripheral and cerebrospinal fluid studies support cross-talk and interconnectedness between various peripheral inflammatory markers and the impact of these on the central nervous system (Di Biase et al., 2021; Halstead et al., 2023; Maxeiner et al., 2014; Riazi et al., 2008). To our knowledge, no study has characterised the combined effects of inflammatory response using a latent variable approach analysis to the association between childhood trauma and cognitive functioning in patients with SZ.

4.1.3. Genetic Risk for Schizophrenia and Cognitive Impairment

Although elevated levels of inflammation have been shown to mediate the relationship between childhood trauma and cognition, not all individuals will show impairments in cognitive functioning despite having experienced adversity. Variation in phenotypic outcomes in SZ have long been proposed to reflect a combination of genetic influences and early life experiences, including childhood trauma. While genome-wide association studies (GWASs) have consistently found evidence that genetic risk variants for SZ are located throughout the genome, the major histocompatibility complex (MHC) - a region synonymous with regulation of immune function-continues to be the most strongly associated single locus (Pardinas et al., 2018; Trubetskoy et al., 2022). Further, SZ risk variants associated with cognition that implicate immune function have been reported at the level of individual genes (e.g., C4A; Donohoe et al., 2018), gene sets (e.g., complement; Holland et al., 2019) and at the cellular level (e.g., microglia; Corley et al., 2021). Interactions between genetic risk for schizophrenia and childhood trauma have also been reported previously (Guloksuz et al., 2019; Tonini et al., 2022). However, it is not yet clear whether these effects combine to influence cognitive functioning, nor has the mediating effects of immune alterations been investigated concomitantly.

4.1.4. The Present Study

The purpose of the present study was to better model the association between childhood trauma and cognition in terms of the mediating effects of inflammatory response and the moderating effects of genetic risk for SZ. In particular, we focused on physical neglect as the aspect of childhood trauma most reliably associated with variation in cognition. Building on previous studies from our group in the same sample suggesting that IL-6 mediates the relationship between physical neglect and cognition (King et al., 2021), we examined whether this mediating role of inflammatory response was better captured by a combined inflammatory latent variable consisting of IL-6, CRP and TNF-α or by any these inflammatory markers alone. Based on the evidence that IL-6, CRP and TNF-α function biologically as a group (Giovannini et al., 2011), and show evidence of association with both trauma (Baumeister et al., 2016) and cognition (Baek et al., 2022; Miller et al., 2009), we used structural equation modelling (SEM) to test the hypothesis that

a latent variable constructed from these markers would mediate a greater percentage of the relationship between physical neglect and cognition than any of these markers alone. We further tested the hypothesis that polygenic risk for SZ, calculated based on the most recent SZ GWAS summary statistics (Trubetskoy et al., 2022) would moderate the mediating role of immune response to the relationship between neglect and cognition. We hypothesised that regardless of diagnostic status, these phenotypic effects on cognition would be stronger for individuals carrying a higher SZ polygenic risk. Analysis was therefore carried out in the total sample first, and then in patients and healthy controls separately.

4.2.   Materials and Methods

4.2.1. Participants

From a total of 311 Irish patients and healthy participants collected as part of the 'Immune Response & Social Cognition in Schizophrenia' (iRelate) research project, 279 patients and healthy controls (n=102 patients and 177 healthy controls) had complete data available. The patient group consisted of clinically stable patients with either a diagnosis of SZ or schizoaffective disorder (SZA). Diagnosis was confirmed using the Structured Clinical Interview for Diagnostic Statistical Manual-IV (SCID) (Spitzer et al., 1992) and patients were recruited from local outpatient clinics and mental health services in Dublin and Galway. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to measure symptom severity of SZ. Healthy participants were recruited from the general population through local and national media advertising in Ireland. Patients were omitted if they had a comorbid DSM-IV Axis I psychiatric disorder. Participants were excluded based on the following criteria: (i) history of acquired brain injury causing loss of consciousness of > 1 minute; (ii) a history of substance misuse disorder six months prior to study commencement, (iii) intellectual disability, (iv) chronic inflammatory illness, and (v) non-steroidal anti-inflammatory drugs (NSAIDs) in the past 24 hours. All participants were aged between 18-65 years. All individuals gave informed written consent prior to the study and assessments were conducted in accordance with the relevant ethics committees' approvals (Appendices D-J). Clinical, cognitive, and demographic characteristics of the total sample are presented in table 4.1.

4.2.2. Measures

4.2.2.1. Cognitive Measures

Cognitive functioning was assessed across three domains including full-scale IQ, logical memory and social cognitive functioning which were available at the time of the study. Full-scale IQ was measured using the abbreviated Wechsler Adult Intelligence Scale- 3rd Edition (Wechsler, 1997a) (WAIS-III) and consisted of Vocabulary, Block Design and Digit Symbol subscales. Several two-

subtest and four-subtest short forms for FSIQ have been validated (Grégoire & Wierzbicki, 2009; Ringe et al., 2002). One of the mostly widely used includes a two-subtest abbreviated form comprising of Vocabulary and Block Design subtests, which correlates strongly (0.92) with the full version (Grégoire & Wierzbicki, 2009). Our study included an additional subtest- digit symbol subtest- as a measure of FSIQ to capture attentional processes which have previously been shown to be impaired in patients with schizophrenia (Dichter et al., 2010). As a complementary analysis, we examined the association between the previously validated two-subtest FSIQ measure to the current three-subtest measure and found a strong positive correlation between both measures (see Supplementary Figure 4.1). Logical memory was examined using the logical memory subtest from the Wechsler Memory Scale, third edition (WMS-III). The Logical memory WMS-III subtest is a reliable measure of verbal episodic memory (Sullivan, 2005). Social cognitive functioning was measured using the Emotion Recognition Task (ERT) - short version from the Cambridge Automated Neuropsychological Test Battery (CANTAB) (Robbins et al., 1994). The total number of correct responses was used as the outcome variable for this test.

4.2.2.2. Childhood Trauma Experiences

The Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003), which is a 28 item self-report measure, was used to examine childhood physical neglect (Appendix K). The CTQ measures five different types of trauma; emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect, and individuals are asked to respond whether they had experienced the event on a Likert scale ranging from '1′ ('never true') to '5′ ('very often true'). The scores of each of the five subscales range from 5-25, and total CTQ scores range from 25-125. Higher scores indicate more traumatic experiences. Across these subtypes, only physical neglect and sexual abuse scores differed significantly across patients with SZ and healthy controls. Based on this, as well as having previously been associated with cognition (Rokita et al., 2020) and having relevance to altered inflammatory cytokine levels (i.e., IL-6; King et al., 2021) we considered the impact of physical neglect separately. Log transformations were applied to reduce skewness of the childhood trauma scores that were not normally distributed.

4.2.3. Inflammatory Marker Measurement

Participant blood samples were collected at approximately the same time of the day (9:30am) and stored in a 6ml EDTA tube (BD367873). Blood was centrifuged at 1,200g for 10 minutes at ambient temperature to generate plasma levels of three inflammatory markers; CRP, IL-6, TNF-α, which were then kept at −80 °C until further analysis. Basal plasma levels of IL-6 (Bio-Techne Catalog Number HS600C), CRP (Bio-Techne Catalog Number DCRP00) and TNF-α (Bio-Techne Catalog Number HSTA00E) were measured using a quantikine high sensitivity enzyme-linked immunosorbent assay (ELISA). CRP was measured using a standard C-reactive protein test. The sensitivity limits of detection for the various inflammatory markers were as follows: IL-6 (0.09 pg/mL), CRP (0.022 ng/mL) and TNF-α (0.049 pg/mL). The assay was conducted based on the protocol given by the manufacturer (Biotechne, R&D). Further details of the performance metrics are detailed in Supplementary Tables 4.1 and 4.2.

4.2.4. Genetic Data

Genetic data were obtained from DNA extracted from whole blood samples and was genotyped using the Axiom Precision Medicine Research Array PMRA r3 (Berlin, Germany). Individual genotype data was phased using Eagle v2.4 and imputed through Minimac4 v1.6.8 using the 1000 Genomes Phase 3 v5 reference panel (http://csg.sph.umich.edu/abecasis/mach/download/1000G.Phase3.v5.html) to yield approximately 8 million single nucleotide polymorphisms (SNPs). Only SNPs that passed quality control (QC) filtering were imputed. Plink 1.9 software was used to perform QC on the data whereby SNPs were excluded if minor allele frequency (MAF) < 0.1%, SNP missingness <5% and Hardy–Weinberg equilibrium $p \leqslant 1\text{x}10^{-6}$ and imputation score < 0.9. Population structure of the sample was examined using multi-dimensional scaling analysis to provide an estimate of ancestry of each participant (see Supplementary Figure 4.2).

4.2.4.1. Polygenic Score (PGS) Calculation

SZ polygenic scores (SZ-PGS) were calculated based on the results from the SZ GWAS meta-analysis (Trubetskoy et al., 2022) using PRSice2 (Choi & O'Reilly, 2019). This consisted of 162,830 nonoverlapping samples from the Psychiatric GWAS Consortium (68,037 cases and 94,793 controls). Variants within the MHC (chr6:25–35 Mb) were excluded from the genotype data due to high linkage disequilibrium (LD) in this region. GWAS results for SNPs in high LD were clumped according to PRSice guidelines (https://choishingwan.github.io/PRSice/command_detail/). Age, gender and genotyping array were controlled for in the PGS analysis.

We examined three arbitrary threshold values based on previously used PGC threshold values (p <10−5, p <0.05, and p <0.5). Using these thresholds, 5,469, 35,539 and 116,034 SNPs in the analysis were included and the percentage of variance explained for each of these PGS was 3.14%, 5.72% and 6.7%, respectively. While it is still unclear what the best approach to selecting a threshold is, for SEM mediation and moderation analysis, we chose to use an effect-size weighted SZ-PGS at a threshold of $p < 0.05$ to reduce multiple testing burden. Further, a p-value of 0.05 has been shown to maximally capture polygenic risk across a large number of independent samples (Pantelis & Bartholomeusz, 2014). For subsequent analysis, a dummy variable coding procedure was applied to stratify the sample based on the median value of the computed PGS (low and high SZ-PGS carrier status) to test for the moderating effect of this variable to the relationship between childhood trauma, inflammation, and cognition. Further details of the subdivision of this variable are detailed in Supplementary Figure 4.3.

4.2.5. Statistical Analysis

A series of t-tests (or Chi-square ($\chi2$) tests, where appropriate) were performed to examine group differences (healthy controls vs patients) on cognitive measures, CTQ scores (total and physical neglect scores), SZ-PGS, and inflammatory response (IL-6, TNF-α and CRP) (see Table 4.1), using the Statistical Package for Social Sciences Version 27 (IBM SPSS Inc., Chicago, IL). Prior to conducting the mediation analysis, a confirmatory factor analysis (CFA) was performed to test

the factor structure of the observed set of inflammatory markers and test whether this latent variable of inflammation mediated the association between physical neglect and cognition. We next examined whether the mediating role of inflammatory response on this association was better captured by a combined latent variable consisting of IL-6, CRP and TNF-α or by any of these inflammatory markers individually. Analyses were first carried out in the total sample and subsequently carried out in healthy controls and patients separately.

4.2.5.1. SEM Mediation and Moderation Analysis

All SEM mediation and moderation analysis were performed in R (version 4.1.2) using the Lavaan package (Rosseel, 2012). The following standard SEM adequacy fit indices were used to determine model fit: the comparative fit index (CFI; > 0.90), the Tucker-Lewis index (TLI; > 0.90), the root mean square error of approximation (RMSEA; < 0.08), the Standardised Root Mean Square Residual (SRMR; < 0.08) and Chi square. To improve convergence, before conducting the SEM analyses, early adversity, genetic, inflammatory, and cognitive measures were standardised. In addition, log transformations were carried out for these variables due to the nonnormal distribution of the inflammatory markers. Missing data were handled using the Maximum Likelihood (ML) method. In our sample, less than 8% of the data were missing. The patterns of missing were consistent with the assumption that the data were missing at random, as determined by Little's (Little, 1988) MCAR test which was nonsignificant and thus an appropriate estimator for the sample.

The total n of the sample with cognitive, environmental, genetic, and immune data available was 279. Based on various recommendations in the SEM literature, we considered this sample sufficient for analysis, including a minimum ratio of at least 10 participants per estimated parameter in the model (Jackson, 2003) or a minimum sample of 200 participants (Martynova et al., 2018). In addition, we conducted an *a posteriori* power analysis using the pwrSEM program (Wang & Rhemtulla, 2021) to estimate the statistical power we had to detect mediation and moderation effects. Analyses were conducted with α = 0.05 and the number of simulations set at 1,000. For the model estimated on the total sample, results revealed an estimated power of > 0.90

for direct and indirect effects. For the model tested in the sample grouped according to high/low SZ-PGS status, an estimated power of > 0.90 for direct associations and 0.70 for interaction effects was found.

4.2.5.2. Genetic Risk for Schizophrenia

We next investigated whether any associations described above were moderated by an individual's genetic susceptibility to SZ, which was grouped according to high vs low SZ-PGS carrier status. Before doing so, we tested for measurement invariance between the SZ-PGS groups by creating a multigroup SEM for each cognitive domain. By imposing a series of increasingly restrictive constraints on factor loadings, intercepts and residual variances, the following four levels of measurement invariance were tested; configural, metric, scaler and strict invariance. If measurement invariance was held across groups, we then sought to examine whether any path coefficients differed according to high vs low SZ-PGS status. See figure 4.1 for a schematic overview of this model.
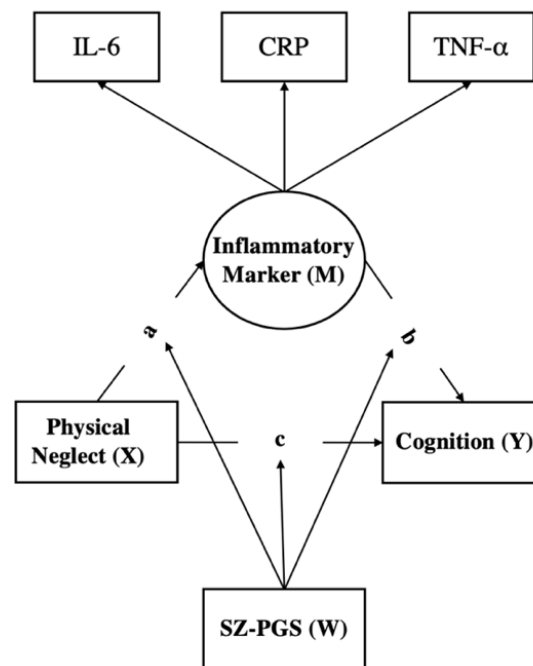
Figure 4.1. Schematic overview of the hypothesised SEM model

X= predictor variable, M= mediator, Y= outcome variable and W= moderator.

4.3.   Results

4.3.1.   Descriptive Statistics

Descriptive statistics are provided separately for patients and healthy participants in Table 4.1. Differences between the clinical and healthy participant groups were observed in age, but not gender. Across the three measures of cognition, healthy controls demonstrated better performance than patients. Total CTQ, physical neglect and sexual abuse scores were significantly higher in individuals with SZ compared to healthy controls, but not for emotional and physical abuse or emotional neglect. Significant differences in IL-6, TNF-α, and CRP were also found such that patients with SZ had significantly higher levels of these immune markers compared to controls. As expected, the SZ-PGSs were significantly higher in participants diagnosed with SZ than in healthy participants.

4.3.2.   Estimating a Latent Factor of Pro-Inflammation

A CFA was conducted on the following three inflammatory markers: IL-6, TNF-α and CRP. All indicators showed significant positive factor loadings on the latent inflammatory variable. Standardised coefficients were 0.641 for IL-6, 0.638 for CRP and 0.402 for TNF-α. Given that the model was just identified (i.e., saturated which had zero degrees of freedom because of the use of three indicator variables), measures of model fit could not be applied. As such, the data was further evaluated using Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. The KMO value was 0.6 and Bartlett's test of sphericity was significant $\chi^2(3) = 74.22$, $p < 0.001$ indicating that the data was adequately sampled, and that factor analysis of these markers was appropriate.

Table 4.1. Descriptive statistics of the total sample and across patients and healthy participants

		Group		Statistic			
	Total *n*	Patients (*M, SD)*	Healthy Participants (*M, SD)*	Test	*df*	*p*-value	Direction
Age	311	43.19 (10.95)	36.19 (12.36)	4.766	277	<0.001	SZ>HC
Sex (female: male)	310	33:69	74:102	2.562	1	0.070	M>F
BMI	298	29.48 (5.09)	24.48 (3.74)	9.058	266	<0.001	SZ>HC
Education	270	14.92 (3.28)	16.79 (3.26)	3.846	266	<0.001	SZ<HC
*Antipsychotic medication (mg)**	83	337.07 (229.31)	-				-
FSIQ	311	94.99 (16.91)	112.53 (16.36)	9.556	277	<0.001	SZ<HC
ERT (Z-Scores)	302	25.05 (6.56)	30.80 (4.27)	8.66	268	<0.001	SZ<HC
Logical Memory	301	8.05 (3.28)	11.71 (2.64)	10.130	267	<0.001	SZ<HC
CTQ Total	280	40.53 (14.11)	36.44 (12.14)	2.47	278	0.014	SZ>HC
Physical Neglect	280	7.39 (2.84)	6.48 (2.43)	2.83	278	0.005	SZ>HC
Physical Abuse	280	6.78 (3.42)	6.46 (2.74)	0.838	278	0.403	SZ>HC
Emotional Neglect	280	10.15 (4.76)	9.44 (4.37)	1.26	278	0.209	SZ>HC
Emotional Abuse	280	9.49 (4.67)	8.53 (4.31)	1.74	278	0.083	SZ>HC
Sexual Abuse	280	6.63 (3.90)	5.53 (1.93)	3.15	278	0.002	SZ>HC
IL-6 plasma (pg/L)	298	3.43 (5.28)	1.53 (1.69)	21.303	295	<0.001	SZ>HC
TNF-α plasma (pg/L)	302	1.202 (1.36)	0.930 (0.38)	6.89	299	<0.001	SZ>HC
CRP Plasma (pg/L)	290	3.616 (4.10)	1.752 (2.82)	20.233	287	<0.001	SZ>HC
SZ-PGS	282	-0.0089 (0.00008)	-0.0090 (0.00007)	55.438	255	<0.001	SZ>HC

Note: HC= healthy participants, SZ= schizophrenia, BMI= body mass index, FSIQ= full scale IQ, ERT= emotion recognition task, CTQ= childhood trauma questionnaire

*Antipsychotic medication were converted to chlorpromazine equivalents and included the following: aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and zuclopenthixol.

4.3.3. Mediating Effects of Inflammatory Response on Physical Neglect and Cognitive Performance

The mediating role of the latent variable of inflammation to the association between physical neglect and cognitive function (logical memory, FSIQ and ERT) was examined in the total sample of patients with SZ and healthy controls. Across all models, the data fit well: logical memory (CFI= 0.971, TLI= 0.928, RMSEA= 0.05, SRMR= 0.034), FSIQ ($\chi2$= 6.32, p= 0.176, CFI= 0.977, TLI= 0.942, RMSEA= 0.048, SRMR= 0.032) and ERT ($\chi2$= 4.33, p= 0.363, CFI= 0.997, TLI= 0.992, RMSEA= 0.018, SRMR= 0.028).

The percentage of variance explained for logical memory, FSIQ and ERT was 14.5%, 13.7% and 18.7% respectively. The latent variable of inflammation was directly associated with both physical neglect and all measures of cognitive functioning. Direct effects of physical neglect on cognitive functioning were observed for FSIQ (β= -0.176, p = 0.004) and logical memory (β= -0.115, p = 0.017) but not ERT (β= -0.09, p = 0.274). Significant indirect effects of the latent variable of inflammation were found across all models, such that the inflammatory marker fully mediated the association between physical neglect and ERT, and partly mediated the association between physical neglect and FSIQ and logical memory (see table 4.2). These associations remained significant after controlling for the effects of age and gender. Further, these associations remained significant for logical memory and ERT (but not FSIQ) after controlling for BMI. In subsequent analyses, which examined patients and healthy controls, the indirect effect of inflammatory response to the relationship between physical neglect and measures of cognition were no longer significant when patients and healthy controls were examined separately (Table 4.2).

Table 4.2. Mediating effects of the latent variable of inflammation on the association between physical neglect across cognitive functioning

	Total Sample (*n*= 279)			Patients (*n*= 88)			Healthy Controls (*n*= 191)			Effect Size (Patients vs Controls)
	B	SE	*p*-value	*B*	SE	p-value	*B*	SE	*p*-value	χ2 (*p*- value)
Logical Memory										
Path a	0.203	0.054	**0.014**	-0.085	0.035	0.543	0.066	0.061	0.542	0.691 (0.406)
Path b	-0.321	0.465	**0.001**	-0.404	2.270	**0.041**	0.038	0.551	0.720	**4.271 (0.04)**
Path c	-0.151	0.208	**0.017**	-0.141	0.307	0.187	-0.159	0.226	0.039	0.025 (0.874)
a*b	-0.065	0.102	**0.036**	0.034	0.541	0.611	0.003	0.024	0.756	5.377 (0.146)
FSIQ										
Path a	0.211	0.054	**0.009**	0.98	0.080	0.177	0.065	0.061	0.550	0.507 (0.476)
Path b	-0.290	2.53	**0.001**	-0.208	4.619	0.205	0.000	3.528	0.998	1.017 (0.313)
Path c	-0.176	1.188	**0.005**	-0.142	1.668	0.192	-0.158	1.431	**0.039**	0.124 (0.725)
a*b	-0.016	0.544	**0.032**	-0.041	0.649	0.331	0.000	0.128	0.998	1.628 (0.653)
ERT										
Path a	0.215	0.052	**0.010**	0.225	0.080	0.166	0.044	0.057	0.690	0.806 (0.369)
Path b	-0.403	0.158	**<0.001**	-0.063	0.344	0.647	-0.266	0.195	**0.034**	0.500 (0.496)
Path c	-0.093	0.065	0.144	-0.180	0.119	0.114	0.024	0.063	0.759	2.367 (0.124)
a*b	-0.087	0.038	**0.021**	-0.014	0.039	0.703	-0.012	0.024	0.693	3.453 (0.031)

Note: path a= direct association between physical neglect and cognition, path b= direct path between inflammatory response and cognition, path c= direct path between physical neglect and cognition, path a*b mediation/indirect effect of inflammatory response on the association between physical neglect and cognition.

4.3.4. Immune Mediated Effects: Comparison of the Latent Inflammatory Variable to Single Measures of IL-6, TNF-α and CRP

After confirming the significance of this proinflammatory mediator, we next sought to examine whether these inflammatory markers individually would show similar or weaker mediating effects to the association between physical neglect and cognitive performance. These associations were examined in the total sample of patients and healthy participants. As shown in Table 4.3, when the latent inflammatory was replaced with IL-6, the mediating effect on the association between physical neglect and measures of cognition remained significant but explained considerably less variance on these aspects of cognition compared to the latent inflammatory variable. In contrast, when examining the effects of CRP and TNF-α as individual mediators, the indirect effects between physical neglect and cognitive functioning were no longer significant.

Table 4.3. Comparison of the latent inflammatory variable (Model 1) to that of a single measure of IL-6 (Model 2), CRP (Model 3) and TNF-A (Model 4) across the different cognitive domains

	Model 1			Model 2			Model 3			Model 4		
	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value	β	SE	*p*-value
Logical												
Path a	0.20	0.079	0.014	0.144	0.061	0.019	0.090	0.063	0.149	-0.028	0.060	0.645
Path b	-0.32	0.077	<0.001	-0.225	0.059	<0.001	-0.158	0.198	0.002	-0.220	0.208	<0.001
Path c	-0.15	0.063	0.017	-0.157	0.059	0.009	-0.164	0.195	0.007	-0.194	0.202	<0.001
a*b	-0.07	0.036	0.036	-0.032	0.016	0.048	-0.017	0.042	0.192	0.006	0.047	0.648
% variance			14.5%			8.6%			6.8%			8.4%
FSIQ												
Path a	0.211	0.077	0.009	0.142	0.060	0.019	0.101	0.061	0.103	-0.010	0.063	0.872
Path b	-0.290	0.076	<0.001	-0.189	0.058	<0.001	-0.149	1.113	0.013	-0.205	1.094	<0.001
Path c	-0.176	0.061	0.005	-0.187	0.058	0.002	-0.214	1.108	<0.001	-0.214	1.134	<0.001
a*b	-0.06	0.028	0.032	-0.032	0.058	0.048	-0.015	0.204	0.172	0.002	0.243	0.872
% variance			13.7%			8.1%			7.5%			8.7%
ERT												
Path a	0.215	0.079	0.010	0.148	0.061	0.016	0.099	0.062	0.115	-0.021	0.064	0.729
Path b	-0.403	0.075	<0.001	-0.240	0.059	<0.001	-0.258	0.061	<0.001	-0.210	0.059	<0.001
Path c	-0.093	0.064	0.144	-0.135	0.059	0.025	-0.129	0.060	0.032	-0.169	0.061	0.004
a*b	-0.087	0.037	0.036	-0.036	0.017	0.039	-0.025	0.017	0.139	0.005	0.013	0.730
% variance			18.7%			8.5%			9%			7.1%

4.3.5. The Association between Inflammatory Response, Physical Neglect and Cognition in High vs Low SZ-PGS Carriers

4.3.5.1. Measurement Invariance

We next tested whether the mediating effect of the latent inflammatory variable on physical neglect and cognition was moderated by SZ-PGS, grouped according to high vs low SZ-PGS carrier status. To test these group differences, measurement invariance was first established to ensure that any differences between high vs low carriers was due to structural differences in path coefficients rather than measurement. Table 4.4 summarises the results of the invariance analyses in which a set of four *a priori* models was specified and tested. The nonsignificant difference in chi-square between the baseline model and the model testing for metric invariance (across all cognitive domains) indicated that the factor loadings were invariant. In the next set of constraints, where both factor loadings and item thresholds were constrained, scalar invariance was held for FSIQ and ERT, but not logical memory, as evidenced by a significant change in chi-square (excellent ($\Delta\chi2(4) = 9.0397$, $p = 0.0288$). Finally in the most restrictive model, strict invariance was established across the different cognitive domains for SZ-PGS groups, demonstrating that overall measurement invariance existed in our data.

Table 4.4. Multigroup analysis: Testing for measurement invariance across high and low schizophrenia polygenic score groups

Measurement Model	χ2	df	Δχ2	Δdf	*p*-value
Logical Memory					
Configural	9.949	8	-	-	-
Metric	11.145	10	1.196	2	0.5498
Scalar	20.185	13	9.04	3	0.0288
Strict	23.308	17	3.124	4	0.5374
FSIQ					
Configural	7.358	8	-	-	-
Metric	7.496	10	0.1376	2	0.9335
Scalar	12.397	13	4.9013	3	0.1792
Strict	15.329	17	2.9318	4	0.5693
ERT					
Configural	6.454	8	-	-	-
Metric	7.044	10	0.58967	2	0.7447
Scalar	7.678	13	0.63405	3	0.8886
Strict	9.2505	17	1.5723	4	0.8138

4.3.6. The Influence of SZ-PGS Status on the Relationship between Physical Neglect and Cognitive Performance

Testing our final hypothesis, we examined whether any differences in structural relationships (direct and/or indirect effects) on cognitive function were influenced by high vs low SZ-PGS carrier status. Figure 4.2 summarises the SEM results for each of the cognitive domains tested. All models fit the data well and demonstrated acceptable fit (CFI > 0.98, TLI > 0.95, RMSEA < 0.05, SRMR < 0.035). Again, the latent inflammatory variable mediated the association between

124

physical neglect and logical memory ($\beta_{indirect}$= -0.098, CI= -0.181 to -0.014, p= 0.022), between physical neglect and FSIQ ($\beta_{indirect}$= -0.092, CI= -0.173 to -0.012, p= 0.024) and between physical neglect and ERT ($\beta_{indirect}$= -0.089, CI= -0.170 to -0.009, p= 0.029). Across all cognitive domains, the SZ-PGS did not significantly moderate this mediating effect. However, the direct pathway between physical neglect and logical memory was moderated by SZ-PGS ($\beta_{indirect}$= -0.244, CI= -0.388 to -0.101, p <0.001) and between physical neglect and FSIQ ($\beta_{indirect}$= -0.154, CI= -0.298 to -0.010, p = 0.038), providing some support for our prediction that the relationship between physical neglect and cognition would vary depending on high vs low SZ-PGS group. All models remained significant after controlling for the effects of age and gender. In addition, logical memory, but not FSIQ or ERT remained significant when the effects of BMI were considered.

(a)

(b)

(c)
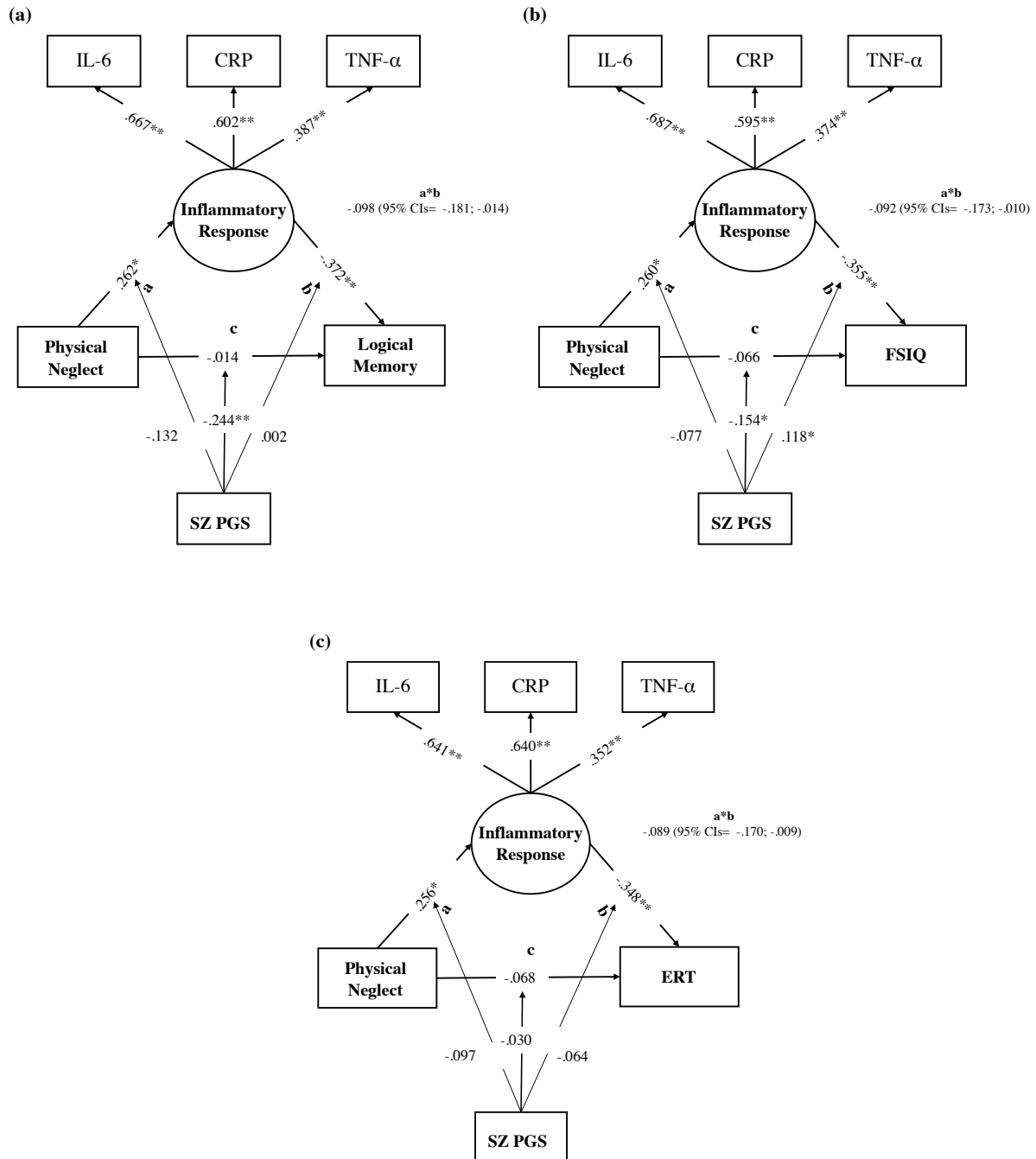
Figure 4.2. SEM moderated and mediated SEM analysis

SZ-PGS directly moderated the association between physical neglect and logical memory and FSIQ, but not ERT. Inflammatory response was a significant mediator between physical neglect and all cognitive domains.

4.3.6.1. Patient and Healthy Participant Group Differences

As an additional post hoc analysis, we conducted a series of multi-group SEM analyses on the above moderated mediated associations for each cognitive domain for both patients with SZ and healthy participants. When patients and healthy participants were considered separately, the mediating effect of the latent inflammatory variable on the associations between physical neglect and cognitive ability were no longer significant. Similarly, SZ-PGS did not moderate the mediating effect of the latent inflammatory variable on the association between physical neglect and cognition in either patient or healthy participant groups. However, for both patients ($\beta_{indirect}$= -0.335, CI= -0.589 to -0.080, $p = 0.010$) and healthy participants ($\beta_{indirect}$= -0.246, CI= -0.430 to -0.062, $p = 0.009$) the moderating effect of the SZ PGS on the direct pathway between physical neglect and logical memory remained significant.

4.4. Discussion

4.4.1. Summary of Main Findings

In this cross-sectional study we tested the hypotheses that the association between exposure to physical neglect and lower cognitive ability would be mediated via an increased inflammatory response and moderated by a higher polygenic risk for SZ. We found that inflammatory response - as measured by a latent variable indexing IL-6, CRP, and TNF-α- mediated the relationship between physical neglect and cognitive ability. Compared to any of these inflammatory markers alone, the latent inflammatory variable explained greater percentage of variance on all aspects of cognition. While SZ-PGS did not moderate the mediating effect of this inflammatory response, we did find evidence that SZ-PGS moderated the direct pathway between physical neglect and measures of cognitive (but not social cognitive) functioning in both patient and healthy participants. In other words, the strength of the association between exposure to physical neglect and lower cognitive ability was greater in those carrying a higher SZ polygenic burden.

4.4.2. The Mediating Role of Immune Response on the Relationship between Physical Neglect and Cognitive Functioning

To our knowledge, this is the first study to examine the mediating effects of inflammatory response (based on multiple inflammatory markers) on the association between physical neglect and cognition in both patients with SZ and healthy participants using SEM. SEM is a powerful statistical tool encompassing general linear modelling, path analysis and regression (Ballen & Salehi, 2021). In the present study we identified a proinflammatory response consisting of three key cytokines - IL-6, CRP and TNF-α- which significantly mediated the already established association between physical neglect and cognition (Davis et al., 2019; King et al., 2021). Among the three cytokines contributing to the latent inflammatory variable, IL-6 had the highest factor loading followed by CRP.

IL-6 has been consistently associated with both ELA and changes in cognitive ability (Davis et al., 2019; Dennison et al., 2013; King et al., 2021), and plays an important role in CRP synthesis

128

(Giovannini et al., 2011). Moreover, IL-6 is postulated to be involved in disrupting integrity of the blood-brain barrier (BBB) resulting in an influx of peripheral cytokines (i.e., CRP and TNF-α) to exacerbate microglial-mediated processes as well as stimulate neuroendocrine release (Dawidowski et al., 2021; Halstead et al., 2023; Momtazmanesh et al., 2019). The current study extends beyond previous work in this area by providing evidence that a combined latent measure of inflammatory better predicts risk associated with exposure to physical neglect and impairments in cognition than the use of IL-6 alone. This aligns with previous work demonstrating interconnectedness between these inflammatory markers (see Cui et al., (2019) for a more detailed review). Although difficult to infer the direction of these results owing to the cross-sectional nature of the data, these results support the hypothesis that ELA alters immune response, contributing to poorer cognitive functioning in adulthood.

4.4.3. Polygenic Risk for Schizophrenia as a Moderator of the Association between Physical Neglect, Inflammation and Cognitive Functioning

As noted earlier, several studies have reported an association between higher SZ-PGS and lower cognitive ability. Variation in cognitive performance has also been associated with SZ-risk variants in gene networks related to immune function (Corley et al., 2021; Donohoe et al., 2018; Fillman et al., 2016; Holland et al., 2019). Based on these findings, we hypothesised that the mediating effect of inflammatory response to the association between physical neglect and cognitive ability would be moderated by increased genetic risk for SZ. However, SZ-PGS was not a significant moderator of this mediating effect, but instead was observed to moderate the direct pathway between physical neglect and cognition. One interpretation of this result is that the contribution of genetic effects to the association between inflammation, physical neglect and cognitive ability was not sensitively indexed by common SZ genetic variation. Immune relevant pathway scores involved in SZ rather than an aggregate genetic risk score for SZ may have been more biologically informative here. Alternatively, genetic variation associated with brain structure or indeed genetic variation associated with childhood trauma may have differentially impacted the inflammatory mediating effects reported in this study.

Importantly, we found a significant interaction of SZ-PGS on the direct path between physical neglect and measures of cognitive functioning, with the strongest association being observed for logical memory performance. These results remained significant after controlling for the effects of age, gender, and BMI. This is notable especially in light of the fact that episodic memory has long been considered an important phenotype for psychosis (Aas et al., 2012). In support of this, a recent meta-analysis found that the association between childhood trauma and memory was stronger than that of overall cognition (Vargas et al., 2019). It is also consistent with previous work carried out in our group (Corley et al., 2021; Donohoe et al., 2018) and others (Sekar et al., 2016) documenting an association between genetic risk variants for SZ and decreased memory performance. Of note, the association between exposure to physical neglect, higher SZ-PGS and non-social cognitive ability did not appear to differ between groups, suggesting that these phenotypic effects were comparable in healthy participants carrying a higher SZ genetic risk burden.

4.4.4. Limitations and Future Directions

The results of the study must be considered in relation to the following limitations. First, physical neglect was measured retrospectively in adulthood, and does not take into account the age of onset or duration of trauma. While the CTQ has shown good reliability and validity in adult patients with SZ (Fisher et al., 2011), further prospective studies and objective measurements of adversity are needed to confirm these findings. A second limitation was the number of confounding variables that we could not accommodate in the analyses due to power issues and multiple testing burden, including alcohol and nicotine consumption and mediation dosage. However, it is noteworthy that the results reported here were comparable in patients and healthy controls, making it unlikely that mediation alone affected our results. Nevertheless, future studies will benefit from the inclusion of drug naïve patients and consider the effects of alcohol and nicotine as these may alter immune cytokine levels (Ribeiro-Santos et al., 2020).

Another limitation concerns the cross-sectional design of the study which informs only the temporal association and not causality. Indeed, it is possible that individuals with cognitive

impairments may be at a greater risk for exposure to childhood trauma. As such we cannot determine whether impairments in cognitive ability might have preceded early life adversity due to the cross-sectional nature of the data and it will be important for future research to examine these associations longitudinally. Fourthly, due to issues of sensitivity as well as availability of cytokines assayed at the time of the study, we were unable to examine the effects of other inflammatory markers (i.e., IL-1β, IL-8, IL-12 and anti-inflammatory cytokines; Il-4, IL-10) which may have relevance here.

Fifthly, while our study used a common approach to characterise genetic risk for SZ involving thresholding and clumping to remove redundant correlated effect caused by LD between variants, a limitation of this method is that it may also remove independently predictive variants that are in high LD. Future work should therefore consider alternative methods such as PRS-CS and LDPred, which implements a Bayesian framework and employs a prior shrinkage approach on SNP effect sizes ((Ge et al., 2019); Rodrigue et al., (2022). Further, newer PGS methods have been developed (LDPred-funct, MegaPRS) that include functional annotation to SNPs to up- or down weight their contributions to the PGS which may improve prediction accuracy and minimise false-positive associations (Ni et al., 2021). Another potential limitation here was that the SZ PGS was performed using a single threshold of $p= 0.05$. Notwithstanding, this threshold was selected to reduce multiple testing burden and minimise type one error. Furthermore, previous work in our group has shown that selecting SNPs based on this threshold had broadly similar cognitive associations to other p-value thresholds (Cosgrove et al., 2017). Future work should therefore consider alternative methods such as PRS-Continuous Shrinkage, which implements a Bayesian framework and employs a prior shrinkage approach on SNP effect sizes. Finally, it was not within the scope of this study to examine brain structural associations. As such, future research should consider the role of brain morphological differences which have been shown to mediate the association between adversity, inflammation and cognitive ability by us and others.

4.5. Conclusions

Increased inflammation and higher genetic risk for SZ represent important factors linking adverse early life experiences to later impairments in cognitive ability in both patients with SZ and healthy controls. These results build on previous work demonstrating that inflammatory response mediates the association between physical neglect and cognitive ability, in a manner that may be independent of genetic risk for schizophrenia.

Acknowledgements

Author Contributions

Conceptualisation: EC, DWM and GD; Methodology: EC, SRP, AL, DWM and GD; Formal analysis: EC and GD; Investigation: EC, SRP, AL, DM, DWM and GD; Writing—original draft preparation: EC and GD; Writing—review and editing: EC, SRP, AL, SK, AC, JK, DM, BH, CM, DWM and GD; Funding acquisition: EC and GD; Resources: GD and AC; Project administration: DWM and GD. All authors contributed to and approved the final version of the paper.

Conflict of Interest

The authors declare that they have no conflict of interest.

4.6.   Supplementary Information

Supplementary Figure 4.1 | Correlations among the 2 and 3 subtest WAIS-III FSIQ measures
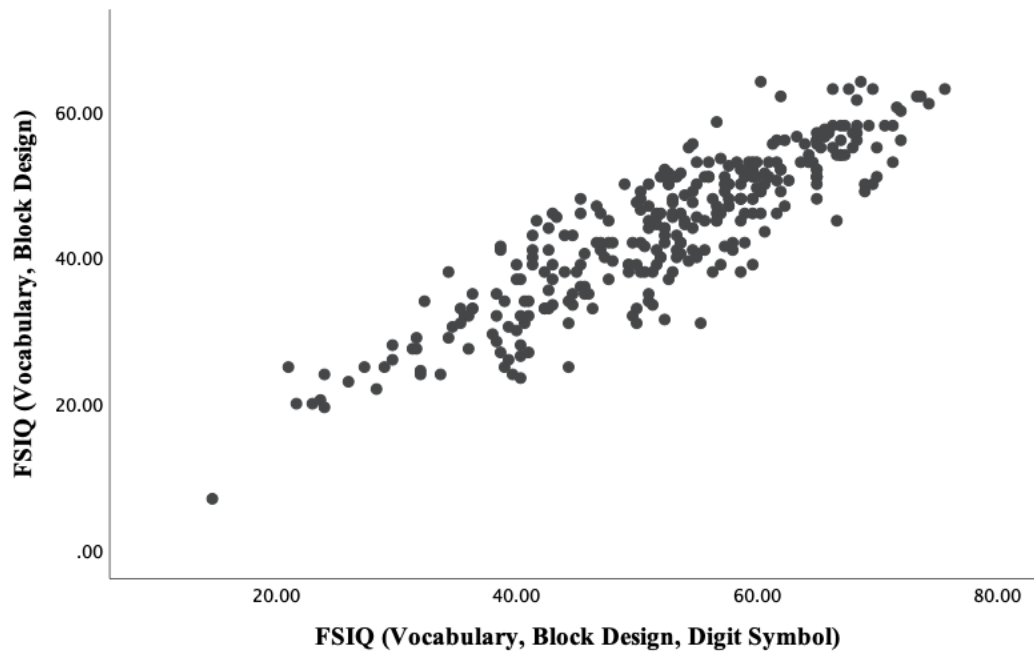
Correlations among the 2-subtest (Vocabulary and Block Design) and 3-subtest (Vocabulary, Block Design and Symbol Digit) FSIQ measures ($r = 0.885$, $p < 0.001$).

Supplementary Figure 4.2 | Multidimensional-Scaling Analysis for Population structure in the iRelate Sample
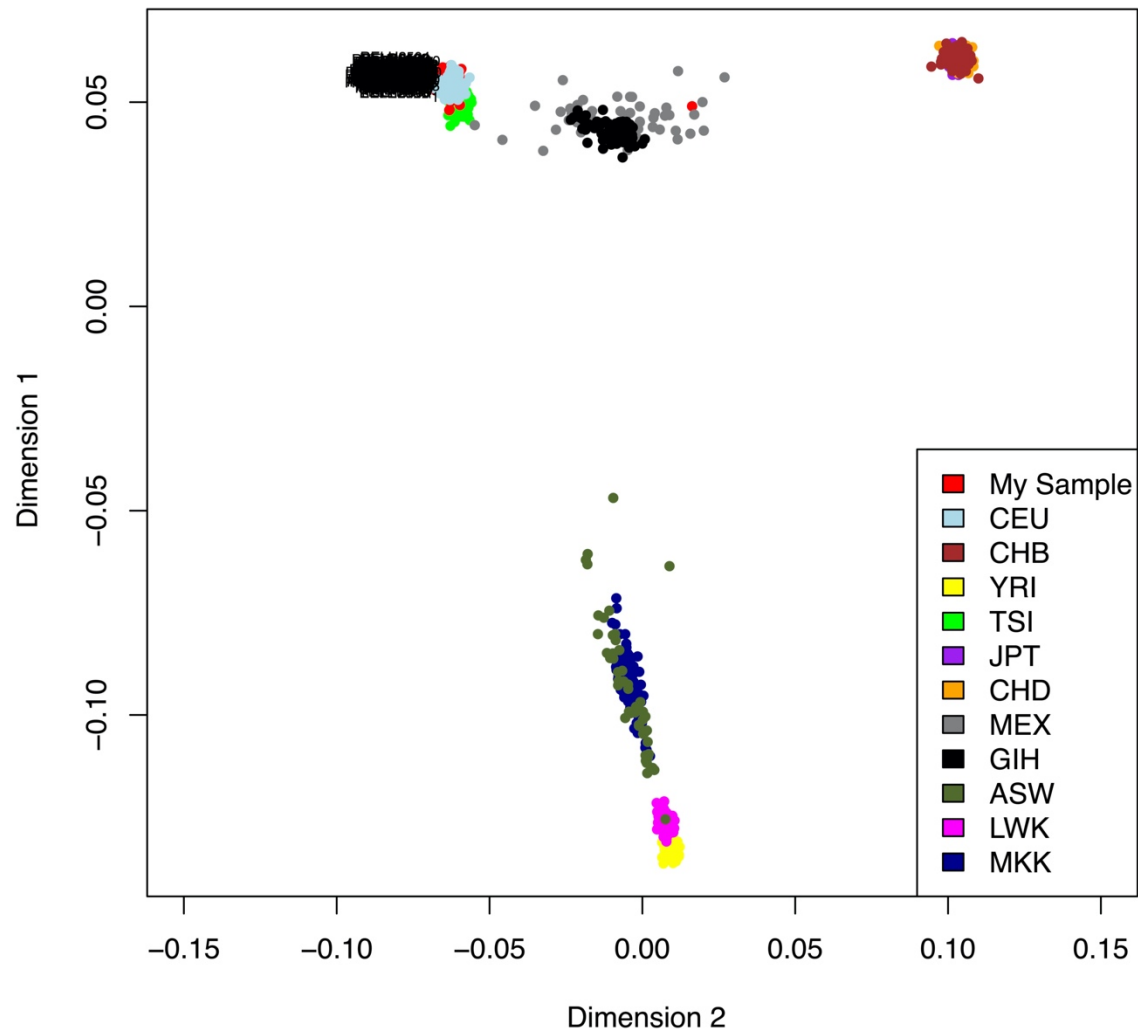
Multidimensional-scaling analysis was used to estimate the ancestry of each individual in our sample (and to remove subjects with non-homogenous ancestry) using the ENIGMA protocol (http://enigma.ini.usc.edu/genetics-protocols/). Within the sample all participants clustered within the European decent except for one participants, was removed due to heterogenous ancestry. The first and second principal components of the multidimensional scaling are plotted against each other for each cohort in the graph. The population codes where assigned to samples collected for the 1000 Genomes project .

Supplementary Figure 4.3. | Schizophrenia polygenic risk score calculation and generation of the schizophrenia-PGS grouping variable
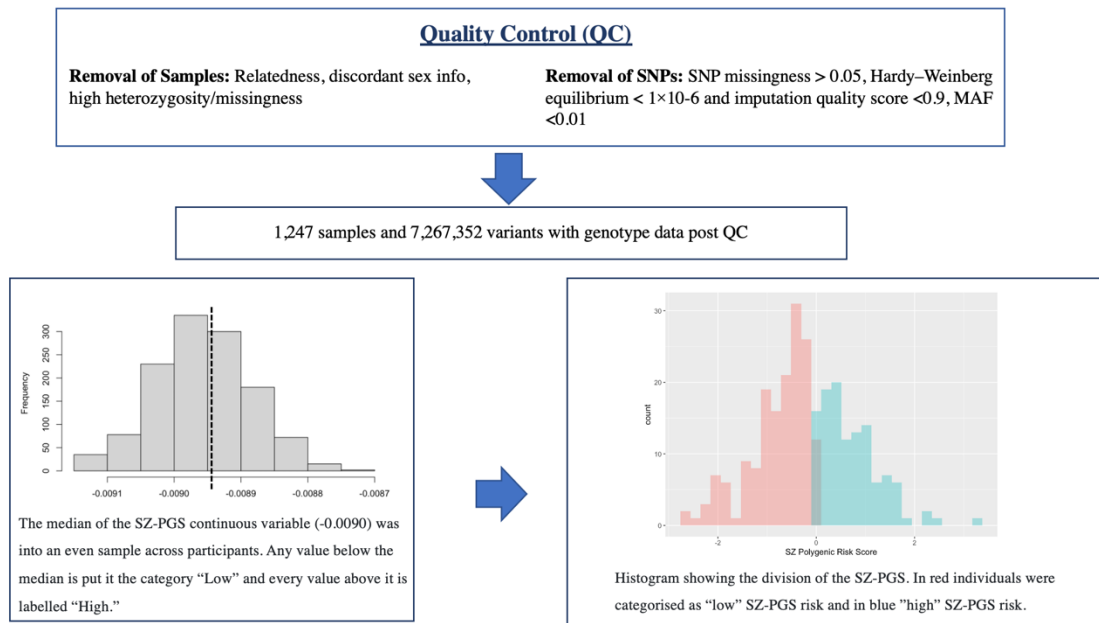
Genotype data was quality controlled to remove samples based on relatedness, discordant sex information, high heterozygosity and missingness. Genetic variants were also removed based on: minor allele frequency (MAF) <0.01, SNP missingness > 0.05, Hardy-Weinberg equilibrium (HWE) $\leqslant$ 1 x 10-6 and imputation score <.0.9. Following this, 1,247 samples and 7,267,352 variants remained. An effect-size weighted SZ-PGS was computed for each individual based on a threshold of $p < 0.05$ for SNPs with the total number of variants used to inform the PGS being 35,539. Of those, 279 participants were recruited as part of the iRelate data and had available cognitive, immune, environment data available. These samples were used to inform the analysis. This continuous measure of SZ polygenic risk was converted into a categorical variable whereby any value that was below the median (-0.0090) was categorised as low SZ-PGS risk and every value above it was labelled as high SZ-PGS risk.

Supplementary Table 4.1. | Performance metrics of the inflammatory markers assayed

		N	Range	Min	Max	Mean	SE	SD	Variance
TNF-α (pg/ml)	HC	201	2.16	0.07	2.23	0.9304	0.02706	0.38371	0.147
TNF-α (pg/ml)	Patients	101	13.67	0.26	13.94	1.2057	0.13518	1.35857	1.846
CRP (pg/ml)	HC	196	24.42	0.04	24.46	1.7524	0.2013	2.81819	7.942
CRP (pg/ml)	Patients	94	23.26	0.11	23.37	3.6183	0.42247	4.09603	16.777
IL-6 (pg/ml)	HC	202	13.99	0.09	14.08	1.5313	0.11918	1.69384	2.869
IL-6 (pg/ml)	Patients	96	45.03	0.19	45.23	3.4426	0.53903	5.28143	27.893

Note. HC= Healthy control

Supplementary Table 4.2. | Average percentage coefficient of variability of the immune markers

	Average % CV of Absorbances
TNF-α (pg/ml)	7.4
CRP (pg/ml)	3.3
IL-6 (pg/ml)	8.3

Chapter 5: Corpus Callosum Microstructural Organisation Mediates the Effects of Physical Neglect on Social Cognition in Schizophrenia

Corpus Callosum Microstructural Organisation Mediates the Effects of Physical Neglect on Social Cognition in Schizophrenia

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Abstract

Exposure to childhood trauma is associated with both increased risk of developing schizophrenia and poorer performance on measures of social cognitive functioning. This study examined whether interleukin 6 (IL-6) and corpus callosum (CC) microstructure mediated the association between childhood physical neglect and social cognition. Fifty-eight patients with a diagnosis of schizophrenia were included. The CANTAB emotion recognition task (unbiased hit rate) was used to assess social cognition. We found that the microstructural organization of the CC significantly mediated the association between physical neglect and emotion recognition. Furthermore, in a sequential mediation analysis that also considered the role of inflammatory response, the association between physical neglect, and lower emotion recognition performance was sequentially mediated by higher IL-6 and lower fractional anisotropy of the CC. This mediating effect of IL-6 was only present when simultaneously considering the effects of CC microstructural organization and remained significant while controlling for the effects of sex, BMI and medication dosage (but not age). Overall, the findings suggest that the association between physical neglect and poorer emotion recognition in schizophrenia occurs, at least in part, via its association with white matter microstructure.

5.1.   Introduction

5.1.1.   Early Life Adversity and Schizophrenia

Exposure to early life adversity (ELA) has been associated with increased risk of developing schizophrenia (SZ) as well as impairments in cognitive functioning. In a metanalysis of 18 case-control studies, Varese et al., (2012) reported that individuals diagnosed with SZ were almost three times more likely to have been exposed to instances of ELA compared to the general population. Associations between ELA and impairments in social cognitive functioning, a key predictor of level of social and occupational function in SZ, have been well documented (Aas et al., 2012; Dauvermann & Donohoe, 2019; Rokita et al., 2020).

Experiencing adversity early in life can have significant and long-lasting effects on the brain by impacting neural development during sensitive periods when neural connections are being established (Peverill et al., 2023). While the association between trauma-exposure and grey matter abnormalities (Begemann et al., 2023; Quide et al., 2021) as well as functional alterations in SZ (Dauvermann et al., 2021; Rokita et al., 2018) has received considerable attention; the study of white matter connections, is largely overlooked in patients with SZ. Investigating changes in white matter in SZ in those exposed to ELA is needed to better understand the nature of biological changes on social cognitive impairments which contribute significantly to the disability of the disorder.

5.1.2.   White Matter Alterations in Schizophrenia

Consistent with the widely held hypothesis that SZ in part reflects disordered brain connectivity, several systematic reviews have reported widespread structural dysconnectivity in SZ, including white matter pathology affecting fronto-temporal and fronto-limbic connections (Samartzis et al., 2014; Najjar & Pearlam, 2015; Kelly et al., 2018). Diffusion tensor imaging (DTI) is a noninvasive MRI technique used to measure *in vivo* water molecule diffusion. While several tensor metrics exist, fractional anisotropy (FA) is a popular scalar metric derived from DTI which uses the three-dimensional motion of water to estimate the homogeneity of diffusion in white matter tissue.

Decreases in FA in patients can occur due to processes such as atrophy, changes in the extracellular matrix, and also due to inflammation (Figueiredo et al., 2022). In the largest DTI study of white matter tracts in SZ, widespread reductions in FA were found across the majority of commissural, projection and association white matter tracts in patients (Kelly et al., 2018). In a follow up study of white matter and cognitive performance led by our group, the functional relevance of these changes was also confirmed (Holleran et al, 2020). The largest differences observed between patients and controls were reported in the corona radiata and the corpus callosum (CC) (Karlsgodt, 2020; Kelly et al., 2018) and similar findings have also been observed in individuals with first episode psychosis (Su et al., 2020; Tao et al., 2023). Furthermore, work to date suggests that in patients with SZ, exposure to ELA is correlated with widespread reductions in FA, with a predilection for cortico-limbic tracts and the corpus callosum (Asmal et al., 2019; Poletti et al., 2015).

The CC is the primary commissural region of the brain, connecting the left and right cerebral hemispheres and has been shown to be relevant to social information processing (McDonald et al., 2018). The CC can be segmented into distinct, but highly functionally correlated neuroanatomical regions known as the genu, body, and splenium. Anteriorly, the genu contributes to the forceps minor and carries fibre tracts connecting the orbital and ventral prefrontal cortex; regions which are implicated in social cognitive processes such as emotion perception (Park et al., 2008). Superiorly, the body fibres form the corona radiata, as well as other large white matter pathways which travel transversely through the cerebral cortex. Posteriorly, the splenium contributes to the forceps major, which connects the occipital lobes, and is relevant for communicating higher order perceptual and semantic processes (Musiek, 1986; Sakai et al., 2017). The splenium is also connected to the posterior insula (Lacuey et al., 2016), a region of the brain implicated in introspection (McDonald et al., 2018). Despite the relevance of this interhemispheric tract to social cognition, the extent to which reductions in FA in the CC contribute to impairments in social cognitive processes in patients with SZ is limited.

Development of the CC is complete by age four with growth continuing until the third decade of life, and albeit at a much slower rate, alterations in its development may be influenced by environmental and early life factors during this developmental period (Tanaka-Arakawa et al., 2015). This extended phase of neurodevelopment makes the CC a region of interest for understanding the effects of early social environment and childhood adversity (Lebel & Deoni, 2018). Recent evidence has found that altered CC microstructure in patients is associated with reduced social cognitive performance (Burke et al., 2022), which suggests that understanding factors contributing to such CC alterations in schizophrenia is essential to understanding functional changes in terms of cognition.

5.1.3. Immune Function and White Matter Alterations

As demonstrated by animal studies, long term stress, including childhood trauma, impacts the typical development of white matter through neuroinflammation and dysregulation of glial cells necessary for myelination (Jauregui-Huerta et al., 2010). CNS-resident astrocytes and microglia, along with circulating immune cells, are typically regarded as the key players coordinating the inflammatory response and emit cytokines that lead to a cascade of events that modulate the neuroinflammatory response. Glial cells also release oxidative and nitrosative products, as well as excitotoxic metabolites that can damage nearby tissue. Prolonged neuroinflammation can lead to brain atrophy by causing the loss of neuronal cell bodies and reducing the extracellular matrix (Frodl & Amico, 2014). In white matter, this response can damage oligodendrocytes and the myelin sheath that surrounds axons, thereby impacting brain network connectivity (Madeira, Hage, Tsirka, 2022; Chew et al., 2013).

White matter structures such as the CC may be particularly vulnerable to the neurotoxic impact of childhood trauma especially during its neurodevelopmental period as above (McLaughlin et al., 2019). Consistent with this hypothesis, elevated interleukin-6 (IL-6), a proinflammatory cytokine, has been reported to be associated with reduced FA of the CC in healthy controls (Michalczyk et al., 2022) and individuals with SZ (Prasad et al., 2015; Wang et al., 2020). It has further been shown to be related specifically to the anterior regions of the CC (Di Biase et al., 2021), and not a

generalised effect associated with all white matter tracts in SZ (Gangadin et al., 2022). Identifying the impact of ELA on immune system regulation and white matter alterations may help elucidate the underlying mechanisms involved in social cognitive processes. To our knowledge, no study has yet investigated whether and how the association between ELA, white matter microstructural organization and cognition is influenced by immune response.

5.1.4. The Current Study

The purpose of the present study was to examine the contribution of CC microstructure and immune response to the association between childhood trauma and social cognition in patients with schizophrenia. ELA was measured in terms of physical neglect based on numerous studies supporting a link between this subtype of trauma and reduced cognitive functioning (De-Nardin et al., 2022; Lakkireddy et al., 2022; Li et al., 2017; Morkved et al., 2020; Ucok et al., 2015; Vaskinn, Engelstad, et al., 2021). IL-6 was selected as the inflammatory cytokine given that it has been shown to be consistently altered in both acute and chronic stages of the disorder (Halstead et al., 2023) and linked to impairments in cognitive ability (Miller et al., 2011; Patlola et al., 2023). DTI was used to quantify water diffusion of the CC tract as a region of interest. Specifically, FA was used to index white matter microstructural organisation of the CC. We hypothesised that reduced FA in the CC and increased inflammatory response would mediate the relationship between childhood physical neglect and emotion recognition outcomes.

5.2. Methods

5.2.1. Ethical Approval

Ethical approval was granted as part of the 'Immune Response and Social Cognition in Schizophrenia' (iRelate) project by the Research Ethics Committee at the University of Galway, Ireland, the University Hospital Galway (Appendix D), and at Tallaght Hospital Dublin (Appendix E).

5.2.2. Participants

Of the total sample recruited to iRelate, n=58 patients with SZ, aged between 18-63 years, completed neuroimaging. Of these, 54 participants had cognitive data. Basal plasma levels of IL-6 were available for 53 participants, and 56 completed the positive and negative symptom scale (PANSS). All participants had a previously established clinical diagnosis of SZ or schizoaffective disorder as outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychological Association, 2010) and confirmed by the Structured Clinical Interview for DSM-IV (SCID; First & Gibbon, 2004). Patients were recruited from outpatient hospital departments and mental health services such as day centres and day hospitals based in Ireland and were determined to be clinically stable by their treating clinical team. Prior to the commencement of the study, participants were required to provide written informed consent (Appendices F-J). Participants undergoing structural MRI were also screened for MRI safety criteria (Appendix L). Patients were omitted if they had a comorbid DSM-IV Axis I psychiatric disorder. Exclusion criteria included: a history of an acquired brain injury; historical or comorbid neurological condition, for example, epilepsy; previous significant loss of consciousness requiring medical attention; intellectual disability (IQ < 70); or a history of substance misuse disorder six months prior to study commencement. Contraindications for undergoing MRI scanning, such as, the presence of a metal implant or device, were also exclusion criteria for both cohorts.

5.2.3. MRI Procedure

Diffusion magnetic resonance imaging (dMRI) was gathered for this project. An initial MRI scan was completed on all participants before disseminating diffusion data. The standard structural MRI scan was conducted using a 3T Philips Achieva MR scanner. The scanner is located in the Centre for Advanced Medical Imaging at St. James' Hospital in Dublin 8, Ireland. Each participant underwent a structural whole-brain MRI scan following a pre-determined acquisition sequence including three-dimensional T1-weighted images using a 'Fast Field Echo' pulse sequence with a spatial resolution of $1mm^3$. The scan 'Repetition Time' (TR) was 8.5 milliseconds (ms), and 'Echo Time' (TE) was 3.9 ms. The 'Inversion Time' from the time elapsed between pulses was 1060 ms with a 'Flip Angle' of 8^0. The acquisition sequence was obtained in millimetres over a distance (field of view) of 256 x 256 x 160 mm^3, and the acquisition time was 7 minutes and 30 seconds in total. Foam padding was used to preserve a secured head position for the MRI scan, and participants were supplied with headphones to dampen noise interference.

Additional information on image acquisition parameters and DTI processing details have been detailed elsewhere (Costello et al., 2023). Briefly, tract-based spatial statistics (TBSS) was used to obtain FA values for white matter tracts using the MNI152 template, resulting in a standard space version of each FA image. Tracts of interest were then registered to a subject-specific target to create a 'mean FA' map which was then 'thinned' to create a WM' skeleton' image which represented the centre of all deep WM voxels common to all subjects. To extract all the variables using diffusion techniques, this study employed the ENIGMA-DTI protocol (https://enigma.ini.usc.edu/protocols/dti-protocols/). The ENIGMA protocol was generated through an international consortium including 29 groups/sites from 14 countries and 4,322 participants in total. The ENIGMA DTI pre-processing steps involve corrections and quality control (QC) steps, including eddy current echo-planar imaging corrections, which can result in image distortion during diffusion imaging (Bodammer et al., 2004). Tensor fitting was also included as a QC step. All DTI pre-processing and QC recommendations can be found at https://enigma.ini.usc.edu/protocols/dti-protocols/.

Using the DTI protocol outlined, the primary analysis of fractional anisotropy (FA) was established, and the CC and cortico-spinal tract (CST) were extracted as the specific regions of interest (ROI). The CST was considered in this protocol to act as a divergent validity marker. The CC can be further segmented into the genu, body, and splenium regions in line with the ENIGMA-DTI protocol, with an 'Average FA across all tracts' also extracted (Holleran et al., 2020). FA values were used to measure white matter microstructural organisation and index the variability of diffusion vectors in different directions at specified voxels. FA is sensitive to changes in biophysical tissue properties, such as alterations in axonal diameter, fibre density and myelin structure (Basser & Pierpaoli, 2011). FA values of zero usually reflect cortico-spinal fluid or free-flowing unrestricted liquid. Values greater than 0.2 signify other tissue types, such as white matter, and values close to 1 are associated with major white matter tracts.

5.2.4. Emotion Recognition Task, Cambridge Neuropsychological Test Automated Battery

The Emotion Recognition Task (ERT) is a computerised task used to measure the ability to identify six basic emotions, including sadness, happiness, anger, disgust, surprise, and fear (Robbins et al., 1994). Participants are asked to choose one out of six emotions describing the emotional expression presented on the screen. In many studies of emotion recognition, accuracy and/or the primary outcome is calculated as the percentage of correctly identified stimuli, or 'Hits', for example, 'Emotion Recognition Task Total Hits' on the CANTAB. However, the percentage-correct score, or total Hit score, does not consider potential response biases towards certain emotions, regardless of whether performance is strategically driven or resulting from a deficit. To overcome this, the *Unbiased Hit Rate* is designed to account for such response bias (Wagner, 1993). The Unbiased Hit Rate is calculated for each participant per emotional subtype, for example, Happy, Sad, Anger etc., and relates to the correct responses for a target emotion, the number of stimuli representing this emotion, and the overall frequency of this emotion category being chosen. The Unbiased Hit Rate ranges from zero to one, which indexes whether all stimuli for a target emotion have been correctly identified and whether the respective emotion has not been falsely chosen for a different emotion.

5.2.5. Positive and Negative Symptom Scale (PANSS)

The PANSS evaluates positive, negative, and general psychopathology symptoms clinically associated with SZ. The scale includes 30 items (Kay et al., 1987), with the following ratings (0 = absent, 1 = minimal, 2 = mild, 3 = moderate, 4 = moderate, 5 = severe, 6 = extreme). The Cronbach's alpha for the PANSS ranges from 0.70 to 0.85 (Van den Oord et al., 2006). This clinical demographic information is included in Table 5.1. The majority of patients were taking antipsychotic medication at the type of assessment and included the following: Aripiprazole, Clozapine, Fluphenazine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Aripiprazole, Chlorpromazine, Clopixol, Quetiapine and Ziprasidone. Medication dosage in terms of chlorpromazine (CPZ) equivalents was also available to include antipsychotic medication as a covariate of no interest in the analysis.

5.2.6. Childhood Physical Neglect

The experience of childhood physical neglect was retrospectively measured using the physical neglect subscale of the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The CTQ is a clinically valid tool which measures five commonly reported categories of trauma: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse (Appendix K). Each subscale includes five items, and individuals are asked whether they had experienced the event on a Likert scale ranging from '1' ('never true') to '5' ('very often true'). The CTQ has strong psychometric properties, as demonstrated in both clinical and non-clinical samples (Scher et al., 2001). The impact of physical neglect was examined here as the aspect of childhood trauma most strongly associated with cognitive performance and inflammatory cytokine levels. Scores for this subscale ranged from 0-20, with higher scores indicating more traumatic experiences.

5.2.7. Interleukin-6 Plasma

Blood samples were taken at approximately the same time of day (9.30 am) from each participant in a 6 ml EDTA tube (BD367873). The sample was centrifuged at 1,200g for 10 min at ambient

temperature. Following centrifugation, plasma was aspirated and stored in 1.5 ml Eppendorf tubes at -80 ∘C until analysed. Basal plasma levels of IL-6 were measured using a quantikine high-sensitivity enzyme-linked immunosorbent assay (ELISA) (Bio-Techne Catalog Number HS600C), which has an assay sensitivity of 0.09 pg/mL and range of 0.156–10 pg/mL and read spectrophotometrially at 450 nm. The assay was conducted based on the protocol given by the manufacturer (Biotechne, R&D).

5.2.8. Statistical Analysis

To test for the presence of an indirect effect of physical neglect on emotion recognition through FA scores of the CC, we carried out a mediation analysis with physical neglect as the predictor variable, FA of the CC as the mediator and emotion recognition as the outcome variable. For comparison, we decided to consider one other tract that was not expected to be related to social cognitive ability or risk for SZ: the CST. We next extended this mediation analysis to test the hypothesis that inflammatory response (as indexed by plasma IL-6) and CC would sequentially mediate the relationship between physical neglect and emotion recognition. A bootstrapping approach was implemented for the mediation analyses using the SPSS macro PROCESS V 4.2 (Hayes, 2012). This allows for estimating direct and indirect effects by applying an ordinary least squares path analytic framework. The significance of an indirect effect is assumed if the 95% confidence interval (95%-CI) does not include zero. The number of bootstrap samples was set to $n = 5000$. Standardised beta regression coefficients and standard errors (SE) are presented for each effect. Pairwise deletion was used in the current study to maximise data available. Sex, BMI, age and antipsychotic medication (as measured in terms of chlorpromazine equivalents) were included as covariates of no interest.

5.3. Results

5.3.1. Correlates and Covariates

Fifty-eight participants with schizophrenia took part in this study. Demographic and clinical details of the participants are outlined in Table 5.1. Physical neglect significantly and negatively correlated with FA within the genu ($r= -0.274, p=0.037$), body ($r= -0.283, p=0.032$), and splenium ($r=-0.387, p=0.003$) of the CC as well as total FA in the CC ($r= -0.329, p = 0.012$). Following multiple testing correction for three domains of CC analysed, only the splenium and total CC survived multiple testing Bonferroni correction ($\alpha = 0.05/3 = 0.016$). Total CC and the subsections were positively correlated with total ERT scores ($p <0.01$). The genu of the CC was also significantly associated with several ERT unbiased hit rate scores, specifically Happy, Sad, Anger, Fear, Surprise, and Disgust, surviving multiple testing correction. The body of the CC, more posterior to the genu, significantly related to three of the ERT outcomes - Happy, Sad, and Anger, while the splenium was associated with Sad stimuli only ($p <0.016$ respectively). Total CC was associated with all emotion stimuli of the ERT and was therefore considered for further analysis (See Figure 5.1).

We examined a number of covariates of no interest prior to running the mediation analysis. There was no significant difference in males and females in FA in the CC ($t_{(56)}= 0.140, p= 0.889$) or on the ERT ($t_{(52)}= 0.583, p= 0.562$). BMI was not significantly associated with ERT ($r= -0.166, p = 0.234$) or the CC ($r= 0.029, p = 0.830$). Similarly, antipsychotic mediation was not associated with the CC ($r= -0.191, p = 0.178$) or the ERT ($r= -0.072, p = 0.632$). Total PANSS total scores were not correlated with ERT ($r= -0.069, p = 0.625$) or FA values in the CC. Age was however, correlated with FA in the CC ($r= -0.436, p <0.002$) and with ERT ($r= -0.458, p <0.001$).
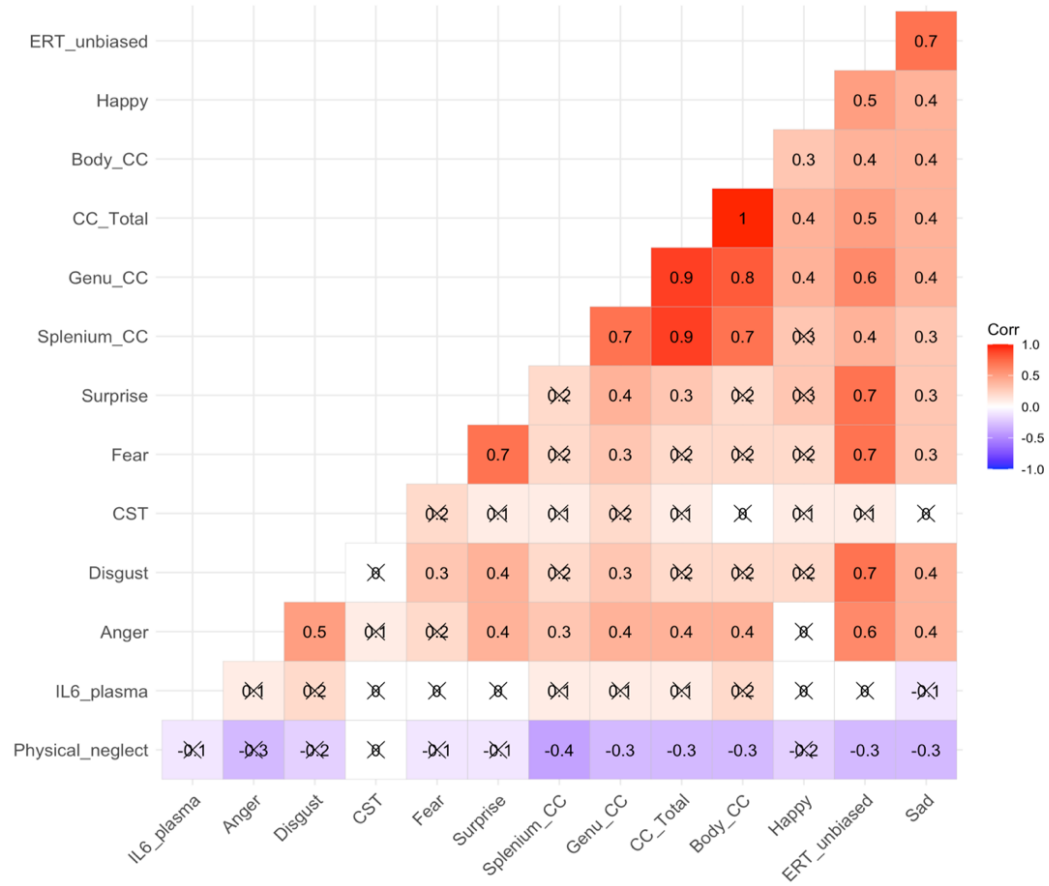
Figure 5.1. Correlations among variables

Positive correlations are shown in red and negative correlations in purple. Nonsignificant associations are marked with X.

Table 5.1. Descriptive statistics of the sample

	n	Range	*M (SD)*
Age	58	18-63	42.40 (11.16)
Gender	58	17 females, 41 males	-
BMI	57	20-40	29.67 (4.63)
CPZ (mg)	49	100-6667	815 (1292)
PANSS (Positive)	56	7-16	8.63 (2.27)
PANSS (Negative)	56	7-21	9.50 (3.71)
PANSS (Total)	56	16-35	20.43 (3.92)
Plasma IL-6 (mg/L)	53	0.37-45.23	3.33 (6.04)
Childhood Trauma			
Total CTQ	58	0-72	16.34 (15.24)
Physical Neglect	58	0-16	2.59 (3.24)
ERT			
(Unbiased Hit Rate)	54	0.37- 3.57	2.09 (0.77)
Happy	57	0.04-1.00	0.54 (0.19)
Sad	57	0.00-0.77	0.39 (0.20)
Fear	55	0.00-0.62	0.19 (0.17)
Anger	55	0.00-0.64	0.29 (0.18)
Surprise	57	0.01-0.89	0.38 (0.19)
Disgust	57	0.00-0.77	0.29 (0.21)
White Matter FA			
CC Total	58	0.59-0.75	0.69 (0.03)
CC Genu	58	0.57-0.73	0.65 (0.04)
CC Body	58	0.55-0.74	0.66 (0.04)
CC Splenium	58	0.63-0.79	0.74 (0.03)
CST Total	58	0.54-0.70	0.63 (0.04)

BMI: Body Mass Index; CPZ chlorpromazine equivalents; IL-6: Interleukin-6; CTQ: Childhood Trauma Questionnaire; ERT: Emotion Recognition Task; FA: Fractional Anisotropy; CC: Corpus Callosum; CST: Corticospinal Tract.

5.3.2. Mediating Effect of Microstructural Organization of the Corpus Callosum on Physical Neglect and Emotion Recognition

Two hypothesised mediation models were tested. The first model examined the mediating role of CC microstructural organization to the relationship between physical neglect and emotion recognition. The second model tested whether both IL-6 and CC microstructural organization sequentially mediated this relationship.

The findings for Model 1 revealed that there was a significant indirect effect of physical neglect on emotion recognition via FA in the CC ($\beta_{indirect}$ = -0.140, SE = 0.071, 95% CI [-0.293, -0.0168]) (Figure 5.2). Physical neglect was directly associated with FA in the CC (β_{direct} = -0.333, SE = 0.014, p= 0.014) and the CC was directly associated with ERT (β_{direct} = -0.422, SE = 0.524, p= 0.002). The direct pathway between physical neglect and ERT was not significant (β_{direct} = -0.182, SE = 0.005, p= 0.160). This suggests that CC FA scores fully mediated the association between Physical neglect and ERT. There were no significant mediating effects for the comparison CST tract ($\beta_{indirect}$ = 0.0010, SE = 0.016, 95% CI [-0.039, 0.029]). Model 1 accounted for 26% of the variance in emotion recognition. This finding remained significant after controlling for the effects of age, BMI, sex, and medication dosage.

Corpus
Callosum FA

a= -0.333*

b= 0.4216**

Physical Neglect

c'= -0.182

Emotion Recognition
(Unbiased Hit Rate)

c= -0.322*

Indirect Effect
a*b= -0.140 95% CIs [-0.293 to -0.017]
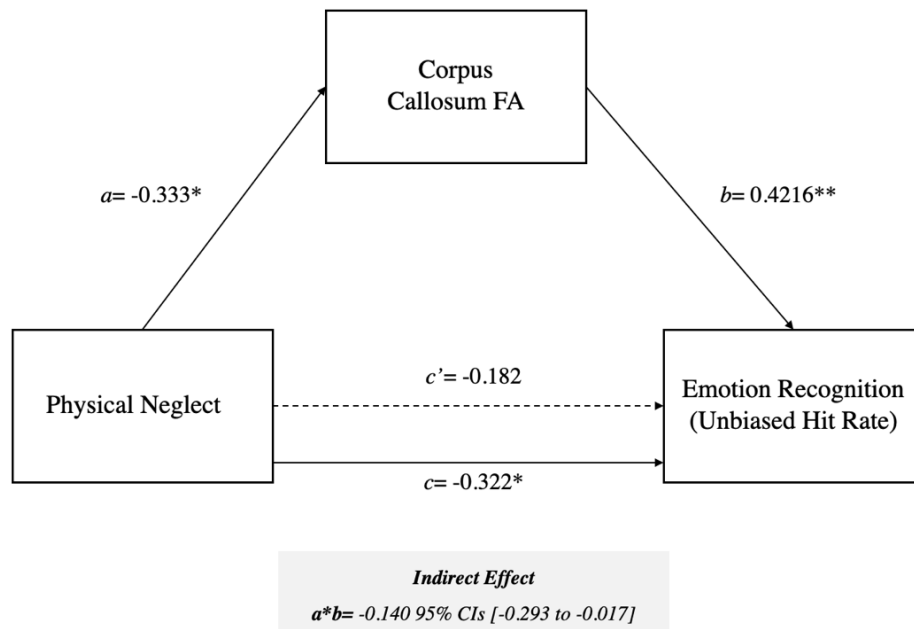
Figure 5.2. The association between physical neglect and emotion recognition as mediated via fractional anisotropy of the corpus callosum

Note: a= path from physical neglect to corpus callosum FA, b= path from callosum FA to emotion recognition, c'= direct effect of physical neglect on emotion recognition and c=total effect of physical neglect on emotion recognition.

5.3.3. Sequential Mediation of IL-6 and FA of the Corpus Callosum on Physical Neglect and Emotion Recognition

The findings for Model 2 revealed evidence of sequential mediation, such that both IL-6 and CC FA scores mediated the relationship between physical neglect and emotion recognition ($\beta_{indirect}$ = -0.005, SE = 0.014, 95% CI [-0.051, -0.008]) (see Figure 5.3). There was no evidence that physical neglect influenced emotion recognition through IL-6 alone ($\beta_{indirect}$ = 0.0009, SE = 0.005, 95% CI [-0.655, 0.042]). Model 2 accounted for 26% of the variance in emotion recognition. There were no significant mediating effects for the comparison CST tract. Again, these results remained significant after controlling for sex, BMI and medication dosage. When we considered the effects

153

of age as a separate covariate, FA in the CC remained significant, however the sequential effects of CC and IL-6 on the association between physical neglect and ERT was no longer significant.
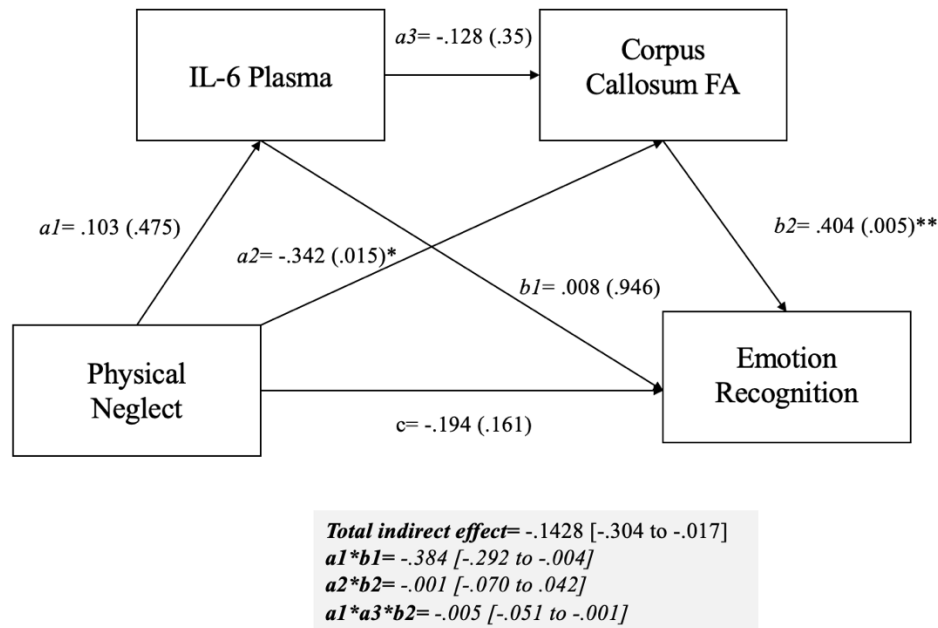
Figure 5.3. The association of physical neglect and emotion recognition as sequentially mediated via IL-6 and fractional anisotropy of the corpus callosum

Note: a1= path from physical neglect to corpus callosum FA, a2= path from physical neglect to corpus callosum FA, a3= path from IL-6 to corpus callosum FA, b1= path from IL-6 to emotion recognition, b2= path from corpus callosum FA to emotion recognition, c=total effect of physical neglect on emotion recognition.

5.4.   Discussion

5.4.1. Summary of Main Findings

In this study we investigated the interplay between physical neglect, inflammation, CC white matter tract microstructure and emotion recognition in patients with SZ. Our study has three main findings. First, lower FA values in the CC were correlated with reduced ERT performance. While these correlations were similar in magnitude across subsections, CC in its entirety and the splenium showed the strongest effect. Secondly, we demonstrated that reductions of FA in the CC mediated an association between greater exposure to physical neglect and reduced performance on the ERT using the unbiased hit rate. This association was observed in the absence of a direct effect, suggesting that the association between physical neglect and emotion recognition was fully mediated by CC microstructure. This mediating effect was observed for the CC and was not present in a comparative tract analysed for the purpose of divergent validity, in line with previous research protocols (Coad et al., 2020). Thirdly, we showed, in a sequential mediation analysis that higher IL-6 levels and lower FA in the CC mediated the association between greater exposure to physical neglect and lower emotion recognition scores. The mediating role of IL-6 was only evident in the sequential mediation model including both IL-6 and CC microstructure and not when IL-6 was considered alone, suggesting that the mediating role of IL-6 was itself mediated by CC microstructure.

5.4.2. The Mediating Effects of White Matter Microstructural Organization of the Corpus Callosum

As mentioned previously, childhood adversity is hypothesised to alter brain development through a number of different mechanisms (McLaughlin et al., 2019). Our findings suggest that CC microstructure represents a critical substrate for the effects of physical neglect on emotion recognition ability in patients. Consistent with previous studies (Rigucci et al., 2013; Zhang et al., 2020; Zhao et al., 2017) lower FA within the CC was associated with lower social cognitive performance on the ERT. Emotion recognition is a complex mental process that depends upon effective communication between multiple cortical regions, including bilaterally. This study

155

supports the role of the CC in potentially mediating the developmental effects of childhood trauma (as measured by physical neglect) on social cognition. Work by our group (King et al., 2021; Rokita et al., 2018) and others (Garcia et al., 2016; Kilian et al., 2018; Kincaid et al., 2018; Vaskinn, Engelstad, et al., 2021; Vaskinn, Melle, et al., 2021) have previously shown that social cognition is particularly susceptible to the effects of childhood neglect in SZ. The effects of childhood trauma are unlikely to be restricted to one metric of brain structure. We have previously reported evidence that an adjacent grey matter structure - the anterior cingulate – also mediates the relationship between physical neglect and emotion recognition (Rokita et al., 2020). The present study extends those findings to suggest that the developmental effects of childhood trauma on social cognition is likely to extend beyond grey matter structure to also include white matter microstructure.

5.4.3. Inflammatory Response as a Sequential Mediator of the Environmental and Brain-Related Underpinnings of Emotion Recognition

Altered inflammatory response has been proposed to be one of the main contributors underlying the association between childhood adversity, brain structure and cognition in patients with SZ. In particular, it has been hypothesised that ELA can trigger an inflammatory response (i.e., via increased proinflammatory cytokines such as IL-6). This altered response is likely to involve astrocytes and microglia, the brain's resident macrophages (Rodríguez-Gómez et al., 2020). This in turn has been hypothesised to lead to changes in both synaptic signalling and altered white matter microstructure (Figueiredo et al., 2022). As reported by Nemes-Baran et al., (2020), the CC is a region in the brain that is highly populated by microglia and oligodendrocytes and may be particularly susceptible to the effect of early life stress.

Based on the above we hypothesised that childhood trauma associated changes in CC microstructure would be at least partially mediated via immune response, as indexed by IL-6 levels. Our data, which provided evidence of sequential mediation involving IL-6 and CC microstructure, supported this hypothesis. Such evidence is consistent with several recent studies that have demonstrated an association between increased levels of IL-6 and reduced FA in several

white matter tracts, including that of the CC (Di Biase et al., 2021; Michalczyk et al., 2022; Wang et al., 2020), although Ushakov et al., (2021) failed to replicate this finding. Regarding why IL-6 was only significant when considered part of a sequential mediation model with CC microstructure, and not alone, is contrary to our expectations based on previous studies from our group. In a larger grouped sample that included both healthy participants (*n*= 207) and people with SZ (*n*= 104), diagnosis did not mediate the effects observed between IL-6 and ERT total hits (King et al., 2021).

5.4.4. Strengths and Limitations

Previous studies on ELA in schizophrenia have focused primarily on brain structural and functional connectivity abnormalities associated with cognitive impairments in SZ. The current findings advance previous research by providing novel evidence that alterations in the CC are linked to variation in inflammatory response associated with early experiences that may led to changes in emotion recognition. A further strength of this study was a more sensitive measurement of emotion recognition using the ERT unbiased hit rate as opposed to a total hit tally score, which measures both the accuracy of responses and false alarms.

The study also had a number of limitations. First, the cross-sectional nature of this study did not permit casual claims or investigations of fluctuations over time. Future work is needed to examine changes in the cytokine levels and the microstructural organization of the CC longitudinally, both as individual variables and their paired relationship. Secondly, although the CTQ is the most widely used measure of childhood trauma, which allows for comparison across studies, the assessment of ELA was retrospective and based on self-report (Bernstein et al., 2003). This may have contributed to the possibility of recall bias (Baldwin et al., 2019). Another limitation concerns the sample size. Although this was consistent with other DTI imaging studies (Fu et al., 2019; Gangadin et al., 2022; Michalczyk et al., 2022; Wang et al., 2020), this may have reduced our power to identify additional significant associations. Notwithstanding, the mediating role of IL-6 and CC on the association between physical neglect and ERT remained significant after controlling for the effect of BMI, sex and antipsychotic mediation.

5.4.5. Future Directions

We did not investigate the role of genetic variation on these associations. Given the growing evidence that genetic factors are associated with immune functioning and cognition in SZ (Corley et al., 2021; Holland et al., 2019; Zhao et al., 2017), investigating the interaction between genetic risk, environment and white matter on cognition is an important avenue for future work. Larger case/control samples, or data from an international consortium, would be required to clarify whether these associations are relevant to patients with SZ only and if the observed effects in social cognitive functioning are specific to the CC or other white matter tracts more broadly. Finally, while the CC in its entirety is likely to be important to social cognitive ability, future research could consider subdividing the CC into sections to determine whether specific projections to the cerebral regions are relevant to the investigated associations on ELA, inflammation, and social cognition.

5.5.   Conclusions

In conclusion, we report for the first time, how CC microstructure mediates the association between physical neglect and emotion recognition. This highlights the potential importance of the CC for understanding the developmental consequences of childhood trauma and their effects on social cognition in patients. We further provide evidence that these associations may be at least partly associated with inflammatory response (as measured by IL-6) suggesting at least one biological pathway by which these changes occur. Confirming any causal significance of these associations will be an important next step towards understanding the effects of childhood trauma on cognition and social cognition.

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Author Contributions

Conceptualisation: EC, TB, DWM and GD; Methodology: EC, TB, SRP, DWM and GD; Formal analysis: EC, TB and GD; Investigation: EC, TB, SRP, AL, DM, DWM and GD; Writing—original draft preparation: EC, TB and GD; Writing—review and editing: EC, CG, EG, MC, SRP, DMC, DPM, JPK, BH, CMD, TB, DWM and GD; Funding acquisition: EC and GD; Resources: GD; Project administration: DWM, TB and GD. All authors contributed to and approved the final version of the paper.

Conflict of Interest

The authors declare that they have no conflict of interest.

Chapter 6: General Discussion

6.1.   Overview

The main focus of this thesis was to model the contribution of ELA, immune response, and genetic risk variants to cognitive outcomes in patients with schizophrenia and healthy participants. This thesis further sought to explore how MRI-derived measures of brain structure mediated these effects on cognitive functioning. In the process of working towards these objectives, the first study (Chapter 2) examined immune-relevant genetic contributions to cognitive impairments. Study two (Chapter 3) then sought to explore the contribution of and interaction between different biological and environmental factors that influence cognition using a rich multivariate dataset from the UK Biobank. Thereafter, studies three and four (Chapters 4 & 5) sought to expand on these associations in a clinical sample of patients with schizophrenia. The findings of this thesis provide novel contributions to gene-environment research, including evidence of immune processes being implicated in cognitive functioning and that exposure to adversity early in life is likely to have long-term consequences on brain structure and cognition.

Studies included in this thesis involved multiple co-authors; their contributions are outlined at the beginning of this thesis. This thesis follows an article-based PhD format. A discussion pertaining to each study has been detailed previously. As such, the key results of the studies included in each chapter of the thesis will be briefly summarised below, followed by a consideration of theoretical and clinical implications. Finally, the strengths, limitations, and directions for future research are discussed.

6.2.   Brief Summary of the Main Findings across each Individual Study

6.2.1. Study One

Given the relevance of cognitive impairments and immune changes in schizophrenia as well as the putative role of the immune system in cognitive dysfunction, the first study of this thesis (Chapter 2) examined the association between microglial genetic risk variants, brain structure and cognitive performance. This study further aimed to investigate whether genes highly expressed within microglial cells would show enrichment for the risk of schizophrenia. In line with the study's first

hypothesis, participants carrying a higher schizophrenia microglial PGS demonstrated poorer performance on measures of cognitive performance, with the strongest association being observed for memory functioning. These findings underscore the relevance of memory functioning as an aspect of cognition that is particularly sensitive to immune genetic risk loci.

In this study, the association between microglial PGS and cognition was further found to be mediated via total grey matter volume, thereby supporting the growing evidence of immune response being associated with changes in brain structure. However, this mediating effect was only observed in the larger replication sample of UK Biobank participants, which may be partially explained by the increase in the sample size leading to improvement in statistical power. Although this effect was modest, this finding is consistent with prior research demonstrating that associations between common variants and the risk of schizophrenia confer relatively small effects on cognitive functioning. Moreover, when comparing the schizophrenia patient group and nonclinical groups in the Irish case/control sample, these associations were no longer significant. Due to issues of power, the division of this sample into patient and healthy groups may have limited our ability to infer an indirect effect of grey matter volume on genetic risk and cognition, particularly in the patient group. Finally, unlike neuronal genes, which did show evidence of enrichment, the microglial gene set was not significantly enriched for schizophrenia. Overall, the results of this study demonstrate that the contribution of microglial PGS on grey matter volume and cognition may not be illness specific. This is further underscored by the absence of microglial enrichment for schizophrenia risk and interpret these data to reflect the broader relevance of microglial-expressed genetic variation to neurodevelopmental processes related more generally to cognition rather than to illness specifically.

6.2.2. Study Two

Based on the findings of study one and of the growing evidence that not just genetic but also environmental factors (e.g., childhood adversity) are associated with cognition, study two (Chapter 3) sought to model the relationship between common genetic variation, grey matter volume, ELA, education, and cognitive ability in the UK Biobank. The UK Biobank dataset is unique in its size and scope and is a powerful resource for population health research. However, a limitation of this

dataset concerns the validity and reliability of the cognitive tests used, which are brief and administered unsupervised. We attempted to overcome this limitation by generating a latent variable of cognition comprising several important domains of cognitive functioning and conducted the analysis using structural equation modelling. In this study, common genetic variation, grey matter volume, and ELA were each significant predictors in the model, explaining ~15% of the variation in cognitive ability.

Contrary to the study's hypothesis, however, grey matter volume did not appear to mediate the relationship between genetic variation and cognition performance. Neither did ELA or educational attainment moderate this relationship, although educational attainment was observed to moderate the association between grey matter volume and cognitive performance. For the present study in which genetic variation was the main predictor variable, the relatively small variation in cognitive function explained by IQ PGSs coupled with the limited genetic overlap between grey matter volume and cognition may have obscured the moderating effects of childhood adversity. While this issue might be addressed by a larger sample size, a more straightforward conclusion is that the model we tested had limited explanatory power.

6.2.3. Study Three

Based on the findings of study two showing modest explanatory value of estimated genetic risk from GWAS, we considered modelling the relationship between biological and environmental variables by including PGS as itself a moderator of other (e.g., environmental) factors rather than as a predictor variable which is itself moderated. That is, we aimed to test whether the association between environment (ELA) and cognitive functioning was moderated via increased genetic susceptibility to schizophrenia. Further, and based on the findings of study one, we explored the mediating effects of inflammatory response on ELA and cognition. Given the large number of studies that have shown a link between physical neglect and reduced neurocognitive functioning and social cognitive ability, this subtype of ELA was investigated. An additional aim of this study was to build on previous studies from our group, which had previously found IL-6 to be a significant mediator of childhood physical neglect and social cognition to include other proinflammatory markers as well as measures of neurocognition.

163

In this third study, we identified a latent proinflammatory variable consisting of three key cytokines - IL-6, CRP, and TNF-α- which significantly mediated the association between physical neglect and cognition. While schizophrenia PGS did not moderate the mediating effect of this inflammatory response, we did find evidence that PGS moderated the direct pathway between physical neglect and measures of cognitive (but not social cognitive) functioning in both patient and healthy participants. Overall, these results suggest that inflammatory response and genetic liability for schizophrenia may independently influence the association between adverse early life experiences and cognitive function in patients and healthy participants.

6.2.4. Study Four

In the fourth and final manuscript, we investigated the interplay between inflammatory response and white matter brain structure to the association between childhood physical neglect and social cognitive performance. Based on previous work showing that altered CC microstructure is associated with reduced social cognitive performance, we hypothesised that reduced FA of the CC and increased inflammatory response would mediate the relationship between physical neglect and emotion recognition in patients with schizophrenia. The results of this study provide a novel contribution to the literature by demonstrating that the relationship between physical neglect and emotion recognition was sequentially mediated by higher IL-6 and lower FA of the CC. This highlights the potential importance of the CC for understanding the developmental consequences of ELA and their effects on social cognition in patients.

6.3.   Integration of the Findings of the Four Studies and Theoretical Implications

The findings of this thesis contribute to the growing body of evidence underscoring the importance of investigating the role of ELA and immune processes in neurodevelopment. Results from the studies are largely in line with the neurodevelopmental and immune hypotheses of schizophrenia, which suggests that several deleterious 'hits' in the form of genetic and environmental risk factors may interact during periods of neurodevelopment to alter brain structure and immune-related processes to contribute to later expression of clinical symptoms such as cognitive deficits (Davis

et al., 2016). Overall, the findings of this thesis add significant and novel data to inform a better understanding of how genetic, biological, and environmental factors are associated with impairments in cognitive ability in patients with schizophrenia and healthy participants. A number of notable theoretical implications of this work are evident and are discussed more thoroughly below.

6.3.1. Immune Alterations associated with Cognition may not be Illness Specific

The contribution of environmental and genetic effects on cognitive functioning observed across the individual studies of this thesis was, for the most part, non-illness specific. In study one, the strength of the association between schizophrenia microglial PGS and cognitive performance was comparable among patients and healthy participants. Similarly, in paper three, the mediating effect of inflammatory response on ELA and cognition was similar in patients and controls. For study two, the results reported were based entirely on a general population sample of UK Biobank participants. These findings suggest that while risk-associated genetic variants and environmental factors may be more prevalent among patients with schizophrenia, the phenotypic effects in healthy participants who carry those risk factors will also be apparent. Indeed, for this reason, it is typical for psychiatric, genetic, and imaging research to investigate these risk factors in healthy participant cohorts first due to the inherent difficulty of genotyping and imaging large samples of cases (Donohoe et al., 2018).

The absence of illness-specific effects coupled with the nonsignificant enrichment of microglial genes as a risk for schizophrenia suggests that changes in inflammatory processes and exposure to ELA may have broader relevance to neurodevelopmental processes related to cognition rather than illness specifically. This is consistent with previous lines of research carried out in our group, showing that a complement component gene set was enriched for IQ (not schizophrenia) and that complement component genetic risk loci were correlated with cognitive functioning (Holland et al., 2019). Notwithstanding, there may be other protective factors acting in concordance with environmental and biological processes to minimise the effects of genetic and environmental factors on psychosis development and/or impairments in cognition, namely safe and nurturing relationships (Crouch et al., 2019), parental bonding (Rokita et al., 2018) and mother-partner

relationships (Walsh et al., 2021). As such, future research should implement a fully data-driven approach to include such factors.

6.3.2. Early Life Adversity and Immune Dysregulation are associated with Neuro- and Social Cognitive Domains

An interesting finding across the studies was that the relationship between ELA, inflammatory response and cognitive performance was observed across multiple cognitive and social cognitive domains. The effect size for the negative association between ELA and memory, general cognitive ability and emotion recognition were comparable in study three and added empirical depth to the wider literature, namely behavioural evidence in schizophrenia demonstrating that these cognitive domains are behaviourally multifaceted and somewhat interdependent (Green et al., 2019). Importantly, these findings extend beyond previous work (Baumeister et al., 2016; King et al., 2021; Li et al., 2022; Quide et al., 2021; Rokita et al., 2020) by demonstrating that the relationship between immune response and cognition is not specific to social cognitive domains, but rather to more general difficulties in overall social and neurocognitive ability.

Notwithstanding, in study one and study three, the genetic contribution of risk to memory ability was larger than that of overall cognition and not a significant moderator of the association between ELA and social cognitive ability. Converging lines of research support that memory deficits, particularly those involving executive functions, may reflect genetically mediated susceptibility to schizophrenia (Horan et al., 2008). Furthermore, it is also notable that the highest loadings on the cognitive ability factor in study two, which examined the association between genetics, brain structure and cognition, were for the Symbol-Digit test and the Trails-Making test part B, both of which measure executive functioning. It is interesting to speculate, therefore, that memory and executive functioning processes may be particularly influenced by genetic factors. Indeed, memory ability has long been considered a critical endophenotype for psychosis (Vargas et al., 2019). The cross-sectional nature of these studies, however, limits causal claims regarding the genetic contributions to global versus specific cognitive functions later in life. However, this is an important first step for future examinations that may allow a stronger understanding of the distinct domains and genetic correlates underlying the observed associations.

6.3.3. Inflammatory Markers are Robustly Associated with Early Environment and Relevant to Understanding Subsequent Cognitive Functioning

Several studies and meta-analytic reviews have consistently shown that inflammatory markers are elevated in individuals who have experienced ELA as well as in individuals with schizophrenia (Baumeister et al., 2016; King et al., 2021; Li et al., 2022; Quide et al., 2021; Rokita et al., 2020) and correlate with changes in cognitive functioning (Patlola et al., 2023). While numerous inflammatory markers have been implicated, the most consistent of these associations have been observed for IL-6, CRP and TNF-α (Baumeister et al., 2016). It is hypothesised that these markers act in concert with one another to contribute to low-grade systematic inflammation in schizophrenia (Becher et al., 2017). This intricacy of inflammatory marker signalling presents several difficulties in understanding the roles and mechanisms of immune markers in neural and cognitive functions. To better account for this complexity, study three of this thesis employed structural equation modelling to examine the contribution of IL-6, CRP, and TNF-α simultaneously to the association of ELA and cognition. A specific advantage of this latent variable approach, beyond being a better representation of inflammatory response than measures of individual markers, is that the variability in inflammatory markers can be combined so that subtle but potentially important patterns can be identified.

Supporting this, study three found that compared to any of the individual inflammatory markers alone, an immune latent inflammatory variable comprising of IL-6, TNF-α and CRP explained a greater percentage of the variance in cognitive functioning. These findings support the notion that multiple inflammatory markers considered collectively are a critical mechanism involved in cognitive processes, specifically for childhood physical neglect. Moreover, these findings add further evidence in favour of the hypothesis of an immune link related to ELA and cognitive impairments (Howes & McCutcheon, 2017). An important theoretical implication of this finding is with regard to identifying subtypes of patients who may be susceptible to low-grade inflammation. Greater detection of this low-grade inflammatory profile may be possible when groups of cytokines are analysed simultaneously and, as such may have important implications for early intervention strategies.

6.3.4. The Association between Early Life Adversity and Cognition is at least partly Mediated via Grey and White Matter Brain Structural Changes

Consistent with a large body of prior work, the findings presented in study four (Chapter 5) of this thesis found that the relationship between childhood physical neglect and cognition was associated with changes in brain structure. Interference with brain structural development from ELA is consistent with a neurodevelopmental view of schizophrenia which postulates that specific environmental factors during developmental periods can induce persistent changes in brain structure and behavioural functions throughout life (Ribeiro-Santos et al., 2014). These factors may also interact with the immune system to further exacerbate changes in cognitive functioning (Khandaker et al., 2015). The findings of the fourth study confirmed the main hypothesis that the effects of childhood physical neglect on social cognitive ability would be mediated via both inflammatory response and brain structure. Specifically, we extended previous brain connectivity findings from our group (Dauvermann et al., 2021; King et al., 2021; Mothersill et al., 2021) and grey matter structure (Rokita et al., 2020) showing for the first time that white matter microstructural organisation of the CC mediates the effect of physical neglect on emotion recognition in patients with schizophrenia.

As demonstrated by animal studies, ELA may alter the typical development of white matter through neuroinflammation and dysregulation of glial cells necessary for myelination (Jauregui-Huerta et al., 2010). In this context, white matter structures such as the CC may be particularly vulnerable to the neurotoxic impact of childhood trauma especially during its neurodevelopmental period, as above (McLaughlin et al., 2019). Consistent with this hypothesis, IL-6 and FA in the CC were found to sequentially mediate the effect of childhood physical neglect and social cognitive ability (namely emotion recognition). This is consistent with previous studies that have shown elevated inflammatory response to be associated with reduced FA in the CC in healthy participants (Michalczyk et al., 2022) as well as in individuals with schizophrenia (Prasad et al., 2015; Wang et al., 2020). Taken together, these findings suggest that immune changes may mediate some of the observable differences in white matter microstructure. However, in the absence of longitudinal data, these cross-sectional associations can be interpreted as indications only. Furthermore, while the CC is likely to be important to social cognitive ability, future research

could consider subdividing the CC into sections to determine whether specific projections to the cerebral regions are relevant to the investigated associations on ELA, inflammation, and social cognition as well as the contribution of other white matter tracts.

6.4. Strengths of this Thesis

6.4.1. Phenotypic Data

The investigation of the relationship between genetics, inflammation, environment, and brain morphology on cognition of the thesis has important strengths, including the large sample size of the Irish case-control sample and the UK Biobank sample. In study one, the Irish case-control sample consisted of approximately 900 patients with a diagnosis of schizophrenia or schizoaffective disorder, which is among the largest single research group dataset of this kind available. Further, to maximise the power to detect effects in study one and study two, we sought to replicate findings in an independent dataset of UK Biobank participants. In studies three and four, data from the iRelate cohort was used to extend these findings to investigate specifically the mediating role of an inflammatory response to the association between ELA and cognition. This dataset consists of rich phenotypic, immune, environmental, and genetic data. Importantly, participants in the iRelate study were extensively phenotyped on multiple domains of neurocognitive and social cognitive ability. In addition, the datasets included in this thesis consisted of highly advanced structural and diffusion imaging acquisition and processing.

6.4.2. Microglial Gene Set and Polygenic Score Analyses

A further strength of this thesis was the methodological approaches taken to characterise genetic, biological, and environmental contributions to cognitive functioning. To the author's knowledge, study one was the first of its kind to characterise a microglial gene set and examine its association with brain structural variation and cognition functioning in patients with schizophrenia and healthy participants. Further, this microglial gene set was based on single-cell RNA-sequencing technology, which is arguably a better method than employing RNA-sequencing in bulk (i.e., gene expression being averaged across all cell types). Moreover, for genetic analyses carried out across

169

this thesis, studies kept up to date with newly published GWASs for schizophrenia and cognition. For example, the schizophrenia PGS that was conducted in study one was based on a sample of 40,675 cases and 64,643 controls, while this number rose to 68,037 cases and 94,793 controls at the time of study three. Lastly, employing PGSs analyses is a notable strength of the thesis, which can better capture the polygenic nature of complex traits such as schizophrenia and cognition compared to single variant analysis. However, as with other approaches, PGS analysis is not without limitations.

6.4.3. Multivariate Statistical Analyses

A particular strength of this thesis relates to the SEM approach taken to characterise the association between ELA, inflammation, and cognition in studies two and three. This expands on prior research, which has primarily used simpler regression approaches to analyse complex relationships between biological and environmental predictors of cognition. The main advantages of SEM are that it considers measurement error among variables and allows testing complex patterns of relationships and hypotheses simultaneously, as well as measuring unobserved variables. Furthermore, SEM allows for residual correlations among variables that may have multicollinearity issues, and it can test invariance effects across different cohorts, which considerably improves the likelihood of identifying significant and meaningful differences in various relationships across group-specific results.

6.4.4. DTI Analysis Tools

Finally, a noteworthy strength of the design of study four is the application of DTI, which is currently the only non-invasive method used to examine white matter microstructural organisation *in vivo*. In the last number of decades, significant advances have been made to improve the specificity of DTI imaging to identify differences in white matter. The utilisation of this metric has helped elucidate white matter changes in patients with schizophrenia beyond that of standard MRI techniques. While there are a variety of different tensor methods available for white matter analysis, such as voxel-based morphometry (VBM) and tract-based spatial statistics (TBSS), the latter approach was used in this as this is generally considered to be the most sensitive to diffusion

changes in schizophrenia (Snook et al., 2007). Both VBM and TBSS allow spatially normalised voxel-wise and ROI analysis. However, TBSS can address specific limitations of VBM pertaining to spatial smoothing and image registration difficulties (Bach et al., 2014).

6.5. Methodological Considerations

The studies presented in this thesis contribute to the growing knowledge regarding the complex interplay between genetics, inflammation, brain structure and cognitive functioning in patients with schizophrenia and healthy participants. However, some methodological considerations should be considered when interpreting the findings of the thesis.

6.5.1. Exploratory Power of Current GWASs of Schizophrenia and Cognition

Across the studies of this thesis, the contribution of genetic risk of schizophrenia to cognitive impairments was evident, albeit of modest effect, suggesting that environmental factors such as ELA may have a more prominent role in the underlying cognitive impairments. However, a general limitation of GWAS data and PGSs relates to their current modest explanatory value of cognitive performance and/or risk of schizophrenia. Moreover, the vast majority of GWASs are based on a general or global cognitive phenotype derived from multiple cognitive domains, which may not fully characterise the genetic architecture of cognition function. Future studies examining specific domains of cognitive phenotypes may be more informative than collapsing different domains under a unitary construct of general cognitive ability. In addition, large samples with genome-wide SNP genotyping and whole genome sequencing, as well as comprehensive measurement of environmental exposures, are needed to increase the predictive power of genetic-environmental influences on cognition. Focus on the formation, transparent multi-site collaborations and data-sharing mechanisms of large-scale genetic, environmental and neuroimaging are therefore needed to advance research in this field. Important progress towards establishing such cohorts is currently underway and includes the ENIGMA Consortium (Thompson et al., 2014), the UK Biobank Project (Bycroft et al., 2018) and Adolescent Brain Cognitive Development Study (Casey et al., 2018).

While the approach taken to pool together multi-site data has been advantageous in many respects, it also comes with some caveats, most notably the re-use of subjects between GWASs, resulting in non-independent datasets for generating PGSs. GWAS data is typically available in the form of summary statistics, whereby data is condensed into one summary statistic per SNP. GWAS summary statistics from multiple sites cannot be made independent by removing subjects unless this is made available by the authors. While the PGC schizophrenia working group allowed for the exclusion of participants collected within our group, for cognition (i.e., summary statistics from Savage et al., 2018) this was not possible. As such, a notable limitation concerning paper two was basing our GWAS and PGS analysis on the Verbal-Numerical Reasoning test in isolation. Large-scale GWASs that comprehensively measure cognition and allow for the exclusion of sample overlap are therefore needed to advance our understanding of genetic contributions to cognitive functioning. A final limitation of GWAS is that it examines each SNP for association with the trait independently and is typically encoded according to an additive model, thereby limiting the discovery of SNPs with nonadditive inheritance. Alternative methods, including FastEpistasis (Schüpbach et al., 2010), as well as machine learning approaches (Chang et al., 2020) such as random forest-like algorithms and GenEpi, have been used to address issues of epistasis but are resource heavy to compute.

6.5.2. Cross-Sectional Nature of the Studies Design

Due to the cross-sectional nature of the studies design, it was not possible to examine the developmental timing of exposure to ELA to the association of brain structural changes or cognitive functioning later in life. The neurobiological impact of ELA may differ depending on factors such as the timing and length of the adversity as well as the severity of the event. The cross-sectional design of this doctoral research prevents us from drawing any firm conclusions about causality. Indeed, for the models tested here, one could equally speculate about whether individuals with reduced cognitive functioning are at greater risk for exposure to ELA, implying reverse causation. It will, therefore, be important for future studies to examine these associations longitudinally. However, conducting cross-sectional analyses is an important step in identifying risk factors and can pave the way for future longitudinal work to explore gene-environment interactions.

On a converging note, studies two, three and four of this thesis measured ELA retrospectively using the CTQ. While the CTQ is a widely used and standardised questionnaire (Bernstein et al., 2003), it is worth noting that some studies have found retrospective reports of ELA to be less reliable and valid compared to prospective assessments (Baldwin et al., 2019). However, other studies have found this issue to be somewhat overrated as prospective and retrospective CTQ reports have been shown to be highly convergent (e.g., Reuben et al., 2016). To address this potential concern, however, future studies utilising a prospective assessment of ELA, which considers the developmental timing of ELA exposure, may help to elucidate whether adversity experienced during a particular developmental period confers more pronounced neurobiological and cognitive deficits in patients with schizophrenia.

6.5.3. Confounding Variables

While the statistical analyses employed across each study controlled for the effects of age, gender, and BMI (where appropriate), there were many other variables not considered (e.g., symptom severity, duration of illness, parental bonding) that may have influenced the findings of the studies. Further, the majority of patients that were included in this thesis were prescribed antipsychotic medication. This is a notable confound to consider as there has been some evidence to suggest that antipsychotics may have immunomodulatory properties (Pandurangi & Buckley, 2020). While we attempted to control for this in studies three and four by including dosage of chlorpromazine equivalents, this is a relatively outdated metric that does not account for individual pharmacodynamics for each medication type, nor does it account for variability in duration of treatment, medication adherence or changes in dose over time. Alternative methods which may be a more accurate representation of antipsychotic equivalent conversion include the WHO's classification of the defined daily dose (DDD), which is the assumed average maintenance dose per day for the medication (Danivas & Venkatasubramanian, 2013). A major advantage of DDDs is that they are available for most antipsychotic drugs and are accepted internationally based on reviews of multiple sources (Leucht et al., 2016). However, DDDs do not consider pharmacologic potencies and may not reflect the actual amount or dose used.

6.6. Future Research

6.6.1. Early Life Adversity as a Transdiagnostic Risk Factor

It is also noteworthy here that ELA represents a transdiagnostic risk factor for several neuropsychiatric disorders. The effects of ELA on brain structural alterations and cognitive impairments have been shown not only in individuals with schizophrenia but also in patients with bipolar disorder (Quidé et al., 2020), post-traumatic stress disorder (Wang et al., 2022b) depression (Zhao et al., 2022), among others. It is therefore, plausible that the connection between ELA and elevated risk for mental health conditions is related more to a group of symptoms (i.e., reduced cognitive functioning) that are shared across various psychiatric disorders rather than a specific diagnosis (McLaughlin et al., 2019). Research aimed at understanding how childhood trauma affects brain structure may benefit from using a transdiagnostic approach model. Focusing only on specific disorders based on a DSM diagnosis may limit our understanding of substantial overlap in neurobiological mechanisms that coexist across multiple psychiatric disorders.

6.6.2. Inflammatory Biomarkers

Significant progress has been made in identifying the effects of specific inflammatory markers in schizophrenia and in those who have experienced ELA. Given the complexity of inflammatory signalling in the brain and periphery, findings from this thesis point towards shifting the focus from individual cytokines to a more network-aligned approach to understand the impact of inflammatory signalling on cognitive functioning. Due to issues of sensitivity as well as the availability of cytokines assayed at the time of the study, we were unable to examine the effects of other inflammatory markers (i.e., IL-1β, IL-8, IL-12, and anti-inflammatory cytokines; Il-4, IL-10) which may contribute to variation in cognitive functioning. As such, future research which includes inflammatory markers beyond that of IL-6, TNF-α and CRP is needed to clarify the extent of these relationships. In addition, it is possible that there is a distinction between peripheral and central inflammation and the symptom domains affected by each, but this would need to be investigated further in a larger sample.

6.6.3. Multimodal Integration of Genetic and/or Imaging Data

Another important area of future research worth exploring is using multimodal imaging techniques to model the association between ELA, brain structure and cognition in patients with schizophrenia. Grey matter and white matter are often examined as though they are separate and distinct structures, but they are in fact parts of the same neuron. To date, structural networks and their association with cognition have primarily been studied unimodally. Modelling the unique and shared covariance among different imaging modalities may shed more insight into the underlying biological mechanisms of cognitive impairments and help determine how their disruption may lead to these deficits. Over the last decade, several techniques for fusing imaging data have been described, including parallel and joint independent component analyses (ICA) and multimodal canonical correlation analysis (MCCA) (Sui et al., 2010). Using the latter approach which combined measures from MRI, dMRI and resting-state fMRI, Sui et al., (2015) identified common deficits in distributed cortical-striatal-thalamic circuits that were significantly associated with cognitive functioning in patients with schizophrenia compared to healthy controls. As such, an interesting area of research would be to explore the structure-function relationship using these fusion techniques to determine if and how exposure to ELA and immune markers impact upon different MRI modalities to contribute to impairments in cognition.

In addition, joint power of multiple discovery GWASs could be adopted in future research by generating a muti-PGS that better predicts cognitive functioning than that of a single PGS based on individual traits. This may be particularly relevant in the context of a transdiagnostic framework which acknowledges the intertwined nature of different psychiatric disorders. Using such an approach in future research may help to uncover individuals' unique functional profiles underlying cognitive deficits. Moreover, newer GWAS methods that combine samples of different ancestries are needed to expand the diversity of results. In a recent trans-ancestry GWAS (Schizophrenia Working Group of the PGC, 2020) a combined PGS of European and East Asian ancestries was better able to predict risk for schizophrenia compared to the matched ancestry GWAS. Future research which seeks to model the inclusion of different ancestries or population groups and the association between environmental risk factors will also need careful consideration. In particular,

other types of adversity may be more prevalent in different cultural contexts, including migration due to war and gun violence (Ford et al., 2015).

6.7. Clinical Implications

6.7.1. Interventions for Social and Cognitive Impairments Linked to ELA

Over the last few decades, significant efforts have been made to understand the impact of ELA and immune dysregulation on cognitive deficits in schizophrenia. The hope is that these efforts will lead to novel approaches to diagnosis, a better biological understanding of the disorder, and improved treatment outcomes. The findings of this thesis have several important clinical implications. First, both social and neurocognitive processes appear to be relevant to ELA. Current trauma-informed care approaches primarily focus on behavioural interventions that help individuals process painful memories, reduce anxiety, improve social functioning, and manage emotion dysregulation (Levenson, 2017). However, interventions that incorporate social as well as cognitive skill elements may offer additional therapeutic value, given that neurocognitive impairments are also linked to adversity early in life. Previous intervention studies that have targeted cognitive and social cognitive impairments prove to be effective in mitigating, at least in part, some of the deleterious effects of ELA on cognitive functioning in patients with severe mental health conditions (Bowie, 2019). Therapies that combine social and cognitive skills training have not only the potential to improve clinical outcomes at an individual level but also have wider, large-scale societal benefits by encouraging higher rates of employment, improving quality of life, reducing job stress, and lowering long-term treatment demands (O'Reilly et al., 2019).

6.7.2. Anti-Inflammatory Interventions

In addition, the findings of this thesis contribute to the characterisation of different risk pathways and mechanisms of cognitive impairments in schizophrenia, namely immune dysregulation, which could potentially refine our capacity to deliver person-based treatments. As described in section 1.3., antipsychotics are largely ineffective in treating cognitive deficits of schizophrenia, despite evidence that cognitive impairments are the most important predictor of functioning (Green & Harvey, 2014). The findings of this thesis, along with previous work carried out by others, suggest

that targeting inflammation may be an avenue worth exploring. However, it is important to mention that anti-inflammatory drug studies thus far, have been adjunctive to stable doses of antipsychotics which may provide additional benefit to these treatments.

Some preliminary lines of evidence indicate that minocycline, a second-generation tetracycline known to inhibit microglial activation, can improve cognitive functioning in patients with schizophrenia (Kelly et al., 2015; Liu et al., 2014; Zhang et al., 2019). Notwithstanding, the intricacies of the immune system and the multifaceted heterogeneity of schizophrenia highlight that a single treatment approach may not be effective for every patient. Within individual studies, there is some evidence to suggest that subgroups of patients with schizophrenia may preferentially respond to anti-inflammatory drugs (e.g., Deakin et al., 2018; Girgis et al., 2018; Quide et al., 2021). It is possible that future stratification of individuals by higher/lower inflammation may result in stronger treatment effects of adjunctive anti-inflammatory drugs. To this end, an additional way to gain insights into drug treatments for future research is through tissue-specific enrichment analyses (i.e., microglia). While the findings of immune-genetic risk had modest explanatory value on cognitive impairments in this thesis, upcoming larger-scale genetic research of estimated polygenic scores will undoubtedly provide additional power to clarify these relationships.

6.8.   Concluding Remarks

The main objective of this thesis was to examine the contribution of and interaction between early life adversity and different biological factors including genetics, inflammation and brain structure that influence cognitive functioning in patients with schizophrenia and healthy controls. The findings of this thesis demonstrate that exposure to ELA, specifically physical neglect is associated with impairments in cognitive ability in adulthood in both patients with schizophrenia and healthy participants. Further, the results suggest that immune processes may mediate the link between ELA and cognitive functioning. Finally, we demonstrate that global grey matter volume and white matter structural alterations are linked to measures of inflammation and cognition. Upcoming larger-scale imaging and genetic studies will undoubtedly provide additional opportunities to clarify the relationships between immune dysregulation, schizophrenia, and cognitive

impairments. Furthermore, leveraging large studies to converge data spanning peripheral inflammation, illness domains, and detailed clinical, cognitive, neurophysiology, and imaging phenotyping will provide further clarity on these complex relationships.

6.9.   Reflection and the PhD Journey

There is so much more to this thesis than these printed pages; it has been quite the journey. I know not everyone feels that way, but at least in my case, the journey was as important and exciting as the publications and the presentations that came about from this PhD. During my time as an undergraduate student I excelled in subjects related to psychology, neuroscience, and research methodology and I had always envisioned myself in a research-orientated career. It was during my MSc research project on neurocognitive deficits in schizophrenia that I realised I wanted to pursue a PhD in this area. I was fascinated by the uncertainty surrounding the underlying biological mechanisms of schizophrenia, and I wanted to contribute, in some way, to understanding this complex disorder. However, I had also come to this project with the personal experience of a parent living with psychosis and there is no doubt that this contributed greatly to my interest to pursue research in this area. I was ambitious, curious, and passionate about this field and perhaps a little optimistic at the start. There were so many unanswered questions, so much uncertainty about how this disorder manifests and the contribution of genetic and environmental factors that were worthy of investigation.

I was fortunate that my MSc supervisor was recruiting for a new PhD student at the time. Even luckier was the fact that the research topic was in an area that genuinely interested me, and that I was offered the role. As I reflect on the past four years, I realise how much of a rewarding experience it was to do a PhD. I have learned a lot- my writing has improved, my ability to digest and analyse information has become much more streamlined and I am more confidence in my abilities. One of the highlights was being part of a large, multidisciplinary team of researchers from diverse backgrounds, including genetics, biochemistry, pharmacology, psychiatry, medicine, neuroscience, and psychology. This undoubtedly strengthened my knowledge in these disciplines, and I greatly benefited from their shared expertise and multi-perspective discussions of theoretical and methodological issues.

Being part of these groups also helped me build connections and engage in professional activities that were new to me. For instance, I learned how to carry out clinical and cognitive assessments and gained knowledge in methods and instruments used to measure the anatomy and physiology

of the brain (e.g., MRI and EEG). In addition, I spent time in the lab learning how to perform DNA and RNA extraction, as well as how to measure peripheral cytokine levels. This training was tremendously valuable and important to me, given that my PhD was based on secondary data. While the use of secondary data provided a means to investigate topics of fundamental importance and was arguably more cost and time effective, I still wanted to gain first-hand experience of data collection and acquire a full appreciation of how this data was generated.

That being said, the use of secondary data presented its own unique learning opportunities. Working with large-scale multi-level data required specific skills and expertise, including knowledge of Linux programming and R. Many of the files I worked with were initially in the form of text files with syntax files for reading the data and creating files for data analysis. Since I had no prior experience in coding or programming, I had to quickly learn these skills. Another challenge was the need for support services to store the data. Fortunately, I had access to an external server, but this was still limited in its capacity for memory storage especially for raw genotyping and imaging files. This was further complicated during the COVID-19 pandemic when many students and staff were working from home on these remote external servers, and it wasn't possible to run high memory jobs. However, I used this time to my advantage, and I developed specific skills that I would need for my future studies, which included structural equation modelling.

Another experience that I found extremely rewarding during my time as a PhD student was attending and presenting at conferences. Opportunities like this were rare during the first two years of my PhD because of COVID-19. However, once these restrictions were lifted in my final year, I took advantage of my unspent funding and I got to present my work at the World Congress of Psychiatric Genetics (WCPG) conference in Florence, Italy, and at the Schizophrenia International Research Society (SIRS) conference in Toronto, Canada. These opportunities helped me gain fresh insights into my research and were deeply enriching, but they were also very nerve-wracking. I remember the first time I had been selected to present my work at the SIRS conference and discussing my anxieties about this with my supervisor. 'Don't worry' he said, 'usually the oral talks are held in small venues, you'll be absolutely fine'. To my horror, the venue I presented in seated up to 500 people! I was determined, however, to not to let my nerves and insecurities

override the benefits this opportunity, even if I felt a bit intimated by the presence of so many established researchers who had been in the field for decades. Overall, these opportunities sharpened my perspective on where my own work fits into the field of schizophrenia research. Moreover, interacting with like-minded academics and professionals who were also passionate about schizophrenia research constantly sparked excitement and motivation in me and confirmed to me that I was in the right career.

Funding applications, papers, teaching, deadlines, results, networking all produced different ups and downs over the four years. Ironically, though, teaching both undergraduate and postgraduate students taught me so much about myself. Although it could be demanding, teaching helped normalise that I don't have to know everything or provide ready-made answers because I am constantly learning too. Interacting with students was extremely rewarding as many of them were curious and determined, and they often asked me questions that would make me think innovatively. In the final year of my PhD, I was asked to teach statistics to doctoral students who had a qualification in clinical psychology that pre-dated the introduction of doctoral-level training. Despite having the requisite knowledge and skills for this position, this was at times a challenging role. Many of these students were working in clinical roles that I had no prior experience in. However, by working with such a diverse group I learned so much more beyond that of my own research topic and it certainly kept me grounded in my own reasons for pursuing a doctoral degree. In addition, teaching different statistical analyses and techniques constantly made me think about the novel ways that I could apply these to my own research or to future projects.

It was through this doctoral programme that I started to really think for myself, to make new conclusions about this field, to contribute. Having a supportive supervisor helped hugely. At the start of my PhD, I relied upon regular face to face meetings, often for reassurance and confidence. However, as time went on, I slowly progressed towards becoming more independent. Of course, different kinds of roles placed different demands on my research. Having a supervisor that recognised those needs and was willing to share his expertise was a blessing as he always encouraged me to develop my own working style. Aside from all the career orientated skills, though, I think my biggest takeaway from doing this PhD was that it helped build my confidence as a researcher and I look forward to the next, exciting chapter in my academic career.

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Appendices

Appendix A: Ethical approval for the Irish Schizophrenia case control cognition sample

1711 2011 SCHOOL OF MEDICINE TRINITY COLLEGE DUBLIN

300 YEARS OF EXCELLENCE
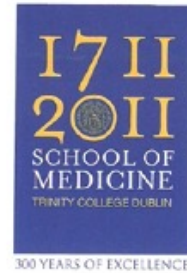
Dr. Gary Donohoe,
Dept. of Psychiatry,
Trinity Centre for Health Sciences,
St. James's Hospital,
Dublin 8

Monday, 13 October 2008

Study Title: Establishing a resource for imaging genomics of brain structure and integrity in Ireland

Dear Dr. Donohoe,

Further to the meeting of the Faculty of Health Sciences Research Ethics Committee on 27th May 2008, I am pleased to inform you that the above project has been approved without further audit.

Yours sincerely,

pp.

Prof. Orla Sheils
Chairperson
Faculty of Health Sciences Ethics Committee

THE UNIVERSITY OF DUBLIN

TRINITY COLLEGE

SCHOOL OF MEDICINE

FACULTY OF HEALTH SCIENCES

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Dr Gary Donohoe,
Psychiatry,
Trinity Centre for Health Sciences,
St. James's Hospital,
Dublin 8
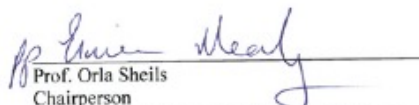
Friday, 29 April 2011

Study: Cognitive remediation in psychoses

Dear Applicant (s),

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in November 2010, we are pleased to inform you that the above project has been approved without further audit.

Yours sincerely

Prof. Orla Sheils
Chairperson
Faculty of Health Sciences Ethics Committee

Schools of the Faculty: Medicine, Dental Science, Nursing and Midwifery, Pharmacy and Pharmaceutical Sciences

COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH   TRINITY COLLEGE DUBLIN

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Dr. Gary Donohoe
Department of Psychiatry,
Trinity Centre,
St. James's Hospital,
Dublin 8

14 November 2012

Study: Establishing A Resource For Imaging Genomics Of Brain Structure And Integrity In Ireland.

Dear Applicant(s),

Further to a meeting of the Faculty of Health Sciences Ethics Committee held in May 2008, and amendment which was approved by the Chair on 26 September 2012, we are pleased to inform you that the above project has been approved without further audit.

Yours sincerely,

PP Cbaye

Dr. Ruth Pilkington
Chairperson
Faculty Research Ethics Committee

Other Applicants:
Prof. Hugh Garavan
Dr. Aiden Corvin

243

COLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH   TRINITY COLLEGE DUBLIN
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Chairperson
Faculty Research Ethics Committee

Other Applicants:
Prof. Hugh Garavan
Dr. Aiden Corvin

HSE

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Central Mental Hospital
Dundrum
Dublin 14

Tel: (01) 215 7400
Fax: (01) 298 9268

5th July 2016

Our Ref: HK/AOC

Professor Aiden Corvin
Consultant Psychiatrist
St. James's Hospital
James's Street
Dublin 8

Re: Genetic Assessment Project for Patients with Schizophrenia and Schizoaffective Disorder at the Central Mental Hospital

Dear Professor Corvin,

Further to our recent conversations I'm happy that ethics clearance for this project to proceed is already in place based on previous stated work. We are therefore ready to start. I am delighted we are able to get going on this work.

With best wishes.

Yours sincerely,

Professor Harry Kennedy, BSc MD FRCPI FRCPsych
Executive Clinical Director, Consultant Forensic Psychiatrist, National Forensic Mental Health Service, Central Mental Hospital
Clinical Professor of Forensic Psychiatry, University of Dublin, Trinity College
Medical Council No: 05923

Appendix B: Consent forms for the Irish Schizophrenia case control cognition sample

CONSENT FORM

Title of Project:
"A structural and functional MRI investigation of genetics, cognition and emotion in schizophrenia"

About the consent form:
This consent forms explains the research study in full. If you have any questions, please ask the researcher. If you are happy to be involved in this study, then please sign this consent form and make it available to the researcher(s).

If you have any questions regarding this research before or after taking part, please feel free to contact any member of the research team (Note: contact information is given at the end of this form).

Information about the Project:

There is evidence to suggest that certain aspects of our genetic make-up influence how we think and feel, and may cause differences in the parts of our brains that control thoughts and feelings. In this study we are interested in looking at how your genes influence your brain structure and function. In order to examine this we will take picture of your brain using Magnetic Resonance Imaging (described below).

The study will take place at the MRI facility located at Trinity College Dublin. The session (including the MRI scanning) will take 2.0 hours. You may withdraw from the study at any time. All information gathered during the course of this research is confidential and is available to you upon request.

What is MRI?

The purpose of functional MRI scanning is to determine which brain regions are activated as someone performs certain tasks. The MRI scanner uses a combination of radio waves and a strong magnetic field to take pictures of your brain while you perform the tasks. While you are inside the scanner you head will be placed inside a special device, known as the head coil. When you have been safely and comfortably placed in the head coil, the bed is moved slowly into the scanner. When your head is in the middle of the magnetic field, radio frequency pulses and magnetic fields are switched on and off to produce a signal which we use for measuring blood flow.

What will I be asked to do while I am in the MRI scanner?

Different types of MRI will be done while you are in the scanner. For some images you will be asked to lie still and relax. For others you will be asked to do tasks while we take the brain pictures (see description below). You will be able to hear us while you are in the scanner and we will explain exactly what you need to do before we start each MRI test run. Individual MRI test runs will last no longer than 10 minutes and

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TCIN   *from molecules to mind*

the entire testing session will be completed within 60 minutes. It is *very* important that you keep still and ***do not move your head*** while we are taking an image of your brain.

Task Description
You will be asked to complete two tasks during scanning. The first task is a working (or 'short-term') memory task.   In this task you will be asked to remember the location of items on a computer screen. You will practice this task on a computer before doing the same task in the scanner. For the second task, you will view a series of video clips showing different facial expressions. You will be asked to watch the video clips carefully. You will be given the information on how to complete the tasks prior to the scan. You must make sure that you understand the tasks before we start scanning. You will see the tasks presented on a screen and the instructor will show you how to respond. These tasks should take no more than 15 minutes to learn and will take less than an hour to complete in the scanner.

What are the risks associated with MRI?

When operated by appropriately qualified individuals, MRI presents virtually no risk, as there is **NO** exposure to x-rays or radioactivity with this procedure. However, there are some potential side effects. The noise produced by the exam has been reported to produce temporary threshold shifts (i.e. decreased ability to hear quiet sounds) in a small percentage of people.   You will be issued with protective headphones and earplugs to prevent damage to your hearing.   Given the confines of an MRI machine, a small percentage of people in the past have reported feeling claustrophobic (fear of being closed in a tight space) when placed into an MRI scanner.   Please let us know before we put you in the scanner if you have experienced claustrophobia in the past. During MRI scanning, you will be in contact with the MRI operator via an auditory communication system. This will be used to regularly check your comfort and to allow you to inform us of any problems or concerns. You will also have a "panic button", which you may press at any time to indicate that you wish to stop the scanning procedure.

As the MRI involves a large magnetic field, it is essential that **NO METAL BE BROUGHT INTO THE SCANNER WITH YOU**.

Items that **must be** removed by individuals before entering the MRI facility include:

- Purse, wallet, money clip, credit cards, cards with magnetic strips;
- Electronic devices such as beepers or cell phones;
- Hearing aids;
- Metal jewellery (in all parts of the body), watches;
- Pens, paper clips, keys, coins;
- Hair barrettes, hairpins;
- Shoes, belt buckles safety pins.

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Other objects that may be hazardous include:

- Metallic spinal rod
- Plates, pins, screws, or metal mesh used to repair a bone or joint
- Joint replacement or prosthesis
- Metal jewellery such as that used with body piercing.
- Some tattoos or tattooed eyeliner (these alter MR images, and there is a chance of skin irritation or swelling; black and blue pigments are the most troublesome)
- Bullet, shrapnel, or other type of metal fragment
- Metallic foreign body within or near the eye (such an object generally can be seen on an x-ray; metal workers are most likely to have this problem)
- Dental fillings (while usually unaffected by the magnetic field, they may distort images of the facial area or brain; the same is true for orthodontic braces and retainers)

If you have any of these items, please inform us immediately.

There may be additional or unknown risks associated with MRI. For example, in very rare cases, the strong magnetic field can induce nerve stimulation (e.g., switching the strong magnetic field gradients during imaging has been reported to cause twitching in the neck muscles). Also, in very rare cases, the radio signals have been reported to cause burns. There may be other risks associated with imaging that are not yet known.

Who shouldn't undergo the MRI procedure?

Research participants who have the following items **should not** undergo an MRI procedure:

- Cardiac pacemaker or an implanted defibrillator
- Catheter that has metal components that may pose a risk of a burn injury
- A metal clip placed to prevent bleeding from an intra-cranial aneurysm
- A medication pump (such as that used to deliver insulin or a pain-relieving drug)
- A cochlear (inner ear) implant

It is essential that you inform the MR operator if you have any metal items in any of the above lists.

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Pregnancy and MRI

For female participants it is also important that you tell us if there is any possibility that you are pregnant. To date there are no known risks of MRI during pregnancy, however as a precautionary safety measure pregnant individuals will not be included in the study. To participate in the current study women of child-bearing potential must be using one of the following acceptable methods of birth-control:

a. oral or transdermal contraceptives
b. barrier (diaphragm or condom) with spermicide
c. intrauterine progesterone contraceptive system
d. Levonorgestrel implant
e. Medroxyprogesterone acetate contraceptive injection
f. complete abstinence from sexual activity

Genetics testing

If you have not done so already, you will be asked to provide a saliva sample. We will extract DNA from this sample and use it for genetics testing. This sample will be stored by us and may be used in the future for other studies. The sample will not be used for any purpose other than to look at how genes impact brain structure and function.

What if the brain imaging finds some abnormality in my brain?

The brain images that are taken are not the kind that are used to look for problems in your brain. We will routinely check images for the presence of a brain abnormality. Should an abnormality be detected, we will contact you immediately and will recommend that you contact your GP to arrange for a clinical-quality brain scan. To make sure that you can be contacted at a later date, you will be asked to provide a name and contact details for a next-of-kin.

Although a significant abnormality is extremely unlikely, you should be aware that if such an abnormality is detected and you are informed, then this knowledge might have consequences for you. Please take the time to consider carefully what it would mean to you if we told you of an abnormality in your brain which might, or might not, affect you later in life. Knowledge of an abnormality may affect your ability to work in certain professions, obtain life or health insurance and other facets of daily living. If you do not want to know, then it is better not to participate in this study.

By providing my consent I agree that:

I have been informed of the discomforts and risks that I may reasonably expect to experience as part of this study. I have been informed that if a brain abnormality is observed, that I will be contacted for a meeting with a radiologist. I have been informed that when used on appropriately qualified individuals, MRI presents virtually no risk. There will be no exposure to x-rays or radioactivity in this study. I understand that noise produced by this exam could be very loud, and that I will wear

earplugs or headphones to prevent damage to my hearing. Even with earplugs, the noise produced by the exam may produce temporary threshold shifts (i.e., decreased ability to hear quiet sounds). I have been informed that I may experience some discomfort from lying in the MRI scanner such as claustrophobia (fear of being closed in a tight space) or tight sensations from having my head restrained to prevent movement. I have been informed that I will also be asked to perform some tasks that I have been trained on, prior to the MRI procedure, which should not cause undue distress.

I have been informed that other risks of injury due to MRI include damage to implanted electronic devices (such as pacemakers), haemorrhage if aneurysm clips are present and trauma if ferrous metal objects are brought too close to the scanner. However, these risks are minimal in a properly administered site. **I do not have any of these items in my body.**

I understand these risks and am agreeing to volunteer to participate in this research. I understand that I can withdraw at any time from the study.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

WITNESS'S NAME: _____

WITNESS'S SIGNATURE: _____

Date: _____

Research Team:

Dr. Gary Donohue, Room 0.19 Trinity Centre, St. James's Hospital, Dublin 8.
 Tel: 01-8962467
donoghug@tcd.ie

Dr. Emma Jane Rose, Room 0.18, Trinity Centre, St. James's Hospital, Dublin 8.
Tel: 01-8962464
rosse@tcd.ie

Mr. Omar Mothersill, Room 0.18, Trinity Centre, St. James's Hospital, Dublin 8.
Tel: 01-8962464
motherso@tcd.ie

GENERAL MRI DATA CONSENT FORM

Trinity College Institute of Neuroscience, (TCIN) is performing research, utilising an MRI scanner at Trinity College, Dublin 2. These research scans, although not full clinical scans, will be read by a radiologist.

In the unlikely event of an irregularity being found, the radiologist, [Dr William Torreggiani of The Adelaide and Meath Hospital Incorporating the National Children's Hospital (AMNCH), Tallaght] will inform the participants GP, that a proper clinical scan may be required to determine whether or not an irregularity is of clinical significance.

To enable us to perform the research scans the participant agrees to give consent/ permission for:
(i)   TCIN to conduct the MRI scan and store MRI scan data of participant;
(ii)   TCIN or Principal Investigator, (PI) to contact participants GP;
(iii)   TCIN radiographer to send MRI scan data to radiologist acting for TCIN;
(iv)   Radiologist to store data in a hospital system with same care as other patient data ensuring participants confidentiality;
(v)   Radiologist/ Clinician (acting for TCIN) to contact participants GP;
(vi)   TCIN to store data on the study for a period of at least 5 years or as specified in the specific consent form.

A dated standard letter signed by the appropriate Principal Investigator will be sent to all participants GP's, it is the responsibility of the Principal Investigator to ensure that this is sent at least two days before scanning to allow for postal delays. The principal investigator is responsible for their project at all times.

The TCIN designated radiologist will be sent data in a form that allows identification so that if a response is required he can act quickly (a copy of this is also held at TCIN). This will be stored in the hospital system with the same rigour and attention to confidentiality as all other medical data, as per the rules of that institution; a copy of this data will also be stored at TCIN. The raw scan data will be stored at TCIN in anonymous form for research purposes as agreed on the consent form of the specific research project.

I agree to the above points and understand that my data will be treated carefully at TCIN and in the hospital system.

Participant Name and Address_____

_____

_____

Signed by Participant:_____

Participants GP Name and Address _____

_____

_____

Date:_____

Appendix C: MRI Information for the Irish Schizophrenia case control cognition sample

MRI Screening Form

Date of Screen:

Demographic Information

Name:

Phone Number:

Alt. Number:

Date of Birth:

Gender: Male ☐ Female ☐

Do you wear glasses or contact lenses: Yes ☐ No ☐

Native language:

If English is not your native language, do you speak English and for how long have you been speaking English?

Handedness: Write? Left ☐ Right ☐

Ball? Left ☐ Right ☐

Fork/Spoon? Left ☐ Right ☐

Marital Status:

Years of Education: Occupation:

Mothers Years of Education: Mothers occupation:

Fathers Years of Education: Fathers occupation:

In what country were you born:

Please give the birth place for:

Mother

Maternal grandmother   Maternal grandfather

Father

Paternal grandmother   Paternal grandfather

Medical Information

Name and Address of GP:

GP Telephone:

Have you ever suffered:

Loss of consciousness? Yes ☐ No ☐   If yes, for how long:

Head injury? Yes ☐ No ☐

If yes, details:

Heart problems? Yes ☐ No ☐

Diabetes? Yes ☐ No ☐

Seizures? Yes ☐ No ☐

Any other major health problems:? Yes ☐ No ☐

If yes, details:

How often do you drink alcohol (please give specific details, e.g. 2 units, twice a week)?

Have you taken any illegal substance in the last 6 months? Yes ☐ No ☐

Are you currently taking any medications? Yes ☐ No ☐

If yes, details:

What is your current health status?

MRI Specific Criteria

Do you have:

Any metal in your body? Yes ☐ No ☐

If yes, details:

[ ]

Any surgical implants (pacemaker, screws, pins)? Yes ☐ No ☐

Any tattoos with ink-containing metal? Yes ☐ No ☐

If yes, where are these located when were these done?

[ ]

Braces, dentures or permanent retainer? Yes ☐ No ☐

Wig, hair extensions or hair piece that cannot be removed? Yes ☐ No ☐

Any piercings that cannot be removed? Yes ☐ No ☐

A history of claustrophobia? Yes ☐ No ☐

Female participants only

Could you be pregnant? Yes ☐ No ☐

If currently sexually active, are you using an approved form (e.g. the pill, condoms, an IUD, hormonal patch or implants) of contraception? Yes ☐ No ☐

Please note, that while there is no evidence that MRI can harm an unborn child, MRI has NOT been proven safe at any stage of pregnancy. If you think there is any chance, at all, that you might be pregnant you must tell us before we scan you

Psychiatric History

Have you ever seen a psychiatrist for an emotional or mental health problem? Yes ☐ No ☐

If yes, please give details:

[ ]

Have you ever been prescribed any psychiatric medication? Yes ☐ No ☐

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If yes, please give details:

Have you ever been hospitalised for a mental health problem? Yes ☐ No ☐

If yes, please give details:

Have you ever felt down or depressed for 2 weeks or more, nearly every day? Yes ☐ No ☐

If yes, please give details:

Have you ever felt so high that others said that you weren't acting like your normal self, or had an inflated self-esteem or other said you were acting 'manic'? Yes ☐ No ☐

Does anyone in your family have a diagnosis of schizophrenia or other mental illness? Yes ☐ No ☐

If yes, please give details:

Availability

Please list days and times that you would be available to come in for testing:

Appendix D: iRelate Ethical Approval for Galway

Saolta
Grúpa Ollscoile Cúram Sláinte
University Health Care Group

Ospidéal na h-Ollscoile, Páirc Mheirlinne
Merlin Park University Hospital
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Room 59
1st Floor
HR Building
Merlin Park Hospital
Galway.

11th February, 2016.

Professor Gary Donohoe
School of Psychology
National University of Ireland
University Road
Galway.

Ref: C.A. 1441 - Immune response & Cognitive performance in Schizophrenia (iRelate)

Dear Professor Donohoe,

I have considered the above project, and I am happy to grant Chairman's approval to proceed.

Yours sincerely,

PP
Dr. Shaun T. O'Keeffe
Chairman Clinical Research Ethics Committee.

Ospidéal na h-Ollscoile, Páirc Mheirlinne, MERLIN PARK UNIVERSITY HOSPITAL,
Galway, Ireland. Tel: 00 353 (0)91 757631

Appendix E: iRelate Ethical Approval for Dublin

SJH/AMNCH Research Ethics Committee Secretariat
Claire Hartin Ph: 4142199
email: claire.hartin@amnch.ie

Prof. Gary Donohoe
Professor of Psychology
School of Medicine
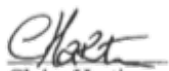NUI Galway
University Road
Galway

10th March 2016

REC Reference: 2015-03 Chairman's Action (11)
(Please quote reference on all correspondence)

Dear Prof. Donohoe,

Thank you for your recent correspondence to SJH/AMNCH Research Ethics Committee in which you queried approval for the above referenced study.

The Chairman, on behalf of the Research Ethics Committee, has reviewed your correspondence and granted ethical approval for this study.

Yours sincerely,

Claire Hartin
Secretary
SJH/AMNCH Research Ethics Committee

The SJH/AMNCH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Appendix F: iRelate Letter of consent for Galway participants

HRB Clinical Research Facility, Galway
Áis Taighde Chliniciúil HRB, Gaillimh

Letter of Consent

The purpose of this study - which is to understand changes in aspects of thinking and behaviour associated with mental health and emotional difficulties – has been explained to me to my satisfaction and I have had an opportunity to read the letter of information.

Participant Initials:_____ Date:_____

Contact details for members of the study team have been made available to me. I have had the opportunity to discuss any questions I may have with the research team, and all questions have been answered to my satisfaction.

1. I voluntarily agree to participate in this study and provide the clinical and cognitive data requested. I understand that I can drop out at any time, and am not required to give a reason, and opting out will not effect my medical care, now or in the future. All clinical and cognitive data will be stored at NUI Galway under Prof. Gary Donohoe's lead.

(Circle as appropriate)   YES   /   NO

Participants Initials:_____ Date:_____

2. I also agree to provide blood samples that will be used for the purposes of genetic, immune and hormone analysis. The study team, led by Prof. Gary Donohoe, is responsible for the blood samples. Blood samples will be given a specific study code without any personal identifying information. Samples will then be stored in the research laboratory facility of Dr. Declan McKernan at NUI Galway, and may be used for future studies seeking to understand the genetic and immune basis of brain development and disorders.

(Circle as appropriate)   YES   /   NO

Participants Initials:_____ Date:_____

The risks associated with having an MRI scan have been explained to me. Specifically, I have been told that there is minimal physical risk and that I will not be exposed to x-rays or radioactivity in this study. I understand that noise produced by this MRI exam could be very loud, and that I will wear earplugs or headphones to prevent damage to my hearing. I have been informed that I may experience some discomfort from lying in the MRI scanner such as fearfulness of being in a tight space or tight sensations from having my head restrained to prevent movement. I have been informed that I will also be asked to perform some tasks that I have been trained on, prior to the MRI procedure, which

iRELATE Study - Letter of Consent – Final [V4.0_CRF_Galway_ 09/01/2019]

should not cause undue distress. I have been further informed that other possible risks of injury due to MRI include damage to implanted electronic devices (such as pacemakers), aneurysm clips or metal objects. I have been informed that if a brain abnormality is observed, that my treating consultant or GP will be informed and that I will be called for a meeting with the radiologist. The MRI data will be stored at NUI Galway under Prof. Gary Donohoe's lead.

I agree to have an MRI scan. (Circle as appropriate) YES / NO

Participants Initials:_____ Date:_____

4. I understand that my neuropsychological and MRI data is likely to be of use in future studies that seek to understand the biological and environmental factors that influence mental health disorders such as schizophrenia. All data will be stored safely and securely, in an anonymised format, in the Psychology building of NUI Galway.
I agree to the future use of my data for these purposes.

(Circle as appropriate) YES / NO

Participants Initials:_____ Date:_____

5. I give permission to authorized personnel to have access to my records to determine if I am eligible for the study. I understand that my personal details will be kept strictly private and confidential, and will only be used for research related to brain, cognition, and mental health.

(Circle as appropriate)   YES   /   NO

Participants Initials:_____ Date:_____

6. I understand that I will not benefit personally from the

study. Participants Initials:_____ Date:_____

7. I understand that I am free to withdraw my consent for the study at any time, and either participating in or withdrawing from this study will not affect that any medical or psychological treatment I receive.

Participants Initials:_____ Date:_____

8. I agree to have my contact details kept on file, which may be used by the same research team to contact me about future studies. If you agree the research team will contact you according to your preferences via phone or email. I also understand that I do not give consent to future studies by agreeing to be re-contacted for future studies. I understand

iRELATE Study - Letter of Consent – Final [V4.0_CRF_Galway_ 09/01/2019]

that this option does not impact on the participation of this study or any future study participation.

Participants Initials:_____Date:_____

PARTICIPANT'S NAME: _____

PARTICIPANT'S   SIGNATURE: _____

Date: _____

WITNESS'S NAME: _____

WITNESS'S SIGNATURE: _____

Date: _____

Research Team:

Prof. Gary Donohoe
Dept Psychology, Room 1040, Arts Millennium Building Extension (AMBE), NUI Galway.
Tel: 353-91-495122
Email: gary.donohoe@nuigalway.ie

Dr. Omar Mothersill
Room 2060, Arts Millennium Building Extension (AMBE), NUI Galway
Tel: 353-091-493457
Email: omar.mothersill@nuigalway.ie

Dr. Maria Dauvermann
Room 1063 Arts Millennium Building Extension (AMBE), NUI Galway.
Tel: 353-91-495953
Email: maria.dauvermann@nuigalway.ie

iRELATE Study - Letter of Consent – Final [V4.0_CRF_Galway_ 09/01/2019]

Appendix G: iRelate Letter of consent for Dublin participants

ST. JAMES'S HOSPITAL
James's Street, Dublin 8
Telephone (+353 1) 410 3000
www.stjames.ie

Immune Response and Social Cognition in Schizophrenia (iRELATE)

Letter of Consent

The purpose of this study - which is to understand changes in aspects of thinking and behaviour associated with mental health and emotional difficulties – has been explained to me to my satisfaction and I have had an opportunity to read the letter of information. Contact details for members of the study team have been made available to me. I have had the opportunity to discuss any questions I may have with the research team.

1. I voluntarily agree to participate in this study and provide the clinical and cognitive data requested. (Circle as appropriate)   YES   /   NO

Participants Initials: _____ Date: _____

2. I also agree to provide blood samples that will be used for the purposes of genetic, immune and hormone analysis. The study team, led by Prof. Gary Donohoe, is responsible for the blood samples. Blood samples will be given a specific study code without any personal identifying information. Samples will then be stored in the research laboratory facility of Dr. Declan McKernan at NUI Galway, and may be used for future studies seeking to understand the genetic and immune basis of brain development and disorders.

(Circle as appropriate)   YES   /   NO

Participants Initials: _____ Date: _____

3. The risks associated with having an MRI scan have been explained to me. Specifically, I have been told that there is minimal physical risk and that I will not be exposed to X-rays or radioactivity in this study. I understand that noise produced by this MRI exam could be very loud, and that I will wear earplugs or headphones to prevent damage to my hearing. I have been informed that I may experience some discomfort from lying in the MRI scanner such as fearfulness of being in a tight space or tight sensations from having my head restrained to prevent movement. I have been informed that I will also be asked to perform some tasks that I have been trained on, prior to the MRI procedure, which should not cause undue distress. I have been further informed that other possible risks of injury due to MRI include damage to implanted electronic devices (such as pacemakers), aneurysm clips or metal objects. I have been informed that if a brain abnormality is observed, that my treating consultant or GP will be informed and that I will be called for a meeting with the radiologist.

I agree to have an MRI scan. (Circle as appropriate)   YES   /   NO

Participants Initials: _____ Date: _____

iRELATE Study - Letter of Consent - Final [V3.0 / 28/11/2017]

ST. JAMES'S HOSPITAL

James's Street, Dublin 8
Telephone (+353 1) 410 3000
www.stjames.ie

4. I understand that my data is likely to be of use in future studies that seek to understand the biological and environmental factors that influence mental health disorders such as schizophrenia. All data will be stored safely and securely, in an anonymised format, in the Psychology Building of NUI Galway. I agree to the future use of my data for these

purposes. (Circle as appropriate)   YES   /   NO

Participants Initials:_____Date: _____

5. I understand that my personal details will be kept strictly private and confidential, and will only be used for research related to brain, cognition, and mental health. I give permission to authorized personnel to have access to my records. (Circle as appropriate)
YES /NO

Participants Initials:_____Date: _____

6. I understand that I will not benefit personally from the

study. Participants Initials:_____Date: _____

7. I understand that I am free to withdraw my consent for the study at any time, and either participating in or withdrawing from this study will not affect that any medical or psychological treatment I receive.

Participants Initials:_____Date: _____

8. I agree to be contacted for future studies by the same research team. I agree that the research team will contact me according to my preferences via phone or email. I also understand that I do not give consent to future studies by agreeing to be re-contacted for future studies. I understand that this option does not impact on the participation of this study or any future study participation.

Participants Initials:_____Date: _____

iRELATE Study - Letter of Consent - Final [V3.0 / 28/11/2017]

ST. JAMES'S HOSPITAL

James's Street, Dublin 8
Telephone (+353 1) 410 3000
www.stjames.ie

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

WITNESS'S NAME: _____

WITNESS'S SIGNATURE: _____

Date: _____

Research Team:

Prof. Gary Donohoe
Dept Psychology, Room 1040, Arts Millennium Building Extension (AMBE), NUI Galway.
Tel: 353-91-495122
Email: gary.donohoe@nuigalway.ie

Dr. Omar Mothersill
Room 2060, Arts Millennium Building Extension (AMBE), NUI Galway
Tel: 353-091-493457
Email: omar.mothersill@nuigalway.ie

Dr. Maria Dauvermann
Room 1063 Arts Millennium Building Extension (AMBE), NUI Galway.
Tel: 353-91-495953
Email: maria.dauvermann@nuigalway.ie

iRELATE Study - Letter of Consent - Final [V3.0 / 28/11/2017]

Appendix H: iRelate Letter of information for Galway participants

HRB Clinical Research Facility, Galway
Áis Taighde Chliniciúil HRB, Gaillimh

Letter of Information to Participants

Project Title: Immune Response & Social Cognition in Schizophrenia (iRELATE)

About this information leaflet:
You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. This Participant Information Sheet will tell you about the purpose of the research, along with its potential risks and benefits.

There will be a screening process to ensure that you are eligible and that it is safe for you to take part in the study. If eligible, and you agree to take part, we will ask you to sign a Consent Form. Only the minimum amount of data necessary for the study is being sought. If there is anything that you are not clear about, we will be happy to explain it to you. Please take as much time as you need to read it. You will also be given a copy of this Participant Information Sheet and the Consent Form to keep. You should only consent to participate in this research study when you feel that you understand what is being asked of you, and you have had enough time to think about your decision.

It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights in any way. Whether or not you agree to take part, any medical care you might be currently receiving will not be changed or affected.

Description:
There is evidence to suggest that certain aspects of our environment and genetic make-up influence how we think and feel. These aspects may cause differences in the parts of our brains that control thoughts and feelings. In this study we are interested in looking at how your environment and genes influence your brain structure and function. A particular focus of the research is on examining whether these effects are related to changes in our immune system – the system that helps us identify infections such as viruses and mount a response. The two questions we want to address in this research are:
(1) Does the effect of genes that are already known to increase illness risk occur because of changes in our immune system? In order to study these genetic and immune system changes we will ask you to give blood (described below).
(2) Does our early social environment (e.g. our childhood relationships) modify this relationship? In order to examine theses influences on thinking and feeling we will ask you some questions and take pictures of your brain using Magnetic Resonance Imaging (MRI - described below).

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The study will consist of three assessment visits. The first visit will be a clinical assessment, which will take about 2.5 hours. The second visit, which will occur one or two weeks later, will involve cognitive assessment, blood draws, and a stress test. This visit will take about 2.5 hours. The third visit will include an MRI scan, which will last around 1.5 hours. The first and second visits will take place at a clinical centre that is in your town (depending on where you live) and the MRI scan in the third visits will take place at the MRI facility located in St James Hospital, Dublin.

(1) Clinical assessment visit
In the clinical assessment will be asked questions about your early childhood experiences (including you relationship to your parents as a child, and whether you experienced any significant trauma or loss in childhood).

(2) Neuropsychological assessment visit
This assessment will consist of three parts. Firstly, you will be asked to do tests that look at memory, concentration and emotion – these include testing your memory, your ability to recognise emotions from pictures of faces, and to 'read' other people's emotions. Secondly, your bloods will also be taken for testing. Thirdly, you will be asked to do a stress test.

What are the risks associated with giving blood?
During the neuropsychological assessment a qualified nurse will take your bloods. This will be done in the routine way using a blood catheter and the equivalent of three tablespoons of blood will be taken. There is minimal physical risk with this procedure.

Storage & future use of blood-based DNA and immune data
Any samples you provide us with will be stored safely and securely in an anonymised format (i.e. with your identifying details such as your name removed). The sample will then be used for the genetic and immune components of the study. These samples, along with the other information you provide, may also be used in the future by us in further studies seeking to understand the genetic and immune basis of brain development and disorders. The samples will not be used for any purposes other than for the purpose of understanding brain and mental health disorders.

(3) MRI scanning visit What is an MRI?
The purpose of this MRI is to determine the size and shape of the brain, and which brain regions are activated as you perform certain tasks. The MRI scanner uses a combination of radio waves and a strong magnetic field to take pictures of your brain while you perform the tasks. While you are inside the scanner your head will be placed inside a special device, known as the head coil. When you have been safely and comfortably placed in the head coil, you are moved slowly into the scanner. When your head is in the middle of the magnetic field, radio frequency pulses and magnetic fields are switched on and off to produce a signal, which we use for measuring blood flow.

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What will I be asked to do while I am in the MRI scanner?
Different types of MRI will be done while you are in the scanner. For some images you will be asked to lie still and relax. For others you will be asked to do tasks while we take the brain pictures. You will be able to hear us while you are in the scanner and we will explain exactly what you need to do before we start each MRI test run. Individual MRI test runs will last no longer than 10 minutes and the entire testing session will be completed within 60 minutes.

Task Description
You will be asked to complete three tasks during scanning. You will practice the first task on a computer before doing the task in the scanner. These tasks include testing your memory, your ability to recognise emotions from pictures of faces, and to 'read' other people's emotions. These tasks are different tasks than the tasks from the neuropsychological assessment. After the MRI scan, you will be asked to do two additional tasks, similar to two of the tasks you will have done previously in the MRI scanner.

What are the risks associated with MRI?
Your MRI scan will be operated by qualified individuals. When done in this way, MRI presents virtually no risk, as there is **NO** exposure to x-rays or radioactivity with this procedure. However, there are some potential side effects. The noise produced by the exam may lead to decreased ability to hear quiet sounds in a small percentage of people. You will be issued with protective headphones and earplugs to prevent damage to your hearing.

Given the confines of an MRI machine, a small percentage of people in the past have reported feeling claustrophobic (fear of being closed in a tight space) when placed into an MRI scanner. Please let us know before we put you in the scanner if you have experienced claustrophobia in the past. During MRI scanning, you will be able to speak to the MRI operator via a microphone. This will be used to regularly check your comfort and to allow you to inform us of any problems or concerns, or to stop the scan if you feel any discomfort.

Benefits
There will not be a direct personal benefit to you from participating in this study. The long-term purpose of the study is to improve our understanding of serious mental health disorders such as schizophrenia. This improved understanding may, we believe, have potential benefits for discovering new treatments for these disorders in the future, and this is why we are asking you to participate.

You will be reimbursed for travel and related expenses incurred with attending for assessments, but you will not be paid for your participation. Feedback on the assessment will not be provided routinely, but you will be able to seek summary feedback on you cognitive assessment if you wish, along with a photo taken from your brain scan.

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Confidentiality and data storage

Your identity will remain confidential throughout and after the study. The signed consent form will be stored on site by the principal's investigator and only members of the research team will be granted access to the form. A reference number will be assigned to the participant's name upon participation in the study as part of ensuring confidentiality. This number will be used to identify all material collected from you. Only the research team will have access to the coded data from the experiment. These members are bound by a contractual code of secrecy that means that members would face disciplinary action who disclose or facilitate unauthorised access to identifiable data. All other data from the study visits (i.e. the clinical assessment visit, the neuropsychological assessment visit and the MRI scanning visit) will be safely stored with Prof. Gary Donohoe, who leads the study, and Dr. Declan McKernan at NUI Galway.

All data that will be provided will be processed by the research team and collective results may be published in scientific journals and/or conferences. However at no point will individual results be interpreted. The results of the research will not be used or disclosed for commercial purposes.

Conditions and withdrawal

It is entirely up to you if you would like to participate in this study. As a participant of this study, you may voluntarily decide to withdraw at any time without any consequences. In the event that you need to withdraw before the day of the experiment, you only need to contact the research team via email. During the experiment, should you experience any discomfort with the blood draws or in the MRI scanner you can easily communicate your discomfort and request the experiment to be discontinued.

Research Ethics Committee

The study has been approved by the Research Ethics Committee at Tallaght University Hospital. No persons, who are carrying out this research, have a link to the Committee or the institution behind the committee.

Lawful basis for the research

This health research is carried out based on the General Data Protection Regulation (Article 6 and Article 9).

Re-Contact

It is optional for you to be contacted by the same research team for future studies. If you agree the research team will contact you according to your preference via phone or email. If you agree to be contacted for future studies, you do not give consent to future studies. This option does not impact on the participation of this study or any future study.

iRELATE Study – Information to Participants – Final V3.0 / 09/01/2019

For further information please contact:
Prof. Gary Donohoe
Room 1040, Arts Millennium Building Extension (AMBE), NUI Galway
Tel: 353-91-495122
Email: gary.donohoe@nuigalway.ie

Dr. Omar Mothersill
Room 2060, Arts Millennium Building Extension (AMBE), NUI Galway
Tel: 353-091-493457
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Dr. Maria Dauvermann
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Appendix I: iRelate Letter of information for Dublin participants

OSPIDÉAL NAOMH SÉAMAS
ST. JAMES'S HOSPITAL

Ospidéal Naomh Séamas, Sráid Shéamais, Baile Átha Cliath 8.
St. James's Hospital, James's Street, Dublin 8.
+353 1 410 3000   www.stjames.ie

Letter of Information to Participants

Project Title: Immune Response & Social Cognition in Schizophrenia (iRELATE)

About this information leaflet:
You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. This Participant Information Sheet will tell you about the purpose of the research, along with its potential risks and benefits.

There will be a screening process to ensure that you are eligible and that it is safe for you to take part in the study. If eligible, and you agree to take part, we will ask you to sign a Consent Form. If there is anything that you are not clear about, we will be happy to explain it to you. Please take as much time as you need to read it. You will also be given a copy of this Participant Information Sheet and the Consent Form to keep. You should only consent to participate in this research study when you feel that you understand what is being asked of you, and you have had enough time to think about your decision.

It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights in any way. Whether or not you agree to take part, any medical care you might be currently receiving will not be changed or affected.

Description:
There is evidence to suggest that certain aspects of our environment and genetic make-up influence how we think and feel. These aspects may cause differences in the parts of our brains that control thoughts and feelings. In this study we are interested in looking at how your environment and genes influence your brain structure and function. A particular focus of the research is on examining whether these effects are related to changes in our immune system – the system that helps us identify infections such as viruses and mount a response. The two questions we want to address in this research are:

(1) Does the effect of genes that are already known to increase illness risk occur because of changes in our immune system? In order to study these genetic and immune system changes we will ask you to give blood (described below).

iRELATE Study – Information to Participants – Final [V2.0 / 07/09/2016]

175

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University Hospital of Trinity College Dublin.
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OSPIDÉAL NAOMH SÉAMAS
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Ospidéid Naomh Séamas, Sráid Shéamais, Baile Átha Cliath 8.
St. James's Hospital, James's Street, Dublin 8.
+353 f 470 3000   www.stjames.ie

(2) Does our early social environment (e.g. our childhood relationships) modify this relationship? In order to examine theses influences on thinking and feeling we will ask you some questions and take pictures of your brain using Magnetic Resonance Imaging (MRI - described below).

The study will consist of three assessment visits. The first visit will be a clinical assessment, which will take about 2.5 hours. The second visit, which will occur one or two weeks later, will involve cognitive assessment, blood draws, and a stress test. This visit will take about 2.5 hours. The third visit will include an MRI scan, which will last around 1.5 hours. The first and second visits will take place at a clinical centre that is in your town (depending on where you live) and the MRI scan in the third visits will take place at the MRI facility located in St James Hospital, Dublin.

(1) Clinical assessment visit
In the clinical assessment will be asked questions about your early childhood experiences (including you relationship to your parents as a child, and whether you experienced any significant trauma or loss in childhood).

(2) Neuropsychological assessment visit
This assessment will consist of three parts. Firstly, you will be asked to do tests that look at memory, concentration and emotion – these include testing your memory, your ability to recognise emotions from pictures of faces, and to 'read' other people's emotions. Secondly, your bloods will also be taken for testing. Thirdly, you will be asked to do a stress test.

What are the risks associated with giving blood?
During the neuropsychological assessment a qualified nurse will take your bloods. This will be done in the routine way using a blood catheter and the equivalent of three tablespoons of blood will be taken. There is minimal physical risk with this procedure.

Storage & future use of blood-based DNA and immune data
Any samples you provide us with will be stored safely and securely in an anonymised format (i.e. with your identifying details such as your name removed). The sample will then be used for the genetic and immune components of the study. These samples, along with the other information you provide, may also be used in the future by us in further studies seeking to understand the genetic and immune basis of brain development and disorders. The samples will not be used for any purposes other than for the purpose of understanding brain and mental health disorders.

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2 | 3

OSPIDÉAL NAOMH SÉAMAS
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(3) MRI scanning visit
What is an MRI?

The purpose of this MRI is to determine the size and shape of the brain, and which brain regions are activated as you perform certain tasks. The MRI scanner uses a combination of radio waves and a strong magnetic field to take pictures of your brain while you perform the tasks. While you are inside the scanner your head will be placed inside a special device, known as the head coil. When you have been safely and comfortably placed in the head coil, you are moved slowly into the scanner. When your head is in the middle of the magnetic field, radio frequency pulses and magnetic fields are switched on and off to produce a signal, which we use for measuring blood flow.

What will I be asked to do while I am in the MRI scanner?

Different types of MRI will be done while you are in the scanner. For some images you will be asked to lie still and relax. For others you will be asked to do tasks while we take the brain pictures. You will be able to hear us while you are in the scanner and we will explain exactly what you need to do before we start each MRI test run. Individual MRI test runs will last no longer than 10 minutes and the entire testing session will be completed within 60 minutes.

Task Description

You will be asked to complete three tasks during scanning. You will practice the first task on a computer before doing the task in the scanner. These tasks include testing your memory, your ability to recognise emotions from pictures of faces, and to 'read' other people's emotions. These tasks are different tasks than the tasks from the neuropsychological assessment. After the MRI scan, you will be asked to do two additional tasks, similar to two of the tasks you will have done previously in the MRI scanner.

What are the risks associated with MRI?

Your MRI scan will be operated by qualified individuals. When done in this way, MRI presents virtually no risk, as there is **NO** exposure to x-rays or radioactivity with this procedure. However, there are some potential side effects. The noise produced by the exam may lead to decreased ability to hear quiet sounds in a small percentage of people. You will be issued with protective headphones and earplugs to prevent damage to your hearing.

Given the confines of an MRI machine, a small percentage of people in the past have reported feeling claustrophobic (fear of being closed in a tight space) when placed into an MRI scanner. Please let us know before we put you in the scanner if you have experienced claustrophobia in the past.

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315

OSPIDÉAL NAOMH SÉAMAS
ST. JAMES'S HOSPITAL

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During MRI scanning, you will be able to speak to the MRI operator via a microphone. This will be used to regularly check your comfort and to allow you to inform us of any problems or concerns, or to stop the scan if you feel any discomfort.

Benefits
There will not be a direct personal benefit to you from participating in this study. The long-term purpose of the study is to improve our understanding of serious mental health disorders such as schizophrenia. This improved understanding may, we believe, have potential benefits for discovering new treatments for these disorders in the future, and this is why we are asking you to participate.

You will be reimbursed for travel and related expenses incurred with attending for assessments, but you will not be paid for your participation. Feedback on the assessment will not be provided routinely, but you will be able to seek summary feedback on you cognitive assessment if you wish, along with a photo taken from your brain scan.

Confidentiality
Your identity will remain confidential throughout and after the study. The signed consent form will be stored on site by the principal's investigator and only members of the research team will be granted access to the form. A reference number will be assigned to the participant's name upon participation in the study as part of ensuring confidentiality. This number will be used to identify all material collected from you. Only the research team will have access to the coded data from the experiment.

All data that will be provided will be processed by the research team and collective results may be published in scientific journals and/or conferences. However at no point will individual results be interpreted.

Conditions and withdrawal
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iRELATE Study – Information to Participants – Final [V2.0 / 07/09/2016]

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4|5

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Re-Contact
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For further information please contact:

Prof. Gary Donohoe
Room 1040, Arts Millennium Building Extension (AMBE), NUI Galway
Tel: 353-91-495122
Email: gary.donohoe@nuigalway.ie

Dr. Omar Mothersill
Room 2060, Arts Millennium Building Extension (AMBE), NUI Galway
Tel: 353-091-493457
Email: omar.mothersill@nuigalway.ie

Dr. Maria Dauvermann
Room 1063 Arts Millennium Building Extension (AMBE), NUI Galway
Tel: 353-91-495953
Email: maria.dauvermann@nuigalway.ie

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5 | 5

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University Hospital of Trinity College Dublin.
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Appendix J: iRelate recruitment letter to consultants- Galway

iRELATE_Information_Sheet_Clinicians_Galway_V2.4_20/09/17

**Immune Response & Social Cognition
in Schizophrenia (iRELATE)**

OÉ Gaillimh
NUI Galway

University Hospital Galway   St. James's Hospital Dublin

Summary of the study

The aim of the study is to gain a better understanding of how the environment and genes influence your brain structure and function. A particular focus of the research is on examining whether these effects are related to changes in the immune system in individuals with schizophrenia.

What is involved in the study?

There are three parts to the study:

1) There is a screening process to ensure the participant is eligible and that it is safe for him/her to take part in the study. Following this, the participant will be asked to complete pen and pencil questionnaires about early childhood experiences and there will be some clinical interviews. This first part of the study will take about 2.5 hours.

2) In the second part of the study, the participant will be asked to complete pen and pencil tests and computer tasks that look at memory, concentration and emotion. In addition, he/she will also be asked to provide small blood samples for immune function and genetic testing. Lastly, he/she will also be asked to participate in a stress task. This part will stake about 2.5 hours.

3) In the third part of the study, the participant will be asked to do new computer tasks while having an MRI scan of the participant's brain done. This part will take about 1.5 hours.

The first and second part of the study will take place at the University Hospital Galway, whereas the third part of the study will take place at St. James's Hospital in Dublin. All travel and related expenses for the study will be fully reimbursed. In addition, we can provide feedback on the pen and pencil tests and computer tests. We also give a DVD containing the MRI scan of the participant's brain.

What individuals can be included in the study?

✓ Patient is between 18 and 65 years old

✓ Patient has a diagnosis of schizophrenia or schizo-affective disorder as defined by DSM-IV

✓ Patient does not currently misuse substances (for at least one month)

Who will be in contact with the participants?

Dr. Maria Dauvermann (Postdoctoral Research Fellow)   Tel: 091 495953

Email: maria.dauvermann@nuigalway.ie

Prof. Gary Donohoe (Principal Investigator)   Tel: 091 495 122

iRELATE_Information_sheet_clinicians_Dublin_v2.3_18/04/17

OÉ Gaillimh
NUI Galway

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Immune Response & Social Cognition in Schizophrenia (iRELATE)

St. James's Hospital Dublin

Summary of the study

The aim of the study is to gain a better understanding of how the environment and genes influence your brain structure and function. A particular focus of the research is on examining whether these effects are related to changes in the immune system in individuals with schizophrenia.

What is involved in the study?

There are three parts to the study:

1) There is a screening process to ensure the participant is eligible and that it is safe for you to take part in the study. Following this, the participant will be asked to complete paper and pencil questionnaires about early childhood experiences and there will be some clinical interviews. This first part of the study will take about 2.5 hours.

2) In the second part of the study, the participant will be asked to complete paper and pencil tests and computer tasks that look at memory, concentration and emotion. In addition, he/she will also be asked to provide small blood samples for immune function and genetic testing. Lastly, he/she will also be asked to participate in a stress task. This part will stake about 2.5 hours.

3) In the third part of the study, the participant will be asked to do new computer tasks while having an MRI scan of the participant's brain done. This part will take about 1.5 hours.

All study parts will take place at St. James's Hospital in Dublin. Travel and related expenses for the study will be reimbursed. In addition, we can provide feedback on the paper and pencil and computer tests. We also give a DVD containing the MRI scan of the participant's brain.

What individuals can be included in the study?

✔ Patient is between 18 and 65 years old

✔ Patient has a diagnosis of schizophrenia or schizo-affective disorder as defined by DSM-IV

✔ Patient does not currently misuse substances (for at least 1 month)

Appendix K: Childhood trauma questionnaire (CTQ)- amended version

Childhood Trauma Questionnaire

Instructions: The questions below ask about some of your experiences growing up as a child and a teenager. Although these questions are of a personal nature, please try to answer as honestly as you can. For each question, circle the dot under the response that best describes how you feel. If you wish to change your response, put an X through it and circle your new choice. If you are not sure about the frequency of a specific event and the age when it happened, please give an estimated answer.

When I was growing up:	Never True	Rarely True	Sometimes True	Often True	Very Often True
1. I didn't have enough to eat.	○	○	○	○	○
2. I knew that there was someone to take care of me and protect me.	○	○	○	○	○
3. People in my family called me things like 'stupid', 'lazy', or 'ugly'.	○	○	○	○	○
4. My parents were too drunk or high to take care of the family.	○	○	○	○	○
5. There was someone in my family who helped me feel that I was important or special.	○	○	○	○	○
6. I had to wear dirty clothes.	○	○	○	○	○
7. I felt loved.	○	○	○	○	○
8. I thought that my parents wished I had never been born.	○	○	○	○	○
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital. Age when this first happened? _____	○	○	○	○	○
10. There was nothing I wanted to change in my family.	○	○	○	○	○
11. People in my family hit me so much that it left me with bruises or marks. Age when this first happened? _____	○	○	○	○	○
12. I was punished with a belt, a board, a cord, or some other hard object. Age when this first happened? _____	○	○	○	○	○
13. People in my family looked out for each other.	○	○	○	○	○

277

14. People in my family said hurtful or insulting things to me.	○	○	○	○	○
15. I believe that I was physically abused. Age when this first happened? _____	○	○	○	○	○
16. I had the perfect childhood.	○	○	○	○	○
17. I got hit or beaten so badly it was noticed by someone like a teacher, neighbour or doctor. Age when this first happened? _____	○	○	○	○	○
18. I felt that someone in my family hated me.	○	○	○	○	○
19. People in my family felt close to each other.	○	○	○	○	○
20. Someone tried to touch me in a sexual way, or tried to make me touch them. Age when this first happened? _____	○	○	○	○	○
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them. Age when this first happened? _____	○	○	○	○	○
22. I had the best family in the world.	○	○	○	○	○
23. Someone tried to make me do sexual things or watch sexual things. Age when this first happened? _____	○	○	○	○	○
24. Someone molested me. Age when this first happened? _____	○	○	○	○	○
25. I believe that I was emotionally abused. Age when this first happened? _____	○	○	○	○	○
26. There was someone to take me to the doctor if I needed it.	○	○	○	○	○
27. I believe that I was sexually abused. Age when this first happened? _____	○	○	○	○	○
28. My family was a source of strength and support.	○	○	○	○	○

Appendix L: CAMI form

Centre for Advanced Medical Imaging (CAMI)
St. James's Hospital, Dublin

RESEARCH SUBJECT - SCAN REQUEST FORM

STUDY DETAILS:

Principal Investigator: Click here to enter text.   **Study name:** Click here to enter text.
Date:_____/_____/_____   **Time:** Click here to enter text.

PATIENT DETAILS:

Forename: Click here to enter text.   **Surname**:Click here to enter text.
DOB:_____/_____/_____   **Sex:** Click here to enter text.

CAMI MRN: Click here to enter text.   **SJH MRN:** Click here to enter text.
Mobility: Walk ☐ Chair ☐ Requires Assistance ☐   **Weight:** Click here to enter text.

PATIENT HISTORY

1. Does the patient have any of the following: (YES / NO)

　　　Cardiac pacemaker ☐
　　　Aneurysm clip 　　☐

2. Any history of renal (kidneyy) disease/failure, dialysis or diabetes? (YES / NO)

　　　Creatine level within 3 months: Click here to enter text.
　　　　　(only for studies using contrast agent)

3. Does the patient have **any** implants / prosthesis? (YES / NO)

　　　Type of Implant: Click here to enter text.   **Model Number:** Click here to enter text.

　　　Name of implant: Click here to enter text.   **Manufacturer:**Click here to enter text.

4. Has the patient ever been injured by metallic object or fragment especially to the eyes? (YES / NO)
　　　(Metallic slivers, shaving, bullet, shrapnel, foreign body)

5. Has the patient prior surgery or an operation of any kind? (YES / NO)
　　　If yes, please indicate the date and type of surgery:
　　　Month: Click here to enter text. **Year:** Click here to enter text.**Type of Surgery**: Click here to enter text.