Genetic and Environmental Influences on Cognitive and Neural Development

Tess Aurora Smith

MRC Cognition and Brain Sciences Unit

University of Cambridge

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DECLARATION

This thesis is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text. I further state that no substantial part of my thesis has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. It does not exceed 60,000 words, the prescribed word limit for the Clinical Medicine and Clinical Veterinary Medicine Degree Committee.

My research has been adapted, published, and posted on a preprint server. Where this is the case, I am the lead author and was responsible for the design, data collection, analysis, and write-up, in collaboration with my supervisor and colleagues.

Tess A. Smith, BSc (Hons), MPhil
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ABSTRACT

The brain self-organises slowly over time, being shaped by both endogenous and exogenous factors. This process results in a unique system for each person, with neuronal circuits shaped by an individual's genetic background and experience. This thesis aims to better understand these multifactorial gene-environment-outcome relationships, and how they relate to human development. Using multiple data types from the Avon Longitudinal Study of Parents and Children (ALSPAC) combined with a diverse methodological approach, I highlight compounding environmental factors which longitudinally interact to predict developmental outcomes, generate meaningful and valid measures of polygenic propensity, and consider the ways the early environment and polygenic heritability influence and interact to influence specific features of the structural connectome, features that are essential for coherent neural communication and brain function.

In the first empirical chapter, I use structural equation modelling to assess whether maternal mental health longitudinally mediates associations between the early socioeconomic status (SES) and key developmental outcomes (i.e., cognitive ability and child mental health). I show that maternal mental health mediates these relationships, and primarily during the first year of life. In the second empirical chapter, I employ polygenic score (PGS) analysis to generate valid and meaningful PGSs for cognitive ability and educational attainment, with the PGSs for cognitive ability ultimately taken forward in the proceeding empirical chapters. The third empirical chapter incorporates measures of socioeconomic status, PGSs for cognitive ability, and diffusion tract imaging data to explore how these data types are associated with global and local features of the connectome. This was made possible by employing graph theory metrics and partial least squares regression analysis. I demonstrate the early child environment and the genome influence the structure of the brain across at least three local metrics of network connectivity (i.e., node strength, degree, and clustering coefficient), with node strength playing a particularly significant role. Drawing on local node strength and generalised linear modelling, the fourth and final empirical chapter considers how measures of SES and polygenic propensity interact to influence developmental outcome and specific features of the connectome that fall under the rich-club framework (i.e., rich-club, feeder, and peripheral nodes, and rich-rich, rich-feeder, and peripheral connection types). Here I show both SES and PGSs to interact to influence developmental outcome, as well as node and connection type. In particular, PGS and the SES-by-PGS interaction appear to relate to the connectivity of a rich-club of highly interconnected nodes most strongly, but these variables do this by shaping so-called 'feeder' connections. Finally, the links between polygenic propensity and connection strength are patterned by gene expression, being strongest across connections that span regions with moderate levels of expression similarity.

This thesis provides new insights made possible by employing a diverse methodological approach in combination with a rich prospective longitudinal dataset. The findings show how it is possible to span multiple levels of analysis within a contemporary developmental science framework, to consider how factors operate at a population level in terms of behaviour, environment, heritability, and brain organisation.

For George and Aldous

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LIST OF ABBREVIATIONS AND ACRONYMS

A	Adenine
ABCD	Adolescent Brain Cognitive Development
ACPC	Anterior Commissure-Posterior Commissure
ADHD	Attention Deficit Hyperactivity Disorder
AHBA	Allen Human Brain Atlas
ALSPAC	Avon Longitudinal Study of Parents and Children
ANT	Advanced Normalisation Tool
ASD	Autism Spectrum Disorders
BLTS	Brisbane Longitudinal Twin Study
C	Cytosine
CCEI	Crown-Crisp Experiential Index
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Confidence Interval
COGENT	Cognitive Genomics Consortium
CUBRIC	Cardiff University Brain Research Imaging Centre
C+T	Cluster and Thresholding
DAWBA	Development and Well-Being Assessment
DICOM	Digital Imaging and Communications in Medicine
DIM	Dimension
DNA	Deoxyribonucleic Acid
DTI	Diffusion Tensor Imaging
DTR	Danish Twin Registry
DWI	Diffusion-Weighted Imaging
EGCUT	Estonian Genome Centre, University of Tartu
ELSA	English Longitudinal Study of Aging
EPDS	Edinburgh Postnatal Depression Scale
FID	Family ID
FIML	Full Information Maximum Likelihood
FoV	Field of View
G	Guanine
GENR	Generational R Study
GfG	Genes for Good
GLM	Generalised Linear Modelling
GO	Gene Ontology
GQI	Generalised Q-Sampling Imaging
GRM	Genetic Relationship Matrix
GSII	Generation Scotland: Scottish Family Health Study

GWAS	Genome-Wide Association Study
HARDI	High Angular Resolution Diffusion-Weighted Images
HiQ/HRS	High-IQ/Health and Retirement Study
HRC	Haplotype Reference Consortium
HWE	Hardy-Weinberg Equilibrium
ID	Individual Identifier
IID	Sample ID
INFO	Imputation Information
INU	Intensity Non-Uniformity
IQ	Intelligence Quotient
IS	Interactive Specialisation
LD	Linkage Disequilibrium
M	Mean
MAC	Minor Allele Count
MAF	Minor Allele Frequency
MCS	Millennium Cohort study
MD	Multiple Demand
MDD	Major Depressive Disorder
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NESCOG	Netherlands Study of Cognition, Environment, and Genes
PC	Principal Component
PCA	Principal Component Analysis
PGS	Polygenic Score
PLS	Partial Least Squares
PPMCC	Pearson's Product-Moment Correlation Coefficient
PRS	Polygenic Risk Score
QC	Quality Control
RMSEA	Root Mean Square Error of Approximation
RNA	Ribonucleic Acid
ROI	Region of Interest
RS	Rotterdam Study
SCZ	Schizophrenia
SD	Standard Deviation
SE	Standard Error
SEM	Structural Equation Modelling
SES	Socioeconomic Status
SMD	Standardised Mean Differences
SNP	Single Nucleotide Polymorphism

SRMR	Standardised Root Mean Square Residual
STR	Swedish Twin Registry
STSA	Swedish Twin Studies of Aging
S4S	Spit for Science
T	Thymine
TE	Echo Time
TEDS	Twins Early Development Study
TI	Inverse Time
TR	Repetition Time
UKB	UK Biobank
UKHLS	UK Household Longitudinal Study
WISC	Wechsler Intelligence Scale for Children
WLS	Wisconsin Longitudinal Study

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1 GENERAL INTRODUCTION

The human brain develops probabilistically (Gottlieb, 1998). That is, its endpoint cannot be predicted by its starting point. This is because over time it self-organises, with this self-organisation shaped, at least in part, by both genetic and environmental factors (Arnatkevičiūtė et al., 2021b; Ilyka et al., 2021; Plomin & Viding, 2022; Scerif, 2010; Tooley et al., 2021). Relative to other species, human brain development is particularly protracted (Benito-Kwiecinski et al., 2021). Indeed, some have argued that the human brain does not reach full maturity until the third decade (Orben et al., 2022). This prolonged process provides maximum opportunity for the brain to adapt to its environmental niche. The end result is a unique system for each person, with neuronal circuits shaped by an individual's genetic background, as well as their experience. This thesis is rooted in these theoretical underpinnings of contemporary developmental science, and aims to better understand these multifactorial gene-environment-outcome relationships and how they relate to human development. To achieve this, a diverse methodological approach must be engaged.

In this opening chapter, I will build the conceptual framework for the empirical work that follows, outlining what is already known about the ways in which the environment and genome influence variability in early child development across multiple levels, including cognitive development, educational attainment, and the structure and organisation of the brain. I discuss the utility of modelling the brain as a system, consider the role of early life adversity for neurodevelopmental outcomes, and highlight the methodologies needed to unpack this multifactorial variability. Throughout this General Introduction, I will highlight the potential opportunities that would flow from addressing the knowledge gaps in the field, and discuss the availability of tools required to bridge those gaps. This is followed by an outline of the fundamental lines of inquiry I aim to address in the thesis, along with a brief summary of the chapters that follow.

1.1 CONTEMPORARY DEVELOPMENTAL SCIENCE

Contemporary developmental science orientates developmental research towards the dynamic interplay between exogenous (i.e., occurring outside) and endogenous (i.e., occurring within) factors that shape neurodevelopment over time (Bronfenbrenner & Evans, 2000). In this way, individual variability in development and functioning can be thought of as a consequence of exposure to various exogenous (e.g., family, social network, and culture) and endogenous (e.g., genomics, neurobiology, and the endocrine system) influences (Cairns et al., 1996). This framework has a number of key ingredients, which include the central importance of timing, the need for multiple levels of analysis, and the consideration of context. The end goal is an enhanced understanding of the *processes* underlying human variability and how we adapt to our niche developmental environment, rather than simply

studying end-states or blindly charting changes across age with little or no explanation of mechanism. It naturally follows that contemporary developmental science acknowledges the importance of concepts and findings across various disciplines, bridging scientific inquiry from anthropology, biobehavioural science, cellular and molecular biology, developmental psychology, sociology, and neuroscience.

At the centre of this theoretical framework sits the brain. As mentioned, the brain self-organises over time. Its developmental components occur in a loop, continually providing and receiving feedback from exogenous and endogenous factors, paving the way for an interactive and specialised cortical network (Johnson, 2011; Kiani et al., 2022). This results in a dynamic and nonlinear progression of the structural and functional development of the brain. This emergent developmental process likely plays a key role in individual variability seen across developmental outcomes. Understanding the mechanisms behind this process could thereby provide meaningful information for informing both policies and interventions that seek to foster positive development at both an individual and population level. However, as will be discussed in detail, the processes by which internal and external factors interact to influence development are complex, and this complexity lends to the challenges faced when trying to understand how individual differences emerge in the first place during development (Astle et al., 2022).

1.1.1 ENVIRONMENTAL AND GENOMIC INFLUENCES ON THE DEVELOPMENT OF COGNITIVE ABILITY AND EDUCATIONAL ATTAINMENT

The early home environment influences a multitude of developmental outcomes. Environmental factors, such as household income, parental education, employment, alcohol consumption, nicotine consumption, household quality, and breastfeeding habits predict a child's cognitive ability, educational attainment, and physiological and psychological health (Bignardi et al., 2022; Dalmaijer et al., 2021; Johnson et al., 2021; Walker et al., 2011). As we will see shortly, interpreting the reason for this prediction is not as simple as it may first appear. Even so, some features of an individual's environment can have long-lasting associations with multiple outcomes. For example, growing up in a household with a library of approximately 80 books is associated with cognitive development and educational attainment in the early years, as well as literacy and numeracy in later life (Sikora et al., 2019). A wide set of environmental factors are linked to subsequent cognition, education, and behaviour. Whilst these factors do not account for *all* the variability in these outcomes, they account for a substantial proportion of it, with some finding over 50% of variability attributable to environmental factors (Bignardi et al., 2022). As we will see in a moment, it is very hard to know if these relationships are themselves *causal*. This notwithstanding, improving early life environments is nonetheless a common goal shared by many governments and is a long-term ambition of many developmental scientists. This goal was echoed globally in the 2021 United Nations Sustainable Development Goals report, which established equitable early childhood development as a cornerstone of its agenda (United Nations, 2021).

Just as the early childhood environment is associated with developmental outcomes, it also provides the optimal setting for parental interventions that encourage typical development during sensitive periods, such as the first three years of life (Nelson III & Gabard-Durnam, 2020). Meta-analyses show that environment-based

interventions, aimed at fostering responsive nurturing care in the home environment, result in significant benefits for early child development (Britto et al., 2017; Jeong et al., 2021; Kumar et al., 2022). One particular meta-analysis (Jeong et al., 2021) consisting of over 100 interventions targeting child outcomes found positive benefits, with significant standardised mean differences (SMD) for motor function (SMD = 0.24), cognition (SMD = 0.32), language (SMD = 0.28), healthy attachment styles (SMD = 0.29), socioemotional development (SMD = 0.19), and reduced behavioural difficulties (SMD = −0.13). Home-based interventions also have the potential for benefits beyond the intended target, such as improvements in parent-child relationship outcomes and maternal mental health (Singla et al., 2015). Whilst meta-analyses of environment-based interventions have highlighted their value, there is still much to be learned about *how* their benefits operate. This is, in part, due to disparity between interventions and a paucity of detailed protocols, making it difficult to decipher the mechanisms behind their benefits (Britto et al., 2017; Jeong et al., 2021; Kumar et al., 2022). This is likely further complicated by the potential for environmental factors to influence developmental outcomes both directly and indirectly, as will be discussed in **Chapter 2**. Nevertheless, it is clear that the environment is closely associated with early childhood development, and this role *can* be causal, as evidenced by the success of interventions improving outcomes for both children and their parents.

Associations between the environment and developmental outcomes can be strong, but they are also complex. One specific environmental factor is unlikely to act in isolation on a specific developmental outcome. For example, factors commonly associated with socioeconomic standing (i.e., parental education, income, and occupation) are broadly related to a diverse range of outcome measures (e.g., cognitive, educational, physiological, psychological, and behavioural), with outcomes often sharing many concurrent environmental predictors (Bignardi et al., 2022; Sikora et al., 2019; Walker et al., 2011). Relatedly, parental education is an important predictor of working memory and vocabulary development, as well as child conduct problems, peer problems, and emotional problems (Bignardi et al., 2022). Put simply, environmental associations are rarely specific. An additional complexity is the plausible mediating role of other environmental factors in predicting developmental outcomes, a point which is considered in detail in **Chapter 2**. For example, some argue that parental education influences developmental outcomes indirectly through parental attitudes and expectations placed on a child, and that opportunities for cognitive stimulation in the home reflect these parental attitudes and expectations (Davis-Kean et al., 2021). Parental education may also be a proxy for other aspects of socioeconomic standing, such as income and occupation, which may be the critical influence on outcomes (Dalmaijer et al., 2021; Johnson et al., 2021).

To summarise briefly: the complexity of environment-outcome interactions makes it difficult to pinpoint *how* the environment influences various aspects of development. This is partially because environmental-outcome associations are rarely specific and may involve one or more mediating steps. By extension, the mechanisms by which environmental prediction operates remain largely unknown. This is clearly a large gap in our knowledge. In order to implement meaningful interventions, and policies that promote equitable childhood development, there is a need for research which addresses this gap.

There is no doubt the environment plays a critical role for a child's developmental trajectory – the success of interventions alone is testament to that. Even so, the environment only accounts for a portion of the variance seen across developmental outcomes. Advancements in genomics, statistical techniques, and accessibility of comprehensive large-scale cohort studies have shed light on the contributing role of heritability for child development (Armstrong-Carter et al., 2021; Collister et al., 2022; Marees et al., 2018; Plomin & von Stumm, 2018). This has been made possible by the application of genome-wide association studies (GWASs) and the subsequent calculation of polygenic scores (PGSs), both of which will be described in detail in **Chapter 3**. Together, these tools enable the stratification of risk based on heritability. Briefly, GWASs are large-scale studies that aim to analyse the genetic variants implicated in genotype-phenotype associations (Chen et al., 2021; Korte & Farlow, 2013; Tam et al., 2019). Whilst an individual's genome is approximately 99.5% identical to that of another, the genetic variations that exist are thought to substantially influence individual differences in health, risk, and phenotypic traits (National Human Genome Research Institute, 2012, 2018). PGS analysis draws upon the variants identified by GWASs to quantify an individual's genetic inclination towards a given disease, phenotypic behaviour, or trait, resulting in a personalised score for each individual in the cohort under study.

The computation of GWASs and PGSs for developmental outcomes, such as cognitive ability and educational attainment, have enhanced our understanding of the heritability of these complex outcomes. Prior to 2017, GWASs for cognitive ability could account for 1% of the variance in cognitive outcomes in independent samples (Plomin & von Stumm, 2018). The calculation of personalised scores summarising the accumulative effects of variants across the entire genome has enabled the proportion of variance in cognitive ability accounted for by the genome to rise to 4% (Okbay et al., 2016). GWASs have now further identified over 1,000 variants associated with educational attainment, with recent GWASs accounting for 10% of the variance seen in educational attainment outcomes (Lee et al., 2018). These effect sizes might not seem large, but at a population level they are substantial. For instance, a one standard deviation increase in PGSs for educational attainment will result in the difference of half a school year (Trejo et al., 2018). The capacity of PGSs to be equally predictive of developmental outcomes at different stages of life, combined with their causal nature given the stability of the genome, has led some to argue their predicative utility extends beyond traditional measures of psychometric testing (Plomin & von Stumm, 2018). Still, it is important to note that just like environmental influences on development, heritability only accounts for a portion of the variance seen across developmental outcomes. Similarly, whilst GWASs and PGS analyses have demonstrated the heritability of cognitive ability and educational attainment, those for other aspects of development have yet to yield predictive capacities of a similar size (Armstrong-Carter et al., 2021). For example, comparative effects have not been identified for internalising and externalising problems or risk-taking behaviours (i.e., driving behaviour, alcohol intake, and nicotine consumption) (Karlsson Linnér et al., 2019).

As was the case when considering environmental influences on child development, the association between heritability and developmental outcomes is not always straightforward. Even when genetic variants are not passed down from parents to children, they can influence development indirectly, because they may influence the early environment (Armstrong-Carter et al., 2020; Kong et al., 2018). This is because non-inherited variants still have the potential to influence parental behaviours, and by extension, the environment in which a child is raised. This

can then have knock-on effects for developmental outcomes. This can be illustrated by drawing again on parental education. Whilst parental education may be partially reflective of socioeconomic standing, it is also highly heritable (Lee et al., 2018). Even where genetic variants associated with educational attainment are not passed down from parents to their offspring, mothers with greater genetic propensity for higher educational attainment are more likely to have optimal prenatal health and greater cognitively stimulating parenting behaviours, such as reading books to their children (Armstrong-Carter et al., 2020; Kong et al., 2018; Wertz et al., 2019). This has been referred to as genetic nurturing, which also influences developmental outcomes (Wertz et al., 2019).

Overall, the genome can have a substantial influence on a child's developmental trajectory. This includes their own genome, as well as the genome of their primary caregivers. In this way, the role of the genome for development can occur both directly and indirectly. Although tools assessing genetic propensity (i.e., GWASs and PGSs) are limited in that they do not pinpoint a specific target gene or mechanism by which variants are associated with variations in developmental outcomes, and can only account for a proportion of the variance seen across developmental outcomes, they go some way to provide insight into the direct and indirect role of heritability for child development (Visscher et al., 2017).

1.1.2 GENETIC AND ENVIRONMENTAL INFLUENCES ON THE STRUCTURE AND ORGANISATION OF THE BRAIN

During the first three years of life, the brain undergoes rapid structural and functional development (Ouyang et al., 2019). This period is often referred to as a sensitive period for development, where the brain undergoes rapid development of cortical grey and white matter, regional cortical thickness, surface area, myelination of white matter connections, fractional anisotropy (i.e., cortical white matter integrity), and the emergence of the default mode network (Dubois et al., 2014; Gao et al., 2009; Knickmeyer et al., 2008; Lyall et al., 2015). Importantly, variance in these structural developments has downstream associations with cognitive and behavioural outcomes. For instance, variability in fractional anisotropy is associated with various aspects of cognitive development, including reading skills and the emergence of neurodevelopmental conditions like dyslexia (De Moura et al., 2016; Vandermosten et al., 2012), cognitive ability and educational attainment (Bathelt et al., 2019), attention and internalising behaviours (Loe et al., 2013), behavioural difficulties (Waller et al., 2017), and psychological health (Muetzel et al., 2018; Waller et al., 2017). By drawing on fractional anisotropy as an example, we can begin to see how the structure of the brain may play an influential role in shaping key developmental outcomes.

Just as developmental outcomes are associated with both genetic and environmental differences, so too is brain structure (Arnatkevičiūtė et al., 2021a; Gilmore et al., 2018; Tanti et al., 2018; Tooley et al., 2021). As will be discussed in **Chapter 5**, research integrating neuroimaging methodologies alongside transcriptional atlas data have highlighted the link between regional differences in brain organisation and regional differences in transcription of the genome (Arnatkevičiūtė et al., 2021a, 2021b). For example, gene expression in the brain mirrors patterns of structural connectivity within and between brain regions (Arnatkevičiūtė et al., 2021b). One possible driving factor behind this is specialised gene expression profiles for metabolic function and cytoarchitecture resulting in gene-derived molecular cues that shape brain connectivity. However, it is important

to note at this stage that it is hard to establish directionality. The efficiency of structural brain connectivity has important implications for developmental outcomes, and in particular, has been associated with variability in behaviour and cognition (Contreras et al., 2015). Take as an example the gene *CYIP1*. This gene has been implicated in brain functional connectivity and callosal functions, and haploinsufficiency of the *CYIP1* gene (i.e., where one copy of the gene is deactivated or deleted) has been associated with perturbations to bilateral brain connectivity and cognitive decline (Domínguez-Iturza et al., 2019). Brain-genome associations are further highlighted by research demonstrating polygenic inheritance to be neurobiologically manifested by morphologic differences in total brain volume during early childhood, with PGSs for cognitive ability and educational attainment positively associated with total brain volume in early life (Alemany et al., 2019).

The emergence of neural organisation is strongly associated with environmental factors. This association is multifaceted, and where the structure of the brain can influence developmental trajectories, the environment can shape the structural trajectory of the brain (Tanti et al., 2018; Tooley et al., 2021). One prominent theory posits that the early life environment can influence the *pace* of brain development. For example, children growing up in high socioeconomic status (SES) households display protracted structural brain maturation, leading to the elongated development of functional network formation and thereby enhanced efficiency within and between brain regions in adulthood (Tooley et al., 2021). Conversely, children growing up in low SES households display accelerated brain maturation, resulting in reduced access to windows of plasticity essential for neural plasticity and cognitive development. It is important to note at this early stage that the caveats about causality I introduced in the previous section also apply here – SES may itself not be entirely environmental. One possible way in which the socioeconomic environment could impact brain development may be via anticipated differences in stress and cognitive enrichment. For example, growing up in a low SES household increases the likelihood of experiencing chronic stress (Sheridan & McLaughlin, 2014), which is subsequently associated with the early onset of puberty (Gur et al., 2019), increased cellular deterioration (Miller et al., 2011), and threat of reduced protection and support (Snell-Rood & Snell-Rood, 2020), all of which have the capacity to increase the pace of brain maturation. Children in low SES households are also less likely to have exposure to a cognitively enriching environment (Rosen et al., 2020), which is associated with protracted synaptic pruning in regions associated with cognitive processes (McLaughlin et al., 2014). The neural correlates of environmental adversity, and in particular household SES, will be returned to at a later point.

1.2 MODELLING THE BRAIN AS A SYSTEM

Neuroscience has often focused on attempting to understand the contribution of specific brain regions when studying environment-outcome associations. Research considering how regions of the brain map onto these associations often focuses on measures of SES in the early life environment. These studies have found early SES to be associated with white matter architecture, visuospatial tract divergence, and fractional anisotropy in the corticospinal tracts, uncinate fasciculus, cingulum bundle, superior longitudinal fasciculus, inferior longitudinal fasciculus, and the fronto-occipital fasciculus (Dufford & Kim, 2017; Gianaros et al., 2013; Gullick et al., 2016). However, there is a rapidly expanding interest to model the brain as an integrated system, often as a network, and connectomics offers a neurobiologically insightful way of achieving this (Bullmore & Sporns, 2009) (see Sporns,

2022, for a recent review). As mentioned, the brain sits at the centre of the contemporary developmental science framework. As will be explored in **Chapter 4**, modelling the brain as a system allows us to comprehensively explore the ways genetic and environmental factors contribute to individual variability in the structural organisation and connectivity of the brain. In turn, this modelling of the brain as an integrated system could provide a vehicle for considering the ways that this system is associated with genomic and environmental variability, and in turn, outcomes like cognitive ability (**Chapter 5**). Thus, there is substantial utility and opportunity in modelling the brain as a system when studying the mechanisms underlying development and variability therein.

1.2.1 CONNECTOMICS

The structural connectome refers to the epitomisation of the brain as a series of networks between elements (i.e., nodes representing cortical grey matter) and their pairwise links (i.e., edges reflecting white matter integrity) within and across brain regions (Rubinov & Sporns, 2010). These nodes and edges define a network's topology. Connectomics refers to the study of these networks, and how they vary between populations. Connectomics can be used to represent all manner of things, including the economy and social networks (Barigozzi et al., 2011; Freeman, 1978; Girvan & Newman, 2002). For example, community structures exist within economic international trade networks (Barigozzi et al., 2011). Trading blocs are considered subunits of this network, and some global cities, such as London or New York, play a more central role to the overall functioning of the global economic system. Crucially, we can use connectomics to model the brain. When applied to complex brain networks, the central thesis of connectomics is the notion that the structural and functional connectivity of the brain can inform an understanding of brain dynamics and behaviours (Behrens & Sporns, 2012).

In this thesis, I will be using structural connectomics. How this is achieved is discussed in detailed in **Chapter 4** and **Chapter 5**, as well as elsewhere (Ciesla et al., 2021). Briefly, this is achieved by converting magnetic resonance imaging (MRI) scans from their native DICOM format to a compact NIfTI-1 format. Images go through a series of standardised quality control (QC) steps to account for things such as motion, field inhomogeneities, eddy currents, and to boost signal-to-noise ratios. Regions of interest (ROIs) are then identified by allocating a parcellation template, which subdivides the cerebral cortex into regions and labels them accordingly. Many parcellation schemes exist, each with its own level of granularity. ROIs undergo tissue classification and anatomical labelling (Fischl et al., 2002). Connectome matrices are then created by estimating and transforming the number of streamlines intersecting at ROIs to a density map for all pairwise combinations of ROIs. Connectome matrices can be binarised, whereby they are labelled as having a connection or not by a pre-specified density threshold. Alternatively, they can be weighted, in which case they include information on the strength of the edges, whilst still pre-specifying a density threshold to reduce the likelihood of spurious or non-significant connections being included in analyses. Once connectomes are created, graph theory metrics can be applied to the data to assess topological features of brain networks.

Graph theory is a branch of mathematics dating back to the 18th century, which involves the analysis of graphs, that is, structures modelling pairwise associations between objects (Bullmore & Sporns, 2009). The application

of graph theory metrics to the structural connectome is therefore a powerful way to assess the topology of brain network data, that is, the properties of these complex brain networks. We can conceptualise connectomics as graphs and use this mathematical framework as a way of understanding these connectome-based graphs. Using a substantial array of network analysis tools, graph theory metrics can be employed to provide insight on local (i.e., nodal), regional, or global (i.e., network-wide) features of network topology, including how integrated or segregated a network is (Bullmore & Sporns, 2009). We can assess the modular organisation of a network, that is, the degree networks are divided into subnetworks, with high-modularity reflecting greater within-module connectivity and predictive of cognitive ability and academic achievement (Chaddock-Heyman et al., 2020). We can further explore the efficiency of a network in distributing information at a global level, that being its small-worldness propensity (Latora & Marchiori, 2001). Small-worldness was conceptualised approximately two decades ago, and over the past decade has been widely applied to the growing field of connectomics (see review by Bassett & Bullmore, 2017). It refers to how effective a neural network is at distributing information at a global level, and is defined by high clustering and short path length (Latora & Marchiori, 2001).

Graph theory metrics can also be employed to assess features of a network's rich-club framework. Previous research has noted that brain networks have some particularly highly connected 'hub' regions, which participate in several communities across a network and play an integral role in a networks overall organisation (Hagmann et al., 2008; Sporns et al., 2007). These hubs have been further shown to be essential for efficient brain communication and healthy cognitive functioning (Bassett et al., 2009). When the hubs of a network form dense connections, where they are more connected to each other than other lower degree nodes, they are said to form a rich-club (Colizza et al., 2006). Rich-club organisation can inform the higher-order network structure, and more specifically, the specialisation, resilience, and hierarchical ordering of a network (Colizza et al., 2006; McAuley et al., 2007). How the study of network topology can inform our understanding of brain development, and the factors that shape it, will be discussed shortly, as well as in **Chapter 4** and **Chapter 5**.

1.2.2 DEVELOPMENTAL CHANGES IN BRAIN ORGANISATION

To date, the application of connectomics to the study of development has provided considerable insight into the structural and organisational changes that take place during typical and atypical development across the lifespan (Cao et al., 2014; Huang et al., 2015; Jones et al., 2021; Khundrakpam et al., 2013, 2016; Vértes & Bullmore, 2015; Zuo et al., 2017). We can see micro- and macro-structural changes taking place and shaping structural networks from the neonatal period through to adolescence (Huang et al., 2015). Modular organisation and small-world attributes are present at birth, and important topological features progressively expand during early development. Indeed, cognitive development itself aligns with important changes in structural and functional brain organisation. For example, between the ages of 5 and 11, children undergo substantial language and cognitive development (Friederici, 2006). During this time, we can see notable network hubs forming in language-dominated regions of the brain, such as the temporal, parietal, and inferior frontal regions, whereas during puberty (i.e., early-late adolescence) these hubs are increasingly less pronounced (Khundrakpam et al., 2013). Instead, during this time, large hubs appear in the frontal lobes, an area frequently associated with the pubertal brain and

the development of social cognition and executive functions (Blakemore et al., 2010). Thus, across development, brain circuitry and cognitive development appear to be closely related.

A strong recurring motif in developmental connectomics is segregation and integration (Fair et al., 2013; Jones et al., 2021; Tooley et al., 2021, 2022; Vértes & Bullmore, 2015). As network topological features emerge during childhood and adolescence, there is a marked increase in segregation and global integration. We can see prominent segregation emerging with age in systems associated with attention and abstract cognition, and increased integration between perceptual and attentional systems (Tooley et al., 2022). This process creates an increasingly specialised but integrated cortical architecture supporting cognitive and socioemotional skills that are developed during this period. Correspondingly, as the human brain slowly develops, segregated and integrated features are fine-tuned, and rich nodes (i.e., highly connected nodes well-linked to each other and the overall network) become more densely connected, forming rich-club hubs that enhance the strength of their connections over time (Vértes & Bullmore, 2015). It is perhaps, in part, for these reasons that the accelerated development associated with low SES in early childhood has implications for neural plasticity and cognitive development (Tooley et al., 2021). The increased rate of development during this crucial period for the development of cortical network structure and organisation, may result in less time for these key topological characteristics to develop, such as well segregated subnetworks and rich-club nodes, which ultimately has consequences for the overall efficiency of the network.

Why are these topological features so important and optimal? One theory postulates that 'small-world' topologies are important because they mean that resources can be efficiently allocated. In particular, 'network control theory' demonstrates that we need these hubs to switch networks between different states (see Medaglia et al., 2017 for a review). For example, Gu and colleagues (2015) used methodologies from control and network theories to mechanistically explore how the brain moves between varying cognitive states by considering the network organisation of white matter microstructure. This resulted in three key findings. First, they found that the default mode network houses densely connected areas, leading the authors to suggest these hubs promote the brain's capacity to move between easily reachable states. Second, weakly connected regions overlapping with cognitive control systems were identified, and were thought to promote the brain's capacity to move between more difficult to reach states. Lastly, there were areas that sat on the boundaries of network communities associated with attentional control systems. These were argued to allow for the integration and segregation of the various cognitive systems. We will return to this idea of 'rich', 'feeder', and 'peripheral' connections in **Chapter 5**. There is also a theory about topological characteristics reflecting economic trade-offs (Behrens & Sporns, 2012; Bullmore & Sporns, 2012). This theory posits that these topological features of the connectome allow for a more complex and efficient system with a lower wiring cost. In this way, long-distance connections are viewed as incurring a large metabolic cost and thereby small world architecture enables an optimal trade-off between minimising wiring costs and maximising metabolically expensive efficiency. Indeed, computational models that explicitly parameterise this economic trade-off do a remarkably good job of simulating the emergence of networks with the topological hallmarks of connectomes (Akarca et al., 2021; Betzel et al., 2016; Hilgetag & Kaiser, 2004; Vértes et al., 2012). It is important to note that these two theoretical accounts are not mutually exclusive – it is possible, indeed likely, that the brain works within resource constraints to optimise an organisation that allows for maximum network controllability.

Modelling the brain as a system, and applying connectomics to achieve this, has substantially added to our knowledge of how the developing brain organises over time, and how those structural and organisational features of cortical networks correspond with what is known about behavioural trajectories during early childhood and adolescence. But many gaps in our knowledge remain. For example, from twin studies we know that there is a genetic contribution to topological differences across connectomes (Fornito et al., 2011; van den Heuvel et al., 2013), and that the early environment can also be strongly associated with connectome organisation (Kim et al., 2019; Van Essen & Barch, 2015), but these two influences have never been considered simultaneously, so we do not know how they interact or overlap. Thus, there is a real opportunity to capitalise on connectomics as a means of exploring developmental variability and the factors that shape it.

1.3 EARLY LIFE ADVERSITY

Exposure to early life adversity, such as chronic stress, poverty, and maltreatment, has long been associated with risk to health outcomes across the lifespan (Bellis et al., 2019). Adverse experiences in early life have been linked with psychological and physiological ill-health and poor educational outcomes in childhood, and health-harming behaviours leading to chronic ill-health in adulthood (Bellis et al., 2014; Gilbert et al., 2009; Hughes et al., 2017). There is now additional evidence that early life adversity can shape development across multiple levels of analysis, including the development of the nervous system, endocrine system, and immune response (Belsky, 2019). Even so, the processes by which early life adversity influences development is not well understood. Existing theories fall broadly into two factions, cumulative risk models, and dimensional models of adversity. Both theoretical schools will be discussed in turn, followed by a discussion of the socioeconomic environment, its implications for developmental outcomes, and the current challenges faced when attempting to disentangle the socioeconomic environment from the genome.

It is also important to note that there is an enormous literature comprising studies which identify a single measure of environmental adversity and relate it to a single outcome, often using correlation or regression-based methods. For instance, some studies explore the relationship between quality language exposure (or lack thereof) and future reading success (Gámez & Levine, 2013; Jasińska & Petitto, 2018), or parental mind-mindedness (or supposed lack of) and children's subsequent Theory of Mind (Hughes et al., 2018; Kirk et al., 2015). These examples and others will not be discussed here for two reasons. Firstly, as will soon become clear, they are not particularly relevant for this thesis. Secondly, in many cases these studies suffer from highly problematic design choices. Often so few measures of the environment are selected that it gives a false impression of the specificity of the association. Or different predictors are compared by controlling for one whilst exploring the other, which almost inevitably creates residual confounding. This again provides a false impression of specificity (see Bignardi et al., 2022 for a discussion of this).

1.3.1 CUMULATIVE RISK MODELS OF ADVERSITY

Cumulative risk models operationalise adversity by calculating a risk score based on the quantity of adverse exposures or experiences during early childhood (Appleyard et al., 2005; Evans & De France, 2022; Evans et al.,

2013; Slopen et al., 2014). The number of experiences is the dominating feature, and adversity type, chronicity, or severity are generally not taken into consideration. In this sense, it is fair to say that cumulative risk models are reductive. There is an underlying assumption that no single form of adversity is more or less consequential (Evans & Kim, 2012, 2013). Rather, distinct types of adversity are argued to influence developmental outcomes in a cumulative manner, with self-regulatory processes and allostatic load as frequent explanatory pathways. For example, one study adopted the cumulative risk model to determine whether cumulative adversity in early childhood is associated with emerging risk factors for long-term health (i.e., weight, height, and blood pressure) (Slopen et al., 2014). In their study, Slopen and colleagues (2014) calculated a score based on the presence or absence of eight social risk factors at four developmental periods during the first seven years of life. Examples of risk factors included were maternal psychopathology, legal involvement, abuse, injury, and financial strain. Results showed that cumulative adversity was associated with behavioural challenges and BMI at age 7 years. However, the timing and chronicity of adversity differentially influenced outcomes.

Whilst this approach has been beneficial for specifying adversity-related health outcomes and enabling efficacious risk prediction, there are glaring limitations. For example, these models fail to specify the underlying mechanisms by which adverse experiences exert their effects on developmental outcomes (McLaughlin et al., 2021). As such, they lack the capacity to enable the identification of clear intervention pathways. Moreover, across multiple studies it is now becoming clear that measures of adversity themselves have a clear structure, and are not in fact combined arbitrarily (Busso et al., 2017; Carozza et al., 2022a; McCrory et al., 2013; Rosen et al., 2018; Sheridan & McLaughlin, 2014). Examples of this can be seen across the developmental literature, with exposure to threat often associated with fear learning, emotion regulation and reactivity, and attentional biases to emotion stimuli, and exposure to deprivation associated with difficulties across cognitive functions, such as executive functioning, language, and problem solving (see Sheridan et al., 2020 for a review).

1.3.2 DIMENSIONAL MODELS OF ADVERSITY

Dimensional models of adversity materialised in response to the pitfalls associated with cumulative risk models (McLaughlin et al., 2014). As such, they attempt to acknowledge the type, chronicity, and severity of early adverse experiences. Dimensional models argue that various types of adversity share features that co-occur with underlying dimensions of environmental experience (McLaughlin et al., 2021). These core underlying aspects of experience are argued to shape development. In the most common instantiation of this dimensional framework posits two domains, *threat* (i.e., threat of harm, such as physical or emotional maltreatment) and *deprivation* (i.e., absence of anticipated environmental inputs, such as cognitive enrichment or social stimulation) (Sheridan & McLaughlin, 2014). This approach views adversity through the lens of adaptability, considering the functional significance of different aspects of experience that are likely to adapt and guide behaviour. Furthermore, these models consider the affective, cognitive, and neurobiological mechanisms underlying dimensions of early experience encompassed by these two core domains. Dimensional models of adversity have catered to some of the shortcomings of the cumulative models which came before, even so, they are not impermeable to their own challenges and limitations. Likewise, the early environment often comprises overlapping adversities that span the supposed boundary demarcated by threat and deprivation (Smith & Pollak, 2021).

There is furthermore a lack of consistency in evidence in support of dimensional models of adversity, with these models not fully supported by the literature (Bignardi et al., 2022; Carozza et al., 2022a; Sapolsky, 2017). For example, where the dimensional account of adversity outperformed the cumulative account in a network analysis assessing dimensions of early adversity, developmental outcomes failed to cluster with distinct forms of adversity, as would have been predicted by the model (Carozza et al., 2022a). There is still much to be learned about the processes underlying early adversity-outcome associations, and the optimal models that define them. Correspondingly, Bignardi and colleagues (2022) employed canonical correlation analysis to explore whether 28 developmental outcomes in early adolescence share the same early environmental risk factors during the first three years of life. It was demonstrated that whilst you can obtain a broad dimension of adversity which predicts multiple general future outcomes (e.g., cognition and parent-rated behaviour outcomes), you also get specific relationships, such as between parental smoking and child smoking. Thus, developmental outcomes may very well share similar environmental risk factors, but exceptions should also be expected.

1.3.3 THE SOCIOECONOMIC ENVIRONMENT

The socioeconomic environment is one particular aspect of a child's early life experience that has received a great deal of attention. One prevalent measure commonly used, and widely linked with multiple developmental outcomes, is SES. SES is typically a continuous measure, usually normally distributed across the population, and comprised of a households parental occupation, income, and education (Baker, 2014; Hagger-Johnson et al., 2011; McMaughan et al., 2020). It is highly predictive of a child's cognitive ability, educational attainment, and physical and psychological health (Bignardi et al., 2022; Dalmaijer et al., 2021; Johnson et al., 2021; Walker et al., 2011). It is particularly important to note at the outset that despite this measure almost always being considered to be purely 'environmental', it is also likely to capture interactions between genetic background and the environment. For instance, PGSs for educational attainment can mediate the association between household SES and education outcomes (Krapohl & Plomin, 2016). Still, SES appears to play an influential role for neurodevelopment, with its implications far-reaching. As such, it is difficult to partition SES from developmental research.

The prevalence of poverty in the UK is as far-reaching as its impact on early child development. As of 2022, more than one in five individuals in the UK are living in poverty (British Government Department of Work and Pensions, 2022). This equates to 14.5 million people in poverty, 4.3 million of which are children. Current poverty rates in the UK are projected to substantially worsen as a result of the recent global pandemic, and subsequent increased cost of living (UK Parliament, 2023). There are several factors that likely contributed to this. For example, the COVID-19 pandemic had a disproportionate impact on those already at risk of low SES, with those working in low-wage sectors (e.g., accommodation and food services) having had reduced opportunities to work from home, and thus at higher risk of employment loss and being furloughed (Joseph Rowntree Foundation, 2022). Furthermore, lone parents, who consistently have the highest rates of in-work poverty compared to all other family types, and are more likely to work in low-wage sectors, had additional childcare responsibilities during the pandemic, adding to their risk of employment loss. Due to COVID-19-related reasons such as these, it is now estimated that by 2024, one in three children will be living in poverty (Joseph Rowntree Foundation, 2022). This is likely to be an underestimation given the cost-of-living crisis the UK population are facing at the time of writing.

This crisis is represented by staggering increases in consumer price inflation and energy expenses, with the Office for National Statistics reporting 93% of adults in the UK to have experienced increases in their cost of living between August-September 2022, alone (United Kingdom Parliament Research Briefing, 2022). Once again, low SES households are anticipated to be disproportionally burdened by these increases, as low SES households on average have greater food and energy bills compared to high SES households.

The prevalence of poverty in the UK has important implications for early development. As has been alluded to, the impact of SES is well-established, even if the mechanisms that drive this association are unclear. There is a wide range of socioeconomically patterned physical and psychological health problems. Even when adjusting for lifestyle factors, SES has been associated with psychiatric difficulties, self-harm, and substance abuse, as well as subsequent liver and renal diseases, ischaemic heart disease, dementia, cerebral infarction, chronic obstructive bronchitis, and lung cancer (see Kivimäki et al., 2020 for review). Relatedly, children from low SES households are two to three times more likely to experience mental ill-health compared to their high SES peers (Kim et al., 2013). The capacity of SES to predict child mental health extends beyond childhood, with childhood poverty-related stressors predictive of so-called 'helplessness' behaviours and emotion dysregulation in adolescence and adulthood (Evans, 2016). As will be discussed in **Chapter 2**, the impact of SES on physical and psychological health is complex, and SES may influence developmental outcomes indirectly through mediating factors in a child's environment. For example, poverty is associated with maternal mental health difficulties, and children whose mother's experience mental ill-health are at a higher risk themselves of experiencing mental ill-health (Fitzsimons et al., 2017).

Socioeconomic disparities are associated with variances in whole brain network organisation. With children growing up in low SES households displaying less efficient network organisation in multiple cortical (i.e., prefrontal cortex, cingulate, and insula) and subcortical (i.e., hippocampus and amygdala) regions (Kim et al., 2019). These findings are particularly pronounced for girls at the lower end of the SES spectrum. Where socioeconomic disparities are associated with variances in cognitive development, with those in low SES household displaying poorer cognitive ability compared to their high SES counterparts, this association is often mirrored by differences in brain structure (Noble et al., 2015; Weissman et al., 2018). For example, minor differences in income have been linked with relatively large differences in the brain surface area of children in low SES households, with income increases corresponding with substantial increases in brain surface area, and income decreases corresponding with substantial decreases (Noble et al., 2015). These relationships are not present to the same degree for children in high SES households, suggesting that this relationship is not linear. Children and adolescents growing up in low SES households have decreased connectivity between the anterior and posterior components of the default mode network, which has been implicated in cognitive skills such as executive functions (Weissman et al., 2018). Interestingly, adolescents in low SES households with an increasing income display greater connectivity proportionate to income change (Troller-Renfree et al., 2022; Weissman et al., 2018). For example, one study supplemented household income by providing low-income mothers with monthly cash payments, and subsequently assessed child brain development after their first year of life (Troller-Renfree et al., 2022). Mothers were randomly allocated one of two payments, receiving either $20 or $333 per month. After one year, the children of mothers who received the greater sum displayed greater neural activity

patterns associated with cognitive, language, and socio-emotional skills in later life (Troller-Renfree et al., 2022). Taken together, these findings show that brain structure and function are significantly influenced by SES during development, and these effects are greatest for those at the lower end of the SES spectrum.

As it stands, there is no question that a child's socioeconomic status is closely tied to multiple outcomes, and that this relationship can be causal (Britto et al., 2017; Jeong et al., 2021; Kumar et al., 2022). The focal question, in hopes of addressing inequity and implementing purposeful interventions or policies to circumvent its effects, is *how* this association is realised at a mechanistic level. The elephant in the room is genetic differences that may well covary significantly with a child's SES. Whilst we can see the negative associations between low SES and child development, this impact is not equivalent for all children. Where numerous children are adversely affected by low SES, there are those who appear to be apparently impervious to its negative influence. Some children display remarkable resilience and seem to flourish despite this adversity, even surpassing their high SES counterparts (Fritz et al., 2018; Luthar et al., 2015; Zolkoski et al., 2012). Whilst this adds to the complexity of SES-outcome associations, it also offers opportunity to assess potential protective factors that may contribute to these developmental outcome differences.

1.4 DISENTANGLING SES AND THE GENOME

Fifty years of genetic twin and adoption studies have profoundly enhanced our understanding of the heritability of complex physical, physiological, and psychological traits (Polderman et al., 2015). They have further highlighted the substantial role the environment plays in the expression of these traits, as heritability only accounts for approximately 50% of individual variability across complex behaviours and traits (Plomin & Viding, 2022). Analyses of the gene-environment interplay have further demonstrated genetic influence on environmental exposure, with environmental measures demonstrating, on average, 25% heritability (McAdams et al., 2013; Plomin & Bergeman, 1991). Moreover, many environmental measures and psychological traits are genetically mediated, with approximately 50% heritability (Plomin, 1994). At the same time, research on adoptees has lent further support for passive gene-environment correlations, with environment-outcome associations being greater for nonadoptive biologically related households (Plomin & Bergeman, 1991). Put simply, 50% of individual variability is argued to be determined by your genome, and within that 50%, 25% occurs as a result of gene-environment interplay. Quantitative and molecular genetics have added to our understanding of heritability and its association with environmental exposure (see Plomin & Viding, 2022 for a review). Even so, where twin and adoptee studies have added to the current body of literature on heritability and gene-environment interplay, they do not allow for the consideration of genomic influence on childhood SES.

By definition, household SES operates between households, not within; SES will be the same for children growing up in the same household. Correspondingly, the quantity of twins reared apart is not substantial enough to detect any potential genomic effects that are made up of the miniscule effects of thousands of inherited variants (Visscher et al., 2021). Assessing genomic influence in non-related samples is therefore pertinent, and genome-wide analyses and the calculation of PGSs offers an avenue to do this. For example, the application of genome-wide complex trait analysis (i.e., a technique comparing matrices of pairwise genomic similarity and pairwise

phenotypic similarity) in a sample of 3,000 unrelated children found that the genome drove the correlation between SES and cognitive ability (Trzaskowski et al., 2014). Still, this influence is likely not straightforward. An individual's genome and household SES have been found to distinctly influence cognitive ability and global cortical surface area during development, and significant associations between SES and cognitive ability can be seen even when accounting for genetic variance (Judd et al., 2020). There are also likely to be other genetic contributors influencing SES-outcome associations, such as the heritability of traits associated with SES, and those which indirectly influence developmental outcomes by way of genetic nurturing (Armstrong-Carter et al., 2020; Kong et al., 2018; Wertz et al., 2019). These findings, and others like them, warrant the need for research which further disentangles the SES environment from the genome. This is particularly pertinent if we are to attempt to identify the mechanisms underlying the ways SES and the genome influence neurodevelopment, both with regards to developmental outcomes, and the structural organisation of the brain.

Taking together the points raised thus far, this thesis aims to ask the broad question of what the underlying environmental and genomic factors are, influencing individual variability across developmental outcome and the structure and function of the brain. Specifically, I want to explore how the early life environment (by way of assessing SES) and genomic factors (by way of PGSs) account for the variability we see across cognitive ability and educational attainment. Moreover, by modelling the brain as a system, and simultaneously considering these multivariate types of data, I want to know how SES and polygenic influence contribute to the structure and organisation of the brain.

1.5 MODELLING MUTLIFACTORIAL INFLUENCE

Contemporary developmental science is inherently interdisciplinary, borrowing tools and techniques from multiple different disciplines and traditions. As such, integrating those methods is itself a challenge. One thing that is clear - as a field we must move past univariate approaches. Relatedly, we must have the statistical means to understand trajectories, assess complex interactions between domains of functioning, and integrate information across different levels of analysis (Pfeifer et al., 2018). To model multifactorial influence in this way, we must go beyond single genes, beyond individual brain regions, beyond single levels of analysis, and beyond individual timepoints or cross-sectional comparisons. Here I will briefly discuss the methodological means we have available to us, how those methods have been deployed thus far, and how we can utilise them to address emerging current knowledge gaps.

1.5.1 BEYOND SINGLE GENES

Following decades of research attempting to test the relationship between single genes and particular outcomes (see overview from Plomin et al., 1994), most of which is likely to be woefully underpowered, we now know that the vast majority of traits of interest to psychologists are likely to be highly polygenic (Plomin, 2019). As discussed further in **Chapter 3**, the accessibility of large-scale cohort studies comprising genome-wide data, combined with advancements in statistical genomics, has provided a platform for modelling this multifactorial influence on developmental outcomes (Armstrong-Carter et al., 2021; Collister et al., 2022; Marees et al., 2018).

This is made possible by the combined utility of GWASs (i.e., large-scale studies implicating genetic variants involved in genotype-phenotype associations) and PGSs (i.e., personalised scores that quantify an individual's genetic propensity for a given developmental behaviour or trait) when applied through the lens of behavioural genetics. Presently, the PGSs scores that account for the most variance in developmental outcomes are those derived for cognitive ability and educational attainment (Armstrong-Carter et al., 2021). For this reason, along with the notable subsequent influence these developmental outcomes have for other areas of an individual's life and well-being (Calvin et al., 2017; Cheng et al., 2012; Lövdén et al., 2020; Malanchini et al., 2020), genomic predictors of cognitive ability and educational attainment remain common proxies for genomic influence on early child development (Plomin & von Stumm, 2018).

Researchers can model the multifactorial interaction between genomic prediction and developmental outcomes by first identifying a GWAS large enough to detect the effects of the multitude of genetic variants which contribute to the developmental outcome under investigation. The genome of a study sample can then be aligned with the variants highlighted by the GWAS to calculate a personalised polygenic propensity score based on the presence of those identified variants in the study sample. These scores can be subsequently correlated with other domains of development to assess association, or perhaps more compellingly, can be combined with rich environmental and developmental outcome measures in downstream analyses that model multifactorial influence on development at various levels of inquiry. For example, PGSs for educational achievement have been incorporated with environmental measures of SES to assess potential genetic mediation in the association between SES and educational outcomes (Krapohl & Plomin, 2016). Genetic influence outweighs that of SES when it comes to number of years a child spends in education. This example illustrates how aspects of an individual's genome combined with environmental measures can shed light on complex environment-genome interactions. Whilst results such as these begin to build a picture of the ways in which a child's genome and environment may interact to influence developmental outcomes, they are limited to furthering our understanding of how this genetic influence may present at a more mechanistic level.

Building on this, research has incorporated neuroimaging data to model the multifactorial influence of PGSs for educational attainment and SES on brain development and cognitive ability (Judd et al., 2020). Results have supported the genetic overlap between SES-outcome associations, and have identified commonalities and differences between the PGSs for educational attainment and measures of SES when it comes to their influence on the structure and function of the brain. For example, PGSs for educational attainment demonstrate global and regional associations with brain development; PGSs related both to total cortical surface area and regional surface area in the right parietal lobe, an area crucial for nonverbal cognitive functions (Judd et al., 2020). On the other hand, SES factors were associated with brain development at a more global level, with lower SES linked with reduced cortical surface area and lower cognitive ability.

Whilst research looking beyond single genes to assess polygenic influence on development has considered PGS-developmental outcome associations, there is still much to be explored. For example, how polygenic propensity and SES concurrently influence the structural organisation of the brain is not yet known. It is furthermore not understood whether an interaction takes places between PGSs and measures of SES, and whether they influence

one another to shape variability in developmental outcomes and features of the connectome. The simultaneous integration of these data types would allow for a more holistic understanding of neurodevelopment and the emergence of individual variability.

1.5.2 BEYOND INDIVIDUAL BRAIN REGIONS

In the past 30 years, the availability of neuroimaging data at scale, in combination with advances in analysis, have changed the way we think about how brain and behaviour are linked. The early developmental literature was dominated by analysis and methods borrowed from an adult neuropsychology framework (see Astle & Fletcher-Watson, 2020 for review). For decades scientists searched for brain regions associated with particular cognitive skills or behaviours, or neurodevelopmental conditions. However, advances in neuroimaging itself, its availability, and the methods at our disposal are allowing us to ask a broader set of questions about how the developing brain is organised and connected (Zuo et al., 2017). Interestingly, despite the relatively recent application of these methods to the developing brain, they hue far closer to developmental theory, which posits a central role for connectivity itself in driving specialisation, adaptation, and development (Johnson, 1995, 2011). Understanding the complex ways in which the environment and genome interact to influence the emergence of network topologies, is likely to be crucial for understanding their variation across the population, and their contribution to subsequent cognition and behaviour (Vértes & Bullmore, 2015). To do this, we must move beyond the exploration of individual brain regions and consider brain organisation as a whole. In **Chapter 4** and **Chapter 5** of this thesis, I aim to address this and use the structural connectome as a way of achieving this. The application of graph theory to connectomics offers us a platform to quantify organisational hallmarks of complex networks, such as the structural connectome. One way of doing this is by first constructing personalised connectomes through the use of a non-invasive magnetic resonance imaging (MRI) technique, diffusion tensor imaging (DTI), which maps the axonal fibre tracks in the living brain (Vergoossen et al., 2021). This information can then be used to devise an adjacency matrix (i.e., a pairwise connection matrix), with rows and columns corresponding to the structural connectivity of the brain. This provides a graph of the networks within the brain. The same process is completed for each individual in a sample, resulting in a personalised connectome for each individual. In this way, individual differences in the connectome can be related to differences in developmental outcomes (Behrens & Sporns, 2012).

Once connectomes are generated for each individual in a sample, topological features of complex brain networks can then be captured by the application of graph theory metrics (Rubinov & Sporns, 2010; Sporns, 2022). To date, the application of graph theory metrics in this way has enabled an abundance of discoveries concerning brain organisation. For example, we can now identify segregated regions of the brain based on their distinctive patterns of connectivity, and assess these, as well as the large-scale networks connecting these regions, in significant detail (Behrens & Sporns, 2012). Graph theory metrics can also inform us on segregated (characterised by decreased short range edges and densely connected regions) and integrated (characterised by increased long range edges and consolidation of specialised information across regions) features of the human connectome (Sporns, 2013). Features which are pivotal for optimal communication and the cohesive integration of networks required for cognitive function (Fair et al., 2007). Importantly, graph theory metrics provide an avenue to better understand the architecture, development, and evolution of the brain (Sporns, 2022). These metrics have the added utility for

downstream analyses to assess the variance in anatomical brain connectivity attributable to multifactorial influence. The integration of connectomics and graph theory analysis, combined with the accessibility of rich data sets, makes asking critical questions to address complex associations involved in early child development possible. To date, these methods have been utilised to assess how neurodevelopment is influenced by various factors, and this has been made possible by advanced neuroinformatics techniques.

1.5.3 BEYOND SINGLE LEVELS OF ANALYSIS

To capture the interaction between exogenous and endogenous factors that likely interact to shape neurodevelopment, there is a need to move beyond single levels of analysis, which do not allow for the simultaneous consideration of multivariate influence. One statistical technique prevalent in neuroinformatics, which allows for the combination of multiple data types, is partial least squares (PLS) regression analysis. Generally speaking, PLS is a data reduction technique which identifies a set of orthogonal factors (i.e., latent variables) across multiple data sets, to detect which factors have the greatest predictive power (Wold et al., 1984). PLS determines whether a relationship is present between data sets, and if a relationship exists, it identifies the specific variables which best model the relationship. Importantly, PLS does not reduce distinct data sets and subsequently examine whether a relationship is present between those dimensions. It rather performs data reduction on the covariance matrix itself. In doing so, the dimensions it produces are optimised for explaining the relationships between different data sets. When applied to the appraisal of multifactorial influence on development, as is done in **Chapter 4**, PLS can handle factors at the level of the environment, genome, and structural brain connectivity.

Relatively recent research has used PLS to combine features of network topology and environmental factors to assess environmental influence on network connectivity (Johnson et al., 2021; Kim et al., 2019). A great example is research carried out by Johnson and colleagues (2021), which employed PLS to assess how measures of childhood SES were associated with the organisation of the human structural connectome. In addition to finding a widespread effect of SES on the connectivity of the brain, the connectome differentially mediated SES-outcome associations. For example, the connectome mediated associations between SES and cognitive ability when it came to measures of matrix reasoning and vocabulary, but not maths or reading, or internalising and externalising behaviour. This study demonstrates the utility of PLS for assessing multifactorial influence, and further echoes the intricacy of the processes underlying SES-outcome associations. PLS regression has also been deployed to identify how gene expression profiles shape the connectome. An example of this can be seen with research employing PLS to explain dimensions of covariance between network topology and gene expression profiles in Huntington's disease (McColgan et al., 2018). These findings highlighted the spatial patterning of gene expression to account for over 65% of the variance in regional corticostriatal and interhemispheric white matter connectivity loss in Huntington's disease. For the purpose of this thesis, PLS offers a flexible tool for the integration of different data types.

1.5.4 BEYOND INDIVIDUAL TIMEPOINTS AND CROSS-SECTIONAL DATA

Development occurs dynamically and nonlinearly over time. There are likely sensitive periods whereby substantial developmental changes occur, and exposure to adversity during these periods may be disproportionately impactful (Nelson III & Gabard-Durnam, 2020). Whilst certain questions necessitate longitudinal data and repeated measure of the same data, analyses including multiple timepoints provide the opportunity to capture dynamic interplay and potentially sensitive periods (Lloyd-Fox et al., 2019; Steele et al., 2012). For similar reasons, there are benefits to moving beyond cross-sectional data, which can often be based on imprecise and inconsistent retrospective self-reports (Cornish et al., 2013; Susser & Widom, 2012). Advanced statistical techniques, combined with data from multiple longitudinal timepoints, allow for modelling environmental factors that may interact and mediate one another to influence development. One good example is structural equation modelling (SEM), a multivariate technique which analyses the structural relations among variables (Gana & Broc, 2019; Iacobucci et al., 2007; Schreiber et al., 2006). As will be discussed in **Chapter 2**, SEM allows for the assessment of direct and indirect associations between all variables included in the model. It facilitates the inclusion of longitudinal data, allows for confirmation that measurement invariance is tenable across multiple timepoints (i.e., the longitudinal measures relate to the latent construct in the same way at each timepoint), and highlights how these direct and indirect associations may vary at different developmental stages and across outcome measures (Cheung & Rensvold, 2002). In this way, SEM, and the model subtypes that fall under this umbrella term, equips contemporary developmental scientists with the means to tease apart the environmental processes underlying early childhood development, and apply research findings to future policy and interventions. For example, this methodology has successfully been employed to identify mediating factors in the early environment that protect against risk factors for mental ill-health in adulthood, resulting in recommendations for future interventions (van Harmelen et al., 2016). Still, there remains an opportunity to utilise SEM with longitudinal samples and across multiple timepoints to further unravel SES-outcome associations through the consideration of domain specificity, potential environmental mediating factors, and sensitive periods of development.

1.6 THE AVON LONGITUDINAL STUDY OF PARENTS AND CHILDREN

Based at the University of Bristol, the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013) aims to address the paucity of longitudinal studies with a rich collection of environmental and genetic factors that contribute to health and development. This world-leading birth cohort study recruited more than 14,000 expectant mothers with a due date between 1st April 1991 and 31st December 1992, and over the last three decades, comprehensive data have been collected from three generations of participating families. Whilst this cohort study suffers from some of the same pitfalls as others currently available, such as high attrition rates for data collected at later timepoints and a limited population demographic (both points which will be returned to throughout this thesis), it remains one of the most detailed and longitudinal studies of its kind. The ALSPAC has obtained environmental data (e.g., measures of SES and maternal mental health), omics data (e.g., whole genome sequencing), brain imaging data (e.g., MRI and DTI), and developmental outcome data (e.g., mental health, cognitive ability, and educational attainment). Although there are other longitudinal studies

available, such as the Millennium Cohort Study (MCS; https://cls.ucl.ac.uk/cls-studies/millennium-cohort-study/) and the Adolescent Brain Cognitive Development (ABCD; https://abcdstudy.org) Study, they currently lack the truly prospective longitudinal nature of the ALPSAC. For this reason, obtaining data from the ALSPAC for the work carried out in this thesis was favourable.

Before I delve into the specific aims and structure of this thesis, it is important to consider how the data obtained from the ALSPAC, and studies like it, are culture and country specific. Even within a country, they are limited by the certain population demographics that make up the study cohort. For example, as is often the case with large-scale population studies based in the UK, the ALSPAC cohort are relatively affluent and highly educated, a point that is drawn upon in **Chapter 2**, **Chapter 4**, **Chapter 5**, and **Chapter 6**. Moreover, the data obtained from studies such as the ALSPAC, MCS, and the ABCD Study only exist in a certain number of countries, and predominantly the UK and the USA. Therefore, they are not sensitive to how constructs, such as SES, are perceived and hallmarked differentially across cultures and countries. The very demographic dimensions included in the ALSPAC (Boyd et al., 2013; Fraser et al., 2013) are, by nature, also culture and country specific. These aspects have shaped the lens by which data are collected, the conclusions we can draw from these data, and for whom the results are most relevant. Future directions for longitudinal cohort studies may be informed by how we move away from studying low income within a high income sample, and collect data that is culturally sensitive. Still, at present, the ALSPAC provides a good dataset for this thesis. Its lifespan aspect, along with its varied data types collected at various snapshots across development, fits the focus of this thesis well.

1.7 THESIS AIMS AND STRUCTURE

The central aim of my thesis is to better understand how environmental and genomic factors shape cognitive and behavioural outcomes, and how they intersect at the level of brain organisation. I report four empirical chapters where I attempt to elucidate this multifactorial influence, working across multiple stages. Firstly, I address compounding environmental factors which may longitudinally interact as they predict developmental outcomes. Secondly, I provide a comprehensive summary of population genetics and how advancements in the field resulted in the computation and application of PGSs for behavioural genetics. In doing so, I appraise the validity, efficacy, and generalisability of PGSs derived from a longitudinal cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013). My purpose in this chapter is to assess the utility of these personalised scores for downstream analyses. Following this, I collate environmental (i.e., measures of SES), genomic (i.e., PGSs for cognitive ability), and connectomic data to assess how measures of SES and PGSs for cognitive ability interact in their associations with structural brain connectivity. Lastly, I consider *how* this interaction operates to influence a key developmental outcome, and explore more specifically how different features of the connectome are related to the socioeconomic environment and the genome.

Chapter 2 considers whether maternal mental health mediates associations between SES and key developmental outcomes (i.e., child mental health and cognitive ability). **Chapter 2** has two primary aims. Firstly, to identify whether maternal mental health in the early years, when the brain is undergoing rapid macro- and microstructural changes, mediates the association between early SES and key outcome domains measured years later. Secondly,

if maternal mental health does in fact mediate this association, I want to identify whether there are sensitive periods wherein the mediating effect is particularly pronounced and thereby most likely to predict risk of mental health and cognitive difficulties. To address these questions I use relatively recent advancements in methodologies that fall under the umbrella of SEM.

Chapter 3 provides a detailed account of the theoretical framework behind population genetics, the rise of GWASs, and our subsequent capacity to generate PGSs for downstream analyses. Following this, I proceed to use appropriate GWASs and follow standard measures of QC to generate PGSs for cognitive ability and educational attainment from scratch. The primary aim of **Chapter 3** is to generate meaningful PGSs for these outcome domains to assess their efficacy and specificity. This is interesting in its own right, but also serves to test the utility of these scores for downstream analyses aimed at evaluating the interplay between the environment, genomics and brain organisation. To meet this goal, I employ dedicated PGS analysis software, alongside multipurpose software, to run stringent QC measures and generate PGSs. I then assess how the resulting scores correlate with their associated outcome measures (i.e., cognitive ability and educational attainment).

Chapter 4 builds on the findings from **Chapter 2** and **Chapter 3**. I take forward environmental measures of SES and the generated PGSs for cognitive ability to elucidate the ways in which SES, genetic propensity for cognitive ability, and structural brain connectivity are related to each other. **Chapter 4** has three primary goals. Firstly, to determine whether genetic propensity and the early child environment influence the structural organisation of the brain. Secondly, if these multifaced data types do influence structural connectivity, I want to identify *how* they are associated with global and local measures of connectivity. Lastly, **Chapter 4** aims to assess whether this influence is heterogeneous between these genetic and environmental factors, and if so, to what extent. By 'heterogeneous' in this context, I mean whether certain predictors explain shared or distinct aspects of brain organisation. In line with the data used in **Chapter 2** and **Chapter 3**, **Chapter 4** draws upon neuroimaging data obtained from the ALSPAC. I employ graph theory metrics to assess global and local measures of connectivity, whilst simultaneously considering segregated and integrated features of the human connectome. I then use PLS regression to assess how these multifaceted factors are associated with structural brain connectivity at global and local levels, and principally whether they make unique or overlapping contributions to this relationships.

Chapter 5 continues to build on the research findings highlighted by its preceding chapters. Utilising the same SES, PGS, and connectome data accumulated in **Chapter 2**, **Chapter 3**, and **Chapter 4**, I consider how SES and PGSs are associated with developmental outcomes for cognitive ability, and subsequently consider how this interaction influences the structural organisation of the brain. This is achieved by employing generalised linear modelling (GLM) to assess unique variance between these complex associations. I then explore more specifically how different features of the connectome relate to the socioeconomic environment and polygenic propensity. Following this, I determine whether we can leverage these findings with post-mortem transcriptomic data, by utilising the Allen Human Brain Atlas (AHBA).

Chapter 6 provides me with an opportunity to draw these empirical strands together, and return to the theoretical framework that I outlined in the current chapter. Here I take stock of the preceding chapters, including highlighting their inevitable theoretical and practical limitations, before identifying potential routes forward for the field.

2 MATERNAL MENTAL HEALTH MEDIATES LINKS BETWEEN SOCIOECONOMIC STATUS AND CHILD DEVELOPMENT

A manuscript closely related to this chapter has been published as: **Smith, T. A.**, Kievit, R. A., & Astle, D. E. (2022). Maternal mental health mediates links between socioeconomic status and child development. *Current Psychology, 1-12*. https://doi.org/10.1007/s12144-022-03181-0.

I was predominantly responsible for the work described in this chapter. Support with the analyses described here was provided by Professor Rogier Kievit and Professor Duncan Astle. I alone was responsible for detailing the work in this thesis and the resulting manuscript, with input and guidance from Professor Rogier Kievit and Professor Duncan Astle.

This work was carried out during the COVID-19 global pandemic, where lab colleagues, collaborators, and I have been influenced in terms of our research, capacity for interaction, and additional childcare and other responsibilities.

2.1 INTRODUCTION

As of 2022, 4.3 million children living in the UK are growing up in a low-income household (British Government Department of Work and Pensions, 2022). As noted in the previous chapter, the impact of poverty on development is well-established, with childhood deprivation associated with negative outcomes for brain architecture, physiological and psychological health, cognitive development, educational attainment, and socioemotional well-being (Evans & Kim, 2013; Hair et al., 2015; Luby et al., 2013; Reiss et al., 2019). These associations start as early as infancy and continue into adulthood (Blair & Raver, 2016; Chen et al., 2002; Tooley et al., 2021). Parental income does not influence development in isolation, but in combination with factors such as parental educational and occupational status, as part of a broader construct called socioeconomic status (SES). The socioeconomically patterned effect on mental and physical health is complex and can often begin with one condition which then goes on to have a cascading effect on a range of various health outcomes (Kivimäki et al., 2020). For example, as noted in **Chapter 1**, socioeconomic disadvantage during childhood is associated with an increased risk of developing psychiatric disorders, substance abuse, and self-harm in later life, which are then subsequently associated with conditions such as liver and renal diseases, brain infarction, dementia, and lung cancer (Kivimäki et al., 2020).

On the other hand, a SES-health gradient exists, where incremental increases in social hierarchy have been linked to improved health (Marmot et al., 1991). Put simply, the association between SES and developmental outcomes are multifaceted, in part because environmental influence does not occur or act in isolation.

2.1.1 CHALLENGES FACED BY THE LITERATURE

Despite a large and growing literature exploring relationships between SES and different outcomes, there are notable remaining empirical challenges. Addressing these challenges provides an opportunity to expand our understanding of SES-outcome associations. The first opportunity comes with including multiple different outcome measures. There have been a large number of studies that have taken single outcome domains and explored pairwise associations with socioeconomic variables (Bøe et al., 2014; Fitzsimons et al., 2017; Kinge et al., 2021; Melchior et al., 2012; Reiss, 2013; Reiss et al., 2019; Wickham et al., 2017). Considering single developmental domains alone makes it difficult to determine whether SES-outcome associations are domain specific or domain general. For example, the scope for explaining SES-childhood health outcomes depends on the health behaviour in question, with stronger associations between injury and low SES in early childhood, and smoking behaviour and low SES in adolescence (Chen et al., 2002). Systematic reviews and meta-analyses further demonstrate that the strength of the association varies across developmental domains, with stronger associations seen within language and cognitive domains, compared to physical and psychological health, emotional maturity, communication skills, and general knowledge (Letourneau et al., 2013; Webb et al., 2017). These findings suggest that it could be important to consider multiple developmental domains simultaneously, in order to establish the specificity of any SES associations.

A second opportunity to further explore the association between SES and developmental outcomes, comes with the consideration of mediating factors. An additional challenge present in the current literature is the scarcity of studies investigating plausible mediating factors. This is problematic, as the complexity of SES-outcome associations is likely in part because they are not direct, but rather the result of multiple intricate processes, such as mediating paths. In this way, the overall effect of SES may depend on specific mediating factors in a child's proximal environment, which have downstream consequences for development (Chen, 2004; Chen & Miller, 2013; Letourneau et al., 2013; Liu et al., 2020; Luby et al., 2013; Pirazzoli et al., 2022). Likewise, pathways operating at the level of a child's neighbourhood, family, individual self, and biology, have all been linked to low SES and child health outcomes (Chen & Miller, 2013). Thus, incorporating potential mediators is crucial if we want to unpack the mechanisms that help explain SES-outcome associations.

2.1.2 POTENTIAL MEDIATING ROLE OF MATERNAL MENTAL HEALTH

One plausible candidate mediating associations with SES is parental mental health. Persistent and transitions into poverty have been associated with an increased risk of maternal mental health difficulties (Fitzsimons et al., 2017; Wickham et al., 2017). In turn, children whose mothers experience mental ill-health during their primary education are at a higher risk of developing mental health problems themselves during this time (Fitzsimons et al., 2017). Correspondingly, maternal depression increases the risk of cognitive difficulties in early infancy (Liu

et al., 2017). Given the emerging literature demonstrating a strong association between early SES and a child's mental health and cognitive development, as well as associations between these measures and maternal mental health, it seems plausible that maternal mental health may mediate the association between SES and child outcomes. Whether maternal mental health amplifies or buffers the effect of poverty on development is a question with little empirical evidence. Of the few studies that have considered the mediating role of maternal mental health, few consider multiple developmental domains or longitudinal measures of maternal mental health (Bøe et al., 2014; Melchior et al., 2012; Reiss, 2013; Reiss et al., 2019; Webb et al., 2017).

Combining the two challenges outlined above – the incorporation of multiple outcomes simultaneously and mediating pathways – it is possible that maternal mental health mediates SES-outcome relationships differentially. For example, according to the dimensional model of early adversities (McLaughlin et al., 2014; 2021; Sheridan & McLaughlin, 2014), a prominent theory within this area discussed in **Chapter 1**, different types of adversity are causally associated with different types of outcomes. Socioeconomic disadvantage results in the relative absence of cognitive and social stimulation and is most strongly associated with cognitive developmental outcomes. In contrast, threatening experiences, such as abuse, are most strongly linked with socioemotional outcomes and mental well-being (Sheridan et al., 2020). According to this theory, whilst we might observe significant relationships between maternal and child mental health (Fitzsimons et al., 2017), the specific SES-mediating role of maternal mental health may be stronger for children's cognitive outcomes. This is simply because SES, an example of 'deprivation' within this framework, ought to most strongly be associated with children's cognitive outcomes (Johnson et al., 2021), and thus there is more to mediate. In short, it is possible that maternal mental health might mediate SES-outcome relationships differentially depending upon the outcome.

A third challenge within the literature is that we do not know whether there are particular windows wherein maternal mental health is *more likely* to have a longitudinal effect on child development. Considering developmental timing is valuable, as there are sensitive periods during development when considerable changes take place. For example, the first three years of life are crucial for brain development, and exposure to adversity during this time may have a disproportionate impact, relative to other developmental periods (Nelson III & Gabard-Durnam, 2020; Ouyang et al., 2019). In addition, substantial and important changes take place during primary education, between the ages of 5 and 11, where cognitive abilities develop rapidly (Spiegel et al., 2021; Van der Ven et al., 2012). This is also the most common time for the onset of mental, behavioural, and developmental difficulties (Robinson et al., 2017). Thus, considering longitudinal measures of maternal mental health in the early years, when the brain is undergoing rapid macro- and microstructural changes, alongside childhood cognitive and mental health during a time of meaningful development, such as during primary education, could provide an opportunity to identify sensitive windows where maternal mental health is most likely to predict risk of childhood mental health and cognitive difficulties. By extension, this could allow for the identification of optimal periods where interventions are likely to have the greatest impact on developmental outcomes.

2.1.3 STRUCTURAL EQUATION MODELLING

Structural equation modelling (SEM) offers a framework by which to address the three aforementioned challenges that are present within the literature on SES-outcome associations to date. SEM is a multivariate technique which uses path modelling and latent variables to analyse structural relationships among variables (Gana & Broc, 2019; Iacobucci et al., 2007; Schreiber et al., 2006). More generally, SEM provides a platform to evaluate the mediating effect that a variable (e.g., maternal mental health) may have on the relationship between other variables (e.g., SES and developmental outcomes). With its use, one can appraise the efficacy of their latent variables by way of latent variable modelling, to specify and test the extent to which the latent variables and observed variables correspond to one another. In addition, the SEM framework enables the assessment of measurement invariance that is, ensuring the longitudinal measures relate to the latent construct in the same way at each timepoint. It further provides information on the direct and indirect association between all variables included in the model. In this current study, SEM could allow for the assessment of the association between SES and key developmental outcomes, such as child mental health and cognitive ability, and how maternal mental health longitudinally mediates this association.

2.1.4 THE CURRENT STUDY

The purpose of this study is to attempt to address these three interrelated challenges by incorporating different outcomes, considering maternal mental health as a potential mediator, and testing for mediating effects across multiple developmental periods. I specifically sought to address the following questions: 1) Does maternal mental health act as a longitudinal mediator for the association between SES and common childhood development outcomes, such as child mental health and cognitive ability? 2) If maternal mental health does in fact mediate the association, are there sensitive periods where the mediating effect of maternal mental health, if any, is particularly strong? I used data from the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013), including measures of early SES, key aspects of child development (i.e., child mental health and cognitive ability), and maternal mental health across three waves. In doing so, I aimed to specify the timing of the mediating effect of maternal mental health on these associations by analysing maternal mental health at three different timepoints. Analyses were carried out within a SEM framework (Gana & Broc, 2019; Iacobucci et al., 2007; Schreiber et al., 2006). It is important to note at the outset that sample attrition rates substantially increased towards later timepoints of data collection. Data missingness and how this was addressed is discussed in the following section of this chapter. Briefly, across the total sample size of 13,855, SES data at 8 months were available for 77% to 84% of the sample. Maternal mental health data at timepoint one (8 months) were available for 80% of the sample. At timepoint two (1 year and 9 months), this decreased to 73% to 74%, and at timepoint three (2 years and 9 months) was further decreased to 68% to 69%. Child mental health data (7 years and 5 months) were available for 58% to 59% of the sample. Lastly, child cognitive ability data (8 years) were available for 53% of the sample.

2.2 METHODS

2.2.1 PARTICIPANT DEMOGRAPHIC

This study was conducted using data from the ALSPAC, a transgenerational cohort study based in the region of Avon, England, where 13,761 eligible pregnant women with an expected delivery date between 1st April 1991 and 31st December 1992 were recruited, with a mean age of 28 ranging from 14 to 46 (*SD* = 5.0) (Boyd et al., 2013; Fraser et al., 2013). Of the mothers who participated in ALSPAC, 79.1% lived in owner-occupier accommodation, 90.8% had a car, 79.4% were married, and 2.2% were non-White. By the third phase of recruitment, data were collected from 14,009 children by way of self-report or on behalf of the biological mother or primary caregiver. Of this cohort, 49.2% were female, 86.5% were White, and 12.5% were from a low-income household. The current study comprised 13,855 of this cohort. The data were obtained from children and their biological mothers when the children were aged 8 months, 1 year and 9 months, 2 years and 9 months, 7 years and 5 months, and 8 years.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. For information pertaining to the ALSPAC Research Ethics Committee policies and supporting documentation, please see https://www.bristol.ac.uk/alspac/researchers/research-ethics/.

2.2.2 MEASURES

2.2.2.1 Socioeconomic Status

SES was assessed by asking mothers to report their social class based on their occupation by selecting one of the following response options: (1) professional; (2) managerial and technical; (3) skilled non-manual; (4) skilled manual; (5) partly skilled; (6) unskilled. Mothers and their partners were further asked to report their level of education by selecting one of the following response options: (0) none; (1) CSE; (2) vocational; (3) O level; (4) A level; (5) degree. Mothers were additionally asked to report the level of difficulty they experienced affording food and paying their rent or mortgage by selecting one of four responses for each scale, ranging from (1) very difficult to (4) not difficult. Reports of social class based on occupation were reverse coded so that higher values represented greater SES, thereby keeping the directionality of responses consistent across all measures of SES. All SES measures were taken at the first timepoint.

2.2.2.2 Maternal Mental Health

Maternal mental health was measured across three waves, when the index children were aged 8 months, 1 year and 9 months, and 2 years and 9 months. At each timepoint, maternal anxiety and depression were measured using the Anxiety and Depression subscales of the Crown-Crisp Experiential Index (CCEI; Birtchnell et al., 1988), a valid, reliable (k = 0.88), and widely used self-reported measure of psychopathology. Anxiety and depression

subscales of the CCEI comprised a summary score from 8-items and included questions such as “Do you get troubled by dizziness or shortness of breath?” and “Do you feel uneasy and restless”. These items were recoded to a 16-point scale, ranging from (0) not anxious or depressed to (16) very anxious or depressed. Depressive symptoms were further measured using the 10-item Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987), which has demonstrated a split half reliability of 0.88. Items from the EPDS (e.g., “I have felt scared or panicky for no very good reason” and “I have been so unhappy that I have had difficulty sleeping”) were recoded to a 29-point scale, ranging from (0) not depressed to (29) very depressed. This globally administered measure of depression during the perinatal period has been shown to be sensitive to changes in depression in both men and women over time (Cox, 2017; Matthey et al., 2001). Maternal mental health scales were recoded so that lower scores were indicative of poorer mental health. Because the respondent for ALSPAC is almost always the mother, data on paternal mental health were not available (Fraser et al., 2013). No maternal mental health data were available prior to the 8-month data collection.

2.2.2.3 Child Mental Health

Child mental health was measured when children were 7 years and 5 months old using symptoms of generalised anxiety, any anxiety disorder, and depression, as reported by parents during a face-to-face clinical assessment and measured using the respective subscales of the Development and Well-Being Assessment (DAWBA; Goodman et al., 2000). Following parent responses to standardised questions during the clinical assessment (e.g., presence and severity of symptoms and the length of time the symptoms have been present) the DAWBA draws upon a computerised algorithm to generate bands based on symptom severity. These bands denote the likelihood of a child having the disorder in question and have been shown to be comparable to clinical-generated diagnoses across varied populations (k = 0.63 - 0.94) (Aebi et al., 2012; Goodman et al., 2011). Child mental health scales were recoded so that lower scores were indicative of poorer mental health. An alternative possibility was to test for relationships between SES, maternal mental health, and children’s behavioural problems. However, I instead opted to use the measures from the DAWBA simply because they are the closest data that we have to clinical information on child mental health and are more directly aligned with our measures of maternal mental health.

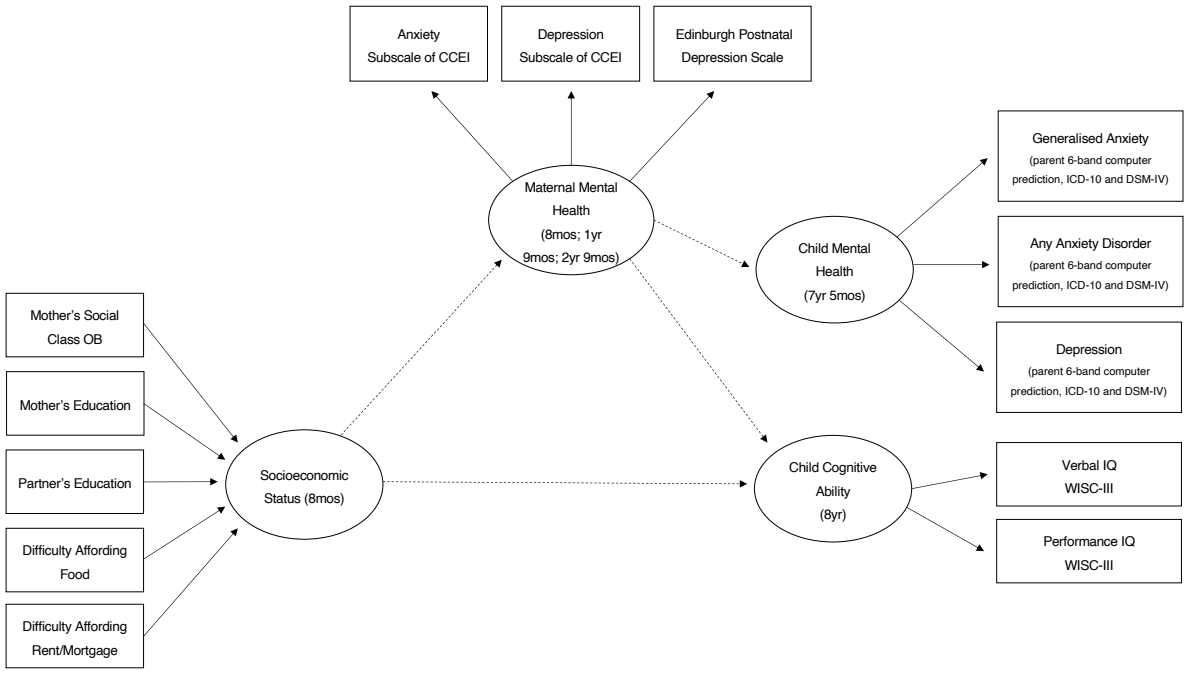
2.2.2.4 Child Cognitive Ability

Cognitive ability was measured at 8 years using Verbal and Performance IQs (intelligence quotients) from the widely used Wechsler Intelligence Scale for Children, 3rd edition, which has demonstrated reliability coefficients ranging from 0.94 to 0.97 (WISC-III; Wechsler, 1991). Both scales yield a standard score (M = 100, SD = 15) by comparing an individual’s scores to those obtained by a representative sample of similarly aged peers. The Verbal scale comprises five subtests including information (i.e., knowledge and long-term memory), similarities (i.e., abstract reasoning and concept formation), arithmetic (i.e., numerical reasoning and computation), vocabulary (i.e., word knowledge), and comprehension (i.e., practical knowledge and social judgement), whilst the Performance scale subtests include picture completion (i.e., visual perception and attention to detail), picture arrangement (i.e., nonverbal reasoning and sequencing), block design (i.e., spatial visualisation and reasoning),

object assembly (i.e., visual perception and organisation), and coding (i.e., visual-motor information processing) See Figure 2.1 for a summary of all measures included in the present study.

Figure 2.1

Summary of Measures



Note. Figure displays all measures included in the present study, including data collection timepoints. *OB* Occupation based; *CCEI* Crown-Crisp Experiential Index; *ICD-10* The International Classification of Diseases, 10th edition; *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, 4th edition; *WISC-III* Wechsler Intelligence Scale for Children, 3rd edition.

2.2.3 DATA COLLECTION

All data were collected by the ALSPAC. Biological mothers were administered questionnaires relating to socioeconomic status when children were 8 months, maternal mental health when children were 8 months, 1 year and 9 months, and 2 years and 9 months, and child mental health when children were 7 years and 5 months. Children were directly administered the WISC-III at 8 years (Wechsler, 1991). For further information on all questionnaires administered by ALSPAC, please see https://www.bristol.ac.uk/alspac/researchers/our-data/questionnaires/. Ethics approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. For information pertaining to the ALSPAC Research Ethics Committee policies and supporting documentation, please see https:// www.bristol.ac.uk/alspac/researchers/research-ethics/. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

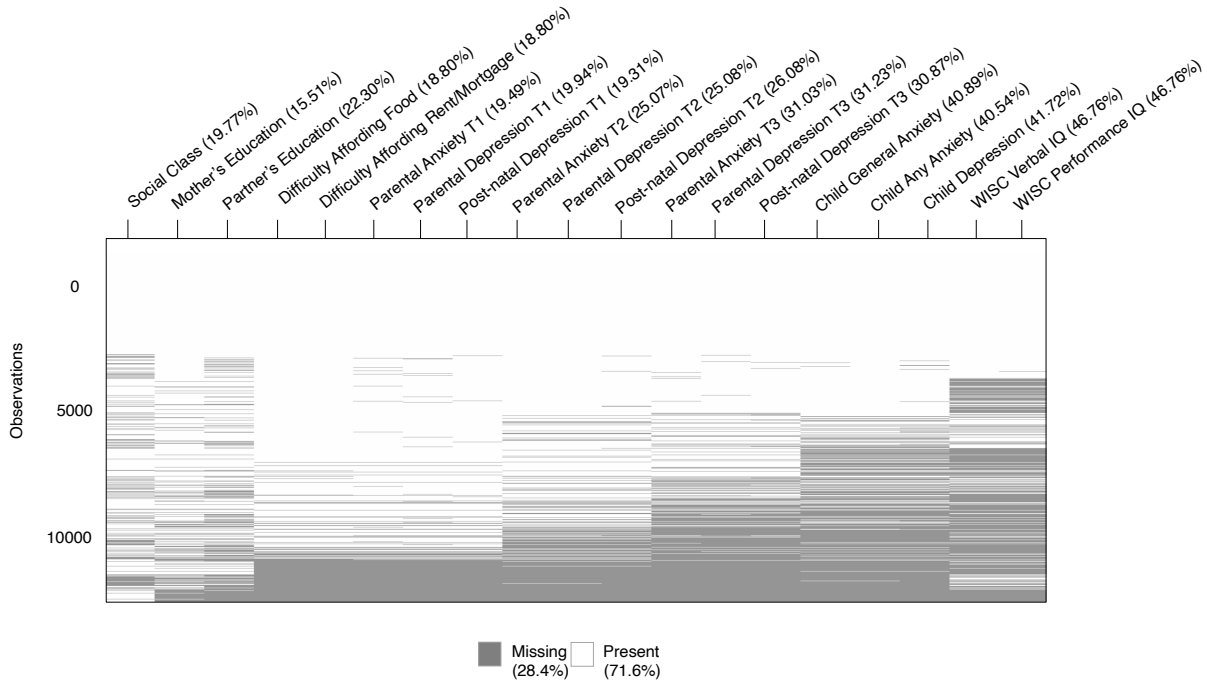
2.2.4 STATISTICAL ANALYSES

To identify whether maternal mental health mediates the association between SES and key developmental outcomes, (i.e., child mental health and child cognitive ability), I used structural equation modelling (SEM), a multivariate technique which uses path modelling and latent variables to analyse structural relations among variables (Iacobucci et al., 2007; Schreiber et al., 2006). Analyses were performed using the lavaan package (Rosseel, 2012) in the R (R Core Team, 2022) and RStudio (RStudio Team, 2022) programming environments.

In the first step, I developed an aggregate SES score. As SES is a formative construct, I used principal component analysis (PCA) instead of confirmatory factor analysis (CFA). To allow the PCA to be run with missingness, I used multiple imputation using the Mice package (Buuren & Groothuis-Oudshoorn, 2011). This allowed for a PCA to be carried out to derive one global metric of SES. The resulting global measure of SES was then integrated with the original pre-imputed dataset, and missing data across the full SEM was accommodated using robust full information maximum likelihood (FIML) with Yuan-Bentler scaled test statistic to correct for deviations from multivariate normality (Rosseel, 2012). When estimating missingness in SEM, such as when data are missing at random, FIML has been shown to be superior to alternative methods in that it produces unbiased estimates, higher efficiency, lower convergence failures, and optimal Type-1 error rates (Cham et al., 2017; Enders & Bandalos, 2001). See Figure 2.2 for detailed missingness across all variables included in the analysis.

Figure 2.2

Detailed Missingness Across Study Variables



Note. Figure displays data missingness prior to imputation for all variables included in the present study. Percentages in brackets for each measure denote the percentage of missing data for that measure pre-imputation. *T1* Timepoint 1; *T2* Timepoint 2; *T3* Timepoint 3; *WISC* Wechsler Intelligence Scale for Children; *IQ* Intelligence quotient.

Overall model fit was evaluated using the model chi-square test with its degrees of freedom and *p* value, the Bentler comparative fit index (CFI; Bentler, 1990), the root mean square error of approximation (RMSEA; Steiger, 1990) with its 90% confidence interval, and the standardised root mean square residual (SRMR; Bentler, 1995), respectively. Evaluation of model fit was interpreted as: CFI (acceptable fit ≥ 0.95, good fit ≥ 0.97), RMSEA (acceptable fit ≤ 0.08, good fit ≤ 0.05), and SRMR (acceptable fit ≤ 0.10, good fit ≤ 0.05) (Schermelleh-Engel et al., 2003). To test whether the observed variables (i.e., psychometric assessments of mental health and cognitive ability) could be accurately captured by a set of a prespecified latent variables (i.e., maternal mental health, child mental health, and child cognitive ability, respectfully), CFA was carried out (Byrne, 2005). To assess the psychometric equivalence of maternal mental health at each of the three waves, measurement invariance was imposed (Putnick & Bornstein, 2016). Both models were further compared by way of evaluating ΔCFI with a cut-off of < 0.01, to confirm measurement invariance was achieved (Cheung & Rensvold, 2002). Standard errors for the defined parameters were computed in lavaan using the Delta method (Rosseel, 2022). Effect sizes were interpreted using guidelines as recommended by Gignac and Szodorai (2016), with $r = 0.10$, $r = 0.20$, and $r = 0.30$ interpreted as relatively small, typical, and relatively large, respectively.

2.3 RESULTS

2.3.1 ESTABLISHING A MEASUREMENT MODEL

Prior to addressing our specific research questions, a measurement model needed to be established. Achieving this was threefold. Each of these steps and their outcomes will be discussed in turn.

2.3.1.1 Latent Variable Modelling

Firstly, to examine the viability of the latent variables (maternal mental health across three waves, child mental health, and child cognitive ability), that is, specify and test the extent to which the latent variables and the observed variables corresponded to one another; latent variable modelling was carried out with CFA (Byrne, 2005). This allowed me to test whether our hypothesised factor structure was compatible with the data. For identification purposes, the two IQ factor loadings of the WISC indicators were constrained to equality. Goodness of fit indices suggested that the model fit the data well ($\chi^2(64) = 778.056$, $p < 0.0001$; CFI = 0.991; RMSEA = 0.032 [0.030, 0.034]; SRMR = 0.041; Yuan-Bentler scaling factor = 1.160).

2.3.1.2 Establishing Measurement Invariance

Next, given that maternal mental health was longitudinally measured across three waves, it was essential to establish measurement invariance to ensure the measures were related to the latent construct in the same way at each wave (Widaman et al., 2010). To do so, I equality constrained key indicators (i.e., the same indicators at wave 1-2-3) and compared it to a model where these same parameters were estimated freely. Model comparison showed notably similar results between the freely estimated ($\chi^2(64) = 778.056$, $p < 0.0001$; CFI = 0.991; RMSEA = 0.032 [0.030, 0.034]; SRMR = 0.041; Yuan-Bentler scaling factor = 1.160) and the constrained model ($\chi^2(63)$

= 502.169, $p < 0.0001$; CFI = 0.994; RMSEA = 0.025 [0.023, 0.027]; SRMR = 0.031; Yuan-Bentler scaling factor = 1.162), with both models fitting the data well. To further establish measurement invariance, the ΔCFI between consecutive models was evaluated and found to be within the designated cut-off point (ΔCFI = 0.003). In other words, imposing the assumption of equal measurement of the latent factors across time did not lead to a substantial reduction in model fit, suggesting measurement invariance was tenable.

2.3.1.3 Developing a Global Metric of Socioeconomic Status

Lastly, whilst the latent variables accounted for thus far (maternal mental health, child mental health, and child cognitive ability) are reflective, in that their association to their allocated observed variables are assumed by CFA to be causal, this is not the case for SES. Unlike the aforementioned variables, this assumption does not hold for SES, which is commonly considered a formative latent variable: An individual's SES is typically formed by their education, occupation and earnings. To derive a single SES metric, the (rescaled) measures of SES were entered into a PCA. Scores on the first dimension of the PCA, which accounted for 40.01% of the shared variance, were extracted and used as our measure of SES in subsequent analyses. For detailed comparisons among PCA dimension factor loadings, refer to Table 2.1.

Table 2.1

Factor Loadings of SES Measures for First PCA Dimension

SES measure	DIM1
Parent (1) social class based on occupation	0.45
Parent (1) highest education qualification	0.53
Parent (2) highest education qualification	0.50
Parent (1) difficulty affording food	0.40
Parent (1) difficulty affording rent or mortgage	0.34

Note. *SES* Socioeconomic status; *PCA* Principal component analysis; *DIM* Dimension; Parent (1) = mother; Parent (2) = partner.

2.3.2 INTERPRETATION OF THE FULL STRUCTURAL MEDIATION MODEL

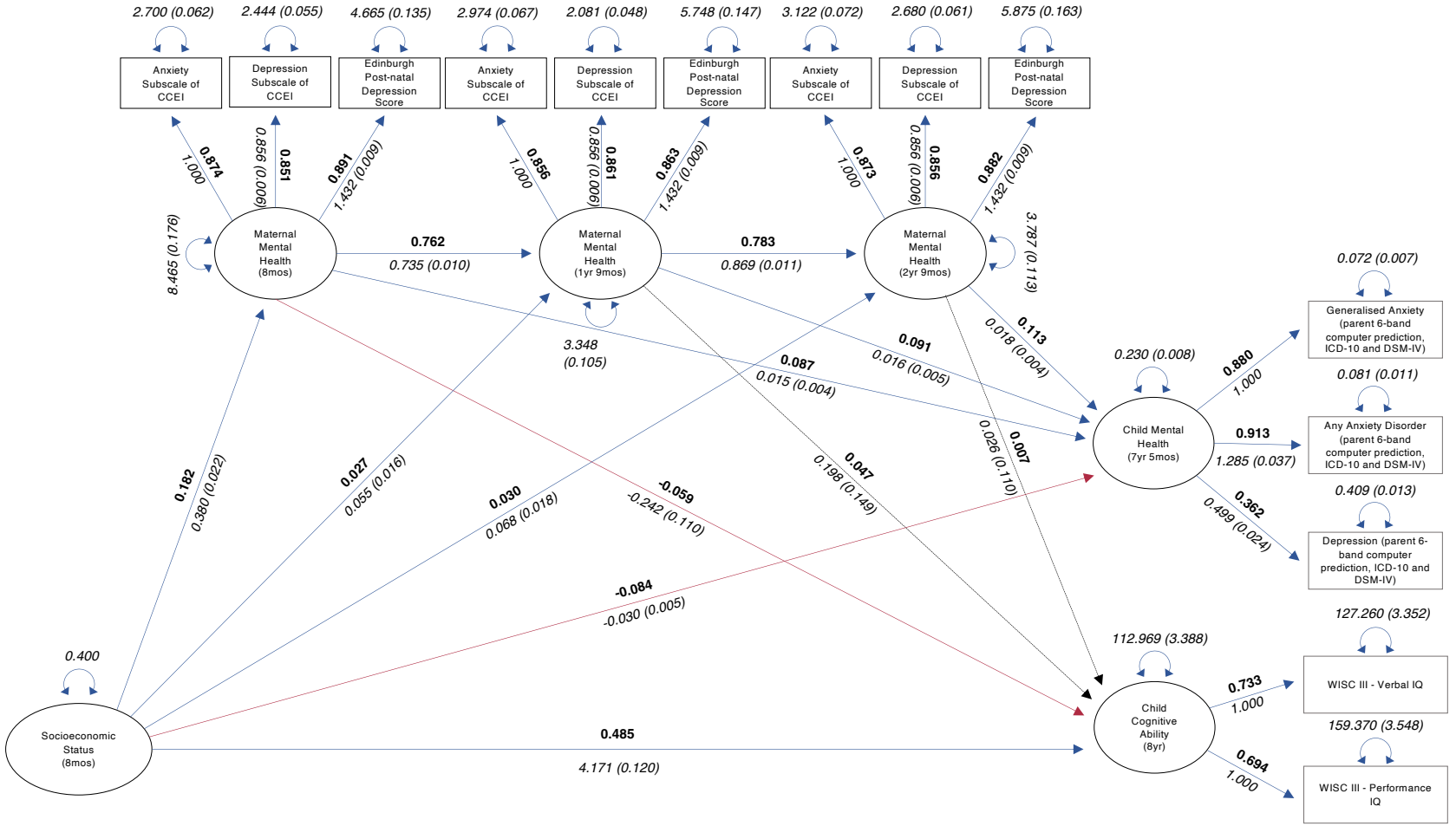
2.3.2.1 Model Fit

Once the measurement model was established, the full structural equation model was fit to the data to examine whether maternal mental health mediates the association between SES and key developmental outcomes (i.e., child mental health and child cognitive ability) and to what extent these effects, if any, were present. The full mediation model fit the data well: $\chi^2(73) = 1089.607$, $p < 0.0001$; CFI = 0.987; RMSEA = 0.034 [0.032, 0.036];

SRMR = 0.037; Yuan-Bentler scaling factor = 1.152. See Figure 2.3 for detailed estimated parameters. The mediating effect of maternal mental health on the association between SES and child mental health, and SES and child cognitive ability will be discussed in turn.

Figure 2.3

Estimated Parameters of the Full Structural Equation Model



Note. Figure displays analysis output for the full structural equation model. Positive and significant ($p < 0.05$) path estimates are denoted by blue arrows, negative and significant path estimates are denoted by red arrows, and non-significant ($p > 0.05$) path estimates are denoted by dashed arrows. Standardised parameter estimates are in roman, unstandardised parameter estimates (with standard errors in parentheses) are in italics, and key standardised parameters of interest have been displayed in boldface. Curved double arrows display (residual) variances.

2.3.3 MEDIATING EFFECT OF MATERNAL MENTAL HEALTH ON MENTAL HEALTH

As illustrated in Figure 2.3, parameter estimates showed a relatively small but significant negative direct effect of SES on child mental health ($b = -0.030$, $SE = 0.005$, 90% CI = [-0.039, -0.020], $\beta = -0.084$, $p < 0.0001$). Children from higher SES households displayed poorer mental health. This association was partially mediated by maternal mental health. The mediating effect was greatest at 8 months ($b = 0.006$, $SE = 0.002$, 90% CI = [0.003, 0.009], $\beta = 0.016$, $p < 0.0001$). Whilst the 1 year 9 months timepoint ($b = 0.001$, $SE = 0.000$, 90% CI = [0.000, 0.002], $\beta = 0.002$, $p < 0.05$) and 2 years 9 months timepoint ($b = 0.001$, $SE = 0.000$, 90% CI = [0.000, 0.002], $\beta = 0.003$, $p < 0.005$) also showed a significant mediating effect, the mediating effect was primarily accounted for by the 8-month timepoint. The cumulative effect of maternal mental health across all three timepoints resulted in a joint partial mediation effect: The direct effect of SES on child mental health was considerably attenuated ($b = -0.022$, $SE = 0.005$, 90% CI = [-0.032, -0.012], $\beta = -0.062$, $p < 0.0001$). Please see Table 2.2 for summary of key findings.

Table 2.2

Key Findings on the Mediating Effect of Maternal Mental Health on the Relationship between SES and Child Mental Health

Defined parameters	*b*	SE	90% CI		β	*p*
Direct effect	-0.030	.005	[-0.039,	-0.020]	-0.084	.0001
Indirect effect (8mos)	0.006	.002	[0.003,	0.009]	0.016	.0001
Total effect	-0.022	.005	[-0.032,	-0.012]	-0.062	.0001

Note. *CI* Confidence interval.

2.3.4 MEDIATING EFFECT OF MATERNAL MENTAL HEALTH ON COGNITIVE ABILITY

Further to be seen in Figure 2.3 is a significant, positive, and relatively large direct effect of SES on child cognitive ability ($b = 4.171$, $SE = 0.120$, 90% CI = [3.936, 4.407], $\beta = 0.485$, $p < 0.0001$). Children with higher SES tended to have better scores on the latent factor of cognitive ability. This association was partially mediated by maternal

mental health at the 8-month timepoint (b = -0.092, SE = 0.042, 90% CI = [-0.175, -0.009], β = -0.011, $p < 0.05$). Whereas parameter estimates for the 1 year 9 months timepoint (b = 0.011, SE = 0.009, 90% CI = [-0.006, 0.028], β = 0.001, $p > 0.05$) and 2 years 9 months timepoint (b = 0.002, SE = 0.008, 90% CI = [-0.013, 0.017], β = 0.000, $p > 0.05$) were non-significant. The effect of maternal mental health on child cognitive ability resulted in an attenuated total effect of SES on child cognitive ability (b = 4.092, SE = 0.122, 90% CI = [3.853, 4.331], β = 0.476, $p < 0.0001$). Please see Table 2.3 for summary of key findings.

Table 2.3

Key Findings on the Mediating Effect of Maternal Mental Health on the Relationship Between SES and Child Cognitive Ability

Defined parameters	*b*	SE	90% CI		β	*P*
Direct effect	4.171	.120	[3.936,	4.407]	0.485	.0001
Indirect effect (8mos)	-0.092	.042	[-0.175,	-0.009]	-0.011	.05
Total effect	4.092	.122	[3.853,	4.331]	0.476	.0001

Note. *CI* Confidence interval.

2.4 DISCUSSION

The present study sought to determine whether maternal mental health acts as a longitudinal mediator for the association between SES and childhood developmental outcomes. Secondly, I aimed to determine whether there are sensitive periods wherein this mediating effect, if present at all, is particularly pronounced. Our design included both measures of mental health and cognition, allowing for the possibility that the effect and timing of maternal mental health may be somewhat domain specific. There are a number of key findings. First, in this relatively affluent sample, SES has a differential association with child mental health and cognitive ability. Second, maternal mental health mediates both of these relationships – the direct relationship between SES and outcome drops significantly when maternal mental health is considered. Third, in both cases this partial mediation happens early, largely before the child's first birthday. Fourth, the partial mediation varies in size depending upon the outcome domain.

2.4.1 SES, MATERNAL MENTAL HEALTH, AND CHILD MENTAL HEALTH

In our data, SES was positively associated with maternal mental health; higher SES levels were associated with better maternal mental health. However, the opposite was found for child mental health, with higher SES levels resulting in poorer child mental health. This association was partially mediated by maternal mental health. The longitudinally mediating effect was primarily accounted for at 8 months. Whilst this mediating effect was relatively small, it suggests the importance of early maternal mental health for critical periods of developmental timing.

Why is higher SES associated with poorer child mental health? It is important to note that our sample was relatively affluent, with a low percentage of participants from low-income households (12.5%). Thus, the majority of the sample were positioned at the higher end of the socioeconomic spectrum. This may be important in interpreting the counterintuitive effect of a negative association between SES and child mental health. Children from affluent backgrounds have been shown to manifest greater anxiety and depression due to parental pressures to achieve at an academic and extracurricular level, as well as isolation due to parental career obligations and intensive schedules (Luthar, 2003; Luthar & Becker, 2002; Parenteau et al., 2020). Considering the sample characteristics and child mental health measures used, it is possible a similar effect is present in our data. This effect is overall partially mediated by maternal mental health, with better maternal mental health weakening the negative relationship between SES and child mental health. But the effect size of this partial mediation is relatively small. One possibility is that the partial mediation effect is relatively small simply because the SES-outcome relationship is relatively small for child mental health. Our SES measure primarily captures the economic circumstances of the family, which may itself be less strongly associated with child mental health, relative to other forms of early life adversity (McLaughlin et al., 2021; Sheridan & McLaughlin, 2014; Sheridan et al., 2020).

2.4.2 SES, MATERNAL MENTAL HEALTH, AND CHILD COGNITIVE ABILITY

In contrast to child mental health outcomes, SES had a relatively large *positive effect* on child cognitive ability (Gignac & Szodorai, 2016); higher SES was associated with better child cognitive ability. Again, it is important to highlight the differential relationships between SES and our developmental outcomes. In our data, socioeconomic status had a stronger and positive relationship with child cognitive performance, relative to the child's mental health, as might be predicted by the dimensional account of early life adversity discussed here and in **Chapter 1** (McLaughlin et al., 2021; Sheridan & McLaughlin, 2014). According to this account, deprivation is thought to have a broad and pervasive impact on child development, via the absence of expected, cognitive, linguistic, and social input. The consequence of this is thought to be primarily observed in terms of widespread neural network formation (Johnson et al., 2021) and cognitive performance measures (Sheridan et al., 2020).

The SES-cognition association was also partially mediated by maternal mental health. Taking maternal mental health into consideration reduces the strength of the direct association between SES and child cognitive ability. As was the case with child mental health, this mediating effect was most influential when children were 8 months old, further demonstrating the important role of a child's proximal environment during the first year of life. The mediating role of maternal mental health could be explained in part by parental buffering and its cascading effects across development. For example, positive parenting behaviour buffers children's emotional and stress reactivity profiles (Brown et al., 2020; Oppenheimer et al., 2016), which in turn influences cognitive ability (Bell & Wolfe, 2004; Bell et al., 2019; Walle et al., 2022; Wass, 2018). Thus, the early benefits of parental buffering may have led to the reduced SES-cognition association. Put simply, whilst early socioeconomic deprivation might reflect reduced cognitive, social, or linguistic stimulation, this can, to some extent, be buffered by maternal mental health.

2.4.3 LIMITATIONS AND FUTURE DIRECTIONS

Irrespective of the strengths in the current study, such as the inclusion of multiple developmental outcomes, its consideration of maternal mental health as a potential mediator, and its longitudinal consideration of developmental periods, it was not without limitations. For instance, measures of child mental health relied on parent reports. Whilst this is common when measuring mental health in this age group, parent reports may have been reflective of parental mental health, as opposed to that of the child. Furthermore, it is possible that the mediating effect of maternal mental health is stronger for certain aspects of SES. For example, even after multiple aspects of SES and genetic confounding are considered, household income is specifically linked to risk of developing mental health problems in childhood (Kinge et al., 2021). Therefore, the mediating effect of maternal mental health may also be specific to certain indicators of SES. This may mean that the SES associations with the aggregated measure may be slightly over or underestimated.

The present study also had limitations by way of sampling. As mentioned, SES distribution weighted towards the more affluent end of the spectrum, with a low percentage of participants from low-income households (12.5%). Likewise, the ALSPAC cohort display high education levels, with 42.6% of mothers educated to an A level or above (Fraser et al., 2013). Whilst this sample allowed me to identify the mediating role of maternal mental health in the association between SES and key developmental outcomes, as well as highlight the negative correlation between high SES and child mental health, future research should aim to incorporate a more evenly distributed sample in terms of SES. Such research could further elucidate the complexity of these associations.

Future research should further consider additional SES timelines during development. For example, as previously noted, SES is more strongly related with childhood injury during early development, and smoking behaviour during adolescence (Chen et al., 2002). By extension, it is possible that the mediating effect of maternal mental health varies depending upon SES during different periods of development, such as infancy, early childhood, and adolescence. Considering multiple SES timelines during development could shed light on the mediating role of maternal mental health in these associations. Building on this, future research should consider additional developmental outcomes where the mediating role of maternal mental health in SES-outcome associations have not yet been considered, such as language and social-emotional domains (Guhn et al., 2020; Luo et al., 2022).

2.4.4 CLINICAL AND HEALTH POLICY IMPLICATIONS

The findings of the current study have both clinical and health policy implications. For example, our findings call attention to the importance of maternal mental health during early childhood, chiefly within the first year of life. At present, and in line with British Government requirements, a clinical postnatal check is carried out with mother's six to eight weeks following the birth of their child (British National Health Service Postnatal Review, 2022). This check includes a general discussion about mental health and well-being. I argue for an extension of the current guidelines, to include regular postnatal mental health checks during the first 12-months after a baby's birth. In view of the role of maternal mental health on these SES-outcome associations, ensuring the mental well-being of mother's during this critical period is paramount.

2.4.5 CONCLUSION

In conclusion, the current study demonstrates that SES has significant longitudinal associations with two domains of child development – mental health and cognitive ability. However, the association is different depending upon the domain. In both cases, maternal mental health mediates the association. The variability of the mediating role of maternal mental health indicates its role is transient and dependent upon the developmental outcome in question. I have emphasised the complexity of SES-outcome associations and add to the current body of literature calling for the consideration of factors in a child's proximal environment that likely mediate this association, in hopes of identifying potential targets for intervention and prevention (Letourneau et al., 2013; Liu et al., 2020; Reiss et al., 2019).

Whilst these findings add to the current literature on the complex ways the environment can influence developmental outcomes, there remains scope for the consideration of how environmental factors operate when genetic propensity is also considered. As noted in **Chapter 1**, both exogenous and endogenous factors interact to influence the development of the brain over time. Thus, to build a mechanistic picture of neurodevelopment, we must consider the role genetic propensity plays, and how it interacts with features of the environment, such as SES, to shape development. In the proceeding chapter, I will begin this process by providing a thorough background on the field of genomics, how it has developed, and how it has enabled us to answer complex questions pertaining to early child development. I will subsequently develop measures of genetic propensity relevant to the current thesis.

3 CONSIDERING GENETIC PROPENSITY

The work described here was carrying out by myself with final protocol summaries overseen by Dr. Varun Warrier at the Department of Psychiatry, University of Cambridge, as has been described in the Statistical Analyses section of this chapter. I alone was responsible for detailing the work in this thesis with input from Professor Duncan Astle.

This work was carried out during the COVID-19 global pandemic, where lab colleagues, collaborators, and I have been influenced in terms of our research, capacity for interaction, and additional childcare and other responsibilities.

3.1 INTRODUCTION

In the previous chapter I considered the longitudinal relationships between socioeconomic status (SES) and cognitive and mental health outcomes. In all subsequent chapters I also wanted to consider the inter-individual genetic variability, which is likely to be associated with both SES and outcomes like cognitive development and educational attainment. The first step towards doing this is to establish the utility, validity and generalisability of population-level genomic measures within the ALSPAC cohort. That is the purpose of this third chapter. Upon reading **Chapter 3**, readers will notice that I have not carried forward the child mental health measures that were included in **Chapter 2**, but have rather included measures of child cognitive ability and educational attainment. Why were the child mental health measures not carried forward? In **Chapter 2**, we found the relationship between SES and developmental outcomes to be much stronger for cognitive ability, and in the expected direction, whereas the relationship between SES and child mental health was much smaller, and the effect was in the opposite direction to that expected. Additionally, the overall explained variance accounted for by PGSs for cognitive ability and educational attainment are some of the largest accounted for in the literature, whereas other aspects of development, such as mental health, have not yet yielded similar predictive capacities (Armstrong-Carter et al., 2021). Correspondingly, this thesis is ultimately interested in unravelling environmental and genomic mechanisms that impact development, and to do so, it is important to have strong relationships to begin with.

As was described in the General Introduction of this thesis, polygenic scores (PGSs), sometimes referred to as polygenic risk scores (PRS), are scores that quantify an individual's genetic propensity towards a given disease, phenotypic behaviour, or trait. This is achieved by calculating the aggregated effects of common variants that are present in an individual's genome (Collister et al., 2022). An individual with a PGS that is above the population average, has a higher probability of developing the disease, or expressing the complex phenotypic behaviour or

trait (Loos, 2020). The generalisability of PGS methods means that PGSs can inform genetic propensity across a plethora of circumstances. When communicated effectively and appropriately, this information can inform personal health management, and identify those most likely to benefit from intervention (Torkamani et al., 2018). Advancements in genetics, combined with increased accessibility to large-scale cohort studies comprising genome-wide data, has led to an increase in both the use and utility of PGS methods (Collister et al., 2022; Marees et al., 2018). A thorough awareness of the efficacy and utility of polygenic scoring is contingent upon an understanding of the theoretical modelling and experimental science of genetic variation, global initiatives to sequence the human genome, genome-wide association studies (GWASs) that were made possible by these initiatives, and the methods developed to increase the functionality of GWASs. As such, these points will be discussed in turn.

3.1.1 POPULATION GENETICS

Population genetics refers to the theoretical modelling and experimental science of genetic variation within and between populations (Charlesworth & Jensen, 2021; Johnson et al., 2019). Its foundations rely heavily on what is known as the Hardy-Weinberg law, which states that in any given large population where mating is random, genotype frequencies remain constant between generations (Charlesworth & Jensen, 2021; Johnson et al., 2019). The Hardy-Weinberg equilibrium is further dependent on the absence of genetic drift, migration, mutation, and natural selection, and females and males having comparative allele frequencies (Johnson et al., 2019). Disruptions to these principles, such as through random genetic drift, migration, mutation, natural selection, and non-random mating (e.g., population stratification, consanguinity, and assortative mating), result in changes to genotype frequencies and equilibrium is no longer tenable (Charlesworth & Jensen, 2021). The application of the Hardy-Weinberg equilibrium can enable population geneticists to obtain knowledge on the population structure of a sample, and answer questions pertaining to genetic diversity within and across populations, evolutionary patterns, contributing factors to common and rare diseases, and the mechanisms by which these vary across populations (Johnson et al., 2019).

To understand how the theoretical underpinnings of population genetics can be applied to the study of genetic variation, it is important to understand the process by which gene variation occurs. During meiosis, when parent sex cells are produced, homologous chromosomes exchange segments of deoxyribonucleic acid (DNA) during the process of recombination, also known as crossing over (Qi et al., 2014). The recombination of genetic material introduces genetic variation, as each chromosome now contains a new combination of alleles. Individuals inherit two alleles for each heritable trait, one from each biological parent. Alleles comprise variations in the sequence of nucleotides which code for a given gene and are located at the same genetic locus on a chromosome. Nucleotides form the building blocks of DNA, and comprise adenine (A), thymine (T), guanine (G), and cytosine (C). These nucleotides form chemical bonds known as base pairs with one another, A with T, and G with C, which connect the strands of DNA inherited by each parent. Variations in nucleotides are often referred to as DNA polymorphisms, and include single nucleotide polymorphisms (SNPs), insertions, deletions, and structural rearrangements. An example of a SNP would be most individuals in a population carrying the C nucleotide at a given base position, and a small percentage of individuals carrying an A nucleotide at this position in the genome.

Whilst the DNA sequence of a human is approximately 99.5% identical to that of another, these genetic variations are thought to substantially influence individual differences in health, risk, and phenotypic traits (National Human Genome Research Institute, 2012, 2018). Thus, an understanding of the human genome, and variations such as these, can not only create a blueprint of that which makes us human, but could also allow for the identification of the genetic variants implicated in health, pathology, and the expression of various complex phenotypic traits.

3.1.2 SEQUENCING THE GENOME

Global initiatives have been undertaken to identify, map, and sequence the genetic architecture of the human genome (Altshuler et al., 2012; Gibbs et al., 2003; Watson, 1990). For example, from its initial conception in 1990, the Human Genome Project successfully sequenced the entire genome of *Homo sapiens* in 2003 (National Human Genome Research Institute, 2018; Watson, 1990). Since then, the project has identified over 3 million SNPs in the human genome. The efficacy of the Human Genome Project further facilitated the initiation of the International HapMap Project, a collaborative effort to construct a haplotype map of the human genome (Gibbs et al., 2003; International HapMap Consortium, 2007). The construction of a haplotype map was made possible by the genomic process of linkage disequilibrium (i.e., the non-random propensity for nearby SNPs on a chromosome to be inherited together during the process of recombination during meiosis). SNPs in high linkage disequilibrium with one another form what is known as a haplotype block. Having a map of the haplotypes that exist in the human genome allows researchers to use tag SNPs that are representative of each haplotype block to identify all the SNPs which exist in the human genome. In this way, researchers can use this map to sequence 500,000 tag SNPs, and by the process of imputation, identify the 10 million SNPs that exist in the human genome with a high degree of statistical accuracy (National Human Genome Research Institute, 2012). This increases the feasibility of a study by reducing the financial and temporal restrictions associated with whole genome sequencing. The HapMap tool has allowed researchers to identify the genes and an ensemble of SNPs implicated in health and disease, as well as those contributing to varying responses to vaccinations, pathogens, pharmaceutical drugs, drug efficacy, and drug metabolism. Relatedly, the HapMap tool provides an opportunity to identify genetic influences on differing responses to environmental factors (Gibbs et al., 2003; International HapMap Consortium, 2007; National Human Genome Research Institute, 2012).

Initiatives such as these have fundamentally advanced our understanding of the human genome and have provided a strong foundation for subsequent genomic investigation. At the same time, advancements in genetics, bioinformatics, and the statistical techniques required to analyse genomic data, have led to an increase in multidisciplinary accessibility to these data types (Collister et al., 2022; Marees et al., 2018). This has paved the way for behavioural genetics, allowing researchers to query how genetic variations within a given population are associated with individual differences in behavioural phenotypes.

3.1.3 ACCESSION OF GENOME-WIDE ASSOCIATION STUDIES

GWASs are one such example of the ways in which the sequencing of the human genome can be applied to the genetic architecture of genotype-phenotype associations. GWASs are large-scale studies which aim to analyse the

SNPs in a samples genome to identify genotype-phenotype associations (Chen et al., 2021; Korte & Farlow, 2013; Tam et al., 2019). In doing so, GWASs often detect genetic variants associated with disease using control and case studies or assess associations between variants and phenotypic and behavioural traits in an unselected sample (Tam et al., 2019). During this process, a sample of DNA from every individual in a sample population undergoes genotyping to identify their inherited alleles and the single nucleotide differences in their DNA sequences. During genotyping, tag SNPs are detected in each sample of DNA, and a reference sample obtained from a database containing all known human haplotypes, such as HapMap, is then used to impute the other SNPs present across all sites of an individual's genome. The collation of SNPs identified during genotyping are often subject to statistical analyses, such as linear or logistic regression, depending on whether the trait of interest is continuous or categorical, respectively, to detect the SNPs associated with a given trait. Whilst genotyping provides details of the genomic location of the single nucleotide variations present in a sample, it cannot pinpoint the exact causal SNPs associated with a trait. This is because whilst the process of linkage disequilibrium increases the feasibility of GWASs given the large sample sizes required to reach statistical significance and detect the accumulative effects of SNPs, it also means that SNPs in high linkage disequilibrium with one another are detected simultaneously. Even so, the application of GWAS methodologies offers a multitude of benefits and utility (Korte & Farlow, 2013; Tam et al., 2019).

3.1.4 MULTIPLE TESTING AND QUALITY CONTROL

Given that GWASs test millions of SNPs, it is crucial that researchers account for multiple testing. This is achieved by adopting a highly stringent genome-wide *p* value threshold (Jafari et al., 2018; Marigorta et al., 2018; Risch & Merikangas, 1996). Traditionally, across many disciplines, the accepted *p* value adopted to reject the null hypothesis is $p < 0.05$. This means for every twenty comparisons in a comparable sample, there is a 5% probability of a type I error (i.e., false positive). However, this traditionally accepted significance level is far too lenient for GWASs given the sizeable quantity of tests performed, and if this threshold were to be adopted, it would lead to over a hundred thousand spurious associations to be classified as statistically significant. To overcome the multiple testing problem, genomic researchers have adjusted for the 5% false positive rate by dividing the traditional threshold by the approximate number of SNPs in the human genome (Jafari et al., 2018; Marigorta et al., 2018). The resulting genome-wide significance threshold typically adopted to declare statistical evidence of an association is $p < 5 \times 10^{-8}$ in GWASs. Whilst having such a stringent *p* value threshold means that there is substantial reduction in the likelihood of false positives and true positives can be teased out, it also means that a large sample size is required to detect the accumulative small effects that SNPs have on complex traits (Marigorta et al., 2018; Risch & Merikangas, 1996). It is therefore common for genomic researchers to retain their samples and make them accessible for future genotype-phenotype association analyses. The resulting SNPs detected by GWAS are often visualised by a Manhattan plot, where SNPs present across all chromosomes are displayed, and those surpassing the genome-wide *p* value threshold form peaks. As specific causal SNPs cannot be identified by GWASs, the SNPs within or near these locations, and the function of their associated genes, are then placed under further scrutiny to identify their potential influence on a specific disease, complex behaviour or trait.

To ensure the efficacy of the genotyping data used by GWASs, these association studies must also take considerable quality control (QC) measures into account (Chen et al., 2021; Korte & Farlow, 2013; Marigorta et al., 2018; Tam et al., 2019). Carrying out accepted standard QC is imperative, as the raw data obtained from the genotyping process is intrinsically flawed (Choi et al., 2020; Collister et al., 2022; Marees et al., 2018). Thus, association studies must undertake fundamental measures to prevent potentially confounding sources from leading to undesirable spurious associations (Choi et al., 2020; Collister et al., 2022; Marees et al., 2018). For example, GWASs must account for population stratification (i.e., genetic variance resulting from ethnic heterogeneity, as opposed to that of genotype-phenotype associations), heterozygosity levels (i.e., levels of heterozygosity which are too high could indicate poor sample quality, and levels that are too low could be indicative of inbreeding), individual and SNP missingness (i.e., where individuals have high proportions of genotype missingness and SNPs are not present in a large portion of the sample, respectively), minor allele frequency (MAF) (i.e., SNPs with a low MAF are prone to errors during the genotyping process, and their rarity means they are also unlikely to enable the detection of genotype-phenotype associations), deviations from the Hardy-Weinberg Equilibrium (HWE) (i.e., variants which deviate from HWE may not be association-specific, but rather indicative of disruptions to HWE, such as population stratification), imputation information (INFO) scores (i.e., SNPs with low INFO scores have lower statistical power and are thus likely to generate type I errors), relatedness within a sample (i.e., relatedness within a sample can inflate the association between SNPs and a phenotype), discrepancies in an individual's reported sex and that indicated by their sex chromosome (i.e., these data are no longer considered reliable due to what could be the result of mislabelled or misreported information), and ambiguous, mismatching and duplicate SNPs. Through the implementation of these QC steps, the results of GWASs can benefit from increased predictability, reliability, and reproducibility.

3.1.5 UTILITY OF GENOME-WIDE ASSOCIATION STUDIES

The implementation of GWASs has elucidated the role of genetic variants associated with many diseases and complex traits, including the heritability of Alzheimer's disease (Marioni et al., 2018), depression (Xie et al., 2017), cognitive ability (Savage et al., 2018), and educational attainment (Lee et al., 2018), to name a few. The recommendations implemented during the initial conception of GWASs to account for multiple testing, small effect sizes, and stringent measures of QC have meant that the results from these studies are highly replicable (Marigorta et al., 2018; Risch & Merikangas, 1996). This recurrent finding is particularly valuable when considering the methodological replicability crisis that many areas of scientific inquiry are facing (Open Science Collaboration, 2015). The many GWAS catalogues freely available as open access, such as the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/) and the GWAS Atlas (https://atlas.ctglab.nl), allow researchers to draw upon large-scale association studies to run their own meta-analysis GWAS with multiple cohorts and thereby increase the statistical power to detect associations, and to investigate additional novel hypotheses on various genotype-phenotype associations. This is made possible by the summary statistics derived from a GWAS, which are made publicly available by catalogues such as those listed above and include information on the chromosome number and position of a SNP identifier, the MAF, effect size for a given trait, standard error, and *p* value. Summary statistics have the added potential to be used for subsequent analyses, such as to calculate an individual's PGS, that is, their predicted likelihood of expressing a particular disease or phenotypic behaviour or trait.

3.1.6 POLYGENIC SCORE ANALYSIS

As of 2021, over 5,700 GWASs have been performed, identifying over 55,000 unique SNPs for approximately 5000 distinct diseases and traits (Loos, 2020; MacArthur et al., 2017; Uffelmann et al., 2021). From the initial conception of GWASs in 1996, to the thousands of GWASs that have since been carried out, GWASs have highlighted the accumulative small effects that SNPs can have on various diseases and complex traits (Marigorta et al., 2018; Risch & Merikangas, 1996). Even so, their limited predictive power means that they do not allow for the stratification of risk or probability of phenotypic expression based on the genetic markers they identify (Dudbridge, 2013, 2016). Statistical techniques have been developed to account for this limitation. Examples of such techniques include linkage disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015a, 2015b) and PGS analysis, also known as polygenic risk score (PRS) analysis (Dudbridge, 2013, 2016; Palla & Dudbridge, 2015). These techniques infer heritability by combining the effect sizes of the SNPs across the genome that have been identified by a GWAS to be associated with a given trait. PGS analysis provides a score that is predictive of whether an individual has a higher likelihood of being diagnosed with a certain disease or expressing a particular phenotypic behaviour or trait. In this way, an individual with a PGS that is above the population average has a higher probability of developing the disease or expressing the behaviour or trait of interest (Loos, 2020). Given the potential efficacy of PGSs, and the growing accessibility of large-scale cohort studies comprising genome-wide data, the implementation of PG scoring methods is increasingly prevalent.

As previously touched upon, to generate a PGS and thereby estimate the explanatory power of SNPs in a prespecified population, a GWAS must first be carried out for a specific disease, behaviour, or trait in an initial training sample (Dudbridge, 2013). The identified common genetic variants are then ranked in terms of their involvement in an association based on their *p* value. This sample, along with a summary of the trait-associated SNPs and their ranking, form the base data which is then used in ensuing PGS analyses. During PGS analysis, the weighted sum of the trait-associated SNPs that are present in an independent replication sample, also known as the target data, form the PGSs, which are calculated for every individual in the sample (Dudbridge, 2013). The potential benefits of calculating the PGSs in a sample are fourfold. First, it allows one to identify the genetic contribution to a disease, behaviour, or trait that is expressed in a target sample. Second, one can determine whether the SNPs deemed by a GWAS to be associated with a disease, behaviour or trait are present in their target data and therefore contributing to the calculated PGSs. Third, and chiefly, they allow for the prediction of behaviour, as well as trait values and disease risk. Lastly, the generated PGSs can be used for downstream analyses to identify the genetic component influencing diseases and complex behaviours and traits, which are likely to be influenced by multiple factors. In this way, PGSs could be incorporated with multiple different data types, such as measures of environmental risk or features derived from brain imaging, in order to understand whether they capture shared or distinct variance with the generated PGSs.

Whilst the advantages associated with PGS analysis were previously limited to those whose research spans the field of genetics, comprehensive protocols for calculating PGSs have since been made available to researchers interested in analysing genomic data across an abundance of fields (Choi et al., 2020; Collister et al., 2022; Marees et al., 2018). This has led to a surge in both the use of PGS methods, as well as their utility (Collister et al., 2022; Marees et al., 2018). Further to this, and similar to GWASs, researchers can now access catalogues and atlas' on

databases, such as the PGS Catalog (https://www.pgscatalog.org) and the atlas of polygenic burden associations across the human phenome (http://mrcieu.mrsoftware.org/PRS_atlas/), respectively. Catalogues and atlas' such as these provide researchers with open access opportunities to obtain previously published PGSs, the annotations of previously derived PGSs, and to carry out subsequent analyses using the data obtained (Loos, 2020).

3.1.7 POLYGENIC SCORES AND CHILD DEVELOPMENT

The efficacy of earlier initiatives to identify, map, and sequence the genetic architecture of the human genome, the development of associative testing with GWASs, and the availability of methods by which to utilise genome-wide summary statistics from large consortia to calculate PGSs have all contributed to the multidisciplinary expansion of genetic inquiry and utility (Collister et al., 2022; Marees et al., 2018). Likewise, there has been a growing trend towards the application of polygenic analyses to assess the predictive power of polygenic scores for key developmental outcomes, such as mental health, cognitive ability, and educational attainment (Allegrini et al., 2022; Morneau-Vaillancourt et al., 2021). In line with this, researchers have employed PG methods to identify whether PGSs have the potential to predict the developmental trajectory of subtypes of social withdrawal (i.e., social weariness and preference for solitude) during childhood (Morneau-Vaillancourt et al., 2021). The results of this study demonstrated the heterogeneous ability PGSs to predict subtypes of social withdrawal during development, with the predictive power of PGSs varying depending on the subtype under examination. For example, PGSs for loneliness significantly predicted the developmental trajectory for social wariness, whereas only PGSs for general mental health were predictive of the tendency to display a high-chronic preference for solitude during childhood. Given the important role of social interactions on a child's development from a socioemotional perspective (Bukowski et al., 2020), these results shed light on the potential for PGSs to identify those at risk of experiencing socioemotional difficulties, thereby highlighting their capacity in a clinical and intervention setting. Even so, it is important to note that typically, even when the predictive capacity of PGSs are significantly higher than chance, the explained variance is often small.

3.1.8 POLYGENIC SCORES, COGNITIVE ABILITY, AND EDUCATIONAL ATTAINMENT

The potential for generating PGSs for cognitive ability and educational attainment has led to an increase in their use to assess their predictive power, as well identify the ways in which they interact with external factors in a child's proximal environment to influence development (Allegrini et al., 2019; Okbay et al., 2022; von Stumm et al., 2020). One such study identified the genomic predictors of cognitive ability and educational attainment in a UK sample of 7,026 children at ages 12 and 16 (Allegrini et al., 2019). Approximately 11% and 16% of the variance in cognitive ability and educational attainment, respectively, could be attributed to PG predictors for both sexes, with an additive effect seen across each timepoint. PGSs have also been calculated in a UK population-based cohort between the ages of 7 and 16, to assess the longitudinal interplay between PGSs for educational achievement and measures of socioeconomic status (SES) in predicting educational achievement (von Stumm et al., 2020). Using latent growth curve models, von Stumm and colleagues (2020) found the predictive capacity of PGSs and SES to steadily increase during development, and by the age of 16, were able to account for 14% and

23% of the variance in education achievement, respectively. Interestingly, these results additionally showed 77% of children with high PGSs and from high SES households had gone on to attend university, compared to the 21% of children with low PGSs and from low SES households. These associations were especially pronounced for children at either end of the PGS-SES distribution. These results demonstrate the ways in which polygenic scores can be used alongside environmental measures, such as SES, to advance our understanding of the multifaceted and longitudinal influences on educational achievement during child and adolescent development.

3.1.9 DOWNSTREAM UTILITY OF POLYGENIC SCORES

PGSs have the additional utility of being used for downstream analyses (Cao et al., 2021; Choi et al., 2020; Collister et al., 2022; Kweon et al., 2021; Marees et al., 2018; Pat et al., 2022). For example, PGSs have been employed to assess plausible mediating factors in the association between genetic liability and psychopathology during early childhood development. In one such study, the mediating role of motivation and cognitive ability, captured as a general intelligence factor, or *g* factor, have been investigated in the link between PGSs for attention-deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD), and the manifestation of these conditions during childhood (Pat et al., 2022). The association between PGSs for ADHD on psychopathology was mediated by reward sensitivity and cognitive abilities, whereas the association between PGSs for MDD on psychopathology was mediated by punishment sensitivity and cognitive abilities. These results elucidate the different mechanisms that help to explain the association between polygenic liability and psychopathology in childhood. Assessing genetic liability by way of PGSs has also been used in analyses which have incorporated PGSs and functional brain network connectivity data to assess the association between polygenic risk for schizophrenia and connectome-wide neural mechanisms (Cao et al., 2021). High PGSs for schizophrenia is associated with lower functional connectivity in a large-scale brain network, a finding consistent with a hallmark feature of schizophrenia, that is, functional brain dysconnectivity (Maher et al., 2019; Zarghami et al., 2020). Additionally, PGSs offer the potential to examine the intersection between genetic, neural, and environmental factors on the well-documented detrimental effects of SES on child development. For example, by calculating PGSs for SES and assessing the influence of polygenic and environmental aspects of SES on brain structure, Kweon and colleagues (2021) demonstrated that the genetic and environmental influences of SES on the anatomy of the brain are highly variable. With brain regions displaying high genetic influence simultaneously showing a proclivity for low environmental influence, such as the prefrontal cortex and the insula, and areas of high environmental influence displaying low genetic influence, such as the cerebellum and lateral temporal region. The current chapter is principally concerned with the construction and validation of PGSs for cognition and education, however, in **Chapter 4** we go on to integrate these genomic predictors with structural brain organisation and standard measures of SES.

In summary, analysing polygenic variability, and using this information to calculate PGSs can further our understanding of child development. When done methodically, following the appropriate protocols for data extraction, QC, and calculating PGSs, polygenic methods can be effectively utilised in downstream analyses. These downstream analyses can provide insight into the complex interplay between genetics, the structural and functional architecture of the brain, and the developmental environment. Likewise, it is plausible that many factors

interact to shape an individual's brain development, cognitive ability, and phenotypic behaviour. A primary obstacle is to disentangle these different factors, and the use of PGSs provides one way of doing this.

3.1.10 THE CURRENT STUDY

The purpose of the current study is to use appropriate GWASs, and actively employ standard measures of QC to generate meaningful PGSs for both cognitive ability and educational attainment. Specifically, I sought to determine whether the resulting scores are correlated with their associated outcome measures (i.e., cognitive ability and educational attainment). By assessing the efficacy of the generated personalised scores, I hope to identify their prospective utility in downstream analyses aimed at evaluating the interplay between genetic, neural, and environmental influences on child development. Our base data comprised summary statistics obtained from GWAS meta-analyses in large-scale cohorts of European descent for cognitive ability (Savage et al., 2018) and educational attainment (Lee et al., 2018). Our target data were formed using data from the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013), including genotyping data and key measures of child cognitive ability and educational attainment. I employed dedicated PGS analysis software programs, PLINK (Chang et al., 2015; Purcell et al., 2007) and PRSice-2 (Choi & O'Reilly, 2019; Euesden et al., 2015), alongside multipurpose software, R (R Core Team, 2022) and RStudio (RStudio Team, 2022), to run stringent QC measures and generate PGSs for assessment.

3.2 METHODS

3.2.1 PARTICIPANT DEMOGRAPHIC

3.2.1.1 Base Data for Cognitive Ability

Base data for cognitive ability comprised a GWAS meta-analysis of cognitive ability in 269, 867 individuals from 14 independent epidemiological cohorts of European ancestry (Savage et al., 2018). Cohorts included individuals from the UK Biobank (UKB), the Cognitive Genomics Consortium (COGENT), the Rotterdam Study (RS), the Generational R Study (GENR), the Swedish Twin Registry (STR), Spit for Science (S4S), the High-IQ/Health and Retirement Study (HiQ/HRS), the Twins Early Development Study (TEDS), the Danish Twin Registry (DTR), IMAGEN, the Brisbane Longitudinal Twin Study (BLTS), the Netherlands Study of Cognition, Environment, and Genes (NESCOG), Genes for Good (GfG), and the Swedish Twin Studies of Aging (STSA). The resulting sample ranged from children to adults with ages ranging from 6 to 60. Older adults ($M > 60$) were removed to reduce the potential of biased performance on tests of cognition due to cognitive decline. A comprehensive description of the participant demographic for all 14 cohorts has been previously delineated by Savage and colleagues (2018).

3.2.1.2 Base Data for Educational Attainment

A GWAS meta-analysis comprising 1,131,991 individuals from 71 cohorts of European ancestry formed the base data for educational attainment (Lee et al., 2018). The sample comprised individuals whose educational attainment

was assessed when they were aged 30 or above. The resulting sample included 59 cohorts previously reported by Okbay and colleagues (2016), as well as an additional 12 cohorts. Additional cohorts included individuals from 23andMe, the National Longitudinal Study of Adolescent to Adult Health (Add Health), Estonian Genome Centre, University of Tartu (EGCUT), the English Longitudinal Study of Aging (ELSA), the Fenland Study (FENLAND), Geisinger Health System (Geisinger), Generation Scotland: Scottish Family Health Study (GSII), the EPIC-Norfolk Prospective Population Study (NORFOLK), UK Biobank (UKB), The UK Household Longitudinal Study (UKHLS), the Viking Health Study (VIKING), and the Wisconsin Longitudinal Study (WLS).

3.2.1.3 Target Data

Target data for the phenotype cognitive ability and educational attainment comprised omics and phenotypic data from the ALSPAC, a transgenerational cohort study based in the region of Avon, England. During its initial conception, 13,761 eligible pregnant women with an expected delivery data between 1st April 1991 and 31st December 1992 were recruited (M = 28, range 14-46, SD = 5.0) (Boyd et al., 2013; Fraser et al., 2013). Over the last three decades, comprehensive data have been collected from three generations of participating families. Elaborate demographic information has been detailed at each wave of data collection for both the index children (Boyd et al., 2013) and their mothers (Fraser et al., 2013). The present study included omics data and phenotypic data for cognitive ability and educational attainment from the ALSPAC index children cohort. To prevent inflated SNP-phenotype associations, only data from unrelated children were included in analyses. Following stringent measures of quality control and related filtering, the total target sample size for unrelated children when generating PGSs for the phenotype cognitive ability was 5,214 (50.3% female). Correspondingly, the target sample size for unrelated children when generating PGSs for the phenotype educational attainment was 1,695 (65.4% female).

3.2.2 MEASURES

3.2.2.1 Genomic Base Data for Cognitive Ability

The GWAS meta-analysis for cognitive ability was performed in individual cohorts using linear or logistic regression analyses where appropriate, and subsequently meta-analysed using the dedicated METAL software (Willer & Abecasis, 2010). Cognitive ability was assessed by way of cognitive testing for fluid domains of functioning. Neuropsychological measures assessed various cognitive domains, including working memory, verbal memory, processing speed, and executive functions. The variance expressed across neuropsychological measures were modelled as *g*, a latent factor of general intelligence, and *g*-factor estimates were taken forward to represent cognitive ability in subsequent analyses (Savage et al., 2018). Stringent QC measures were carried out with the summary statistics for each GWAS cohort included in the meta-analysis, and SNPs were filtered based on the following parameters: minor allele count (MAC) < 100, imputation quality information (INFO) score < 0.6, Hardy–Weinberg equilibrium $p < 5 \times 10^{-6}$, mismatch of alleles, and allele frequencies that varied more than 20% from the Haplotype Reference Consortium (HRC) genome reference panel. Duplicate, multiallelic, monomorphic, and ambiguous SNPs were also removed during QC. The meta-analysis resulted in 12,110 variants indexed by 242 lead SNPs in approximate linkage equilibrium ($r^2 < 0.1$) reaching genome-wide significance ($p < 5 \times 10^{-8}$).

3.2.2.2 Genomic Base Data for Educational Attainment

The GWAS for educational attainment performed a sample-size-weighted meta-analysis of 71 individual cohort-level results files using METAL software (Willer & Abecasis, 2010). Educational attainment was measured as the number of years of schooling completed by individuals in each cohort, as indicated at age 30 and above. Questionnaires included questions such as "What is the highest level of education that you have achieved to date" and "What is the highest level of schooling you completed". Stringent measures of QC were carried out, with varying thresholds adopted depending on the cohort study under assessment, as detailed by Lee and colleagues (2018). Thresholds were set to filter SNP- and subject-specific exclusions based on minor allele frequencies, SNP call rates, Hardy–Weinberg equilibrium, population stratification, sex mismatches, duplicates, relatedness, and heterozygosity. The meta-analysis identified 1,271 approximately independent ($r^2 < 0.1$) SNPs at genome-wide significance ($p < 5 \times 10^{-8}$).

3.2.2.3 Target Data Genomics

All target data were obtained directly from the ALSPAC. Omics data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Index children were genotyped using Illumina HumanHap550 quad chip genotyping platforms. The genome-wide data were then subject to standard QC, where SNPs and individuals were excluded from the sample based on sex mismatches, heterozygosity levels, individual missingness (> 3%), SNP missingness (>1%), and insufficient sample replication (IBVD < 0.8). Population stratification was assessed, and individuals with non-European ancestry were removed from the sample. Variants were further filtered based on MAF (< 1%), call rate (< 95.5), Hardy–Weinberg equilibrium violations ($p < 5 \times 10^{-7}$), and cryptic relatedness (IBD > 0.1). The remaining SNPs (n = 500,527) and individuals (n = 9,115) were retained for subsequent phasing and imputation.

For the present study, only omics data for unrelated children were carried forward for downstream QC measures and PGS calculations. Unrelated children were identified by the ALSPAC based on genetic relationship matrices (GRMs). Once GRMs were calculated, an individual from each pair where relatedness was greater than 0.05 was arbitrarily removed, and the remaining sample formed the unrelated children cohort. The resulting sample size post-ALSPAC standard QC and genetic relationship filtering was 7,856. This was further filtered in the current study based on the phenotypic data availability for unrelated children. This resulted in a sample size of 5,214 for the phenotype cognitive ability and 1,695 for educational attainment.

3.2.2.4 Phenotypic Target Data for Cognitive Ability

Cognitive ability was measured when children were age 8 using the Verbal and Performance subscales of the commonly used Wechsler Intelligence Scale for Children, 3rd edition (WISC-III; Wechsler, 1991). This widely used scale has demonstrated reliability coefficients ranging from 0.94 to 0.97. Both subscales yield a standard score (M = 100, SD = 15) by comparing an individual's score to that of a representative sample of similarly aged peers. The Verbal scale comprises five subtests on information (i.e., knowledge and long-term memory), similarities (i.e., abstract reasoning and long-term formation), arithmetic (i.e., numerical reasoning and

computation), vocabulary (i.e., word knowledge), and comprehension (i.e., practical knowledge and social judgement). The Performance scale includes picture completion tasks (i.e., visual perception and attention to detail), picture arrangement (i.e., nonverbal reasoning and sequencing), block design (i.e., spatial visualisation and reasoning), object assembly (i.e., visual perception and organisation), and coding (i.e., visual-motor information processing). The total sum of the scores for the Verbal and Performance subscales formed the global measure of cognitive ability, which was then taken forward for PGS tests of association.

3.2.2.5 Phenotypic Target Data for Educational Attainment

Educational attainment was assessed by self-reported measures of education levels achieved when participants were aged 18 and above. Items included whether the respondent had obtained GCSE grades A*-C qualification, GCSE/Vocational GCSE or equivalent qualification, and/or A-level/Vocational A-level/GCE in applied subjects or equivalent qualification. Response options were (1) yes or (2) no. Response items were recoded so higher values represented higher levels of education. Response items were then scored, with a score of 1 accredited for each no response, and a score of 2 accredited for each yes response. The total sum of these scores represented the global educational attainment score for each individual, which was then taken forward for downstream analyses.

3.2.3 TARGET DATA COLLECTION

All target data were collected by the ALSPAC. Omics data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Children were directly administered the WISC-III at 8 years (Wechsler, 1991). Questionnaires pertaining to educational attainment were administered when index children were age 18 and above.

Ethics approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

3.2.4 SOFTWARE

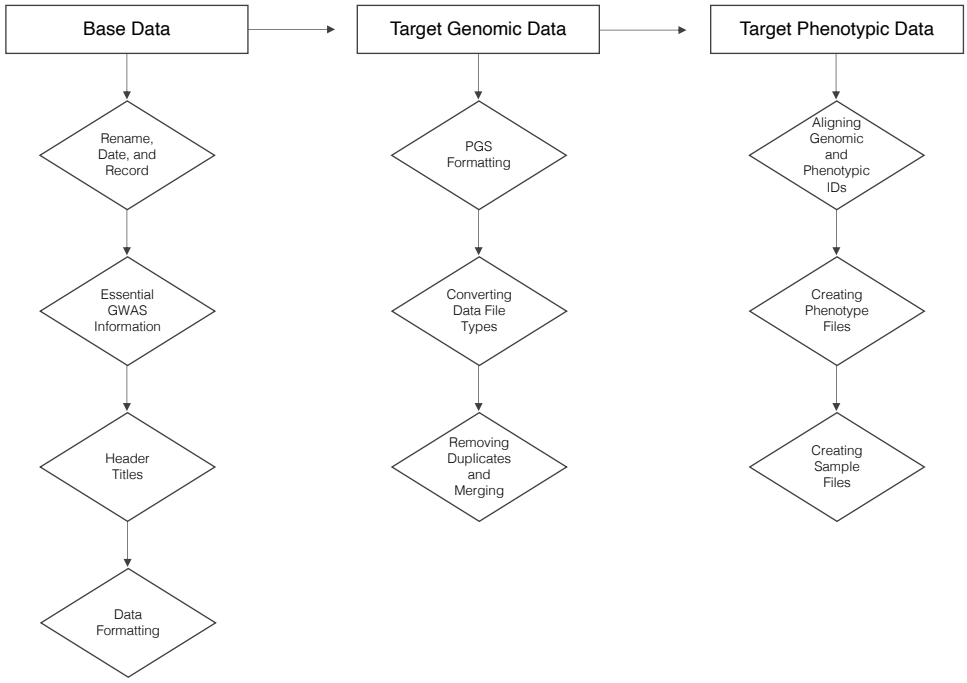
Formatting, pre-processing, QC measures, and PGS analyses were carried out using a combination of dedicated PGS software programs alongside multipurpose software. This included the use of PLINK (Chang et al., 2015; Purcell et al., 2007) and PRSice-2 (Choi & O'Reilly, 2019; Euesden et al., 2015), alongside R (R Core Team, 2022) and RStudio (RStudio Team, 2022), respectively. Whilst it is possible to predominantly carry out PGS analyses in multipurpose programming environments, such as R and RStudio, it is more advantageous to use dedicated programs with user-friendly methods to ensure optimal data formatting, pre-processing, QC, and PGS calculations (Marees et al., 2018). Correspondingly, when compared with alternative PGS software, such as LDpred, PRSice-1, and lassosum, PRSice-2 offers a memory-efficient and substantially quicker calculation time, whilst maintaining comparable predictive power (Choi & O'Reilly, 2019).

3.2.5 DATA FORMATTING AND PRE-PROCESSING

As required by standard PGS protocols and dedicated software, all data were subject to formatting and pre-processing prior to analyses (Choi et al., 2020). The completed formatting and pre-processing steps can be distinguished into those required for the base, target, and phenotypic dataset, respectively. These steps have been outlined for clarity in Figure 3.1. The steps required for the base and target genomic data will be discussed in turn.

Figure 3.1

Summary of Data Formatting and Pre-Processing



3.2.5.1 Base Data Formatting and Pre-processing

3.2.5.1.1 Rename, Date, and Record

The GWAS summary statistics obtained in the current study were downloaded from an open access consortium. Base data were downloaded and placed in a directory housing all data required for analyses. Data files were renamed, dated, and the publication for each GWAS was recorded.

3.2.5.1.2 Essential GWAS Information

It was important to ensure the summary statistics contained the relevant information as required by PGS software when employing QC measures and computing PGSs. This involved confirming the presence of SNP identification references (in the form of rsID, chromosome:position, or chromosome:position_allele1_allele2), chromosome numbers, base pair positions, effect allele (i.e., risk allele, reference allele, and coded allele), non-effect allele (i.e., the alternative allele or other allele), z-score for the effect allele, and the discovery stage sample size. During

this stage, header titles were assessed to ensure required data was present, and data presentation was reformatted where necessary to ensure continuity between the base and target data sets (Choi et al., 2020).

3.2.5.2 Target Data Genomic Formatting and Pre-processing

3.2.5.2.1 Required Formatting for PGS Analysis

When using PGS software, certain genomic target data formats are required. For instance, PLINK and PRSice-2 require data to be formatted as either text or binary files. Given the large file sizes synonymous with genomic data, reading genomic text files would be cumbersome (Choi et al., 2020). Thus, files containing genotype information should be in binary format prior to analysis. The three files required by PLINK and PRSice-2 for PGS analysis include one binary .bed file, and two text .bim and .fam files. The binary .bed file comprises individual identifiers (IDs) and genotypes, and its binary format means it is unreadable to the human eye. The .fam file includes information on the individuals in a sample, including the family, individual, paternal, and maternal IDs, sex, and phenotype information. The .bim file includes information about the genetic variants, including chromosome number, SNP ID, genetic distance, base-pair position, and the nucleotides for the effect and non-effect allele (Marees et al., 2018).

3.2.5.2.2 Converting Target Data File Types

Omics data obtained from ALSPAC were received in chromosome-specific .bgen format with their associated .sample files, a format less compatible with the intended PGS software to be used for analyses. These data were therefore required to undergo reformatting prior to their use. This was achieved in PLINK by converting all 22 autosomal chromosome .bgen files to PLINK-friendly .bed/.fam/.bim files. This resulted in a set of 22 .bed/.fam/.bim files, one for each autosomal file.

3.2.5.2.3 Removing Duplicates and Merging Files

For ease of analyses, all 22 files were then merged into one set of .bed/.fam/.bim files. To do this, all duplicate SNPs first needed to be removed from the .bim files. This step was pivotal, as duplicate SNPs can cause PGS software programs to crash during the merging process, and therefore need to be removed prior to analysis. This was achieved in PLINK and RStudio, where a text file was created in RStudio detailing all unique SNPs in each set of .bed/.fam/.bim files for each chromosome. These SNPs were then extracted from the files in PLINK. A text file was created stipulating the 22 .bed/.fam/.bim file names to be merged. All files were then merged in PLINK, and the resulting single set of .bed/.fam/.bim files were taken forward for subsequent QC and PGS analyses.

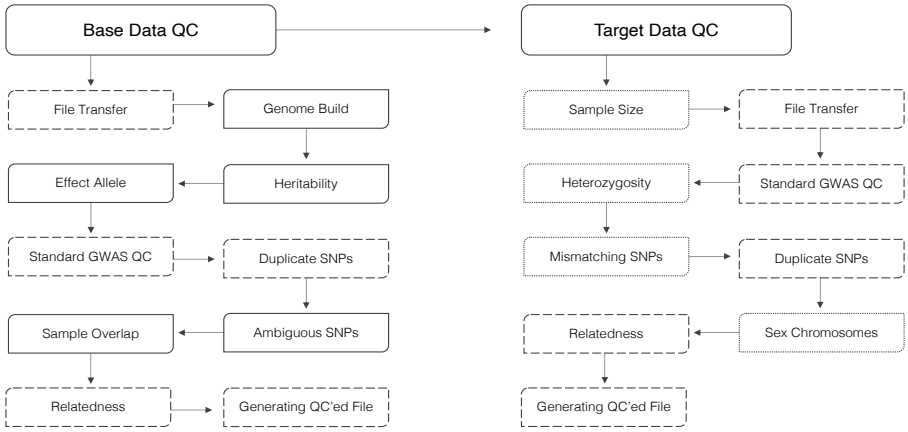
3.2.6 QUALITY CONTROL

Following data formatting and pre-processing, both base and target data sets underwent stringent measures of QC, as outlined thoroughly by Choi and colleagues (2020). The numerous QC steps which were carried out with the

base data for cognitive ability and education, along with the target data for cognitive ability and educational attainment, will be discussed. For clarity, these steps have also been briefly outlined in Figure 3.2.

Figure 3.2

Summary of Quality Control Steps Undertaken with Base and Target Data Sets



Note. Solid border indicates steps completed with the base data only. Round dot border indicates steps taken with the target data only. Long dash indicates steps which were completed with the base and target data.

3.2.6.1 Base Data Quality Control

3.2.6.1.1 File Transfer

The genome-wide summary statistics for cognitive ability and educational attainment were downloaded from open access consortiums. The integrity of all files was confirmed by ensuring the files were not corrupted during the file transfer process. This was achieved by aligning the md5sum hash (i.e., string of characters assigned to a file) indicated by the GWASs, and that of the downloaded files. The string of characters generated from the downloaded files matches those indicated by the GWASs, indicating that the files were not corrupted during the transfer.

3.2.6.1.2 Genome Build

All base and target data sets were assessed to confirm they were on the same genome build. Genome builds must be standardised prior to PGS analyses, as each build uses distinct parameters to label and present SNPs. Thus, differences in genome builds could lead to variations in SNP labelling and presentation. This could additionally lead to variants being incorrectly identified, having downstream consequences for PGS calculations (Collister et al., 2022). Both GWA studies and the ALSPAC omics data were on genome build 37, and thus, this prerequisite was met.

3.2.6.1.3 Heritability Check

It is recommended that only genome-wide summary statistics with a SNP heritability (h^2_{SNP}) threshold > 0.05 are used for PGS analyses. SNP heritability refers to the amount of variance in a phenotypic trait that can be explained by the accumulation of SNPs (Evans et al., 2018). Given the standard errors in effect size estimates generated during PGS analyses, taken together with the difference that will undoubtably exist between base and target data sets, the predictive power of PGSs is considerably lower than h^2_{SNP}. Whilst larger samples increase the predictive power of PGSs, it is important to set an appropriate h^2_{SNP} threshold to avoid type I (i.e., false positive) and type II (i.e., false negative) errors. This was assessed for the GWAS summary statistics, and the SNP heritability requirement was met.

3.2.6.1.4 Effect Allele

Information regarding the identity of the effect allele must be indicated by the GWAS selected for PGS analyses. It is essential that this information is obtained from the GWAS and not presumed, as identifying the incorrect allele as the effect allele can lead to the generation of PGSs that are in the opposite direction, and result in inaccurate conclusions to be drawn from the results. Therefore, the effect allele was pre-identified in both genome-wide studies.

3.2.6.1.5 Standard GWAS Quality Control

As noted, the base and target data should be subjected to the same standard stringent QC steps performed by the initial GWASs. For both base data sets, this included filtering the SNPs according to MAF and INFO score, and SNPs with MAF < 1% and INFO < 0.6 were removed from the data at this stage. This was carried out in R using packages 'data.table' and 'R.utils', and only including SNPs with MAF > 0.01 and INFO > 0.6. In the base data for cognitive ability, a total of 1,085,690 SNPs were removed during filtering, resulting in a total of 8,209,428 SNPs taken forward. In the base data for educational attainment, 1,855,262 SNPs were removed, resulting in a total of 8,970,068 SNPs taken forward.

3.2.6.1.6 Duplicate SNPs

As noted, PGS software programs, such as PLINK and PRSice-2, do not allow for duplicate SNPs. Thus, all duplicate SNPs were removed from both base data sets prior to analyses. This was completed in R using the 'dplyr' package. No duplicates were present in the base data for cognitive ability. A total of 35,804 duplicates were removed from the base data for educational attainment, resulting in a total of 8,934,264 SNPs taken forward.

3.2.6.1.7 Ambiguous SNPs

There is a possibility that different genotyping chips were used when generating the base and target data, and the chromosome strand for either is unknown. If this is the case, then it is not possible to align the alleles of ambiguous SNPs between data sets. Attempting to infer which alleles align based on allele frequencies when the base and target data are gathered from different populations can lead to systematic errors. Therefore, instead of attempting

to remediate ambiguous SNPs, it is recommended to remove them from the data entirely (Choi et al., 2020). This was achieved in R using the 'dplyr' package. A total of 1,151,571 ambiguous SNPs were removed from the base data for cognitive ability, resulting in a total of 7,057,857 SNPs taken forward. A total of 1,383,493 ambiguous SNPs removed from the base data for educational attainment, resulting in a total of 7,550,771 SNPs taken forward for downstream analyses post QC.

3.2.6.1.8 Sample Overlap

It is important to confirm that there is no sample overlap between the base and target data, as this will lead to substantially inflated associations being drawn between the PGSs and the phenotype of interest (Wray et al., 2013). For this reason, individual's whose data are present in the base and target data must be removed from the sample prior to further analyses. Considering the rise in meta-analysis GWASs using multiple cohorts to increase sample size and thereby statistical power, such as those used in the current study, it is possible the base data includes the large-scale cohort data selected for the target data. Here, the GWAS for educational attainment included data from the ALSPAC cohort. Therefore, a copy of the summary statistics with this cohort removed were obtained prior to running PGS analyses.

3.2.6.1.9 Relatedness

In addition to sample overlap leading to inflated association results, so too can a high degree of relatedness between the base and target samples (Choi et al., 2020). Relatedness within the base data was tested with the target data.

3.2.6.1.10 Generating QC'ed Base Data Sets

Following QC, the final base data to be used for PGS calculations for cognitive ability and educational attainment, respectively, were generated. For cognitive ability, the final QC'ed base data comprised a total of 7,057,857 SNPs. For educational attainment, the final QC'ed base data included a total of 7,550,771 SNPs.

3.2.6.2 Target Data Quality Control

3.2.6.2.1 Sample Size

It is recommended that PGS analyses are only carried out with target data comprising a sample of at least 100 individuals. However, the larger the sample, the higher the statistical power, and in terms of statistical power, a sample size of 2,000 is ideal. Whilst this condition was met with the cognitive ability sample, n = 5,296 the educational attainment sample size was less than ideal, with n = 1,716. Nevertheless, as this sample size was still substantial, the data were taken forward for subsequent analyses.

3.2.6.2.2 File Transfer

As the target data were obtained from an external source (i.e., the ALSPAC), the integrity of the downloaded files needed to be confirmed to ensure the files were not corrupted during the transfer. The md5sum hash values were cross-referenced with the values provided by ALSPAC, and file integrity was confirmed.

3.2.6.2.3 Standard GWAS Quality Control

As a minimum, target data must undergo QC methods to the same standards implemented by GWA studies (Choi et al., 2020). In the current study, SNPs with low genotyping rates (> 0.01 sample missingness), low MAF (< 0.01), and those deviating from the Hardy-Weinberg Equilibrium ($p < 1 \times 10^{-6}$) were excluded. Individuals with a high genotype missingness rate (> 0.01 SNP missingness) were also excluded. Standard QC was carried out in PLINK using the applicable flags and setting the appropriate thresholds (i.e., --geno 0.01; --maf 0.01; --hwe 1e-06; --mind 0.01). Standard measures of QC were carried out on the full ALSPAC omics dataset, and target data subsamples based on phenotypic availability (i.e., cognitive ability and educational attainment) were extracted using the --keep flag in PLINK following QC. Thereby, for the target data for both cognitive ability and educational attainment, 136 individuals were removed due to missing genotype data (i.e., --mind), 2,782,184 SNPs were removed due to missing genotype data (i.e., --geno), 146 SNPs were removed due to Hardy-Weinberg exact test (i.e., --hwe), and 13,549,168 SNPs were removed due to minor allele threshold (i.e., --maf). This resulted in 4,970,097 SNPs and 17,680 individuals passing standard target data filters and QC.

3.2.6.2.4 Extreme Heterozygosity

Individuals with either very low or high heterozygosity rates (beyond three standard deviations from the mean) were excluded from the target data. This required the use of PLINK to generate a .het file containing the *F* coefficients estimates for assessing heterozygosity. Individuals whose *F* coefficients were more than three standard deviations from the mean were then removed in R. This generated a new sample file, which was then taken forward for subsequent filtering and QC. During filtering, 75 individuals were removed from the sample due to heterozygosity rates. This resulted in a total sample size of $n = 17{,}605$.

3.2.6.2.5 Mismatching SNPs

There is a possibility of SNPs having resolvable mismatching alleles reported between the base and target data (e.g., A/C in the base data and G/T in the target). This can be remedied by strand-flipping the alleles to the correct corresponding allele (Choi et al., 2020). Non-resolvable mismatching SNPs (e.g., C/G in the base data and C/T in the target data) were removed altogether. This QC step was performed automatically in PLINK during PGS calculations.

3.2.6.2.6 Duplicate SNPs

As noted, PGS software programs, such as PLINK and PRSice-2, do not allow for duplicate SNPs. All duplicate SNPs were removed during the pre-processing and formatting stage to allow for the autosomal data files to be merged.

3.2.6.2.7 Sex Chromosomes

The mislabelling of a sample can lead to invalid results, and one indication of mislabelling during the genotyping process is a difference between an individual's reported sex and that indicated by their sex chromosomes. Whilst this could be due to a difference in gender identify and sex, it could also be the result of mislabelling or misreporting. This data is then classed as unreliable, and where there is a discrepancy between reported sex and that indicted by the sex chromosomes, participants are removed from the data. This step was carried out by the ALSPAC directly, as part of their standard QC protocols prior to making omics data available. The current PGS analyses aimed to solely model autosomal genetics, as is often the case with PGS analyses. Therefore, and in line with PGS guidelines (Choi et al., 2020), sex chromosomes were further removed from the data to minimise the possible influence of non-autosomal effects on the results.

3.2.6.2.8 Relatedness

Relatedness within the sample is typically calculated and those with high relatedness are removed. As noted, unrelated children were identified by the ALSPAC based on genetic relationship matrices (i.e., relatedness greater than 0.05 was arbitrarily removed), and the remaining sample formed the unrelated children cohort. This resulted in a list representing the IDs of the unrelated children in the ALSPAC omics data. This text file was used to extract data from unrelated children only using the --extract function in PLINK. This ensured only unrelated children in the target data were carried forward for PGS calculations.

3.2.6.2.9 Generating QC'ed Target Data

After completing the above QC steps, a final QC'ed target data set was generated in PLINK. Subset files for individuals with both genomic and phenotypic data available (i.e., cognitive ability and educational attainment) were further generated in PLINK using the --keep function. This resulted in two sets of .bed/.bim/.fam files, one for the cognitive ability (n = 5,214), and one for educational attainment (n =1,695), with 4,970,097 SNPs passing filters and QC. These files were taken forward for PGS calculations.

3.2.7 STATISTICAL ANALYSES

The statistical analyses required for the current study were threefold. First, principal component analysis (PCA) was employed to account for population stratification. Second, PGSs were calculated using standard cluster and thresholding (C+T) methodologies in PRSice-2. Third, Pearson correlation coefficients were computed to assess PGS performance compared to the phenotype outcome measures on which they were based. These analytic steps will be discussed in turn. I performed all data pre-processing and formatting of the base and target data sets, and

generated the pipelines required for completing PGS analysis specifically with the ALSPAC genomic and phenotypic data. To confirm accuracy of these pipelines, the protocols I devised providing a thorough account of each step taken and the resulting outcome were overseen by Dr. Varun Warrier at the Department of Psychiatry, University of Cambridge.

3.2.7.1 Population Stratification

As part of the PGS analyses, population stratification must be accounted for. Population stratification refers to the genetic variance resulting from ethnic heterogeneity, as opposed to that of genotype-phenotype associations, and is a principal source of systematic bias (Marees et al., 2018). It is therefore essential to test for and account for population stratification in the target data during PGS analyses. There are many ways that this can be achieved (Price et al., 2010). A common method, as detailed by Choi and colleagues (2020), is to account for population stratification by incorporating principal components (PCs) as covariates in a covariance matrix alongside participant family ID (FID), sample ID (IID), and participant sex, which are then incorporated into the PGS analyses. This method was adopted in the current study, and PCs were calculated in PLINK using the --pca flag and indicating the number of components for return. The number of PCs chosen is typically arbitrary, but it is common practice to use that which is typically seen in the literature for the phenotype of interest. When calculating PGSs for cognitive ability and educational attainment, 10 PCs are predominately calculated and added to the covariance matrix (Allegrini et al., 2019). The first 10 PCs generated were then merged with the FID, IID, and participant sex information. This was carried out in R for cognitive ability and educational attainment samples, separately.

3.2.7.2 Calculating Polygenic Scores

After the appropriate formatting, pre-processing, QC measures, and steps to account for population stratification were completed using PLINK and R software programs, PGSs were then calculated for both cognitive ability and educational attainment in PRSice-2. Whilst the individual steps to calculate PGSs can be carried out manually in PLINK and enable an enhanced depth of understanding of the processes involved in PGS calculations, these steps are fully automated by alternative software programs, such as PRSice-2 (Choi et al., 2020). Scores were generated in PRSice-2, which implements the standard cluster and thresholding (C+T) method. The C+T method enables one to control for linkage disequilibrium, which makes identifying the causal independent SNPs particularly challenging (Choi et al., 2020; Privé et al., 2019). During C+T, SNPs were clumped based on those most associated with the phenotype of interest. This does not mean that only SNPs highly associated with the phenotypes of interest were retained, however, they were preferentially selected during the clumping process. Correspondingly, if there were multiple effects present in the same region, multiple SNPs were retained. PGSs were then calculated using the clumped subset of partially independent SNPs which exceeded the PRSice-2 default GWAS *p* value threshold. The C+T method was automatically carried out using PRSice-2 default parameters to generate PGSs. Once scores were calculated for each phenotype, PRSice-2 provided output files containing the generated scores, the *p* value thresholds which generated the 'best-fit' PGSs, and the proportion of the phenotypic variation explained by the 'best-fit' PGSs.

3.2.7.3 Correlation Coefficients

Following the calculation of PGSs, Pearson's product-moment correlation coefficients (PPMCCs; Pearson, 1895) were computed to assess the linear relationship between PGSs and their phenotypic counterparts. PPMCC values range from -1 to 1, with -1 denoting a negative association between any two given variables, 0 denoting no linear correlation between two variables, and 1 denoting a position association between two variables. PPMCCs were computed to determine the association between PGSs for cognitive ability and the phenotypic outcome measure cognitive ability, as measured by individual performance on the WISC-III (Wechsler, 1991), and between PGSs for educational attainment and the phenotypic outcome measure educational attainment, as measured by self-reported measures of education levels achieved. PPMCCs were additionally computed for PGSs for cognitive ability and the phenotypic measure of educational attainment, as well as PGSs for educational attainment and the phenotypic measure of cognitive ability. Given the interweaving nature of cognitive ability and educational attainment (Allegrini et al., 2019), this allowed me to further assess the efficacy of the generated PGSs. Effect sizes were interpreted as small where *r* ranged from .1 to .3 to -.1 to -.3, medium where *r* ranged from .3 to .5 or -.3 to -.5, and large where *r* was.5 or greater or -.5 or greater (Rosenthal, 1991).

3.3 RESULTS

3.3.1 POLYGENIC SCORES FOR COGNITIVE ABILITY

I calculated PGSs (i.e., the SNP effect size weighted sums of the number of alleles associated with cognitive ability) based on summary statistics from a GWAS meta-analysis of cognitive ability (Savage et al., 2018). High-resolution PGSs were calculated in PRSice-2 at the following *p* value thresholds: 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1, as recommended by PGS analysis guidelines (Choi et at., 2020; Marees et al., 2018). A summary of the best model fit when generating PGSs for cognitive ability has been detailed in Table 3.1. As illustrated in Table 3.1, the threshold which generated the 'best-fit' PGS was $p = 0.1$. Further to be seen in Table 3.1, the 'best-fit' PGSs accounted for 8% of the variance in the full model when covariates were accounted for ($R^2 = 0.084$, $p = 3.05887E^{-94}$).

Table 3.1

Summary of the Best Model Fit for the Phenotype Cognitive Ability and Gene Set

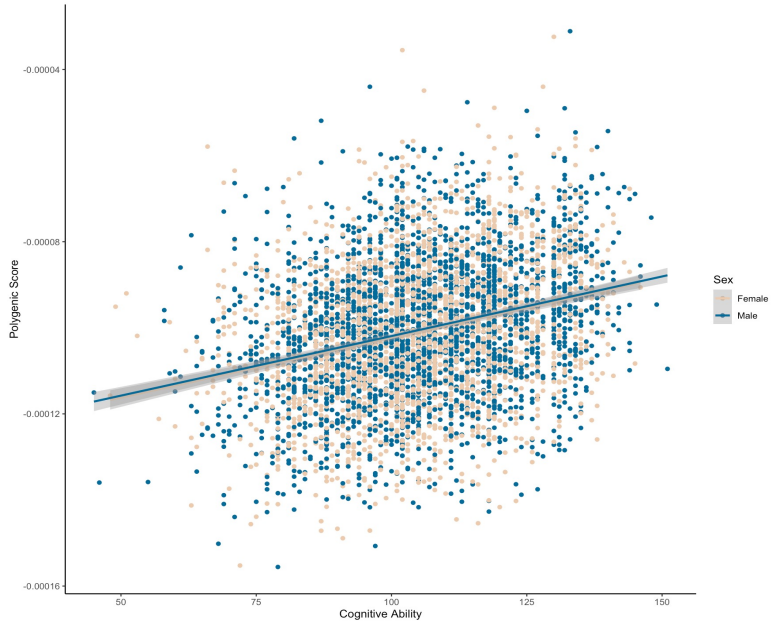
Set	Threshold	PGS R^2	Full R^2	Null R^2	Coefficient	*SE*	*p*	*SNP*
Base	0.097	0.078	0.084	0.007	283754	13498.1	$3.05887E^{-94}$	48261

Note. Set refers to the name of the gene set. Threshold refers to the best *p* value threshold. PGS R^2 refers to the variance explained by the PGS. Full R^2 refers to the variance explained by the full model, including covariates. Null R^2 refers to the variance explained by covariates. Coefficient refers to the regression coefficient of the model, denoting the directionality of the effect. *p* refers to the *p* value of the model fit. SNP refers to the number of single nucleotide polymorphisms (SNPs) included in the model.

The PGSs generated for cognitive ability were then assessed to determine their performance relative to their associated phenotype, cognitive ability, as represented by performance on the Verbal and Performance subscales of the WISC-III (Wechsler, 1991). A Pearson correlation coefficient was computed to assess the linear relationship between PGSs for cognitive ability and WISC-III performance. There was a small-medium positive correlation between the two variables, $r(5212) = .28$, $p < 2.2e\text{-}16$. See Figure 3.3 for plotted correlation between PGSs for cognitive ability and measure of cognitive ability, separated according to sex.

Figure 3.3

Correlation Between the 'Best-fit' Polygenic Scores and Cognitive Ability



Note. Coloured according to sex.

3.3.2 POLYGENIC SCORES FOR EDUCATIONAL ATTAINMENT

I calculated PGSs based on summary statistics from a GWAS meta-analysis of educational attainment carried out by Lee and colleagues (2018). High-resolution PGSs were calculated in PRSice-2 at the following *p* value thresholds: 0.001, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1, as recommended by PGS analysis guidelines (Choi et at., 2020; Marees et al., 2018). A summary of the best model fit when generating PGSs for educational attainment has been detailed in Table 3.2. As illustrated in Table 3.2, the threshold which generated the 'best-fit' PGS was $p = 0.1$. In Table 3.2 readers can see that the 'best-fit' PGSs accounted for 5% of the variance in the full model when covariates were accounted for ($R^2 = 0.053$, $p = 9.66973e\text{-}17$).

Table 3.2

Summary of the Best Model Fit for the Phenotype Educational Attainment and Gene Set

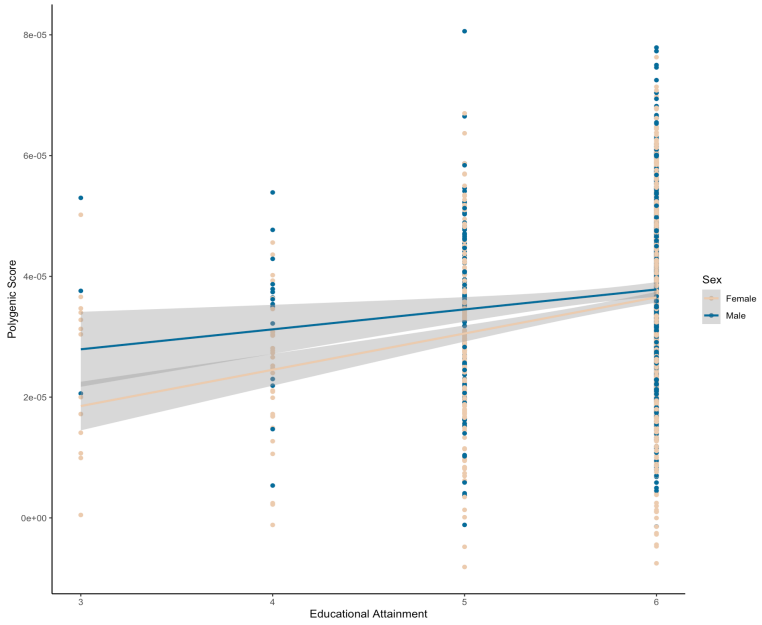
Set	Threshold	PGS R^2	Full R^2	Null R^2	Coefficient	*SE*	*p*	*SNP*
Base	0.055	0.040	0.053	0.013	7820.04	931.472	9.66973E-17	37742

Note. Set refers to the name of the gene set. Threshold refers to the best *p* value threshold. PGS R^2 refers to the variance explained by the PGS. Full R^2 refers to the variance explained by the full model, including covariates. Null R^2 refers to the variance explained by covariates. Coefficient refers to the regression coefficient of the model, denoting the directionality of the effect. *p* refers to the *p* value of the model fit. SNP refers to the number of single nucleotide polymorphisms (SNPs) included in the model.

The PGSs generated for educational attainment were then assessed to determine their performance in relation to their associated phenotype, educational attainment as measured by self-reported measures of education levels attained. A Pearson correlation coefficient was computed to assess the linear relationship between PGSs for educational attainment and educational levels attained. There was a small positive correlation between the two variables, $r(1693) = .20$, $p = 2.2e\text{-}16$. See Figure 3.4 for plotted correlation between PGSs for educational attainment and measure of educational attainment, separated according to sex.

Figure 3.4

Correlation Between the 'Best-fit' Polygenic Scores and Educational Attainment



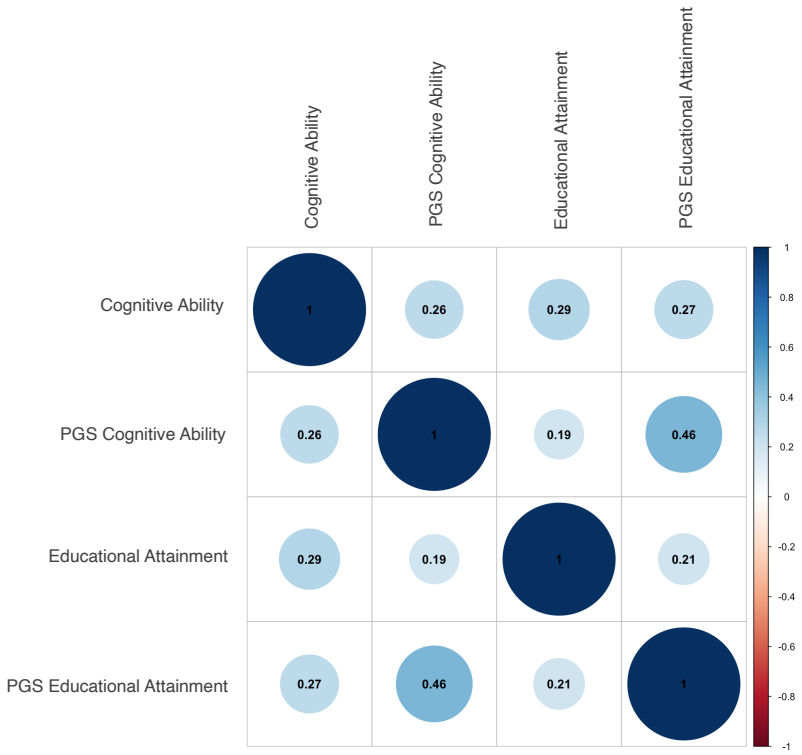
Note. Coloured according to sex.

3.3.3 CORRELATIONS BETWEEN POLYGENIC SCORES AND PHENOTYPIC MEASURES

In this next comparison I just considered the n = 1,485 with complete data across all the genotypes and phenotypes. This allowed me to directly compare the strength of correlations within subjects. Correlations between all measures of interest (i.e., PGSs for cognitive ability, PGSs for educational attainment, phenotypic measure of cognitive ability, and phenotypic measure of educational attainment) were visualised by way of a correlational heatmap matrix (Figure 3.5). All measures were positively correlated with one another, with particularly positive correlations seen between the generated PGSs for cognitive ability and educational attainment. Pearson correlation coefficients were then computed to assess the linear relationships between the generated PGSs and their phenotypic counterparts, along with the relationship between the PGSs themselves.

Figure 3.5

Correlation Heatmap Displaying Associations Between Polygenic Scores and Phenotypic Measures

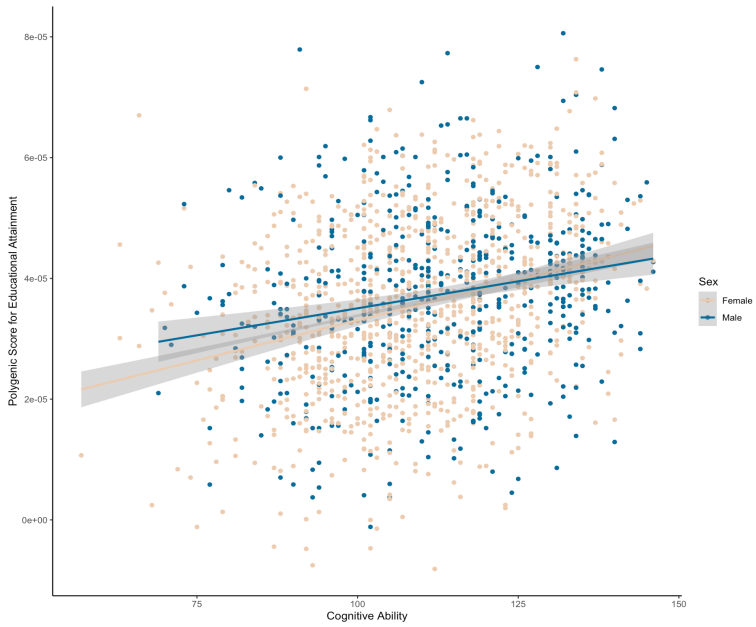


Note. Positive correlations denoted in blue; negative associations denoted in red. Correlation values range from -1 to 1.

The association between PGSs for educational attainment and the phenotypic measure of cognitive ability was evaluated using a Pearson correlation coefficient. There was a small-medium positive correlation between the two variables, $r(1483) = .27$, p = 2.2e-16 (Figure 3.6). In other words, the PGS for education is also significantly associated with cognitive ability.

Figure 3.6

Correlation Between the 'Best-fit' Polygenic Scores for Educational Attainment and Phenotypic Measure of Cognitive Ability

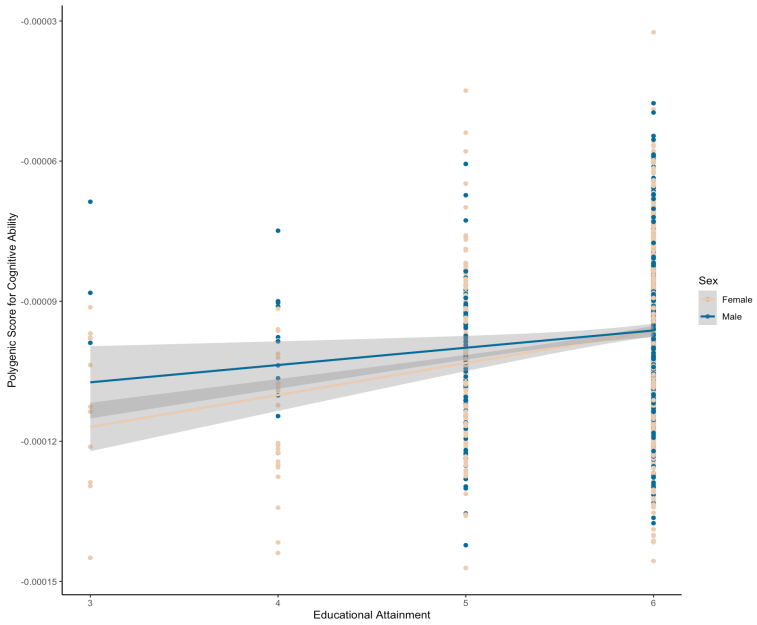


Note. Coloured according to sex.

Following this, the association between PGSs for cognitive ability and the phenotypic measure of educational attainment was evaluated, also using a Pearson correlation coefficient. There was a small positive correlation between the two variables, $r(1483) = .19$, $p = 5.129e\text{-}14$ (Figure 3.7). Again, this suggests that the PGS for cognition also predicts educational attainment.

Figure 3.7

Correlation Between the 'Best-fit' Polygenic Scores for Cognitive Ability, and Phenotypic Measure of Educational Attainment

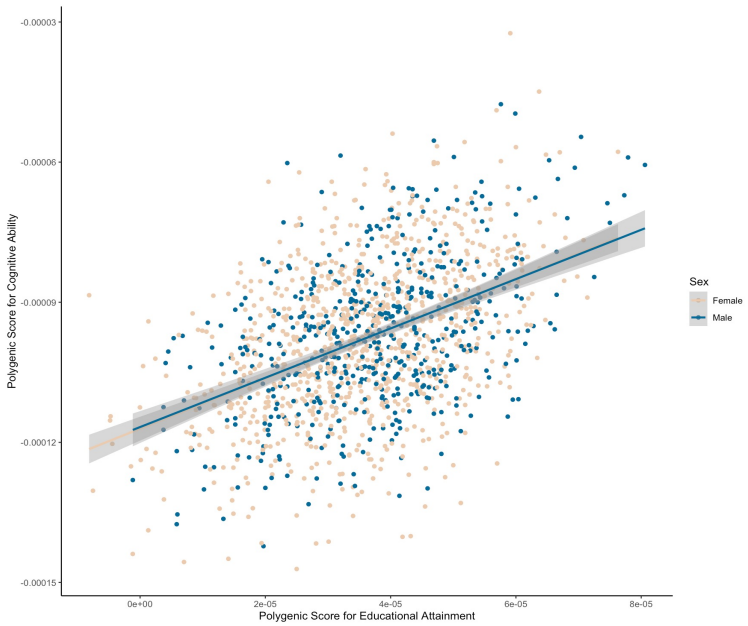


Note. Coloured according to sex.

The association between PGSs for cognitive ability and PGSs for educational attainment was evaluated. A Pearson correlation coefficient was computed to assess the linear relationship between these PGSs. There was a medium-large positive correlation between the two variables, $r(1483) = .46$, $p = 2.2e\text{-}16$ (Figure. 3.8). Put simply, the two PGSs are significantly correlated with each other.

Figure 3.8

Correlation Between the 'Best-fit' Polygenic Scores for Cognitive Ability, and the 'Best-fit' Scores for Educational Attainment



Note. Coloured according to sex.

Finally, I tested the relative specificity of the PGS-phenotype associations, using a *z* transform to compare the strength of the relationships empirically. I first tested whether cognitive ability can be predicted by the PGSs for cognitive ability *significantly better* than it can be predicted by the PGSs for educational attainment. The answer is that it cannot (z = -0.388, p = 0.349). That is, the education PGSs capture variance that is highly related to cognitive performance, in fact, just as much as PGSs for cognition do. Secondly I tested whether educational attainment can be predicted by the PGSs for educational attainment significantly better than it can be predicted by the PGSs for cognitive ability. The answer is that it cannot (z = 0.76, p = 0.223). In other words, each phenotype can be predicted equally well by either PGS.

3.4 DISCUSSION

In this chapter I sought to draw upon GWASs for cognitive ability and educational attainment to generate PGSs. Specifically, I sought to determine whether the resulting scores were correlated with the associated outcome measure for cognitive ability during primary education, a period of meaningful development in childhood (see **Chapter 2**), and educational attainment in later life when individuals were aged 18 and above. By employing substantial pre-processing and formatting, followed by rigorous measures of QC, I generated meaningful PGSs for both cognitive ability and educational attainment. An assessment of the resulting PGSs for cognitive ability and educational attainment, as well as of the associations between the generated PGSs and their respective

phenotypes, will be discussed briefly, followed by important caveats particularly relevant for their utility in downstream analyses.

3.4.1 POLYGENIC SCORES FOR COGNITIVE ABILITY

In our data, I found that PGSs for cognitive ability are significantly associated with performance on the WISC-III (Wechsler, 1991). Individuals with higher PGSs for cognitive ability displaying higher levels of cognitive ability compared to those with low PGSs for cognitive ability. These findings are in line with previous research aiming to derive PGSs for cognitive ability from GWASs, which typically account for 1-4% of individual variance in cognitive ability (Plomin & von Stumm, 2018). Further to this, our tests of correlation between the calculated scores and performance on the WISC-III have highlighted a small-medium positive correlation between PGSs for cognitive ability and WISC-III performance, a finding that was similar across females and males in the sample. These findings provide support for the efficacy of the scores generated for cognitive ability in the current study, lending to their potential utility in subsequent analyses. For example, PGSs such as these could be used to assess how multivariate traits, like cognitive ability, are influenced by gene-environment interactions.

These results shed light on the genetic underpinnings of cognitive ability. They further raise the question of why cognitive ability can be predicted by an individual's genome in the first place, and what molecular neurobiological mechanisms may be behind the predictive capacity of PGSs? One possibility is that the SNPs associated with cognitive ability are important for genetic architecture relating to healthy cognitive development. For instance, one genome-wide association meta-analysis on cognitive ability, which was carried out in over 78,000 individuals, identified 336 associated SNPs for cognitive ability to be predominantly expressed in brain tissue (Sniekers et al., 2017). Subsequent Gene Ontology (GO) pathway analysis highlighted an associated gene set comprising four genes that reached genome-wide significance, *SHANK3*, *DCC*, *ZFHX3*, and *BMPR2*, with many others displaying weaker associations (Sniekers et al., 2017). The first three of these genes are implicated in neuronal function and development, including synapse formation, encoding of a netrin receptor involved in axon guidance and putamen volume, and the regulation of myogenic and neuronal differentiation, respectively. The fourth gene is implicated in embryogenesis and bone tissue development. Pathway analysis further identified four GO gene sets with the lowest *p* values, which indicated the gene functions driving the observed association, and these were involved in regulating the development of the nervous system, negatively regulating dendrite development, myelin sheath, and neuron spine. These findings shed light on the neurobiological mechanisms behind the predictive potential of PGSs for cognitive ability. Even so, PGSs for cognitive ability only accounted for 8% of the variance in cognitive ability in the current study. Thus, these findings lend support for the complex multifaceted nature of development, and thereby the consideration of multiple factors which may interact to contribute to cognitive development.

3.4.2 POLYGENIC SCORES FOR EDUCATIONAL ATTAINMENT

In addition, I found the PGSs for educational attainment to be significantly associated with levels of educational attainment. Individuals with higher PGSs for educational attainment had higher levels of educational attainment compared to those with lower PGSs. Whilst the variance accounted for by the PGSs for educational attainment

were lower than that observed with the PGSs for cognitive ability, this could have been due to differences in sample size. Where the widely accepted sample size for target data used in PGS analysis is a sample size of n = 500, the optimal sample size to detect the accumulative effect of SNPs on the phenotype of interest is n = 2,000. The number of individuals with both genomic and phenotypic data available for educational attainment in the current study was n = 1,695. This was substantially lower than the sample size obtained for cognitive ability (n = 5,214). Thus, it is possible that there was less capacity to detect the accumulative effect of SNPs on the phenotype educational attainment, and a larger sample size could equate to a larger effect being observed. Going forward, comparisons between PGSs for cognitive ability and educational attainment in more comparable sample sizes may provide clarity on whether the observed effect was a true effect, and not reflective of differences in sample size. Still, the variance accounted for by PGSs for education were substantially lower than that typically seen across the literature (Donnellan et al., 2021), with PGSs leaving a large portion of variance unaccounted for.

A related point worth mentioning relates to the quality of phenotypic behavioural measures obtained in the present study. For example, the phenotypic behaviour of cognitive ability was measured by way of employing the WISC-III, a widely used, reliable, and valid scale for cognitive ability (Wechsler, 1991). Alternatively, educational attainment was measured by obtaining self-reported measures of education levels achieved when participants were 18. Response items were scored, and the total sum of these scores represented the global educational attainment score for each individual. Whilst it is common to assess educational attainment by considering education levels or years in education, assessing the phenotype in this way means that the quality of the measure of cognitive ability was substantially higher than that of educational attainment. As such, this could have influenced the variance accounted for by PGSs for educational attainment. Similarly, the heritability of educational attainment has been shown to be highly heterogeneous, with one international meta-analysis finding its heritability to be largely influenced by geographical location, shared environment, and unshared environment (Branigan et al., 2013). These findings demonstrate that the heritability of educational attainment is largely contingent on an individual's environment, both at a macro and micro level, and to fully unpack the role of genetic propensity when it comes to educational attainment, it is important to consider PGSs within a wider social mobility framework.

3.4.3 ASSESSING ASSOCIATIONS BETWEEN MEASURES

In addition to assessing the variance accounted for by the generated PGSs for cognitive ability and education, and correlating these scores with their respective phenotypic counterparts, I assessed correlations between all the remaining genomic and phenotypic measures. All measures were positively correlated with one another, with particularly strong medium-large positive correlations seen between the generated PGSs for cognitive ability and educational attainment. The finding that our PGSs and their associated phenotypes correlate well with one another is in line with related research, which has showed that when combined together, multipolygenic scores generated from GWASs of cognitive ability and educational attainment can now predict over 10% of the variance in cognitive ability, and account for more than 20% of the 50% of cognitive ability that can be accounted for by heritability (Plomin & von Stumm, 2018). Thus, the finding that our generated PGSs are correlated well with one another, as well as their phenotypic counterparts, carries additional support for their efficacy.

It is plausible that the association between our measures suggests that the genetic underpinnings of these two outcomes are interrelated. Crucially, either set of PGSs predicts both cognitive ability and educational attainment equally well. PGSs generated for different psychiatric disorders have demonstrated that their genetic underpinnings are substantially related (Hindley et al., 2022; O'Donovan & Owen, 2016). Thus, it is conceivable that something similar is occurring with our measures of cognitive ability and educational attainment. The associations between our measures could further reflect to the potential for cognitive ability to influence multiple aspects of an individual's life, including the decisions they make regarding healthcare, education, occupation, partnerships, and family units (Gottfredson, 1997). The capacity for cognitive ability to flow throughout multiple components of an individual's life is argued to be the reason why cognitive ability commonly predicts education (Lövdén et al., 2020), occupation (Cheng et al., 2012) and health outcomes (Calvin et al., 2017). It would follow on from this that cognitive ability, and thereby PGSs for cognitive ability, would be associated with phenotypic and genomic measures of educational attainment. Nevertheless, it is important to note that even when cognitive ability predicts various outcomes, its predictive capacity varies depending on other internal and external factors in an individual's environment included in the analysis, as these factors interact with cognitive ability to influence the outcome under investigation (Cheng et al., 2012). To give a concrete example: factors such as schooling quality could conceivably shape the overall impact of the genome on both cognitive development and educational attainment, thereby inflating their pairwise association. Thus, to fully unpack the mechanisms involved in these associations, analyses must also be multifaceted in nature to capture these interactions and the processes by which they go on to influence developmental outcomes.

3.4.4 CAVEATS AND DOWNTREAM ANALYSES

PGSs can be utilised as time-invariant predictors of developmental outcomes, such as cognitive ability and educational attainment, given that an individual's DNA sequence does not vary during their lifespan. However, the inferences that can be drawn from these PGSs and the downstream analyses utilising the resulting PGSs are restricted to population demographics similar to those used in the present study (Allegrini et al., 2022). In this way, the PGSs and inferences that are drawn off the basis of them in subsequent downstream analyses are specific to European populations with a similar demographic to that of the ALSPAC cohort. Correspondingly, it is of importance to note that the ALSPAC target data cohort, whose genomic data allowed for the generation of PGSs for cognitive ability and educational attainment, weighted towards the more affluent end of the SES spectrum, with only 12.5% of participants living in low-income households (Fraser et al., 2013). This cohort also displays relatively high educational levels compared to other regions in the UK, with 42.6% of mothers educated to an A-level or above (Fraser et al., 2013). Furthermore, when compared to rates in Avon and the UK as a whole, the ALSPAC mothers are more likely to live in owner-occupied accommodation and have access to a car, and less likely to have more than one person per room in the household and be non-White (Fraser et al., 2013). As such, the predictability of the generated scores relate to the sample demographic of the present study, and may not generalise to samples weighted towards the less affluent end of the SES spectrum.

Even so, PGSs for cognitive ability and educational attainment are argued to be the most influential genetic predictors of behaviour across the behavioural sciences (Allegrini et al., 2019). Correspondingly, the PGSs

generated here have potential utility for downstream analyses that aim to examine the intersection between environmental, neural, and genetic factors influencing child development. Such research could advance the current body of literature aiming to unravel complex SES-outcome associations (Blair & Raver, 2016; Evans & Kim, 2013; Hair et al., 2015; Luby et al., 2013; Reiss et al., 2019; Ridley et al., 2020; Smith et al., 2022; Tooley et al., 2021). As previously discussed, research has begun to do just this by generating PGSs for SES and assessing the influence of polygenic and environmental aspects of SES on brain structure using data from the UKB (Kweon et al., 2021). Whilst these findings have advanced our knowledge on the ways in which an individual's genetics and environment influence the anatomy of the brain, this research area is in its infancy, and additional work is required to further understand the complicated interaction between SES and development. The creation of PGSs for developmental outcomes displayed here (i.e., cognitive ability and educational attainment), could add to the current body of literature by implementing these scores in further analyses which incorporate other factors likely to influence SES-outcome associations. For example, these PGSs could be carried forward alongside measures of SES and connectomes mapping the neural connectivity of the brain. (**Chapter 4**). This could allow for the initial assessment of variance amongst these developmentally influential factors, followed by the inclusion of key developmental outcome measures to further elucidate the multifactorial role of these factors on development (**Chapter 5**).

3.4.5 CONCLUSION

In conclusion, the present study demonstrates that when conscientiously following appropriate guidelines for generating PGSs, meaningful PGSs can be generated. I have shown in the current sample that the variance explained by these PGSs differs according to the phenotype of interest, with PGSs for cognitive ability accounting for a larger portion of the variance in its respective phenotype during associative testing and subsequent correlation coefficient analyses, compared to PGSs for educational attainment. I have highlighted potential neurobiological mechanisms that may be behind the predictive capacity of PGSs and discussed the ways in which the quality of phenotypic behavioural measures may influence the predictive capacity of PGSs. I have further assessed the associations displayed between PGSs and their phenotypic counterparts, and what mechanisms may be behind these associations. I have also acknowledged the limitations associated with these scores but have also emphasised the potential utility of PGSs for downstream analyses that aim to assess the interplay between environmental, neural, and genetic factors for key developmental outcomes, in hopes of unpicking the multifaceted mechanisms that interact to shape brain development, cognitive ability, and phenotypic behaviour during early childhood development. Given the small number of participants with PGSs for educational attainment, only PGSs for cognitive ability were taken forward for downstream analyses. This was done to reduce the likelihood of inflated and unpredictable associations, which is common with these data types when small samples are used (Marek et al., 2022).

4 GENES AND SES COLLECTIVELY SHAPE THE CONNECTOME

The work described in the following chapter was completed as part of a collaborative effort by Professor Duncan Astle, Dr. Danyal Akarca, and me. All brain imaging data were previously obtained as part of the Avon Longitudinal Study of Parents and Children, and all processing and formatting for connectome construction was carried out by Dr. Danyal Akarca. Analyses were carried out by myself, alongside input and guidance from those noted above, and I alone was responsible for detailing the work in this thesis with input from Professor Duncan Astle.

4.1 INTRODUCTION

Within the broader construct of contemporary developmental science sits the theoretical framework of neuroconstructivism, which centres on how representations in the developing brain are constructed. Neuroconstructivism conceptualises neurodevelopment occurring in the context of multifactorial constraints across various levels, from cellular to environmental conditions (Westermann et al., 2007). A critical ingredient of neuroconstructivism is cognition itself. As cognitive functions develop, their engagement *itself* drives the organisation of neural networks and the specialisation of particular neuronal assemblies (Johnson, 2011), with cognition providing a vehicle by which genetic background and environmental experience interact as neural structures self-organise (Westermann et al., 2007). However, it is incredibly challenging to conduct research that incorporates the multiple levels of analysis – including cognition, genetic and environmental factors - necessary to understand the emergence of individual differences in neurodevelopment (Astle et al., 2022).

Just as brain organisation is shaped by both a person's genetic background and their experience, the same is true of functional outcomes, like cognitive ability. Individual variability in cognitive ability is highly heritable and polygenic, as has been demonstrated by twin studies and polygenic scores (Allegrini et al., 2019; Plomin & von Stumm, 2018; Savage et al., 2018). From studies such as these, we estimate that around 11% of the variance in general cognitive ability, sometimes termed IQ, can be explained by an individual's genetic background (Allegrini et al., 2019). Even so, cognitive development is not simply the unfolding of genetic destiny. As discussed in detail in **Chapter 1**, cognitive ability is also associated with environmental factors, such as socioeconomic status (SES), which is also often associated with outcomes for neurocognitive systems and differences in the pace of brain

development (Engelhardt et al., 2019; Hackman et al., 2010; Reiss et al., 2019; Tooley et al., 2021). In practice, the dynamic emergence of brain organisation across development, in which both genetic background and environmental experience shape trajectories, can make it very difficult to disentangle the source of individual variability.

4.1.1 POLYGENIC PROPENSITY

Polygenic propensity has been discussed at length in **Chapter 3**. To summarise briefly, advancements in human genomics and the statistical techniques required to assess genomic influence provide a key component that we need in order to address the challenge of incorporating multiple levels of analysis to understand individual differences in neurodevelopment (Altshuler et al., 2012; Choi et al., 2020; Dudbridge, 2013; Gibbs et al., 2003; Watson, 1990). Using a polygenic score (PGS) analysis, the heritability of cognitive ability can be inferred by combining the aggregated effects of single nucleotide polymorphisms (SNPs) associated with cognition, and calculating a score based on the presence of these SNPs in an individual's genome (Collister et al., 2022). SNPs associated with cognitive ability have been shown to be important in the genetic architecture required for healthy cognitive development, including the development of myelin sheath, neuronal function, synapse formation, and dendrite regulation (Sniekers et al., 2017). As such, PGSs for cognitive ability could provide an effective proxy by which to identify the influence of heritability on structural brain organisation.

PGSs have been used to assess the ways in which genetic propensity interacts with external factors in a child's proximal environment to influence development (Allegrini et al., 2019; Mitchell et al., 2020; von Stumm et al., 2020). Readers may remember from **Chapter 1** and **Chapter 3** that a great example of this is the PGSs for educational attainment. These scores have been used to assess the interplay between PGSs for educational attainment and SES in predicting educational achievement (von Stumm et al., 2020), and associations between PGSs for educational attainment and the structure and function of the brain (Mitchell et al., 2020). Whilst these findings provide support for the role of both genetic and environmental factors in shaping developmental outcomes, this research area is in its infancy. In this next chapter, I intend to build on the findings from the previous chapter – namely that we can calculate and validate PGSs for cognition in a large number of the ALSPAC cohort members – to start exploring how polygenic propensity and SES are associated with brain organisation. The principal question for this chapter is: do genetic and environmental predictors make relatively independent predictions of brain organisation, or do they explain overlapping variance? However, in order to explore how factors shape neurodevelopment, we first need a systematic way of exploring brain organisation.

4.1.2 THE STRUCTURAL CONNECTOME

As mentioned in **Chapter 1**, topological features of the complex brain networks that make up the structural connectome can be captured by the application of graph theory (Rubinov & Sporns, 2010). Graph theory metrics capture the *organisational characteristics* of complex networks and can thereby capture individual differences in the structural connectome at a local (nodal), regional, or global (network-wide) level. During development, whole-brain networks gradually segregate (i.e., characterised by decreased short range edges and densely connected

regions) and integrate (i.e., characterised by increased long range edges and consolidation of specialised information across regions) (Sporns, 2013). Efficient segregation and integration within the structural connectome is pivotal for optimal communication and the cohesive integration of networks required for cognitive function (Fair et al., 2007). Thus, integrating these types of structural connectome metrics with genomic and environmental data could allow us to assess how the early life environment and polygenic propensity influence differences in brain organisation.

Progress in connectomics and imaging genetics has provided us with the capacity to assess the genetics of neuronal connectivity in the human brain. In particular, twin-based heritability studies are a powerful tool for understanding the overall contribution of the genome to the configuration of the human connectome (Arnatkevičiūtė et al., 2021b; Posthuma et al., 2003; Zyphur et al., 2013). In studies such as these, monozygotic twins (commonly referred to as identical twins) are assumed to have identical genomes, whereas dizygotic twins (also known as non-identical twins) share approximately half of their genetic information. These studies work under the assumption that both monozygotic and dizygotic twins are similarly influenced by environmental factors, whereas non-twin siblings encounter dissimilar experiences starting in utero and continuing throughout development (Jinks & Fulker, 1970; Mark et al., 2017). Thus, the inclusion of non-twin siblings into study designs often allows for a better understanding of heritability. These studies are then able to quantify heritability, which is commonly done by employing a classical ACTE structural equation model (SEM). Heritability (h^2) is computed by considering the additive genetic (A) and common environmental factors that are twin-specific (T), twin non-specific (C), and unique for each person (E). Assessing heritability in this way allows for the quantification of the proportion of phenotypic variance accounted for by the genome with the following equation.

$$h^2 = \frac{A}{A+C+T+E}$$

One twin-based study carried out by Arnatkevičiūtė and colleagues (2021b) used diffusion-weighted magnetic resonance imaging with twins and non-twin siblings to assess genetic influences on hub connectivity in the human cortical connectome. They employed a connectome-wide heritability analysis using the classical ACTE model. A SEM was fit to the biometric model for each connection in the connectome, providing genetic and environmental estimates for each edge. This was proceeded by a transcriptional coupling analysis utilising post-mortem transcriptional data from the Allen Human Brain Atlas (AHBA), which was mapped onto the regions of the connectome parcellation scheme. Values assigned to each edge were compared across connection types. The similarity of gene expression profiles across parcels was predictive of the connectivity strength of different regions of the connectome. Transcriptomic coupling analysis further highlighted the specificity for the coupling of transcriptional activity in hub regions, which was related to metabolic and cytoarchitecture similarity. These results were subject to further tests by way of comparing several generative models of network growth. Stochastic (i.e., simple wiring rules reflective of geometric parameter restrictions) processes alone could not explain the wiring tendencies of hubs, and the inclusion of genetic constraints improved the model. The implication is that experience dependent, stochastic processes cannot explain the entirety of connectome configuration. Genomics, and the graded expression therein, likely provide crucial signals that drive the wiring of certain aspects of organisation, and in particular, rich-club connectivity. An interesting way of furthering this research area would

be via polygenic scores, and exploring their contribution to the formation of structural connectivity across features of the connectome.

In parallel to the ongoing study of genomic influences on brain organisation, such as those described above, many have argued that neural network connectivity is shaped by the environment. For example, it is argued that SES impacts on structural brain development, with high childhood SES resulting in prolonged structural brain development, promoting the structural trajectory of network segregation and thereby encouraging effective and robust cortical networks (Tooley et al., 2021). Conversely, low childhood SES is argued to result in protracted structural brain development, and thereby less efficient and resilient cortical networks in the long run (Tooley et al., 2021). One possible explanation is that the early life environment can shift the economic conditions that shape the formation of the structural connectome, thereby adjusting the timing of the emergence of key topological features, like network segregation and modularity (Carozza et al., 2022b). Using a mouse model organism, in combination with a computational model that simulates the formation of complex networks, Carozza and colleagues showed that early adversity alters the wiring economy of the connectome, resulting in a more stochastic process, that is, enhanced randomness during the structural development of the connectome (Carozza et al., 2022b). Crucially, in this example, because the early adversity is induced experimentally, we can know that this influence is *causal*. Whilst it is plausible these alterations serve an adaptive function in the short term, such as helping an organism to operate successfully in a more chaotic and unpredictable environment, they may have long-term negative influences on cognition. Computational analyses have demonstrated the initial explosion of connections followed by a slow and steady pruning, thereafter, enables optimal network structure formation that is both more efficient and robust (Navlakha et al., 2015).

These findings start to build a mechanistic picture of how environmental influence can drive variability in the development of the brain, and by extension, cognitive outcomes. Whilst valuable, a limitation is that this reflects a particular kind of adversity – in this case early life stress is induced by removal from the mother and extreme scarcity of resources – which is thankfully exceptionally rare in humans. For humans in a western society, the most common dimension of adversity is socioeconomic (Carozza et al., 2022a, 2022b). Moreover, this study controls for genetics with selective breeding of the mice, meaning that we necessarily cannot explore how genes and the environment overlap in the aspects of brain organisation that they drive. An important next step, therefore, is to consider whether and how the genetic underpinnings of cognitive ability and childhood SES *converge* to influence structural brain connectivity. The consideration of multifactorial influence combined with segregated and integrated measures of structural brain connectivity could further build this mechanistic picture, and in doing so, enhance our understanding of the ways these factors interact to shape one another and thereby influence development.

4.1.3 THE CURRENT STUDY

The purpose of the current study is to integrate multiple data types to elucidate the ways in which genetic propensity and SES shape structural neural connectivity over development. We specifically sought to answer the following questions: 1) Do genetic propensity and the early childhood environment influence the structural

organisation of the brain? 2) If so, do they explain distinct aspects of structural brain organisation, or shared aspects of brain organisation? 3) Is this influence heterogeneous among environmental factors, and if so, to what extent? Put simply, do all components of SES equally influence the structural connectome, or are some features of SES more influential than others?

We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013), including measures of early SES (i.e., parental educational levels, maternal occupation, and level of difficulty affording food and rent or mortgage), genetic propensity (i.e., PGSs for cognitive ability), and global and local measures of structural brain connectivity (i.e., global modularity, global efficiency, local node degree, local node strength, local node clustering coefficient, and local node betweenness centrality). A PGS analysis was initially carried to generate PGSs for cognitive ability, in line with comprehensive guidelines for generating PGSs (Choi et al., 2020). Details of this can be found in the previous chapter. Connectomes were constructed for each individual in the sample using tractography data derived from diffusion tract imaging (DTI) during a magnetic resonance imaging (MRI) session. We subsequently employed partial least squares (PLS) regression, a data reduction technique which identifies a set of orthogonal factors (i.e., latent variables) across multiple data sets, to detect which factors have the greatest predictive power (Wold et al., 1984). Rather than address genomic and environmental measures separately, I intend to combine them in a single analysis. This will allow me to test how polygenic propensity and multiple measures of SES are associated with global and local measures of the structural connectome, simultaneously. Thus allowing me to highlight any specificity of these relationships, should any exist.

4.2 METHODS

4.2.1 PARTICIPANT DEMOGRAPHIC

The present study comprised genomic, neural, and phenotypic data from children and parents enrolled in the ALSPAC (Boyd et al., 2013; Fraser et al., 2013). Of the mothers who enrolled in ALSPAC, 79.1% lived in owner-occupier accommodation, 90.8% had a car, 79.4% were married, and 2.2% were non-White. Elaborate demographic information has been detailed at each wave of data collection for the index children (Boyd et al., 2013) and their mothers (Fraser et al., 2013). Genomic, neuroimaging, and cognitive ability data were obtained from the ALSPAC index children cohort, and SES data were obtained from their primary caregivers. To prevent inflated associations between single nucleotide polymorphisms (SNPs) and phenotype associations when generating polygenic scores for cognitive ability, only data from unrelated children were included in these analyses. PGSs were generated following stringent measures of quality control (QC) and related filtering (Choi et al., 2020), with a resulting sample size of n = 5,214, of which 49.7% were female. This sample size was subsequently reduced based on the availability of neuroimaging data. As the neural data comprised a predominantly male sample, this resulted in an overall sample size of n = 685, of which 27.2% were female. Data were obtained from children and their biological mothers when the children were aged 8 months (i.e., measures of SES), 8 years (i.e., genomic and cognitive ability data), and between the ages of 18 and 24 (i.e., neuroimaging data).

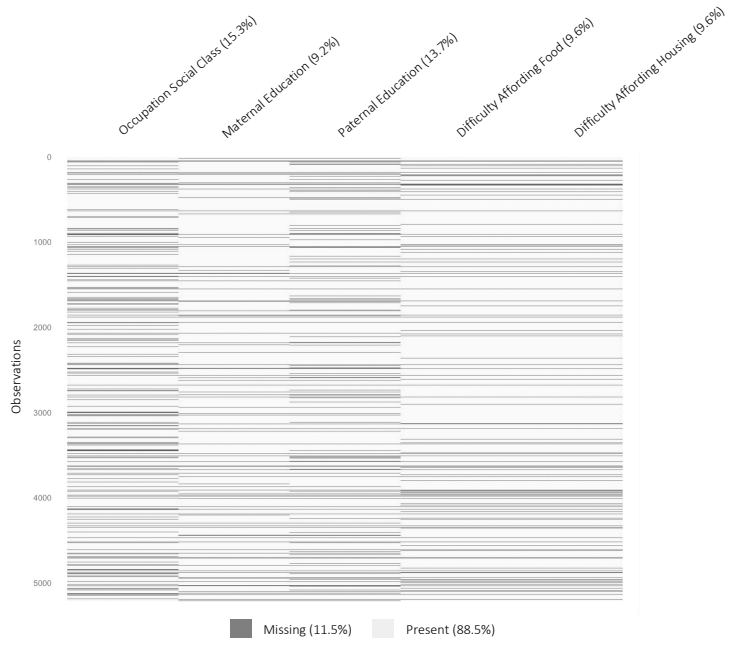
4.2.2 MEASURES

4.2.2.1 Socioeconomic Status

Measures of SES comprised the same self-reported measures of maternal social class based on occupation, maternal and paternal education levels, and maternal self-reported levels of difficulty affording food and housing (i.e., rent or mortgage) which were acquired in **Chapter 2**. As such, for a detailed summary of these measures, please refer to **Chapter 2**. Measures of SES were assessed when the index children were age 8 months. All SES measures were subjected to imputation using the Mice package (Buuren & Groothuis-Oudshoorn, 2011) in R (R Core Team, 2022). See Figure 4.1 for detailed missingness across SES variables prior to imputation.

Figure 4.1

Detailed Missingness Across Socioeconomic Variables



Note. Figure displays data missingness prior to imputation for all socioeconomic variables in the present study. Percentages in brackets on the top edge of figure represent missing data per variable.

4.2.2.2 Polygenic Scores for Cognitive Ability

This analysis employed the polygenic scores for cognitive ability which were generated and discussed in detail in **Chapter 3**. As such, please see **Chapter 3** for a detailed outlining of how these data were acquired and processed. For brevity, this information has been succinctly detailed below.

4.2.2.2.1 Base Data Genomics

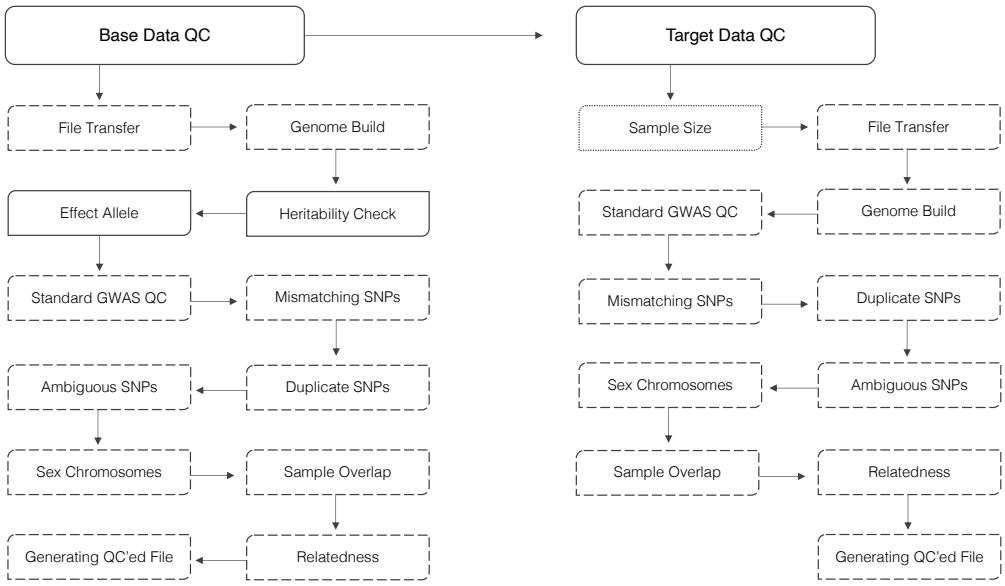
PGSs for cognitive ability (i.e., the SNP effect size weighted sums of the number of alleles associated with cognitive ability) were derived from summary statistics from a genome-wide association study (GWAS) meta-analysis of cognitive ability (Savage et al., 2018). This meta-analysis of cognitive ability in 269, 867 individuals from 14 independent epidemiological cohorts of European ancestry formed the base data in our PGS analysis.

4.2.2.2.2 Target Data Genomics

Omics data from the ALSPAC, which formed the target data in our PGS analysis, were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Index children were genotyped using Illumina HumanHap550 quad chip genotyping platforms.

Figure 4.2

Summary of Quality Control Steps Undertaken with Base and Target Data Sets



Note. Solid border indicates steps completed with the base data only. Round dot border indicates steps taken with the target data only. Long dash indicates steps which were completed with the base and target data.

4.2.2.2.3 Phenotypic Measure of Cognitive Ability

PGS efficacy was confirmed by way of tests of association with measures of cognitive ability. Cognitive ability was assessed by performance on the widely used Wechsler Intelligence Scale for Children, 3rd edition (WISC-III; Wechsler, 1991) when children were age 8. The total sum of the scores for the Verbal and Performance subscales formed the global measure of cognitive ability, which was then taken forward for associative testing.

4.2.2.3 Constructing Connectomes

Connectomes were constructed using brain imaging data made available through the ALSPAC. Brain imaging data were acquired during the course of three separate sub-studies with varying recruitment criteria. As such, all work to obtain these data were carried out by Fonville and colleagues (2019), Lancaster and colleagues (2018), and Björnholm and colleagues (2017). Data were obtained from the index children when they were between the ages of 18 and 24. For information on the criteria adopted for each study, please refer to the comprehensive summary provided by Sharp and colleagues (2020). Briefly, it is worth noting that one study in particular, with the largest sample size of the three (n = 513), was a testosterone study that selected for males-only during recruitment (Björnholm et al., 2017). Details of how these data were obtained and the MRI protocols employed will be briefly discussed here.

4.2.2.3.1 Magnetic Resonance Imaging Data Acquisition

MRI data were acquired when the ALSPAC index children were between the ages of 18 and 24. A subset of children were invited take part in three neuroimaging studies. The first sub-study comprised a sample of n = 252, with a mean age of 20.03 (range 19.08 to 21.52), of which 35% were male (Fonville et al., 2019), the second comprised a sample of n = 196, with a mean age of 22.75 (range 21.12 to 24.55), of which 48% were male (Lancaster et al., 2018), and the third comprised a sample of n = 513, with a mean age of 19.62 (range = 18 to 21.50), of which 100% were male (Björnholm et al., 2017). Multimodal neuroimaging data were acquired at Cardiff University Brain Research Imaging Centre (CUBRIC) using a 3 Tesla General Electric HDx (GE Medical Systems) with an 8-channel head coil. Scanning protocols were coordinated between the three studies where possible. A detailed overview of all neuroimaging data acquisition and associated samples of each sub-study has been detailed elsewhere (Sharp et al., 2020). Briefly, during structural MRI data acquisition, coronal T1-weighted volume scans were obtained using 3D fast spoiled gradient echo with 168-182 oblique-axial AC-PC slices, 1 mm isotropic resolution, and a 20° flip angle. Repetition time (TR) was 7.9 ms, echo time (TE) was 3.0 ms, and inverse time (TI) was 450 ms. A voxel size of 1mm x 1mm x 1 mm was implemented, with 1mm slice thickness, and a 256 x 192 mm matrix field of view (FoV).

DTI data were acquired for each sub-study (Björnholm et al., 2017; Fonville et al., 2019; Lancaster et al., 2018). For the first sub-study (Fonville et al., 2019), a cardiac-gated diffusion-weighted spin-echo echo-planar imaging sequence was used to obtain high angular resolution diffusion-weighted images (HARDI). Whole brain coverage was obtained with 60 gradient orientations and 6 unweighted (b = 0 s/mm^2) images with TE = 87 ms, acquisition matrix = 96 × 96, zero-padded matrix = 128 × 128, and FoV = 230 × 230 mm. The reconstructed image resolution for the HARDI scans was 1.8 × 1.8 × 2.4 mm. For the second sub-study (Lancaster et al., 2018), HARDI data were obtained using a cardiac-gated, peripherally gated twice-refocused spin-echo EPI sequence. Whole brain coverage was acquired with 60 gradient orientations and 3 non-diffusion-weighted (b = 0 s/mm2) images, with effective TR/TE of 15R-R intervals/87ms, FoV = 230 × 230 mm, acquisition matrix = 96 × 96, zero-padded matrix = 128 × 128. The reconstructed image resolution for the HARDI scans was 1.8 × 1.8 × 2.4 mm. Sets of 60 contiguous 2.4-mm thick axial slices were obtained, with diffusion-sensitizing gradients applied along 30 isotropically distributed gradient directions (b = 1,200 s/mm2). For the third sub-study (Björnholm et al., 2017),

data were acquired using a dual spin-echo, single shot echo-planar imaging sequence. Whole brain coverage was obtained with 30 gradient orientations and 3 non-diffusion-weighted images (b = 0 s/mm^2) with a resolution of 2.4 x 2.4 x 2.4 mm, a FoV matrix of 230 x 230 mm, acquisition matrix of 96 x 96, and slice thickness of 2.4 mm. TE = 87 ms (effective), b = 1200 s/mm^2, T1 = 0, flip angle = 90°, number of excitations = 1, and parallel imaging acceleration factor = 2;30.

Data from all three sub-studies were subject to reconstruction and stringent measures of cortical and sub-cortical QC as detailed by Sharp and colleagues (2020). Following cortical QC, sub-study one comprised a sample of n = 238, the sample for sub-study two comprised n = 193, and sub-study three comprised n = 465. There were n = 11 overlapping individuals between sub-study one and two, n = 22 between sub-study one and three, n = 33 between sub-study two and three, and n = 3 individuals took part in all three studies (Sharp et al., 2020).

4.2.2.3.2 MRI Pre-processing and Reconstruction

MRI pre-processing and reconstruction was completed by Dr. Danyal Akarca at the MRC Cognition and Brain Sciences Unit, University of Cambridge. The acquired MRI data across all three samples were subject to pre-processing and reconstruction using QSIPrep 0.14.2, an integrative software platform based on Nipype 1.6.1 (Gorgolewski et al., 2011). The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) using the N4 bias field correction algorithm in the Advanced Normalisation Tools (ANTs) software program (Avants et al., 2014), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped using brain extraction with antsBrainExtraction.sh (ANTs 2.3.1), with OASIS as target template. Spatial normalisation to the ICBM 2009a 152 Nonlinear Asymmetrical MNI template (Bowring et al., 2022) was performed through nonlinear registration with antsRegistration (ANTs 2.3.1), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid, white-matter, and grey-matter was performed on the brain-extracted T1w using the FMRIB Software Library (FSL 6.0.3: b862cdd5) FAST-based boundary correction method (Patenaude et al., 2011). Any images with a b-value less than 100 s/mm^2 were treated as a b = 0 image. MP-PCA denoising as implemented in MRtrix3's dwidenoise1 was applied with a 5-voxel window (Tournier et al., 2019). After MP-PCA, B1 field inhomogeneity was corrected using dwibiascorrect from MRtrix3 with the N4 algorithm. After B1 bias correction, the mean intensity of the diffusion-weighted imaging (DWI) series was adjusted so all the mean intensity of the b = 0 images matched across each separate DWI scanning sequence.

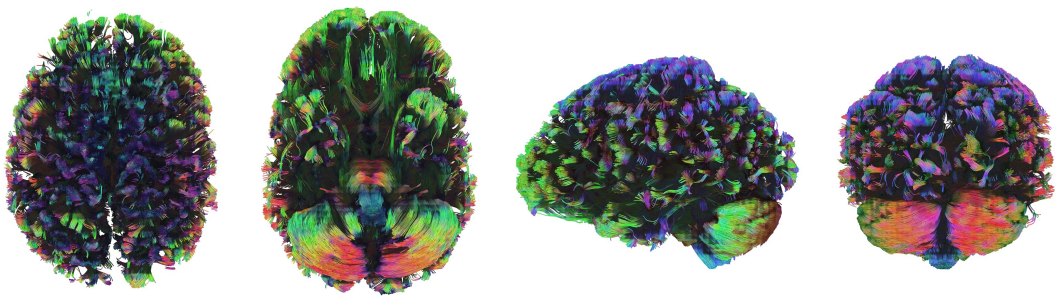
FSL Eddy was employed for head motion correction and current correction (FSL 6.0.3: b862cdd5). FSL's Eddy was configured with a q-space smoothing factor of 10, a total of 5 iterations, and 1000 voxels to estimate hyperparameters. A linear first-level model and a linear second-level model were used to characterize Eddy current-related spatial distortion. Q-space coordinates were forcefully assigned to shells. Field offset was attempted to be separated from subject movement. Shells were aligned post-Eddy. Eddy's outlier replacement was run. Data were grouped by slice, only including values from slices determined to contain at least 250 intracerebral voxels. Groups deviating by more than 4 standard deviations from the prediction had their data replaced with imputed values. Final interpolation was performed using the jac method.

Several confounding time-series were calculated based on the pre-processed DWIs. Framewise displacement was calculated using the implementation in Nipype, following the definitions outlined by Power and colleagues (2014). The head-motion estimates calculated in the correction step were added to the corresponding confounds file. Slicewise cross-correlation was additionally calculated. The DWIs time-series were resampled to anterior commissure-posterior commissure (ACPC), generating a pre-processed DWI run in ACPC space with 1mm isotropic voxels.

Diffusion orientation distribution functions were reconstructed using generalized q-sampling imaging (GQI; Yeh et al., 2010) with a ratio of mean diffusion distance of 1.25. 5 million streamlines were created with a maximum length of 250mm, minimum length of 30mm, random seeding, a step size of 1mm. Many internal operations of QSIPrep use Nilearn 0.8.0 (Abraham et al., 2014) and Diffusion Imaging in Python (Dipy; Garyfallidis et al., 2014). Further QSIPrep procedures have been previously detailed (Cieslak et al., 2021), and additional documentation and pipeline information can be accessed on the following page https://qsiprep.readthedocs.io. See Figure 4.3 for tractography visualisation.

Figure 4.3

Visualisation of Average Three-Dimensional DTI Derived Tractograms



Note. From left to right displays top side, bottom side, lateral view of left hemisphere, and back side. The colour red represents transverse orientation, green represents anterior-posterior or posterior-anterior orientation, and blue represents craniocaudal orientation of fibres.

4.2.2.4 Data Harmonisation

Although all participants are cohort members scanned on the same scanner, as readers will see from the scanning sequences, there is a risk of some systematic differences. Something also not listed is the almost inevitable replacement of component parts over a scanner's lifetime. Accordingly, once we had extracted our global and local connectome measures we first passed them through the neuroCombat package in MATLAB (Fortin et al., 2017, 2018) before proceeding with the subsequent analysis. Initially developed for genomic data, neuroCombat has been adapted for neuroimaging data (Fortin et al., 2017; Johnson et al., 2007). NeuroCombat accounts for non-biological variance that may result from variations in MRI scanners and protocols by harmonising values acquired across data sets, and removing unwanted sources of variability that may result in spurious findings and

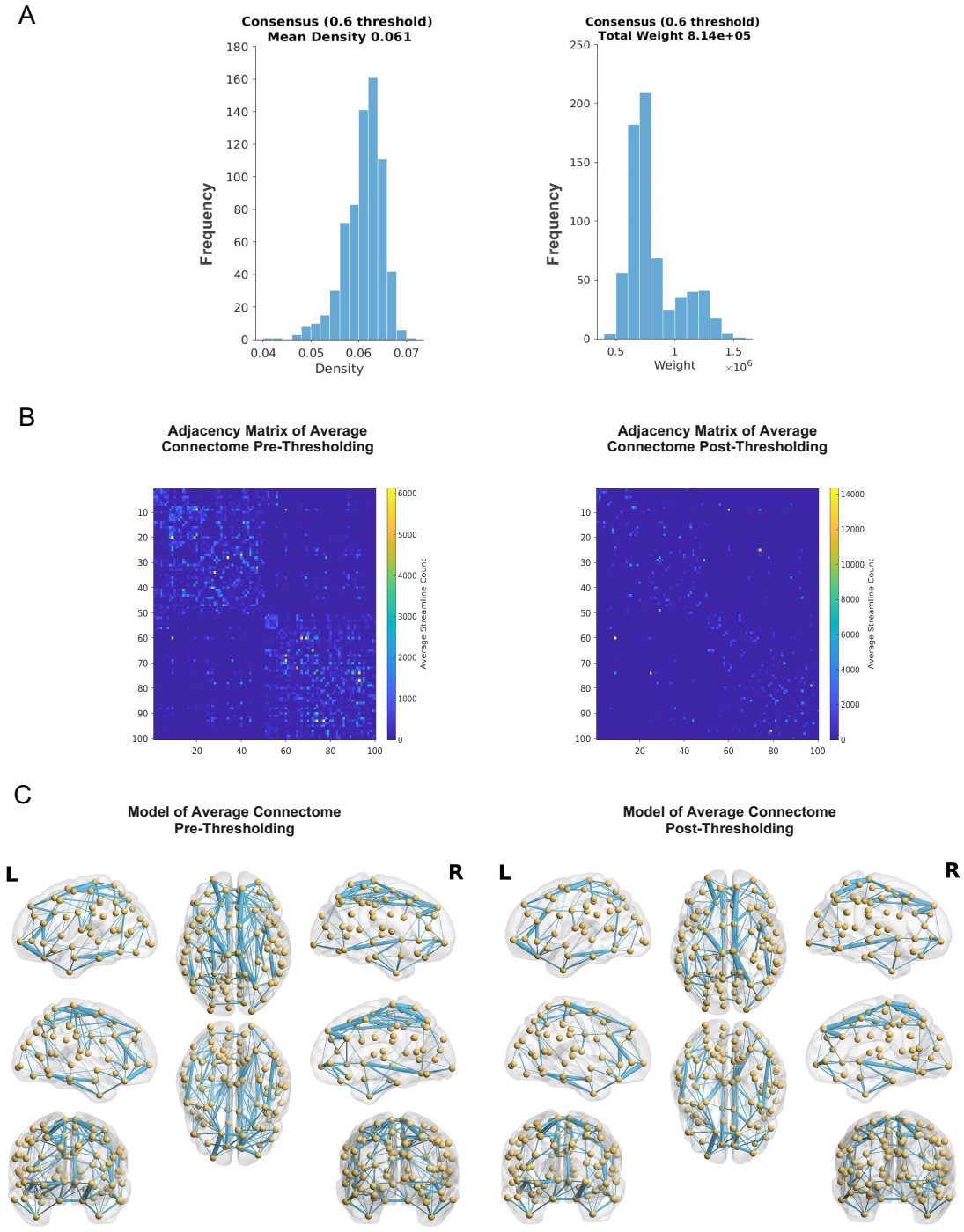
detract from covariates of interest (Fortin et al., 2018). This is achieved by obtaining the imaging features, adjusting the values, and producing a cohort that can be assessed as though their imaging data were produced by the same MRI scanner (Richter et al., 2022). Value estimations are computed using a linear model, with biological variance (i.e., age and sex), and additive and multiplicative scanner effects as predictors in the model (Fortin et al., 2018). To better estimate the model parameters for small-scale studies, empirical Bayes is employed.

4.2.2.5 Connectome Parcellation and Thresholding

Several parcellation schemes exist which map the human brain into distinct regions, each with its own level of granularity (Luppi & Stamatakis, 2021). This allows for meaningful networks, comprised of elements (nodes) and their pairwise links (edges), to be derived from neuroimaging data (Sporns, 2022). In the current study, we employed the 100-node Schaefer parcellation, which has demonstrated biologically meaningful representations of brain connectivity and alignment with histologic and visuotopic boundaries (Schaefer et al., 2018). In the end, there is no 'correct' parcellation to use, but the Schaefer-100 is relatively widely used (Cruces et al., 2022; Luppi & Stamatakis, 2021; Pan et al., 2022; Royer et al., 2022) and provides a good granularity for integration with gene expression data (see **Chapter 5**; Dear et al., 2022). We applied edge filtering to prevent weak and non-significant edges, which are likely to reflect spurious connections, from masking the topology of strong and significant edges (Buchanan et al., 2020; Rubinov & Sporns, 2010). In doing so, 100-node structural connectomes were subjected to a consensus threshold of 60%. Put simply, anatomical connections were classified as genuine if edges were present in 60% of participants. Again, as with parcellation choices, there is no 'objective' criteria for what the threshold should be. Nonetheless, a 60% is widely used in the literature (e.g., de Reus & van den Heuvel, 2013; Zdorovtsova et al., 2022). At these set thresholds, a mean density of 6.1% was calculated across all connectomes. See Figure 4.4 for summary of mean density and total weight post-thresholding, and visualisation of average connectome pre- and post-consensus thresholding.

Figure 4.4

Visualisation of Average Connectome Pre- and Post-Consensus Thresholding



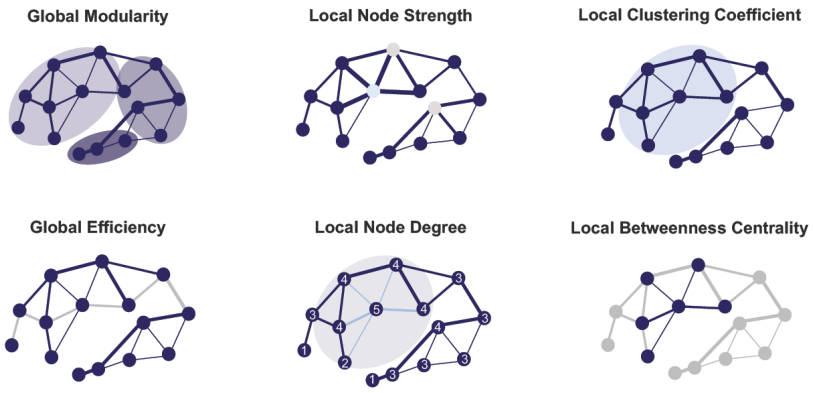
Note. (A) Bar graph displaying mean density and weight post-consensus thresholding. (B) Adjacency matrix of average connectome pre- and post-thresholding across the sample. Average streamline count refers to the average number of white matter pathways connecting two different regions of the brain. (C) Visualisation detailing average connectome pre- and post-thresholding across the sample. Yellow spheres represent nodes, and blue lines represent edges. The first row of each model from left to right displays lateral view of left hemisphere, top side, and lateral view from right hemisphere. The second row from left to right displays medial view of left hemisphere, bottom side, and medial view of right hemisphere. The third row displays frontal side and back side.

4.2.2.6 Graph Theory Metrics

Topological features of complex brain networks can be captured by the application of graph theory metrics (Rubinov & Sporns, 2010; Sporns, 2022). The characterisation of these features primarily falls into one of two categories, the global and local properties of an individual's connectome, and may include binary, weighted, or directed networks (Farahani et al., 2019). The application of graph theory methods to evaluate the anatomical tracts or functional associations between brain regions further allows for the appraisal of two primary obstacles for neural information processing, that is, the segregation and functional integration of specialised information, and how these features vary between populations (Fair et al., 2007). We employed two global and four local graph theory metrics to assess brain connectivity architecture, comprising a measure of segregation (i.e., global modularity), and integration (i.e., global efficiency), each of which will be discussed in turn. See Figure 4.5 for illustration of graph theory metrics included in the present study.

Figure 4.5

Diagram Illustrating the Properties of the Employed Global and Local Graph Theory Metrics



4.2.2.6.1 Global Modularity

Modularity refers to clusters of nodes (i.e., modules), where interconnectivity within a module is greater than its connectivity with nodes in other modules (Bassett & Bullmore, 2009; Newman, 2006). The density of nodes within a module augments the efficiency of communication within, whilst its sparse connections between different modules simultaneously facilitates the intermodular integration of information (Farahani et al., 2019). Modularity is a prevalently used metric to quantify topological segregation in networks and has been shown to reflect known functional specialisation across brain regions (Rubinov & Sporns, 2010; Salvador et al., 2005). Moreover, modularity is associated with morphological variation in cortical thickness across these specialised regions, which is likely reflective of the underlying cytoarchitecture and connectivity of these regions (Chen et al., 2008). Here, the modularity statistic calculates the degree to which the network can be subdivided into discrete groups, maximising within-group edges and minimising between-group edges, using Newman's spectral community detection (Rubinov & Sporns, 2010).

4.2.2.6.2 Global Efficiency

Global efficiency is a small-world principle that refers to how effective a neural network is at distributing information at a global level (Latora & Marchiori, 2001). This metric is based on the average inverse path length between all nodes in a network, it can be calculated for connected and disconnected networks, and is primarily based on short paths, making it an optimal measure of integration (Achard & Bullmore, 2007; Rubinov & Sporns, 2010). The efficiency of a network can be influenced by a multitude of factors, including age-related deficits, as well as perturbations to rich-club networks that positively influence global network structure (Achard & Bullmore, 2007; van den Heuval & Sporns, 2011).

4.2.2.6.3 Local Node Strength

Links connecting a node to others in a network hold various weights, and local node strength refers to the sum of the weights of these links at the nodal level. Whilst studies often omit link weights in favour of binarisation to simplify characterisation, this information can provide essential information on network organisation, and can be useful to identify and remove weak and non-significant links (Rubinov & Sporns, 2010). Additionally, a primary feature of hubs, which act as connectors linking nodes in different modules, are defined by high local node strength (Sporns et al., 2007). As such, considering local node strength could provide information on the functional integration of a network (Fornito & Bullmore, 2015).

4.2.2.6.4 Local Node Degree

Local node degree refers to the number of connections linking a node to the overall network. Network node degrees form a degree distribution, with random networks, which are all equally probable, displaying Gaussian and symmetrically centred distributions (Amaral et al., 2000). On the other hand, complex networks (e.g., complex brain networks) typically have non-Gaussian degree distributions, and demonstrate fast decaying tails towards higher node degrees (Amaral et al., 2000). In addition to being an essential metric, local node degree provides the foundation of the majority of all other graph theory metrics (Bullmore & Sporns, 2009).

4.2.2.6.5 Local Node Clustering Coefficient

Local node clustering coefficient is a measure of segregation that refers to the fraction of triangles around a node, that is, the probability two connected nodes connected to a third are also connected to one another (Fornito & Bullmore, 2015). This metric is equivalent to the fraction of a node's neighbours that are neighbours of each other (Bullmore & Sporns, 2009). Put simply, the clustering coefficient of a network reflects the prevalence of clustered connectivity around a given node (Rubinov & Sporns, 2010). Local node degree forms the foundation of this metric, which is indicative of small-world attributes (Sporns et al., 2007).

4.2.2.6.6 Local Node Betweenness Centrality

Local node betweenness centrality refers to the fraction of shortest paths that contain a node in a network (Bullmore & Sporns, 2009). This metric informs on the degree a brain region is involved in the set of shortest

paths between any pair of vertices in a neural network. Local node degree forms the foundation of this metric, which provides a sensitive metric of centrality, which is essential for the governance of the dispersion of information across a network (Rubinov & Sporns, 2010). As with local node degree, betweenness centrality allows for the identification of hubs (defined by high betweenness centrality) and thereby the appraisal of the functional integration of a network (Sporns et al., 2007).

4.2.3 DATA COLLECTION

All data were initially collected by the ALSPAC. Biological mothers and fathers were administered questionnaires relating to SES when children were age 8 months. Children were directly administered the WISC-III at 8 years (Wechsler, 1991). Omics data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Brain imaging data were acquired from the index children when they were between the ages of 18 and 24. Brain imaging data were acquired during the course of three different studies with varying recruitment criteria (for a detailed summary of the criteria adopted for each study, please refer to Sharp et al., 2020). Briefly, it is worth noting that one study in particular, with the largest sample size of the three (n = 513), was a testosterone study that selected for males-only during recruitment (Björnholm et al., 2017).

4.2.4 STATISTICAL ANALYSES

4.2.4.1 Polygenic Score Analysis

The polygenic scores for cognitive ability computed in **Chapter 3** were carried over to the present analysis. Thus, please see **Chapter 3** for a detailed account of how PGSs for cognitive ability were generated and what steps were taken. A brief description will be provided here.

4.2.4.1.1 Population Stratification

Population stratification was accounted for by incorporating principal components (PCs) as covariates in a covariance matrix alongside participant family ID (FID), sample ID (IID), and participant sex (Choi et al., 2020). The first 10 PCs were generated, and subsequently merged in R with the FID, IID, and participant sex. This data file was then included as covariates in PGS calculations.

4.2.4.1.2 Calculation of Polygenic Scores

PGSs were generated for cognitive ability in using a dedicated PGS analysis software program, which implements the standard cluster and thresholding (C+T) method (Choi & O'Reilly, 2019; Euesden et al., 2015).

4.2.4.1.3 Software

Formatting, pre-processing, QC, generating PCs for population stratification, PGS calculations, and tests for association were carried out using a combination of dedicated PGS software programs alongside multipurpose software. This included the use of PLINK (Chang et al., 2015; Purcell et al., 2007) and PRSice-2 (Choi & O'Reilly, 2019; Euesden et al., 2015), alongside R (R Core Team, 2022) and RStudio (RStudio Team, 2022), respectively.

4.2.4.2 Partial Least Squares Regression

We employed PLS regression to assess the covariance between measures of SES, PGSs for cognitive ability, and measures of structural brain connectivity. PLS is a data reduction technique that implements features from principal component analysis (PCA) and multiple linear regression to identify a set of orthogonal factors (i.e., latent variables) across multiple data sets, to detect which of these factors have the greatest predictive power (Wold et al., 1984). In doing so, PLS transforms the original predictor space into a new component space and determines whether a relationship is present between multiple data sets, and if so, highlights the measures within the data sets that optimally model the relationship (Wold et al., 1984). Given the large number of variables present in connectome data, alongside multiple measures of SES and PGSs for cognitive ability, the use of PLS was well-suited to assess the complex relationship between these environmental, genomic, and connectome data sets (Abdi et al., 2010; Johnson et al., 2021). Correspondingly, when used to assess connectome-based predictive models, PLS models have been shown to outperform linear regression models (Yoo et al., 2018).

Using the 'plsregress' function in MATLAB, we applied a two-block canonical PLS to assess the relationships between measures of SES, PGSs for cognitive ability, and measures of structural brain connectivity. Due to the nature of calculating global and local graph theory metrics, we considered these in two separate sets of PLS analyses. The first PLS analysis considered the two global metrics, with subsequent PLS analyses assessing the four local metrics in turn. For both types of PLS, the first block comprised the five measures of SES and PGSs for cognitive ability, and the second block comprised the connectome measures. For the first PLS, we used the two global graph theory metrics as the response block. Because they are on difference scales, all predictor and global response variables were standardised (with a mean of zero and standard deviation of one) before the PLS. For the subsequent PLSs, we took each local measure in turn, as a vector of 100 values, one local metric per parcel. Local connectome measures were left in their native space. We used permutation testing (n = 1000) to assess the significance of the relationship between the latent variables, whilst controlling for sex, age, sub-study, and residual head motion, defined as maximum frame-wise displacement (Krishnan et al., 2011). During permutation testing, a new data set was obtained by randomly redistributing the rows of the sample data in the first block, leaving the second block unchanged. A PLS regression was then fitted to the new data, and the correlation was assessed. This process was repeated 1000 times. Significance was determined by testing whether the actual strength of the relationship between the latent variable fell into the tails of the null distribution derived from the permutation samples. If the relationship does not fall in the tails then we conclude that no relationship between data sets exists (Good, 2013).

To estimate the standard errors and thereby assess the reliability of outer weights for significant components, we used bootstrapping (n = 1000 with replacement). Put simply, this step is designed to establish the measures that load significantly onto the respective latent components. Bootstrapped weightings were utilised to construct 95% confidence intervals. Loadings with bootstrapped confidence intervals that did not pass zero were classified as loading significantly onto the other latent variables. Bootstrapping with replacement resamples a dataset of N participants using the original dataset, by selecting N participant rows from the dataset, with the capacity for any row to be selected more than once. The reliability of outer weights were determined based on how they varied between bootstrap samples. The bootstrap process commonly results in axis reflection, whereby sign-flipping occurs during resampling (Krishnan et al., 2011). To correct for this, a Procrustes rotation was applied to the imputed outer weights, where outer weights for each dataset and component were rotated onto the equivalent set for the initial imputed dataset. This process was repeated (n = 1000) for each imputed dataset.

4.3 RESULTS

4.3.1 PARTIAL LEAST SQUARES REGRESSION ANALYSIS

We employed a two-block canonical PLS to assess the covariance between measures of SES (i.e., maternal occupation, parental education, and maternal reported levels of difficulty affording food and housing), PGSs for cognitive ability, and measures of structural brain connectivity (i.e., global modularity, global efficiency, local node strength, local node degree, local node clustering coefficient, and local node betweenness centrality). The PLS analysis could produce multiple potential outcomes. First, there may be no significant components that explain the relationship between the predictor variables and the measures of brain organisation. In other words, it could be that SES within the first year of life, PGS, and structural brain organisation around 20 years later, are not significantly related to each other. Second, there may be a single dimension/component that explains the relationship between predictors and outcomes. This would mean one common dimension of genomic and environmental variation is related to a common dimension that captures variation in structural brain organisation. Third, there may be multiple different components, with the environmental measures and PGS each explaining relatively distinct aspects of brain organisation. Such a finding would suggest that the aspects of brain organisation that are associated with genomics are somewhat different from those aspects that are associated with the environment. To foreshadow the result, we found the second potential outcome best described our results, which will be detailed in turn.

4.3.1.1 Global Measures

The correlation between the first pair of latent variables from each dataset (Block 1: SES and PGS; Block 2: global modularity and global efficiency) was r = 0.092321, p = 0.15878, and did not survive the permutation procedure p(permuted) = 0.352. No subsequent components were significant either. In short, at a global level, within this sample, there is no significant relationship between our predictors and brain organisation.

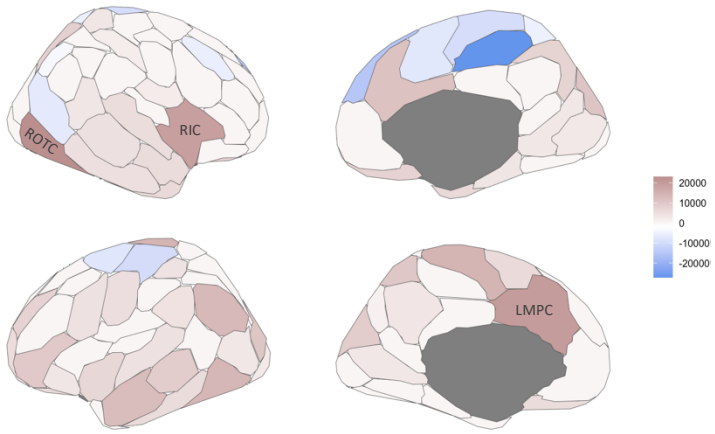
4.3.1.2 Local Measures

4.3.1.2.1 Node Strength

The correlation between the first pair of latent variables from each dataset was $r = 0.23368$, $p = 6.7247e\text{-}10$, but did not survive the permutation procedure $p(\text{permuted}) = 0.092$. The correlation between the second pair of latent variables from each dataset was $r = 0.28693$, $p = 2.2586e\text{-}14$, $p(\text{permuted}) < 0.001$. This second component explained 21.81% of the covariance between the data sets. In the predictor block, this variable captured significant positive loadings for maternal occupation (2.4809, 95% [2.2982 ± 2.6636]), maternal education (2.4059, 95% [1.6363 ± 2.7788]), paternal education (1.6790, 95% [1.5985 ± 1.7595]) and PGSs for cognitive ability (0.5386, 95% [0.5292 ± 0.5480]), and negative loadings for the difficulty affording food (-3.2501, 95% [-4.2102 ± -3.0517]) and difficulty affording mortgage or rent (-4.9331 [-5.7249 ± -4.6548]). In the response block this variable captured significant loadings across a very broadly distributed set of brain regions, which can be seen in in Figure 4.7. Loadings were particular high in the left medial prefrontal cortex (and to some extent the right hemisphere equivalent), right insular cortex, and right occipital temporal cortex.

Figure 4.7

Significant Node Strength Loadings Overlaid on 100-Node Schaefer Parcellation



Note. Scale denotes unstandardised loadings. Loadings range from positive to negative, and are represented by the colours pink and blue, respectively. *LMPC* Left medial prefrontal cortex; *RIC* Right insular cortex; *ROTC* Right occipital temporal cortex.

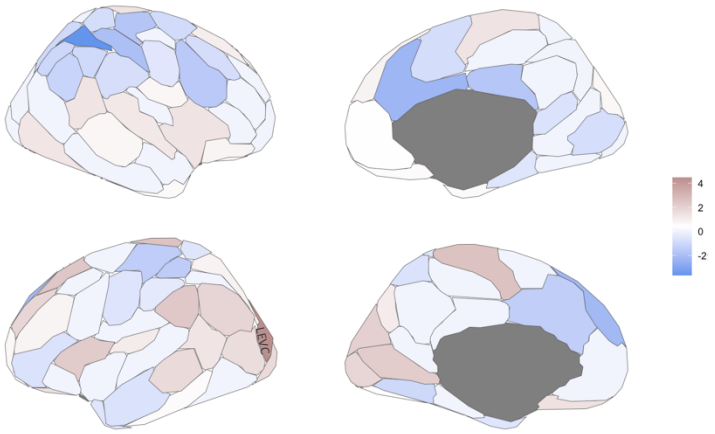
4.3.1.2.2 Node Degree

The correlation between the first pair of latent variables from each dataset was $r = 0.19206$, $p = 4.4232e\text{-}07$, but did not survive the permutation procedure $p(\text{permuted}) = 0.961$. The correlation between the second pair of latent variables from each dataset was $r = 0.31061$, $p = 1.0697e\text{-}16$, $p(\text{permuted}) = 0.051$. This second component explained 21.375% of the covariance between the data sets. In the predictor block, this variable captured significant positive loadings for maternal occupation (1.1605, 95% [1.0820 ± 1.2391]), maternal education (1.7913, 95% [1.6363 ± 1.9463]) and PGSs for cognitive ability (0.4690, 95% [0.4170 ± 0.5210]), and negative

loadings for paternal education (-0.3418, 95% [-0.3809 ± -0.3026]), difficulty affording food (-3.9960, 95% [-4.2102 ± -3.7818]) and difficulty affording mortgage or rent (-5.3936 [-5.7249 ± -5.0623]). In the response block, this variable captured significant loadings, mostly positive, across multiple brain regions, highlighted in Figure 4.8. Loadings were particularly high in the left extrastriate visual cortex.

Figure 4.8

Significant Node Degree Loadings Overlaid on 100-Node Schaefer Parcellation



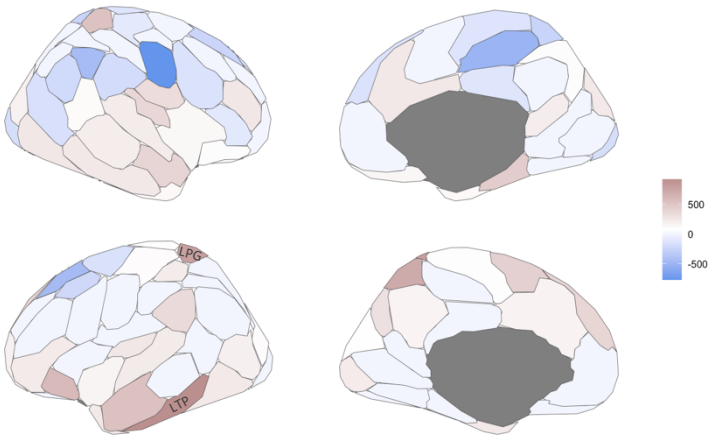
Note. Scale denotes unstandardised loadings. Loadings range from positive to negative, and are represented by the colours pink and blue, respectively. *LEVC* Left extrastriate visual cortex.

4.3.1.2.3 Node Clustering Coefficient

The correlation between the first pair of latent variables from each dataset was r = 0.26277, p = 3.2296e-12, but did not survive the permutation procedure p(permuted) = 0.073. The correlation between the second pair of latent variables from each dataset was r = 0.27211, p = 5.019e-13, p(permuted) = 0.023. This second component explained 21.043% of the covariance between the data sets. In the predictor block, this variable captured significant positive loadings for maternal occupation (1.9499, 95% [1.8043 ± 2.0954]), maternal education (0.8406, 95% [0.7495 ± 0.9317]), paternal education (0.4479, 95% [0.3953 ± 0.5005]) and PGSs for cognitive ability (0.7012, 95% [0.7006 ± 0.7018]), and negative loadings for the difficulty affording food (-3.9042, 95% [-4.1084 ± -3.7001]) and difficulty affording mortgage or rent (-5.3634 [-5.6958 ± -5.0313]). In the response block, this variable captured significant loadings, mostly positive, across multiple brain regions, with the parcels most strongly driving the effect highlighted in Figure 4.9. Loadings were highest in the left postcentral gyrus and left temporal pole.

Figure 4.9

Significant Node Clustering Coefficient Loadings Overlaid on 100-Node Schaefer Parcellation



Note. Scale denotes unstandardised loadings. Loadings range from positive to negative, and are represented by the colours pink and blue, respectively. *LPG* Left postcentral gyrus; *LTP* Left temporal pole.

4.3.1.2.4 Node Betweenness Centrality

The correlation between the first pair of latent variables from each dataset was $r = 0.23873$, $p = 2.7925\text{e-}10$, but did not survive the permutation procedure $p(\text{permuted}) = 0.895$. No subsequent components approached significance following the permutation procedure.

4.4 DISCUSSION

The present study sought to integrate multiple data types to establish the interrelationships between genetic propensity, SES, and structural brain organisation. Specifically, we sought to determine whether genetic propensity and the early childhood environment are associated with measures of the structural organisation of the brain. To do this, we created individual level PGSs for cognitive ability for each participant, used five measures of SES collected when the index children were 8 months old, and created connectomes from diffusion imaging data acquired around 20 years later. We used a technique called PLS analysis to integrate these different data types. PLS is a data reduction technique adapted for multiple blocks of data, designed to determine precisely this kind of distinction. There were multiple possible results – it could have been that SES and PGSs are associated with distinct aspects of brain organisation, alternatively they could share their associations with brain organisation.

There are several key findings. First, there were no significant relationships between our predictor variables and our global network effects at either the level of segregation or integration. Second, we identified a number of significant local effects, including significant effects of predictor measures on node degree, node strength, and node clustering coefficient. Third, all significant local effects were captured by *shared* genetic and environmental relationships. Put simply, the PLS identified single components upon which both environmental and PGS measures loaded significantly. Lastly, the results of the current study highlighted the heterogeneity of this

influence through individual SES components – in the ALSPAC cohort, it is particularly the occupation and education measures of social status, rather than the financial difficulty measures, that appear to associate with brain organisation. These findings will be discussed in turn.

Before we delve into the detailed interpretation of the PLS results, it is important to consider carefully the interpretation of second order components. In all of our analyses, only the second components survived the permutation procedure. In essence, it is only with the second components that we can be confident that the relationships identified do not reflect noise. Just like with a PCA, the second components in a PLS analysis reflect the variance captured that's not captured by the first component (Wold et al., 2001). In practice, the first component often captures all predictors – much like the first PC capturing shared variance across all measures. The second component then will likely split the variables, necessarily capturing variance that is common to some but not others. For instance, in the current analysis, the second components always capture the educational and occupational aspects of SES, but not the level of difficulty affording food and housing aspects. The negative loadings for the level of difficulty measures should *not* be interpreted as absolute negative relationships with the variables in the response block. Instead the differential in loadings should be interpreted as indicating that this component captures the variance explained by maternal occupation and parental education *relative* to the level of difficulty affording food and housing aspects of SES. As to why the first components never survive the permutation procedure is an interesting question in itself, which we touch upon later. One possibility is that we are controlling for so many sample biases, including sex differences and scanner protocols, and that despite this, these creep into the PLS analysis and are captured by the first component. When we then permute the components, they are no longer significant.

4.4.1 NODAL STRENGTH, DEGREE, AND CLUSTERING COEFFICIENT ARE ASSOCIATED WITH BOTH EARLY LIFE SES AND PGS

Variations in local node strength were captured by positive loadings for predictor measures maternal occupation, parental education, and PGSs for cognitive ability, and negative loadings for level of difficulty affording food and housing. Note the above explanation of the interpretation of second components (i.e., this component reflects the shared variance across maternal occupation and parental education aspects of SES and PGS, *relative* to the level of difficulty afford food and housing aspects of PGS). These loadings were primarily positive, and seen across multiple brain regions, including those found within the dorsal attention network, the salience ventral attention network, and the sensorimotor network. These are networks which are implicated in orientating focus to a particular task, attention and response to unexpected salient stimuli in the environment, bottom-up attentional processes, and preparing the brain to perform and coordinate motor tasks, respectively (Cai et al., 2016; Hsu et al., 2020). Variations in local node degree were captured by a second component with positive loadings for predictor measures maternal occupation, maternal education, and PGSs for cognitive ability, and negative loadings for paternal education, and level of difficulty afford food and housing. Loadings were positive, and primarily represented in the visual central network, which is implicated in visual processing (Ungerleider, 2020). Lastly, variations in local node clustering coefficient were captured by a second component with positive loadings for maternal occupation, parental education, and PGSs for cognitive ability, and negative loadings for level of

difficulty afford food and housing. These loadings were primarily positive, and most strongly correlated with the limbic network and the dorsal attention network. These are networks which are implicated in lower order emotional processing and input from sensory stimuli (Morgane et al., 2005), and orientating focus towards a particular task (Ho et al., 2022), respectively.

Why are these effects so distributed? This is in part due to the nature of PLS, which is modelling the covariance structures of measures of SES and PGSs, and the structural connectome. It is designed to identify relationships between these two 'spaces' without isolating region specificity. However, it is still noteworthy that the widely distributed effects reflect the fact that differences in brain organisation associated with environmental and genetic influences are not specific (Johnson, 2011; Westermann et al., 2007). This is not simply the case for the links between the environmental and genetic influences on the developing brain, many cognitive functions are highly distributed. For example, cognitive mathematical problem-solving skills ubiquitously manifest across a distributed network of parietal, prefrontal, and ventral temporal-occipital regions in the brain (Iuculano et al., 2015).

Why was nodal strength particularly important? Among our nodal measures, nodal strength is unique in that it captures the weighted structure of a network, not just its topological organisation. This may be why it is by far the most strongly related to the predictor variables. Local node strength can inform us on the functional integration of a network given its defining role for hub formation (Fornito & Bullmore, 2015). The functional integration of a cortical network is increasingly linked to SES (Tooley et al., 2021, 2022). Thus, nodal strength could be particularly important in the current study specifically because we are looking for links with SES as a broad proxy for environmental influence. Current findings linking SES with functional cortical network formation would predict that higher SES would equate to higher local node strength, and that is exactly what we found in our structural networks: certain features of SES (namely maternal education and occupation - which themselves are highly polygenic) and PGSs for cognitive ability are positively associated with a distributed pattern of nodal strength, particularly picking out portions of the frontal lobe. Interestingly, this metric is often omitted in favour of more simplified binary graph theory metrics (Rubinov & Sporns, 2010). These findings argue for the importance of its inclusion when addressing the functional integration of a network. In the current context, nodal strength provides stronger relationships than nodal degree. Again, this is likely because even though these two measures are related, nodal strength captures additional *weighted information* not seen in degree metrics.

4.4.2 SHARED PREDICTION

To date, low SES has been associated with less efficient network organisation in cortical and subcortical regions, reductions in brain surface area, and decreased connectivity between the anterior and posterior components of the default mode network (Kim et al., 2019; Noble et al., 2015; Weissman et al., 2018). But neurodevelopment can also be genomically influenced, with cognition-specific SNPs having molecular neurobiological underpinnings, being predominantly expressed in brain tissue, and implicated in neuronal function and development (Sniekers et al., 2017). What is not yet known is whether these effects are independent of one another or shared. Here, using PLS, a method ideally suited to test this notion of shared relationship, we show they are not independent. In

possibly the first empirical study of its kind (at least, the first we have been able to identify), we demonstrate shared prediction from maternal occupation, parental education, and PGSs for cognitive ability, relative to the level of difficulty affording food and housing aspects of SES. One strong possibility is that these specific SES measures and the PGSs predict shared aspects of brain organisation due to their inherent genomic entanglement (Plomin & Bergeman, 1991; Plomin & Viding, 2022). For example, education and occupation are highly heritable (Allegrini et al., 2019; Okbay et al., 2022; von Stumm et al., 2020), and quantitative genetic analyses with twin and adoption studies have demonstrated that environmental factors are strongly influenced by an individual's genome when they are incorporated in PGS analyses as phenotypes of interest (Plomin & Bergeman, 1991). Likewise, it is possible that the SNPs associated with cognitive ability may also be associated with genetic propensity for occupation and education, which could further explain the shared variance demonstrated in the current study.

The overarching deliberation to be had, based on this finding in particular, is whether this shared prediction is because the environmental factors are actually genetic, or because those polygenic morphisms are tapping into parental behaviours which then shape the environment. It is important to remind ourselves that PGSs can only speak to the *variance* across a specific phenotypic behaviour or trait within the specific population on which they were based. We therefore cannot stipulate that these SNPs are specifically coding biological or cellular pathways specifically related to the behaviour itself. That being said, it appears plausible that the answer is as multifaceted as developmental processes. For example, we know educational attainment is highly heritable (Allegrini et al., 2019; Lee et al., 2018; von Stumm et al., 2020). It naturally follows that this aspect of SES is genomically influenced. Educational attainment is also likely to map onto an individual's occupation. Moreover, there is evidence of crosstalk occurring between genetic variants, allele-specific DNA methylation patterns, and environmental factors when it comes to disease risk (Wang et al., 2019). It is possible this crosstalk occurs more generally and influences aspects of SES-genomic-outcome associations. In this way, the maternal occupation and parental education aspects of SES may be genomically guided, influencing child development in one way, while at the same time, crosstalk between endogenous and exogenous factors may lend further contribution. In summary, these two potential accounts – SES is primarily genetic and these genes may relate indirectly to parenting behaviours – are not mutually exclusive.

4.4.3 ASPECTS OF SES ASSOCIATE WITH CONNECTOME MEASURES

Why do measures of financial difficulty (i.e., level of difficulty affording food and level of difficulty affording rent or mortgage) not load on the same components as other measures of SES (i.e., maternal occupation and parental education)? As direct income data were not available for the ALSPAC cohort, we obtained measurements that best represented income by proxy. However, it is possible that these measures do not represent household income. Similarly, these measures may better reflect the level of support a household receives by way of government or otherwise assisted benefits, financial support, or subsidised housing. The level of additional support outside of household income may buffer against the difficulties experienced in affording food and making payments towards rent or mortgage. A less interesting explanation is that the proxy measures we used are self-report, and to be blunt, are not very good. Unlike the prescriptive measures of, say, education or occupation, these

ratings are subjective. As such, they may be capturing something other than the intended household income. In the future it would be wise to discount this possibility by identifying alternative measures of financial difficulty in the ALSPAC cohort, or an alternative longitudinal cohort study comprising income-specific data that may better capture household income and overall SES.

Why do some measures of SES (i.e., maternal occupation and parental education) relate more closely to polygenic propensity than others? As noted in **Chapter 2**, the ALSPAC cohort is a relatively affluent sample, with only 12.5% of participants being from low-income households. It is therefore plausible that the economic elements of SES do in fact relate to polygenic propensity in a similar way, but rather, the sample is simply not dynamic enough across the SES spectrum to capture these effects. A further plausible explanation for the finding of heterogeneity across aspects of SES relating to PGSs for cognitive ability, is perhaps partially because what the PGSs are really capturing is not necessarily 'cognition' per se, but rather are mapping onto features of the social environment that the parents co-create. This explanation hues closely to the idea of genetic nurturing, which was discussed earlier in **Chapter 1**; even when genetic variants are not passed down from parents to their offspring, parental heritability can influence how the early environment is shaped by promoting cognitively stimulating behaviours, such as whether parents frequently read books to their children (Armstrong-Carter et al., 2020; Kong et al., 2018; Wertz et al., 2019). Similarly, the PGSs may be capturing aspects of the wider family environment, such as maternal mental health (**Chapter 2**), school readiness, availability of childcare, and the opportunities a child has for socioemotional development. To investigate these points further, it would be useful to replicate the current study with an alternative longitudinal cohort comprising a more SES-representative sample, which includes aspects of the wider family environment, and incorporates parental polygenic propensity into analyses. This would allow for the confirmation of whether there are, in fact, differences between maternal occupation and parental education aspects of SES and financial difficulty aspects of SES, and provide further information on whether PGSs are capturing aspects of the wider family environment and elements of genetic nurturing.

4.4.4 LIMITATIONS AND FUTURE DIRECTIONS

Irrespective of the strengths in the current study, it is not without limitations. For example, as mentioned, it is plausible the measures of financial difficulty do not capture household income. It would be useful for future research to address this limitation by considering the use of an alternative sample cohort comprising environmental, genetic, and neural data, with an emphasis on obtaining a sample with the potential data to capture robust standard measures of SES. It is also worth pointing out that the ALSPAC cohort is a relatively affluent sample, as discussed heavily in **Chapter 2**. In addition, the current study considered polygenic propensity through its consideration of PGSs for cognitive ability, alone. Thus, it would be beneficial to integrate additional PGSs for further phenotypes of interest to examine how the influence of polygenic propensity in shaping neurodevelopment varies according to phenotype. Whilst we computed PGSs for educational attainment alongside PGSs for cognitive ability (as detailed in **Chapter 3**), the PGSs for educational attainment were not included in the current study. This was due to the small number of participants with educational attainment data available, which was less than that required for this type of analysis (Marek et al., 2022). Moreover, the variance accounted for by these PGSs was substantially lower than that typically seen across the literature, with a large portion of

variance left unaccounted for (Donnellan et al., 2021). We have highlighted several reasons why this may be the case, pertaining to limitations in sample size, quality of educational attainment measures, and the nature of its heritability (**Chapter 3**). It is likely that alternative PGSs for other phenotypes of interest may yield more positive and informative results within the ALSPAC cohort, further enabling a deeper understanding of the processes underlying neurodevelopment.

There are also limitations with the neuroimaging data available. The most obvious of which are the sample imbalances and other unwanted sources of variability that needed to be accounted for. For example, there was a disproportionate number of males in the final sample including data across all levels of analysis. This was due to the neural data comprising a predominantly male sample, resulting in an overall sample size of n = 685, of which 72.8% were male. Nevertheless, this imbalanced sex was accounted for in the PLS analysis to ensure this source of variability did not result in spurious findings and detract from covariates of interest. Further to this is the issue of combining neuroimaging data sets across three separate studies, which may have introduced scanner-specific differences in the data obtained. These sources of variance were accounted for in the present study by harmonising the three data sets using neuroCombat (Fortin et al., 2017, 2018). Whilst there are tools available to account for inevitable unwanted sources of variability, such as those noted here, it is impossible for us to know whether we have resolved these issues. For example, why do the first components never come out as significant after controlling for the permutations? It is perhaps possible that these first components capture sample biases. Future research could aim to further address these sources of variability. We discuss this idea in more depth in the General Discussion.

4.4.5 CONCLUSION

In conclusion, the current study demonstrates that both genetic propensity and the early child environment influence the structural organisation of the brain across at least three local metrics of network connectivity. We have shown this influence is shared, with key elements of SES and PGSs for cognitive ability both mapping onto differences in the structural connectome at the local level (i.e., node strength, degree, and clustering coefficient). We have emphasised the heterogeneous nature of this association, with certain components of SES (i.e., maternal occupation and parental education) consistently displaying positive local node strength, degree, and clustering coefficient loadings, relative to other components of SES (i.e., difficulty affording food and housing). Moreover, nodal strength was particularly important - presumably because unlike the other measures included in the analysis, it captures the weighted aspects of connectivity, rather than pure topology. There would be additional utility in delving further into the specifics of how features of the connectome (e.g., node and connection type) are shaped by the interaction between environmental and genomic influence, and whether these effects are mirrored by gene expression patterns.

5 SES AND THE GENOME INTERACT TO SHAPE COGNITION AND THE CONNECTOME

The work described in the following chapter was completed as part of a collaborative effort by Professor Duncan Astle and me, using the connectomes generated in the previous chapter by Dr. Danyal Akarca. I alone was responsible for detailing the work in this thesis with input from Professor Duncan Astle.

5.1 INTRODUCTION

Chapter 4 considered how socioeconomic status (SES) and the polygenic scores (PGSs) are associated with the structural organisation of the brain using partial least square regression (PLS) analysis. This demonstrated that genetic propensity and the early childhood environment are collectively associated with the structural organisation of the brain (i.e., local node strength, degree, and clustering coefficient) around 20 years later. It further highlighted the heterogeneity across SES measures, with the PLS loadings identifying the differential between certain aspects of SES (i.e., maternal occupation and education) versus other aspects (i.e., difficulty affording food and housing). However, a couple of key questions remain. The first obvious one pertains to the *interaction* between SES and PGSs, that is, whether they influence one another, and if so, how? A second obvious question is *how* do to these two factors, or their interaction, shape the connectome? In this final empirical chapter, I aim to address these two remaining questions. To do this, I use generalised linear modelling (GLM) to explore the interaction between PGS and SES in their prediction of cognitive ability. Secondly, I explore the relationship between these predictors, and their interaction, across the connectome in order to understand the topological role of the nodes and connections that most strongly relate to genetic propensity, the environment, or their interaction. Finally, I test whether or how these effects mirror the patterning of gene expression, using post-mortem data.

Within the connectome, not all nodes are equal. Different nodes are thought to have different topological roles within the network. When we model the brain as a network, as is done with connectomics, the arrangement of its edges (i.e., white matter integrity) and nodes (i.e., cortical grey matter) are essential for the efficiency and cohesiveness of the networks overall functioning (Rubinov & Sporns, 2010; Sporns, 2022). The connectome is organised into modules (i.e., sets of nodes), which are distinguished by greater within-module connectivity and

sparser outside-module connectivity (Girvan & Newman, 2002). A rich-club refers to a core subnetwork of brain regions, where a node that is rich in connections forms an elite club (Colizza et al., 2006; Zhou & Mondragón, 2004). Rich-clubs are metabolically costly and provide a high-capacity backbone essential for coherent communication and brain function (van den Heuvel et al., 2012). With this framework, we can divide the connectome into different node types: rich-club nodes (i.e., central and densely connected nodes), feeder nodes (i.e., nodes connected to rich-club nodes), and peripheral nodes (i.e., nodes sharing no connection to the rich-club node). Here, we will use this rich-club framework to assess how SES, genetic propensity, and their interaction influence node type (i.e., rich-club, feeder, and peripheral) and connection type (i.e., rich-rich, rich-feeder, and peripheral-peripheral). This may provide telling information on the mechanisms underlying associations between the early environment, the genome, and the developing brain.

We previously considered in **Chapter 4** how the strength of connectivity across the human connectome is, in part, associated with genetic influence. This was done using PGS for cognitive ability. But there is another important way to consider genetic variability, and that is the patterning of gene expression across the brain. Gene expression refers to the process by which the information carried by a gene is operationalised to serve a function (National Human Genome Research Institute, 2023). This is primarily achieved through the process of transcription. Generally speaking, during transcription, deoxyribonucleic acid (DNA) is transcribed to ribonucleic acid (RNA) molecules that code for proteins with the assistance of messenger RNA (mRNA). One way gene expression can be measured is with high-density DNA microarray assays that measure the mRNA expression of every gene in the genome, and through reverse transcription, identify the genes being expressed (Lockhart & Winzeler, 2000). A great example of how DNA microarray-based gene expression profiling has been utilised can be seen with the Allen Human Brain Atlas (AHBA; https://human.brain-map.org). The AHBA is a multimodal atlas of gene expression and anatomy across the adult human brain (Hawrylycz et al., 2012; Shen et al., 2012). It is the most extensive atlas of gene expression to date, and is freely and globally available. The AHBA has mapped all genes across the cerebrum, cerebellum, and brainstem using post-mortem tissue samples. This data has also been histologically mapped into a unified 3D anatomic framework established on the grounds of MRI. Whilst limited in some ways, a point that will be returned to later, the AHBA has revolutionised genetic neuroimaging. Researchers can leverage the AHBA gene expression data to explore how components of the genome contribute to cell and organism function during development, health, and pathology on the basis of their gene expression profiles (Lockhart & Winzeler, 2000).

Gene expression is closely related to brain geometry. The expression profiles of different brain regions seems to be related to the role of those regions, and their interconnections in the network (Akarca et al., 2021; Arnatkevičiūtė et al., 2021b; Oldham et al., 2022). One possibility is that the expression profiles of genes preferentially influences the strength of hubs in the connectome, with gene-derived molecular cues shaping connectivity between regions (Arnatkevičiūtė et al., 2021b). Research assessing neurodevelopmental diversity in the structural organisation of the brain has lent further support for the role of gene expression in shaping the connectome (Akarca et al., 2021). For example, as part of a wider study, Akarca and colleagues (2021) assessed whether genetically coded processes steer neurodevelopmental diversity in structural brain organisation. They used generative network modelling, whereby connections were formed probabilistically in a spatially embedded

network whilst adhering to predetermined parameters. Adjusting the set parameters governing the network allowed for the identification of the constraints most representative of human connectomes. This subsequently enabled the identification of the topological features most representative of the connectomes within the sample, which were then taken forward to specify gene expression profiles that co-located spatially with these topological features. The resulting gene lists underwent Gene Ontology (GO) enrichment analysis to identify the biological pathways underlying their enrichment. Results showed that co-located gene expression profiles are predominantly involved in biological and cellular processes implicated in synaptic signalling, neuronal projection, protein transport, and catabolic intracellular processes. Another example is demonstrated by work from Oldham and colleagues (2022), who sought to model various constraints on human brain connectivity, including spatial, topological, developmental, and physiological constraints. They explored the implications of using transcriptional similarity as a node-wide measure in generative models. Results showed that model performance improves upon taking transcriptional similarity into account, leading the authors to argue for the role of genetics in shaping the connectivity of the connectome. One interesting way of furthering this would be to see whether more granular topological features of the structural connectome, such as connection type, mirror genetic similarity, and whether this similarity shapes the relative influence of SES or polygenic propensity on that connection.

5.1.1 THE CURRENT STUDY

The current study addresses two broad aims. First, to understand the interaction between genetic propensity and SES, and second, to understand how this shapes connectome organisation. To address these aims we ask a series of interlinked questions: 1) Does SES and PGSs for cognitive ability predict cognition, and if so, do they interact? (To state the obvious: the PGSs should predict cognition, as shown in **Chapter 3**. The question is whether this prediction overlaps with that made by SES and whether there is any interaction between these terms.) 2) Does SES and PGSs for cognitive ability predict specific features of the structural connectome (i.e., node and connection type), and if so, do they interact? 3) Do certain types of connections mirror genetic similarity?

As with the previous empirical chapters, we used data from the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013). Measures of early SES comprised maternal occupation, and maternal and paternal education levels. We omitted the economic measures because of our reservations about those specific metrics, as outlined in **Chapter 4**. Genetic propensity was measured by computing PGSs for cognitive ability. Specific features of the structural connectome included node type (i.e., rich-club, feeder, and peripheral) and connection type (i.e., rich-rich, richer-feeder, peripheral-peripheral). A PGS analysis was performed in the first instance to generate PGSs for cognitive ability adhering to extensive guidelines detailed in **Chapter 3** and elsewhere (Choi et al., 2020). Connectomes were constructed for each individual in the sample using tractography data derived from diffusion tensor imaging (DTI) during a magnetic resonance imaging (MRI) session. We then employed generalised linear modelling (GLM) to perform multivariate regressions to assess the unique variance accounted for by SES, PGSs for cognitive ability, and their interaction on cognition and features of the connectome.

5.2 METHODS

5.2.1 PARTICIPANT DEMOGRAPHIC

The present study comprised the same genomic, neural, and phenotypic data outlined in **Chapter 4**. For a detailed summary of this cohort and demographic information, please refer to the preceding chapter.

5.2.2 MEASURES

5.2.2.1 Socioeconomic Status

Measures of SES were similar to that of **Chapters 2-4**, and comprised self-reported measures of maternal social class based on occupation, and maternal and paternal education levels. Following the results of **Chapter 4**, we chose to solely focus on the maternal occupation and parental education aspects of SES. Details of how these aspects of SES were measured and coded for are provided in **Chapter 2**. Measures of SES were assessed when the index children were age 8 months. All SES measures were subjected to imputation using the Mice package (Buuren & Groothuis-Oudshoorn, 2011) in R (R Core Team, 2022). See **Chapter 4** Figure 4.1 for detailed missingness pre-imputation. For the current purposes we calculated the first principal component (PC) across the included measures, which explained 62.20% of the variance across the raw measures, with high loadings for occupation (0.474), maternal (0.596) and paternal education (0.657). This PC was used as our measure of SES in the model, but we rescaled it before using it to calculate the interaction term, such that it only contains positive numbers. This is important: a PC is usually normalised with a mean of zero, meaning that half the values will be negative. If these negative numbers are then used within an interaction it can create results that are uninterpretable.

5.2.2.2 Polygenic Scores for Cognitive Ability

5.2.2.2.1 Base Data Genomics

PGSs for cognitive ability were derived from summary statistics from Savage and colleagues (2018) genome-wide association study (GWAS) meta-analysis of cognitive ability. Base data genomics and the employed QC steps have been thoroughly described in **Chapter 3**. Briefly, this meta-analysis of cognitive ability in 269, 867 individuals from 14 independent epidemiological cohorts of European ancestry formed the base data in our PGS analysis.

5.2.2.2.2 Target Data Genomics

Target data were acquired from the ALSPAC. These data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Index children were genotyped using Illumina HumanHap550 quad chip genotyping platforms. Please see **Chapter 3** for a detailed outline of the target data, and the QC steps employed.

5.2.2.2.3 Phenotypic Measure of Cognitive Ability

As detailed in **Chapter 3**, PGS efficacy was confirmed by way of tests of association with measures of cognitive ability. Cognitive ability was assessed by performance on the widely used Wechsler Intelligence Scale for Children, 3rd edition (WISC-III; Wechsler, 1991) when children were age 8. The total sum of the scores for the Verbal and Performance subscales formed the global measure of cognitive ability, which was then taken forward for associative testing. See **Chapter 3** for a detailed outline of the WISC-III Verbal and Performance subscales.

5.2.2.3 Cohort Connectomes

The connectomes used in the present analysis were obtained using protocols outlined in **Chapter 4**. For a thorough outline of the steps undertaken to construct the cohort connectomes, please refer to **Chapter 4**. Briefly, MRI data were acquired over three neuroimaging studies (Björnholm et al., 2017; Fonville et al., 2019; Lancaster et al., 2018) when the ALSPAC index children were between the ages of 18 and 24. The first sub-study comprised a sample of n = 252, with a mean age of 20.03 (range 19.08 to 21.52), of which 35% were male (Fonville et al., 2019). The second comprised a sample of n = 196, with a mean age of 22.75 (range 21.12 to 24.55), of which 48% were male (Lancaster et al., 2018). Lastly, the third sub-study comprised a sample of n = 513, with a mean age of 19.62 (range = 18 to 21.50), of which 100% were male (Björnholm et al., 2017). DTI data were acquired during MRI sessions, and data from all three sub-studies were subject to reconstruction and stringent measures of cortical and sub-cortical QC (see Sharp et al., 2020 for a detailed summary of all sub-studies). Acquired MRI data across all three samples were subject to pre-processing and reconstruction using QSIPrep 0.14.2, an integrative software platform based on Nipype 1.6.1 (Gorgolewski et al., 2011).

5.2.2.4 Constructing the Rich-Club Framework

5.2.2.4.1 Building a Distance-Dependent Consensus Network from Cohort Connectomes

In order to define the rich-club network, we needed to create a group distance-dependent consensus network. This creates a binary group average connectome, which can be used to calculate representative topological characteristics at a group level (Betzel et al., 2019). The alternative would be to calculate this rich-club for each individual participant. However, this then makes subsequent analysis stages very difficult, because the rich-club network will be subtly different for each individual. Prior to making the group consensus network, we needed to threshold each participant's connectome. This time we used proportional thresholding to set each participant's connectome to a density of 6%, which is comparable to other studies, and to the density achieved with the 60% consensus thresholding employed in **Chapter 4**. We could not use the consensus thresholding in the present chapter, as when combined with the distance-based consensus procedure, prior consensus thresholding results in the loss of *all* long-range connections. Whilst cortical networks favour short-range connections due to their cost reduction mechanisms, longer connections are essential to offset their costs, and their preservation is pivotal for group-representative networks (Bullmore & Sporns, 2012; Vértes et al., 2012). This is why we thresholded individuals to a density of 6% prior to the group consensus process and binarisation. A distance-dependent consensus network is an alternative approach to the commonly adopted uniform consensus-based approach which favours short-range connections and thus results in higher short-range frequencies not representative of individual

connectomes. Distance-dependent thresholding on the other hand, results in networks more representative of the edge length distributions seen across individual connectomes (Betzel et al., 2019). Put simply, it achieves this by allocating connections to bins, and preserving those most commonly exhibited within each bin. As seen in Figure 5.1, distance-dependent networks optimally mirrored the distance profile of the individuals within our cohort when compared to uniform consensus networks. Figure 5.2 illustrates the average connectome across all participants under a distance-dependent network.

Figure 5.1

Distance and Uniform Consensus Networks Compared to Distance Profile of Cohort

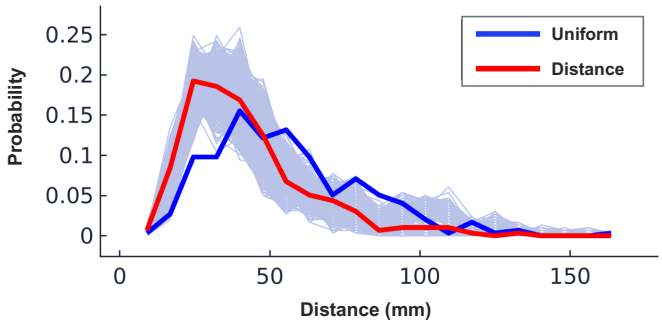
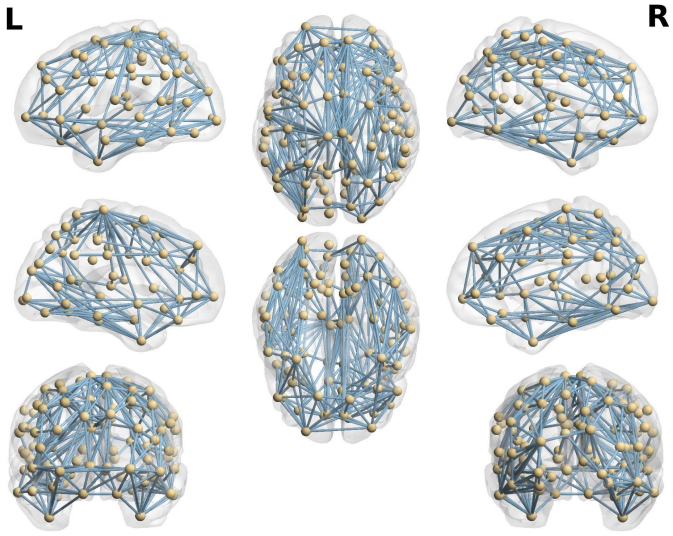


Figure 5.2

Group Distance-Dependent Consensus Network Connectome



Note. Figure displays binarised connections across the group distance-dependent consensus network. Yellow spheres represent nodes, and blue lines represent edges. The first row from left to right displays lateral view of left hemisphere, top side, and lateral view from right hemisphere. The second row from left to right displays medial view of left hemisphere, bottom side, and medial view of right hemisphere. The third row displays frontal side and back side.

5.2.2.4.2 Defining the Rich-Club Topology

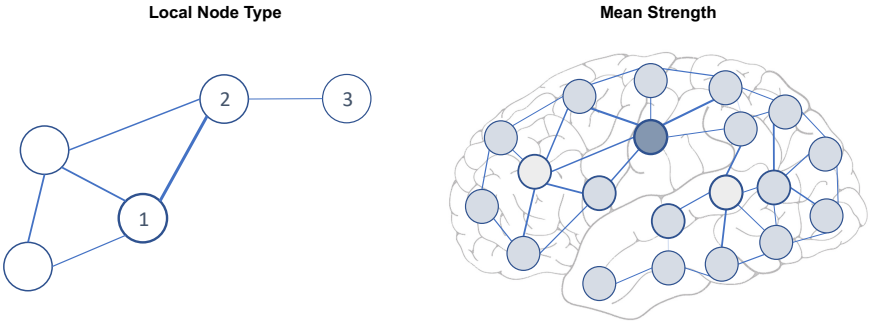
We used the rich-club coefficient from the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/; Rubinov & Sporns, 2010), a commonly used method to identify rich-club topology, to calculate the proportion of shared connections and different levels of node degree (termed K). This coefficient tells us what proportion of connections between nodes of K or higher are shared. Importantly, this number naturally rises with rising node degree, even in a random network. This is because as nodes have more connections it becomes more likely that a subset of nodes will *share* more connections, just by chance. Therefore, we needed to deduce how much connectedness increases with node degree. This was done by creating 1000 null models, each of which preserves the degree distribution of the original consensus network. As our consensus network was binary, there was no need to maintain strength or weight distributions. We calculated the rich-club coefficient for each of these random networks. Following this, for each value of K, we calculated the upper 95th percentile of rich-club coefficients from the 1000 random networks. Only when the rich-club coefficient from the equivalent K value in our consensus network exceeded the respective 95th percentile, did we consider nodes of that K and higher to be members of a rich-club. In our data, nodes of K = 10 or higher were classified as being members of a rich-club. That is, nodes with 10 connections or more shared a disproportionate number of their connections with one another, even when considering their overall connectedness. We then calculated which nodes connected to these rich-clubs, but were not themselves members of the rich-club. These nodes were termed 'feeder' nodes. The remaining nodes were classified as 'peripheral nodes'.

5.2.2.4.3 Identifying the Mean Strength of Node Connection Types

The links connecting a node to others in a network hold various weights, and node strength refers to the sum of those weights. Node strength is a primary feature of hubs, which are defined by high node strength and argued to be the communication backbone for cogent neural dynamics (Arnatkevičiūtė et al., 2021b). Calculating node strength and subsequently the mean strength of node types and connections within the rich-club framework, allows for the comparison of mean strength across node and connection types when SES and PGSs are considered. We calculated the mean strength for each of the predefined node types and their connections, across each participant. Crucially, this must be done for each individual participant, not least because it is the individual participants' connectomes that contained that weighted information, whereas our group consensus is a binary network. In each case, we used a GLM containing SES, PGS, PGS*SES, sex, age, and study to test for associations between the strength of different node types and these variables. All connectomic metrics were submitted to neuroCombat before conducting the GLMs (Fortin et al., 2017, 2018). See **Chapter 4** for an overview of the utility and manner of data harmonisation using neuroCombat. Figure 5.3 illustrates the properties of the rich-club framework incorporated in the present chapter.

Figure 5.3

Diagram Illustrating the Properties of the Rich-Club Framework



Note. Local node type illustrates rich-club (1), feeder (2), and peripheral (3) node types. Mean strength refers to the mean strength for each node and connection type.

5.2.3 DATA COLLECTION

As detailed in **Chapter 4**, all data were initially collected by the ALSPAC. Biological mothers and fathers were administered questionnaires relating to SES when children were age 8 months. Children were directly administered the WISC-III at 8 years (Wechsler, 1991). Omics data were generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Brain imaging data were acquired from the index children when they were between the ages of 18 and 24. Brain imaging data were acquired during the course of three different studies with varying recruitment criteria (for a detailed summary of the criteria adopted for each study, please refer to Sharp et al., 2020). It is worth reminder readers that one study in particular, with the largest sample size of the three (n = 513), was a testosterone study that selected for males-only during recruitment (Björnholm et al., 2017).

5.2.4 STATISTICAL ANALYSES

5.2.4.1 Polygenic Score Analysis

The polygenic scores computed in **Chapter 3** and subsequently used in **Chapter 4** were carried over to the present analysis. Please see **Chapter 3** for a detailed account of how PGSs for cognitive ability were generated and what steps were taken. A brief description, similar to that provided in **Chapter 4**, will be provided here.

5.2.4.1.1 Population Stratification

We accounted for population stratification through the classification of principal components (PCs), participant family ID (FID), sample ID (IID), and participant sex as covariates in a covariance matrix (Choi et al., 2020). We

generated 10 PCs which were merged with the FID, IID, and participant sex in R. The merged file was included as covariates in subsequent PGS calculations.

5.2.4.1.2 Calculation of Polygenic Scores

PGSs for cognitive ability were generated using a dedicated PGS analysis software program which implements the standard cluster and thresholding (C+T) method for PGS calculations (Choi & O'Reilly, 2019; Euesden et al., 2015). These PGSs were used within the GLM, but before using the scores to calculate the interaction with SES we rescaled them, such that all of the values were positive. As with the SES PC, negative values introduced to an interaction term are very hard to interpret.

5.2.4.1.3 Software

PGSs and validation testing were carried out using a combination of dedicated PGS software programs alongside multipurpose software. This included PLINK (Chang et al., 2015; Purcell et al., 2007), PRSice-2 (Choi & O'Reilly, 2019; Euesden et al., 2015), R (R Core Team, 2022), and RStudio (RStudio Team, 2022).

5.2.4.2 Generalised Linear Models

We employed GLMs (Nelder & Wedderburn, 1972) to assess main effects and interactions. A GLM removes redundant restraints on model parameters, allowing for the compact performance of multivariate regressions to assess variance and covariance. In the present chapter, we used GLMs to account for the unique variance of SES and PGSs for cognitive ability and specific features of the structural connectome. Importantly, in our GLMs we can easily include an interaction term between these variable, and examine how this interaction influences the aforementioned outcomes. Another key feature of GLMs, is that where linear models employ either least square or maximum likelihood, providing the same results due to the prior assumption of normal distribution, GLMs only employ maximum likelihood. Here, we employed the following GLMs to express covariates $\boldsymbol{x}$ and response $\boldsymbol{y}$ in a linear additive manner, regardless of whether underlying relationships are either linear or additive. Using GLMs further allowed us to account for potential effects attributable to the age of the participant when they had their scan, their sex, and the sub-study data were collected for, allowing for a more accurate representation of the effects and interactions resulting from the variables of interest.

$$(x_1) + (x_2) + (x_1 * x_2) + \text{error}$$

$$\text{Cognitive Ability} = (\text{SES}) + (\text{PGS}) + (\text{PGS*SES}) + (\text{Age}) + (\text{Sex}) + (\text{Study}) + \text{error}$$

$$\text{Mean Strength of Node/Connection Type} = (\text{SES}) + (\text{PGS}) + (\text{PGS*SES}) + (\text{Age}) + (\text{Sex}) + (\text{Study}) + \text{error}$$

5.3 RESULTS

5.3.1 EFFECT OF SES, PGS, AND THEIR INTERACTION ON COGNITION

5.3.1.1 Effect of SES on Cognition, Effect of PGS on Cognition, and the SES and PGS Interaction

First we modelled SES and PGS as predictors of cognition in separate models. In the first model, SES significantly predicted cognitive ability, SES: $t(681) = 12.0845$, $p < 0.001$; Age: $t(681) = 1.3719$, $p = 0.1705$; Sex: $t(681) = -0.6849$, and $p = 0.4936$; Study: $t(681) = 0.0441$, $p = 0.9648$. In the second model, we assessed whether PGS was predictive of cognitive ability. Reassuringly, PGS was a strong predictor of cognitive ability, PGS: $t(681) = 7.6288$, $p < 0.001$; Age: $t(681) = 0.7693$, $p = 0.4420$; Sex: $t(681) = -1.2027$, $p = 0.2295$; Study: $t(681) = -0.5077$, $p = 0.6118$. It may seem obvious that this would be the case, but it is reassuring to see this effect in the subset of the ALSPAC cohort with good neuroimaging data. Lastly, we included both SES and PGS in the same model, alongside an interaction term: the impact of SES reduced when considering PGS but was still significant, and the impact of PGS reduced when considering SES but was likewise still significant, SES: $t(679) = 6.9975$, $p < 0.001$; PGS: $t(679) = 4.5955$, $p < 0.001$; PGS*SES: $t(679) = -3.1769$, $p = 0.0016$; Age: $t(679) = 0.8978$, $p = 0.3696$; Sex: $t(679) = -0.5885$, $p = 0.4326$; Study: $t(679) = -0.1659$, $p = 0.8683$. The significant interaction term implies that the PGS and the SES measures influence each other in how they associate with cognition. The fact that it is negative suggests that it is an *under-additive* interaction. That is, when the value of one variable is low, the impact of the other is magnified, and vice versa. To make this interpretable we conducted a small follow-up analysis. We split the sample into two halves: above average and below average SES, i.e., a mean split. If this under-additive interaction is a good interpretation of the data then we should expect that when SES is low the impact of the PGS on cognition is greater, whereas when SES is high the impact of the PGS should be smaller. We tested this with two GLMs, one in each half of the data, and this is exactly what we found. In the low SES portion of the data the association between PGS and cognition is strong: PGS: $t(314)=5.7292$, $p < 0.001$; Age: $t(314) = 1.6408$, $p = 0.1018$; Sex: $t(314) = -1.2743$, $p = 0.2035$; Study $t(314) = 0.4951$, $p = 0.6209$). Whereas the effect of PGS was much weaker in the high SES portion of the sample: PGS $t(363) = 2.9578$, $p = 0.003$; Age: $t(363) = 0.1318$, $p = 0.5925$; Sex: $t(363) = -0.5357$, $p = 0.8952$; Study: $t(363) = -0.1961$, $p = 0.8446$. In summary, both SES and PGS are significantly associated with cognitive ability, but they also interact. Children growing up in lower SES households show a larger effect of polygenic propensity on cognition than those growing up in higher SES households.

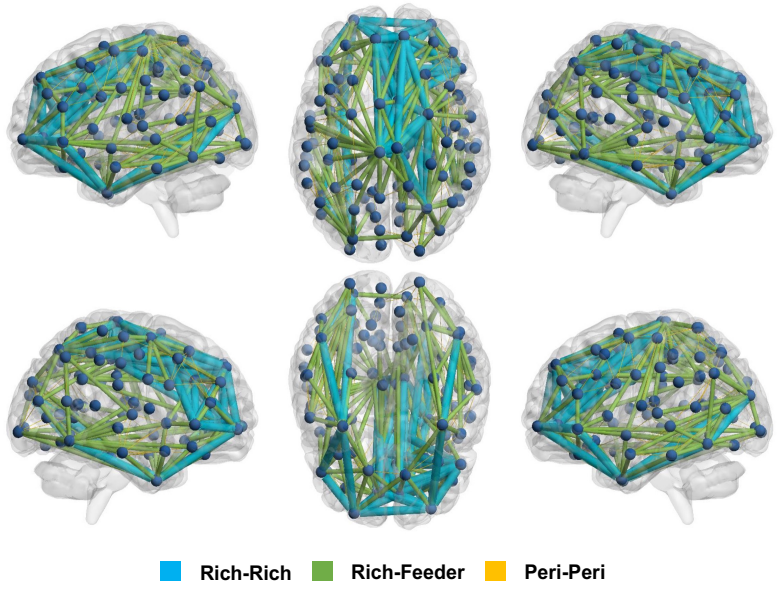
5.3.2 EFFECT OF SES, PGS, AND THEIR INTERACTION ON CORTICAL NETWORKS

5.3.2.1 Defining the Rich-Club

In our cohort consensus connectome, K ranged from 1 ~ 20. Across our data, we found nodes of K = 10 or higher to be members of a rich-club, and there were 21 ‘rich-club’ nodes in this grouping. There were 60 ‘feeder’ nodes, which were connected to the rich-club nodes, but were not themselves part of the rich-club. The remaining 19 nodes were termed ‘peripheral’ nodes. For an illustration of connectome connection types across all participants, see Figure 5.4.

Figure 5.4

Illustration of Connectome Comprising Rich-Rich, Rich-Feeder, and Peripheral-Peripheral Connection Types



Note. *Peri* Peripheral. Connectome displays connection type, including rich-rich, rich-feeder, and peripheral-peripheral connections across participants. Connectomes have been differentiated based on colour and thickness, with rich-rich connections being the thickest, rich-feeder connections being moderately thick, and peripheral connections appearing the least thick.

5.3.2.2 Comparing Nodal Degree and Strength Across Node Types

Before we proceeded with the more interesting analyses, we first carried out some sanity checks on the data. We formally tested whether our node types do indeed differ at a group and individual level, both in terms of node degree and node strength.

Within our group consensus network, as we would expect, rich-club nodes have the highest average node degree (12.57 connections), followed by feeder connections (5.15 connections), followed by peripheral nodes (1 connection). These differences are significant, using a one-way ANOVA ($F(2,99) = 129.19$, $p = 4.4613e\text{-}28$), with Tukey's procedure confirming that all the pairwise differences are significant (*ps* < 0.001). We used the node classifications to calculate the average nodal strength of each connection across participants. Rich-club nodes have the highest strength (2.1801e+04 streamlines), followed by feeder nodes (1.1637e+04 streamlines) and finally peripheral nodes 5.1991e+03 streamlines). These differences are significant at a group average level ($F(2,99) = 60.5640$, $p = 8.5296e\text{-}18$), with post-hoc Tukey's tests confirming that all the pairwise comparisons were significant (*ps* < 0.001). Put simply, it seems that our classification of node types using the group-based consensus network has produced the distribution of nodal degree and strength we would expect, at least at a group average level.

Next we tested whether this holds at an individual level. Readers will remember that we are essentially combining connectomes we reconstructed across three tranches of neuroimaging data (Björnholm et al., 2017; Fonville et al., 2019; Lancaster et al., 2018). This inflates the risk that whilst this classification might work at a group level, it may be a poor account of node type at an individual subject level. For this reason we repeated the analysis above, but at an individual subject level. Every single subject shows the same significant pattern for node degree, with the *p* values ranging from $p = 0.0203$ to $p = 6.2795e\text{-}15$, with a mean of $p = 1.3962e\text{-}04$. The post-hoc Tukey's tests reveal that for 629/685 participants the rich-club nodes have a higher degree than the feeder nodes ($ps < 0.05$), this is 100% of the participants from the first tranche of data, 85% from the second tranche of data, and 92% from the third tranche of data. For every participant, the rich-club nodes have a higher degree than the peripheral nodes ($ps < 0.05$) (i.e., 100% across all three sets of data). For 492/685 the feeder nodes have a significantly higher node degree than the peripheral nodes ($ps < 0.05$), this is only 16% of the participants from the first tranche of data, 86% from the second and 89% from the third. In short, node degree differs across node type both at a group level and, to a large extent, at an individual subject level.

The above within-subject comparison was repeated for the nodal strength values. At a within-subject level, 682/685 participants show the same significant effect as was apparent at the group level, with *p* values ranging from $p = 0.1138$ to $p = 3.5246e\text{-}16$, with a mean of $p = 0.0014$. The post-hoc Tukey's test reveal that for 645/685 there is a significant difference in strength between the rich-club nodes and the feeder nodes ($ps < 0.05$), which is 88% from tranche one, 95% from tranche two, and 96% of participants from tranche three, all at $ps < 0.05$. For 681/685 participants there is a significant difference in strength between the rich-club and peripheral nodes ($ps < 0.05$), which is 98% from tranche one, 100% from tranche two, and 99% from tranche three, all at $ps < 0.05$. For 386/685 there is a significant difference in nodal strength between feeder and peripheral nodes ($ps < 0.05$), which is 10% of tranche one, 40% of tranche two and 85% of tranche three, all at $ps < 0.05$. In short, node strength largely follows a similar patter to node degree.

In summary, at a group level the categorisation of node type (rich-club, feeder, and peripheral) strongly mirrors the node degree and nodal strength pattern we would expect. Even though the dataset is made up of three sets of connectomes, this group level classification of node type works relatively well at an individual subject level. There is a very clear and consistent distinction between both the nodal degree and nodal strength between the rich-club and feeder nodes, for between 85-100% of participants, and between rich-club and peripheral nodes for between 98-100% of participants. However, at an individual subject level the distinction between feeder and peripheral nodes is patchier. Whilst still present in an overall majority of participants, this distinction appears to be weak in the first tranche of data (Fonville et al., 2019).

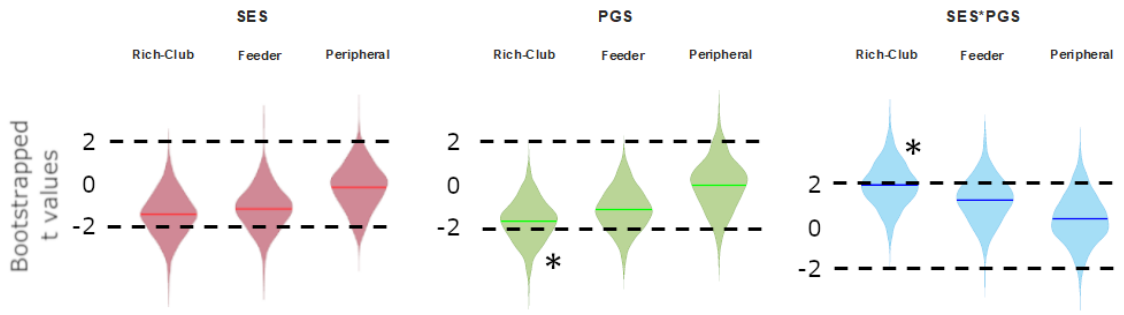
5.3.2.3 Comparing Strength Across Node Types

Having double checked that our nodal classification works well at a group, and to a large extent, at an individual subject level, we then proceeded to explore whether and how different node types differed according to SES, PGSs, and their interaction. For each participant, we calculated the mean strength from their individual proportion thresholded connectome. This was done for all three node types (i.e., rich-club, feeder, and peripheral). The only

effects that approached significance were for the rich-club nodes, with SES: $t(678) = -1.4647$, $p = 0.1435$; PGS: $t(678) = -1.7468$, $p = 0.081$; PGS*SES: $t(678) = 1.9537$, $p = 0.051$; Age: $t(678) = 0.2657$, $p = 0.7906$; Sex: $t(678) = 1.4204$, $p = 0.1559$; Study: $t(678) = 0.5421$, $p = 0.5879$. See Figure 5.5 for an illustration of how strength of relationships varied across node types for SES, PGSs, and the PGS*SES interaction.

Figure 5.5

Strength of Relationships Across Node Types for SES, PGS, and the Interaction Between SES and PGS



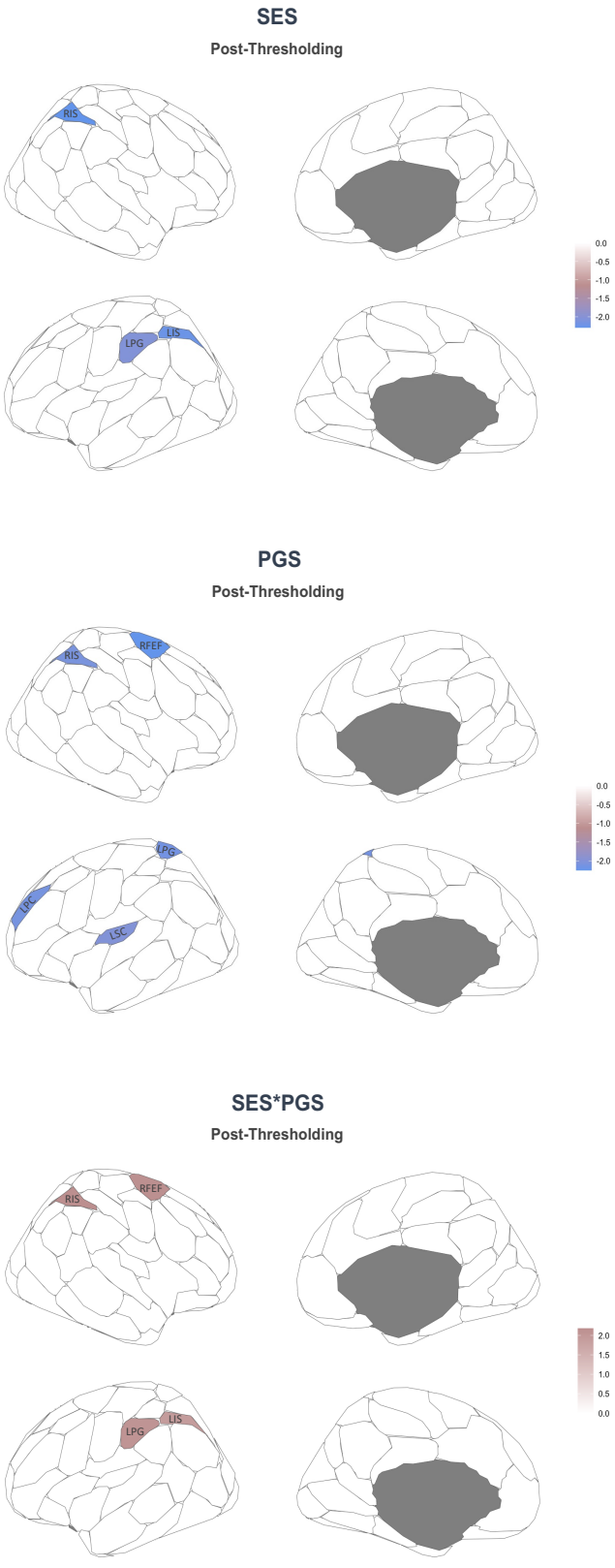
Note. Violin plots illustrate bootstrapped samples for SES, PGS, and the interaction between SES and PGS. The strength of the relationship can be seen across rich-club, feeder, and peripheral nodes. The '*' corresponds to trend level effects for the rich-club nodes.

5.3.2.4 Looping the Model Across Nodes in the Connectome

Using node strength as the outcome, we obtained a *t* value for *each node*, per measure in the regression. This was permuted with 1000 shuffles of the response variable (i.e., shuffling the node strength measure) to produce distributions of *t* which we then used to threshold each parcel. This provided us with a way of testing whether these effects would have occurred by chance, controlling for multiple comparisons. This produced three 100 value vectors which were plotted over the 100-node Schaefer parcellation employed in **Chapter 4**. This allowed us to assess the alignment of node strength across network topology boundaries. Figure 5.6 illustrates loadings overlaid on 100-node Schaefer parcellation for each GLM predictors following the permutation thresholding (SES, PGSs, and the interaction between PGSs and SES). For SES, significant effects were present for the left postcentral gyrus, and both the left and right interparietal sulcus. For PGSs, significant effects were present for the left somatomotor cortex, left postcentral gyrus, left prefrontal cortex, right frontal eye field and the right intraparietal sulcus. Lastly, for the interaction between SES and PGSs there were significant effects for the postcentral gyrus, the left and right intraparietal sulcus, and the right frontal eye field.

Figure 5.6

Thresholded Node-Wise Effects Overlaid on 100-Node Schaefer Parcellation



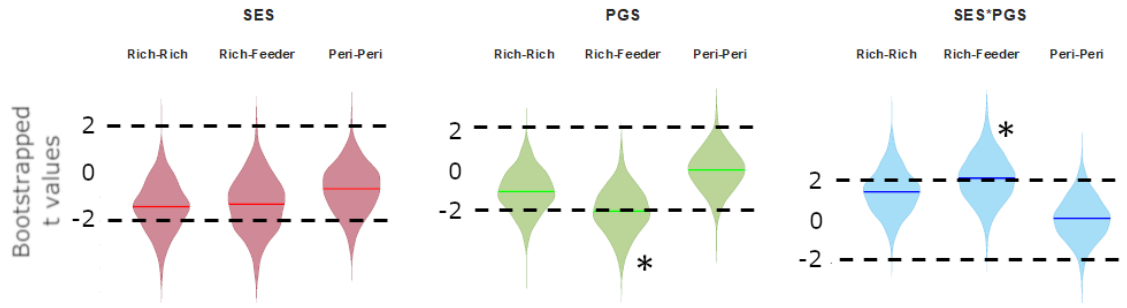
Note. Scales denote unstandardised loadings. Loadings range from positive to negative, and are represented by the colours pink and blue, respectively. *LPG* Left postcentral gyrus; *LIS* Left interparietal sulcus; *RIS* Right interparietal sulcus; *LSC* Left somatomotor cortex; *LPC* Left prefrontal cortex; *RFEF* Right frontal eye field.

5.3.2.5 Comparing Strength Across Connection Types

For each participant, we calculated the strength of their rich-rich, rich-feeder, and peripheral connections. Significant effects were only on the rich-feeder connections, with SES: $t(678) = -1.2822$, $p = 0.200$; PGS: $t(678) = -2.0131$, $p = 0.0445$; PGS*SES: $t(678) = 2.0266$, $p = 0.043$; Age: $t(678) = 0.9553$, $p = 0.3398$; Sex: $t(678) = 2.5091$, $p = 0.0123$; Study: $t(678) = 0.1715$, $p = 0.8638$. Figure 5.7 illustrates the strength of relationships across connection types for SES, PGSs, and the PGS*SES interaction. The significant interaction term is tricky to interpret. Because it is positive we interpreted it as being an additive interaction, that is, the effect of SES is higher when PGS is also higher. We tested this by splitting the dataset into two halves – those with high versus low PGS scores – and repeating the GLM in each half. The impact of SES on connection strength is significant in children with a higher PGS: SES: $t(328) = 2.445$, $p = 0.0150$; Age: $t(328)=1.6573$, $p = 0.0984$; Sex: $t(328)=1.3651$, $p = 0.1732$; Study: $t(328) = -1.1038$, $p = 0.2705$. Whereas SES has no significant impact on connection strength in children with a lower PGS: SES: $t(347) = 0.1412$, $p = 0.8878$; Age: $t(347) = -0.5474$, $p = 0.5845$; Sex: $t(347) = 2.2972$, $p = 0.0222$; Study: $t(347) = 1.2380$, $p = 0.2166$. In other words, the impact of SES on feeder connections seems to be strongest in children with a higher PGS. (We also tried to break the interaction down by splitting the sample by SES, however the PGS effect is not significant in its own right in either half of the split, so it does not help much with the interpretation.)

Figure 5.7

Strength of Relationships Across Connection Types for SES, PGS, and the Interaction Between SES and PGS



Note. *Peri* Peripheral. Violin plots illustrate bootstrapped samples for SES, PGS, and the interaction between SES and PGS. The strength of the relationship across rich-rich, rich-feeder, and peripheral-peripheral connections. The '*' corresponds to the significant effects for the rich-feeder connections.

5.3.2.6 Assessing Genetic Similarity Amongst Certain Types of Connections

In this final analysis, we wanted to explore whether the connection types mirrored genetic similarity. To do this we used post-mortem samples. Regional microarray expression data were provided from the AHBA (http://human.brain-map.org/; Hawrylycz et al., 2012), and comprised six post-mortem brains from donors with no history of neurological or neuropsychiatric conditions (1 female, ages 24.0-57.0, 42.50 +/- 13.38). Only two of the six brains contained right hemispheric data, and as such, only left hemispheric data were included in analyses. Data were processed with the abagen toolbox (version 0.1.1; https://github.com/rmarkello/abagen) using a 100-region volumetric atlas in Montreal Neurological Institute (MNI) space. Microarray probes were reannotated using data made available by Arnatkevičiūtė and colleagues (2019). Probes without parallel valid Entrez ID were discarded. Probes were subsequently filtered on the basis of expression intensity comparative to background noise (Quackenbush, 2002). Probes where expression measures failed to exceed the background in >50% of samples were discarded. Where the expression of the same gene was indexed against multiple probes, the probe with the most consistent pattern of regional expression to RNA-seq data was selected. Put simply, we calculated the Spearman's rank correlation between each probes' microarray expression and RNA-seq expression data of the corresponding gene, and the probe with the highest correspondence was selected. Here, regions correspond to the structural designations provided in the ontology from the AHBA.

The MNI coordinates of tissue samples were updated to those generated via non-linear registration using the Advanced Normalization Tools (ANTs; https://github.com/chrisfilo/alleninf). Samples were assigned to brain regions in the provided atlas if their MNI coordinates were within 2 mm of a given parcel. Tissue samples not aligned with a brain region in the atlas were discarded. Inter-subject variation was addressed by normalizing tissue sample expression values across genes using a robust sigmoid function (Fulcher et al., 2013):

$$x\_norm = 1/(1 + \exp(-(x-\langle x\rangle)/IQR\_x))$$

where $\langle x\rangle$ is the median and IQR_x is the normalized interquartile range of the expression of a single tissue sample across genes. Normalized expression values were then rescaled to the unit interval:

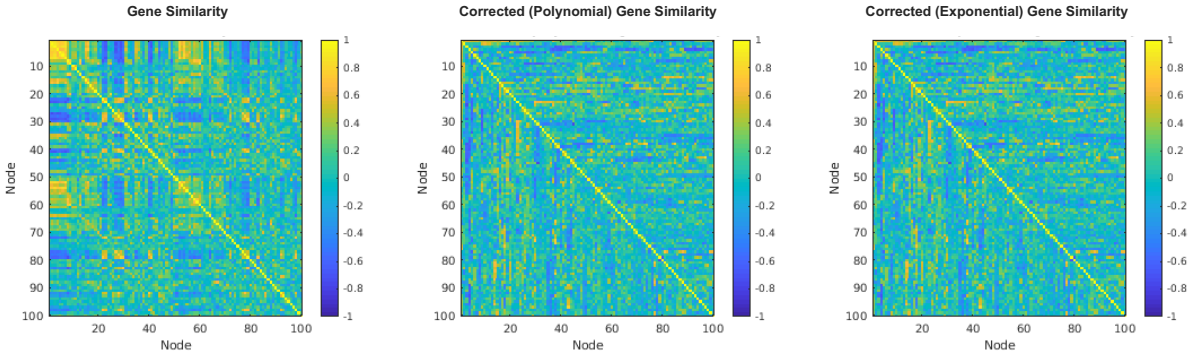
$$x\_scaled = (x\_norm - \min(x\_norm))/(\max(x\_norm) - \min(x\_norm))$$

Gene expression values were then normalized across tissue samples using an identical procedure. Samples assigned to the same brain region were averaged separately for each donor and then across donors, yielding a regional expression matrix. The fully pre-processed gene data comprised a 50 by 13,562 matrix of microarray array gene expression data. We could then use these data to calculate the similarity of gene expression across our 50 nodes using a Pearson correlation. The end result is a 100 x 100 adjacency matrix showing the relative similarity in gene expression across brain regions in our parcellation. We could then use this in downstream analyses to test whether or how differences in gene expression similarity mirror structural connectivity. Each analysis was done twice, the first time using the basic gene similarity matrix. We also regressed Euclidean distance from this using a third order polynomial to create a distance-controlled gene expression similarity adjacency matrix (Figure 5.8). This is important because some have argued (Krienen et al., 2016; Richiardi et al., 2015;

Vértes et al., 2016) that expression similarity is highly related to distance, and thus, because distance and connection strength are strongly related, distance could confound the relationship between gene similarity and connection strength.

Figure 5.8

Matrices Displaying Basic, Corrected Polynomial, and Exponential Gene Similarity



Note. Pearson correlation values for node-by-node similarities in gene expression.

The first analysis simply tested whether connection type predicts gene expression. We calculated the gene expression for each connection and then compared them for the rich-rich, rich-feeder, and peripheral connections using a one-way ANOVA. These differed significantly ($F(2,247) = 4.65$, $p = 0.0104$), but differences were in the opposite direction to that expected, with the peripheral connections showing the strongest absolute similarity ($M = 0.4271$) relative to the rich-feeder connections ($M = 0.3719$) and rich-rich connections ($M = 0.2787$). Post-hoc Tukey's test show that the peripheral connections are significantly more similar than the rich-rich connections ($p = 0.0092$), but not the rich-feeder connections ($p = 0.1747$). Rich-rich and rich-feeder connections do not differ significantly ($p = 0.1403$). This surprising result is almost certainly the result of distance confounds – put simply the peripheral connections span a shorter anatomical distance, and that is why their gene expression is more similar. When we repeat the analysis with the distance-controlled expression similarity data the effect goes away entirely ($F(2,247) = 0.16$, $p = 0.8524$). Indeed, if we were to just compare the different connection types on the basis of distance (rather than gene expression similarity) then the connection types differ significantly ($F(2,247) = 18.21$, $p = 4.2187\text{e-}08$), with rich-rich connections being significantly longer than rich-feeder connections ($p = 0.0135$), and relative to peripheral connections ($p < 0.001$), and rich-feeder connections significantly longer than peripheral connections ($p < 0.001$). Generally speaking, the rich-rich connections span a greater distance than the rich-feeder connections, and in turn the peripheral connections.

In the second analysis using the gene expression data, we tested whether there is any relationship between expression similarity and the impact of SES, PGSs or their interaction on connection strength. To do this, we used the same GLM used in previous sections, with SES, PGS, PGS*SES, age, sex, and study as predictors, to identify the relationship between our regressors of interest and the strength of each connection. Then, with connection-wise beta values we could conduct a second-level analysis, testing whether the strength of these betas varies

depending upon the expression similarity of the nodes the connection spans. Or in other words, does the impact of PGSs or SES on a given connection depend upon its relative genetic similarity? In doing this, we fit both standard linear and quadratic relationships. We did this because the above connection type analysis indicated that mid-range rich-feeder connections seem to show the effects of these regressors most strongly. Both the linear and quadratic term for the SES regressor were significant ($t(245) = 1.9765$, $p = 0.0492$; $t(245) = 2.7066$, $p = 0.0073$, respectively). The quadratic ($t(246) = 4.5485$, $p = 8.5021e\text{-}06$) but not the linear term ($t(246) = -0.8376$, $p = 0.4031$) was significant for the PGS regressor. Neither the linear nor quadratic effect were significant for the PGS*SES interaction: quadratic ($t(245) = 1.3498$, $p = 0.1783$); linear term ($t(245) = -1.5207$, $p = 0.1296$). Importantly, some of these effects still hold when controlling for geometric distance. When repeating the analysis with the distance-controlled gene expression data there are no significant effects for SES: linear ($t(245) = -1.6817$, $p = 0.0939$); quadratic effect ($t = -1.2815$, $p = 0.2012$). However, for the association with PGS there is still a significant quadratic relationship ($t(246) = 3.3978$, $p < 0.001$) but no linear effect ($t = -0.8012$, $p = 0.4238$). For the PGS*SES regressor there is still no significant quadratic effect ($t(245) = 1.5583$, $p = 0.1205$) or linear effect ($t(246) = -1.3829$, $p = 0.1678$). In summary, the effect of PGS on connection strength seems to vary according to the gene expression similarity of the nodes that connection spans, and this relationship is best accounted for by a quadratic term.

5.4 DISCUSSION

The present chapter sought to build on its preceding chapter by testing the interrelationships between genetic propensity, socioeconomic status, cognitive ability, and features of the structural connectome. First, we tested whether SES and PGSs interact to predict cognition. Second, we tested whether specific node-wise or connection-wise features of the structural connectome are significantly predicted by this same set of regressors. Third, we tested whether there is a relationship between the spatial patterning of gene expression and the association between these regressors and connection strength. To do this, we carried forward individual level PGSs for cognitive ability for each participant, the occupation and education measures of SES collected when participants were 8 months old, and connectomes from DTI data acquired an average of 20.34 years later ($SD = 1.47$). To establish the topological role of different nodes and connections in the structural connectome, we created a group distance-based consensus network. This binary model provides a group average result that is not biased towards short-range connections (Betzel et al., 2019). With this network we could establish the topological role of different nodes, by establishing the rich-club, defined as the set of nodes that are disproportionately well connected to each other. This was done using random null models to control for overall node degree. Once we had established our rich-club within the group network we could identify feeder nodes (i.e., those that connect to, but are not themselves, rich-club members) and peripheral nodes. This information allowed us to establish rich-rich connections, rich-feeder connections and peripheral connections. We used GLMs to assess the capacity of SES, PGSs, and their interaction to predict cognition, and node and connection types.

There are several key findings. First, both SES and PGSs for cognitive ability were predictive of cognition. SES was seen to have greater predictive capacity compared to PGSs, but nevertheless, an effect was seen across both variables. SES and PGSs further *interacted* to predict cognitive ability, whereby the effect of one was dependent

on the other. The predictive potential of SES was reduced when PGSs were considered. PGSs, and the interaction between SES and PGSs predicted the mean strength of rich-club node types, but not the other two node types. Although it is important to note that this is only a trend-level effect. The reason for this trend is likely because these variables influence the feeder connections, that is, they influence the connections that pass information to and from the rich-club, rather than those within the rich-club itself. These rich-feeder connections show significant PGS and PGS*SES effects. Finally, we discovered that these relationships overlap with post-mortem gene expression data, albeit not linearly. The PGSs seem to be most strongly associated with connections that span nodes with a *moderate* degree of genetic similarity.

5.4.1 SES AND PGS INTERACT TO INFLUENCE COGNITION

As anticipated given the results of **Chapter 2** and **Chapter 3**, SES and PGSs for cognitive ability independently predicted cognitive ability. These results are similar to previous research findings, which have demonstrated independent associations between SES and PGSs for educational attainment on cognitive ability (Judd et al., 2020). Unique to this study, we further explored whether an interaction exists between SES, PGSs, and cognitive ability. Crucially, we found a significant interaction between PGSs and SES. When one measure gets higher, the impact of the other reduces. In this way, at high SES levels, the impact of PGS is reduced, relative to at low SES levels. The capacity of SES and PGSs to influence developmental outcomes weighs heavily on the nature of their circumstance. In the General Discussion we will provide a more in depth theoretical account of why this might be, but regardless, the presence of this under-additive interaction underscores the importance of policy which aims to improve early developmental environment conditions, such as by introducing more cognitively enriching environments with a decreased threat of reduced protection and support (Rosen et al., 2020; Sheridan & McLaughlin, 2014). It is of interest to note that whilst both SES and PGSs were predictive of cognitive ability, the predictive capacity was greater for SES. However, when PGSs are in the same model as SES, the strength of SES as a standalone predictor drops by around half. The implication of this finding is that much of the variance captured by SES alone is also being captured by PGSs, but the SES-by-PGS interaction remains a significant stand-alone predictor. The finding that the interaction between PGS*SES operates to substantially reduce the stand-alone effect of SES suggests that the SES measures are, in part, reflective of what is being captured by the PGSs (**Chapter 4**). A point that will be returned to in the final chapter of this thesis.

5.4.2 SES AND PGS INTERACT TO INFLUENCE NODE TYPE

Why were effects of PGS and the SES-by-PGS interaction only seen in the rich-club? Here, we showed that PGS and PGS*SES interact for nodal strength in the rich-club only. Rich-club topology is argued to be essential for coherent neural dynamics and brain functioning (van den Heuvel et al., 2012), which is closely related to cognitive ability (Siugzdaite et al., 2020). The genome is further posited to play a substantial role in the formation of the connectome, and in particular, rich-club hubs (Arnatkevičiūtė et al., 2021b). This may explain why our PGSs appears to be related to the strength of the rich-club – albeit only at trend level. Perhaps a more novel finding is the association between the SES-by-PGS interaction and rich-club strength. If we remind ourselves of the literature discussed in **Chapter 1** regarding SES, the pace of brain development, and the development of rich-

club hubs, we can build a clearer mechanistic picture of what these results may indicate. For example, SES is argued to be associated with the pace of brain development, with lower SES linked to accelerated brain maturation and high SES linked with protracted maturation (Tooley et al., 2021, 2022). The protracted maturation of the brain enables the robust development of rich-clubs, which enhance their strength of connections during the slow process of neurodevelopment (Vértes & Bullmore, 2015). The current study shows however, that much of this SES effect exists as an *interaction with* PGSs, and in this case this interaction appears to be related to the strength of rich-club nodes. Why is the interaction additive? One simple explanation is that these two variables ultimately form a kind of 'virtuous' cycle, where the genes are actually coding for skills that shape the social environment, which are in turn shared with parents both in terms of shared genetic background *and* the co-created environment. As one increases, it enhances the relevance of the other - as the parent creates a social environment, the child's capacity to engage in that environment becomes more relevant for development. This notion also holds relevance for aspects of the wider family environment (as discussed in **Chapter 4**), whereby parental mental health, sibling mental health, family dynamics, and community support may further contribute to how the social environment is shaped, and thereby influence the relevance for a child's capacity to engage in that environment.

When plotted on regions of the brain and connectome, our results implicate the frontoparietal cortex, with the majority of significant nodes located in this region – including the left frontal eye-field, the bilateral intra-parietal sulcus and the left prefrontal cortex. This distribution is somewhat reminiscent of the results in **Chapter 4**. The frontoparietal cortex houses the multiple-demand (MD) network, and in particular, the inferior frontal sulcus, anterior insula and frontal operculum, pre-supplementary motor area, dorsal anterior cingulate, prefrontal cortex, frontal eye field, and the intraparietal sulcus (Duncan, 2010). The MD network is a commonly demonstrated pattern of activity in the frontal and parietal regions of the brain, which are frequently linked with a variety of cognitive demands (e.g., task encoding, goal setting, response inhibition, control of attentional bias, vocabulary learning, general cognitive *g* factor, and is activated during tests of fluid intelligence (Crittenden et al., 2016; Duncan, 2010; Sliwinska et al., 2017)). Given the role of this network in executive functioning, and the capacity of SES, PGSs for cognitive ability, and their interaction to predict its development, these findings shed light on the associations seen in the literature and within the chapters of this thesis, that is, that SES and PGSs influence developmental outcomes such as cognitive ability and educational attainment. Here, we provide a potential mechanistic explanation for these associations. However, this mechanistic link is better detailed as we move on to examine relationships with connection type.

5.4.3 SES AND PGS INTERACT TO INFLUENCE CONNECTION TYPE

Why is it the feeder connections that show significant effects of PGSs and their interaction with SES? One plausible reason is because the rich-club connections are so strongly genetically programmed, as illustrated by the twin study carried out by Arnatkevičiūtė and colleagues (2021b). This strong genetic programming could result in minimal variation in rich-rich connections. This would explain the lack of relationship between these and our predictors. In this way, the feeder connections, which still play a critically important topological role but are rather more variable and amenable due to their lesser genetic control, may be more likely to be influenced by PGS and PGS*SES interactions. The analysis involving the gene expression data tell a subtly different, but potentially

complementary, story. We found that the PGS term is strongest for connections that have a medium degree of gene expression similarity. One possibility is that gene similarity is a proxy for a zone of malleability or variability. That is, connections that are very strongly genetically programmed and emerge extremely early in development, may have less scope for variability. Whereas there is a zone in which genetic expression profiles are still important but in a way that allows for flexibility and adaptability. This is perhaps why we see the PGSs associating with those connections most strongly. This is an idea we return to in the final chapter.

A final piece of the puzzle is the direction of these effects. For the nodal strength and the connection type findings, it appears that PGSs are negatively linked with either the aggregated or node-wise values. Why might that be, when, generally speaking, the PLS analysis in **Chapter 4** found positive relationships? The key difference, relative to **Chapter 4**, is that in **Chapter 5** we are also modelling the PGS-by-SES interaction. By including this in our model, the SES and PGS standalone measures become metrics that capture the *unique* contribution of their respective domains. The positive interaction between SES and PGS on nodal or connection strength is more readily interpreted because of our follow-up analysis on the connection type data. When PGS is high, the SES measure is more strongly associated with the strength of feeder connections, whereas when PGS is low, there is no relationship between SES and the strength of feeder connections. In other words, when children have a strong genetic propensity for high cognitive ability, certain aspects of their brain organisation are more sensitive to the environment. In our case, it appears to be the strength of the connections that feed into the rich-club, rather than the strength of the connections within the rich-club itself. Returning to the explanation above, regarding genetics and co-created environments, one possibility is that these form a mutually reinforcing mechanism that shapes the strength of connections into the rich-club. In addition, there was a significant effect of sex that was seen when comparing strength across connection types. Whilst significant sex effects were found, this may have been attributable to differences in study samples across the three separate tranches of neuroimaging data. For example, readers will remember that in one such sub-study (Björnholm et al., 2017), 100% of the sample were male, and this sub-study formed the largest portion of our total sample (n = 513).

5.4.4 LIMITATIONS AND FUTURE DIRECTIONS

A clear limitation in this chapter's analyses come from the issue of separate tranches of data. This introduced a number of issues, likely in part due to the different recruitment strategies, but also possibly because of small changes in scanner protocol. Correspondingly, the node type sanity checks carried out to confirm expected distinction between node strength and degree for rich-club, feeder, and peripheral nodes, showed the data from tranche one to have weaker distinctions between the feeder and peripheral node types. Readers may remember that tranche one neuroimaging data were acquired as part of a psychosis study, with 65% of the sample being female (Fonville et al., 2019). In contrast, tranche three neuroimaging data were acquired as part of a testosterone study, and as such, 100% of the sample were male (Björnholm et al., 2017). Future research could explore this further to better understand these findings by considering sex differences and acquiring neuroimaging data from one cohesive cohort, ideally with a single set of scanner protocols. An alternative might be to pursue different harmonisation strategies. However this would require harmonising raw connectomes, which as we will outline in the final chapter, is very difficult.

Another fundamental limitation pertains to sample size and recruitment variability. Whilst the ALSPAC acquired data from several thousand participants, once we filtered for the data types required for these analyses, we were left with a sample size of n = 685. A sample of this size is sufficient for research of this kind; however, it is possible that the effects derived from this relatively small sample may be driven by variability within the sample itself, and therefore may not translate to other populations (Marek et al., 2022; Poldrack et al., 2017). For example, within-sample variability can lead to inflated and unpredictable associations between neuroimaging and environmental data types (Marek et al., 2022). To further assess whether this is the case here, future research should aim to obtain a larger sample and replicate analyses detailed here. An additional note worth considering, is that here we have considered how SES and PGSs interact to influence measures of cognitive ability at age 8 years, as well as features of the structural connectome between the ages of 18-24. As such, caution should be made when making inferences between the results of these separate analyses. The interaction between SES and PGSs on these outcomes may, and likely do, operate differentially across the lifespan. Future research should aim to collect these data types at similar timepoints across the lifespan, as doing so would enable a more thorough understanding of how these multifactorial interactions operate to influence neurodevelopment.

5.4.5 CONCLUSION

In conclusion, by building on the results in **Chapter 4**, the current study demonstrates that SES and PGSs both independently influence cognitive ability, and further interact to influence cognition. The association between cognition and SES drops when you consider PGS in the same model. The significant interaction between these terms is because children with higher SES have a reduced effect of polygenic influence, relative to low SES children. By identifying a rich-club framework across the connectomes in our sample, we further identified the role of PGSs and their interaction in shaping specific features of the connectome. We showed that PGSs, and the interaction between SES and PGSs, weakly predict the strength of rich-club nodes, but these effects are significant for rich-feeder *connections*. Lastly, by enlisting transcriptomic data from the AHBA, we describe the quadratic role of the genome in shaping these specific features of the connectome, with PGSs strongest for connections spanning nodes with a moderate degree of genetic similarity. Next, a General Discussion follows which aims to remind readers of the scope and central aims of this thesis, provide a brief overview of the empirical findings, highlight the main themes derived from its chapters, and discuss its limitations and future directions.

6 GENERAL DISCUSSION

6.1 SCOPE AND CENTRAL AIMS OF THE THESIS

This thesis is rooted in developmental science, seeking to integrate different forms of data to better understand how the early life environment and the genome are associated with individual variability across developmental outcomes and the structural organisation of the brain. Using a diverse range of methods and modelling the brain as a system, I endeavoured to address the following aims across four empirical chapters using data from the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013; Fraser et al., 2013). First, I wanted to know whether compounding environmental factors interact longitudinally to predict developmental outcomes. Second, I aimed to test the validity, efficacy, and generalisability of polygenic scores (PGSs) for cognitive ability and educational attainment, and their utility for downstream analyses. Third, I sought to combine measures of the early life environment by way of socioeconomic status (SES), the genome by virtue of PGSs for cognitive ability, and connectomic data to determine how the early life environment and an individual's genome may interact at the level of structural brain connectivity. Lastly, I wanted to assess how this interaction operates to influence cognitive ability, and explore in more detail how the socioeconomic environment and the genome can influence distinct topologically meaningful features of the structural connectome.

6.2 EMPIRICAL FINDINGS – A BRIEF SUMMARY

6.2.1 CHAPTER TWO

In **Chapter 2** I used structural equation modelling (SEM) to assess whether maternal mental health longitudinally mediates associations between early SES and key developmental outcomes (i.e., child mental health and cognitive ability). I further sought to explore whether there are sensitive developmental periods, wherein the mediating effect of maternal mental health is particularly pronounced. My results highlighted domain specificity, with SES being differentially associated with measures of mental health and cognitive ability. For example, SES was negatively associated with child mental health, and positively associated with cognitive ability. Maternal mental health partially mediated both of these associations, with the association between SES and both developmental outcomes significantly reduced upon taking maternal mental health into consideration. A second key finding was that the mediating effect of maternal mental health predominantly occurred during the first year of life.

6.2.2 CHAPTER THREE

Chapter 3 drew upon genome-wide association studies (GWASs) for cognitive ability and educational attainment to compute PGSs for these behavioural phenotypes, and assessed their capacity to correlate with measures of cognitive ability and educational attainment during meaningful periods of development. The end goal being to use these PGSs in downstream analyses in the proceeding empirical chapters. Whilst I demonstrated the capacity to generate meaningful PGSs for the ALSPAC cohort by meticulously following appropriate protocols for PGS computation, differences emerged in the capacity of the resulting PGSs to correlate with their intended phenotypic behavioural measures. PGSs for cognitive ability accounted for a substantially larger portion of the variance in cognitive ability compared to the PGSs for educational attainment and their respective outcome measure of educational attainment. Importantly, these PGSs are not specific - each phenotype can be predicted equally well by either PGS. There was a substantially smaller number of participants with educational attainment data available. As such, only the PGSs for cognitive ability were taken forward for subsequent analyses to reduce the likelihood of inflated and unpredictable associations between these data types due to small sample size (Marek et al., 2022).

6.2.3 CHAPTER FOUR

Building on the results from **Chapter 2** and **Chapter 3**, **Chapter 4** incorporated neuroimaging data to explore how measures of early SES, PGSs for cognitive ability, and structural brain connectivity are related to one another. Specifically, I wanted to know how these multifaceted data types are associated with both global and local features of the structural connectome, and whether deconstructed aspects of SES and PGSs have shared or distinct contributions to the organisation of the brain. Utilising graph theory metrics and employing partial least squares (PLS) regression analysis, I showed that both the genome and early child environment influence the structure of the brain across at least three local metrics of network connectivity (i.e., node strength, degree, and clustering coefficient). This influence was shared between aspects of the exogenous and endogenous measures included in the analysis, with aspects of SES (i.e., maternal occupation and parental education) mapping onto PGSs for cognitive ability to influence the structural organisation of the brain. In contrast, other aspects of SES (i.e., difficulty affording food and housing) consistently displayed negative loadings for these metrics. Readers may remember the issues with interpreting the second order components in dimensionality reduction methods like PLS – this does not mean that these financial difficulty measures are negatively associated with the response variables in absolute terms, but rather that they represent distinct variance relative to the other aspects of SES with respect to this component. Local node strength played a particularly important role in these associations, likely given the weighted aspects of connectivity captured by this metric (the other measures can all be calculated from binary connectomes). As such, this metric was taken forward for subsequent analyses.

6.2.4 CHAPTER FIVE

Building on its preceding chapters, **Chapter 5** employed generalised linear modelling (GLM) to consider how measures of early SES and PGSs for cognitive ability are uniquely associated with developmental outcomes for cognitive ability, and how this interaction relates to the structural organisation of the brain. SES and PGSs for

cognitive ability predicted cognitive ability, with SES having greater predictive capacity compared to the PGSs. SES and PGSs further interacted to predict cognitive ability. It seems important that when PGSs and the PGS*SES interaction are included in the model, the SES effect drops in magnitude substantially. This may suggest the SES effects initially observed are, at least in part, reflective of what is being captured by the PGSs. The reason for the significant interaction term is because children with higher SES have a reduced association between PGS and cognition, relative to lower SES children. Moving onto the connectomics, PGS and the SES-by-PGS interaction seem to be weakly associated with the strength of rich-club nodes, and more robustly associated with the strength of the connections that feed into that rich-club. Looping the model over nodes highlighted areas in fronto-parietal cortex, which is perhaps not surprising given that this is where many rich-club nodes reside. These results were further leveraged with post-mortem transcriptomic data using the Allen Human Brain Atlas (AHBA). Whilst we could not replicate recent findings suggesting that the rich-club nodes have more similar gene expression profiles to one another, relative to that between other nodes (Arnatkevičiūtė et al., 2021b), we did unearth interesting findings on the relationship between expression similarity and the association with PGS. Put simply, the PGSs seem to most strongly be associated with connections with a moderate degree of genetic similarity.

Having given a brief summary of the main results, I will now proceed to provide theoretical integration of some of the main overarching themes that have emerged over the course of this thesis.

6.3 WHEN AND HOW DOES THE EARLY ENVIRONMENT INFLUENCE DEVELOPMENT?

6.3.1 SENSITIVE PERIODS FOR DEVELOPMENT

A prominent question in developmental research is whether there are particularly sensitive windows *when* the early environment is likely to have a more impactful role for developmental outcomes. As noted in **Chapter 2**, we know there are sensitive periods during early childhood development from a biophysiological perspective, with considerable architectural changes taking place in the brain during the first three years of life (Nelson III & Gabard-Durnam, 2020; Ouyang et al., 2019). There are sensitive periods during primary education between the ages of 5 and 11, when we can see the rapid development of cognitive abilities, with cognitive flexibility, goal setting, and information processing skills rapidly developing (Anderson, 2002; Spiegel et al., 2021; Van der Ven et al., 2012). Cognitive challenges and mental ill-health can also emerge during this time, with children of mothers with maternal depressive symptoms displaying lower cognitive scores around the age of 5, compared to children with non-symptomatic mothers (Fitzsimons et al., 2017; Liu et al., 2017).

In **Chapter 2** I found that the socioeconomic environment in the first year of life seems to be particularly important. But *why* is this first year of life so important? Literature on the first 1000 days of life illustrates that during this time neuronal proliferation, myelination, synaptogenesis, growth, and differentiation rapidly occur as the sulci and gyri take the brain from resembling an unconvoluted coffee bean to a complex walnut-like adult brain (Linnér & Almgren, 2020; Lloyd-Fox et al., 2017). Exposure to adverse events during this time may disrupt

these processes, leading to epigenetic changes with downstream consequences for health and development (Linnér & Almgren, 2020; Walker et al., 2007, 2011). Another key consideration is to consider how static SES data are, with SES being highly correlated across data collection waves in similar studies to the ALSPAC (Hanscombe et al., 2012). This is because the ingredients of SES, such as maternal education, occupation, or income, are relatively fixed across a child's lifetime. This is testament to the woefully poor social mobility within countries, such as the UK. This has likely worsened in the last decade, with most leading indicators suggesting regressive governmental policies have likely reduced support for families and narrowed the scope for social mobility (Joseph Rowntree Foundation, 2020). As a result, it is possible that these SES data may simply not have the granularity to pull out the differential effects that may exist over time. Correspondingly, some have argued for the removal of SES as a measure of early adversity, and instead advocate for directly indexing the early environment in terms of its opportunities for sociocognitive development (DeJoseph et al., 2022). My view is that this measure is still meaningful and useful, however, we need to be mindful of other factors it is capturing and, in turn, what mediators in the child's proximal environment might be important for understanding (and mitigating) its impact. More to the point, the position that SES should not be measured because it cannot be changed is itself rooted in an attitude that poverty and relative deprivation are inevitable. I would reject this attitude and position entirely. On the contrary, forward thinking governments worldwide have shown that this is not the case. Bold programmes, like the introduction of a universal basic income, can have a substantial cascading impact on families and children (Joseph Rowntree Foundation, 2021; Wilson & McDaid, 2021).

6.3.2 MEDIATING ROLE OF MATERNAL MENTAL HEALTH IN SES-OUTCOME ASSOCIATIONS

In **Chapter 2** I further addressed *how* the early environment influences development by considering the mediating role of maternal mental health in SES-outcome associations, and exploring the domain specificity of these associations. In my findings, maternal mental health partially mediated the association between SES and key developmental outcomes (i.e., child mental health and cognitive ability). So, why is maternal mental health relevant for these developmental outcomes? Maternal depression has been shown to influence a mother's cognitive processes, and is associated with reduced decision-making capacity, perception of social support, and self-esteem, and an increase in life-stressors (see Atif et al., 2015 for a review). This is likely to have downstream consequences for the early life environment and the level of support a child receives. For example, postnatal depression has been linked with early cessation of breastfeeding, reduced offspring gross and fine motor development, language development, and adverse influences on infant cognitive development (Ali et al., 2013). Ali and colleagues (2013) argued that these findings are linked, and likely to be, at least in part, the result of reduced mother-child interactions. In support of this notion, maternal depressive symptoms play a substantial role in the quality of mother-child interactions, with symptoms positively associated with less communication, sensitivity, affection, enjoyment, engagement, reciprocity, and higher rigidity in mothers, and less compliance, affection, engagement, and gentleness in children (Albright & Tamis-LeMonda, 2002). These findings hold regardless of the provision of play materials, organisation of the early environment, absence or presence of a partner, mother's IQ, or SES. Thus, highlighting the role of maternal mental health, and providing some indication

as to why it may be so important in mediating SES-outcome associations. For the avoidance of doubt, none of this is the fault of the mother, but rather of a systemic failing in mental health support and social care.

The analysis carried out in **Chapter 2** further highlighted the domain specificity of the mediating effect of maternal mental health, with much smaller effect sizes seen for its mediating role in SES-child mental health associations. In line with the dimensional account of adversity discussed in **Chapter 1**, which posits different types of adversity are causally associated with different types of outcomes, it is possible the household income aspects of our SES measure are less strongly associated with child mental health outcomes, as opposed to other types of adversity (McLaughlin et al., 2021; Sheridan & McLaughlin, 2014; Sheridan et al., 2020). Correspondingly, the mediating effect of maternal mental health on SES-child cognitive ability associations were more pronounced, and discussed in terms of the potential role of parental buffering in positively influencing children's emotional and stress reactivity profiles (Brown et al., 2020; Oppenheimer et al., 2016), and their cognitive ability, thereafter (Bell & Wolfe, 2004; Bell et al., 2019; Walle et al., 2022; Wass, 2018). It is possible the mediating role of maternal mental health had more of an effect on SES-cognition associations due to SES being an example of 'deprivation' within the dimensional account of adversity framework. Along these lines, SES would be expected to relate more strongly to cognitive outcomes, and, in plain language, there would be more of a relationship to mediate.

6.3.3 HETEROGENEITY ACROSS MEASURES OF SES

The scope of this thesis allowed for the identification of additional heterogeneity across specific aspects of SES. This was established in **Chapter 4**, which considered the deconstructed components of the SES measures used throughout the preceding chapters of this thesis. This was made possible through the use of PLS analysis (Wold et al., 1984), which allowed for the identification of a set of orthogonal factors across the SES, PGSs, and local and global measures of the structural connectome. Thereby allowing for the detection of which measures had the greatest predictive power, and highlighting the specificity of these relationships. Results from the PLS analyses in **Chapter 4** called attention to the important role of the *maternal occupation and parental education* aspects of SES for both the structural organisation of the brain, as well as the overall convergence between these measures and PGSs on local measures of the structural connectome. I showed that particular aspects of SES (i.e., maternal occupation and parental education) *and* PGSs for cognitive ability positively influence at least three local measures of brain organisation (i.e., node strength, degree, and clustering coefficient). Financial difficulty aspects of SES on the other hand, did not share this variance.

We considered why this heterogeneity between these aspects of SES exists in our data. One possibility being the genetic entanglement between these measures. In other words, it could be that the genetic scores themselves are somehow coding for downstream behaviours that relate more closely to a child's early social environment (Kong et al., 2018). However, it is also important to say that many other studies have found that occupation and education aspects of SES do appear to have the strongest relationships with developmental outcomes such as cognitive ability and educational attainment – in other words, you do not need the genetic data to pull out these measures of SES. For example, employing ordinary least squares regression in a Swedish cohort (n = 28,000) Erikson (2016)

found parental education and social class to better predict educational attainment compared to household fiscal earnings. With approximately one third of the effects to be transmitted by way of cognitive ability (Erikson, 2016). But why are occupation and education aspects of SES more important than pure material sources? Some have argued that whilst interrelated, these aspects of SES are inherently different. Along these lines, financial aspects of SES are argued to represent spending capacity, housing, medical access, and diet, whereas occupation and education aspects reflect skills required for acquiring positive social, psychology, and economical resources (Winkleby et al., 1992). It is also worth reminding readers of the questionable quality of the financial difficulty measures available for the ALSPAC cohort, which may not accurately capture household income, as will soon be discussed in the limitations portion of this chapter.

6.4 WHAT DO POLYGENIC SCORES REALLY MEASURE?

A worthwhile question raised by the results in **Chapter 3**, and echoed throughout **Chapter 4** and **Chapter 5**, is: *what are polygenic scores really measuring?* In **Chapter 3**, I demonstrated PGSs for one phenotype predict outcomes for another, with PGSs for cognitive ability predictive of cognitive ability, as well as educational attainment. Likewise, PGSs for educational attainment were predictive of both educational attainment and cognitive ability. Indeed, in a direct comparison both cognitive ability and educational attainment can be equally well predicted by either PGS. So, what are PGSs measuring?

Drawing on the literature on genetic p factors for psychopathology, it is possible the PGSs generated for this thesis are actually capturing a general dimension that encompasses aspects of both cognitive ability and educational attainment. For example, behavioural difficulties in childhood are typically phenotypically highly correlated. This has led some to argue that a general dimension of psychopathology exists, often referred to as a p factor (Allegrini et al., 2020; Caspi et al., 2014). Not dissimilar to the general intelligence, *g* factor, discussed in **Chapter 3** (Pat et al., 2022). Genetic analyses have lent support for the notion of a p factor (Allegrini et al., 2020; Caspi et al., 2014). For example, Allegrini and colleagues (2020) used twin data to assess genetic and environmental influences on p by considering various measures of behavioural difficulties in children between the ages of 7-16, as rated by children, parents, and teachers. Examples of questionnaire items include those pertaining to depressive traits, peer difficulties, and emotional difficulties. Longitudinal twin modelling was employed to assess the stability of genetic and environmental influences across timepoints. A genetic p factor was then calculated in an unrelated sample based on eight polygenic scores for various adult psychiatric disorders to assess how genetic predisposition to these disorders were related to the childhood p factor. The p factor was found to be highly heritable (50% - 60%), with behavioural difficulties correlating both phenotypically and genetically across ages and ratings from children, parents, and teachers. Along these lines, it is possible the PGSs generated for this thesis are capturing a general dimension for cognitive- and education-related skills and abilities.

In **Chapter 4** and **Chapter 5**, the influence of PGSs on brain structural organisation and developmental outcomes overlapped extensively with measures of SES. For example, PLS analyses in **Chapter 4** demonstrated shared prediction from PGSs for cognitive ability and features of SES (primarily maternal occupation and parental education) on local measures of structural brain organisation. **Chapter 5** additionally showed that SES and PGSs

interact in their prediction of cognitive ability, and that the relationship between SES and cognitive ability reduces substantially when you include PGSs in the model, implying that a large proportion of the variance in cognition that is captured by SES is also captured by the PGSs. Crucially, we further investigated the significant under-additive interaction. When SES is high the impact of PGS is smaller, relative to when SES is low. In our case, then, it seems that whatever the PGS is coding for, it seems to be particularly important when children are developing in lower SES environments. This speaks to an overlapping and nuanced relationship between SES and PGSs. Why are these features of SES and PGSs so closely related in how they shape developmental outcomes? There are a few plausible reasons why this might be the case. PGSs may be capturing aspects of a child's social environment which is co-created with their parents - this has been referred to as passive gene-environment correlations. In this way, the environments co-created with parents align with parental genotype, and thereby, the genotypes of their children.

Passive gene-environment correlations can heavily influence the capacity of PGSs to predict cognitive traits, with some suggesting SES operates to influence between-family prediction through passive gene-environment mechanisms (Selzam et al., 2019). For example, when comparing PGS predictions in unrelated and related children to identify different sources of prediction, Selzam and colleagues (2019) found prediction estimates for cognitive traits to be 60% greater between families than within. That is, until they controlled for SES, when much of this difference went away. This led the authors to conclude SES is a primary source of between-family prediction through gene-environment mechanisms. Similarly, SES itself is partly heritable, with twin studies estimating approximately 50% heritability (Branigan et al., 2013; Polderman et al., 2015). Occupation and education aspects of SES are also inherently entangled with polygenic propensity for cognitive ability (Plomin & Bergeman, 1991; Plomin & Viding, 2022). For example, a primary component of SES includes parental educational attainment, which as we saw in **Chapter 3**, is not only heritable but also highly correlated with cognitive ability (which is also heritable), and has close links with occupation (Allegrini et al., 2019; Okbay et al., 2022; von Stumm et al., 2020). In our case it seems that this genetic nurturing becomes increasingly important in lower SES households.

6.5 THE ENVIRONMENT, GENOME, AND CONNECTOMICS

Previous work had shown that a particular network of hubs, sometimes call rich-clubs, are particularly genetically programmed (Akarca et al., 2021; Arnatkevičiūtė et al., 2021b; Oldham et al., 2022). Evidence for this came from twin studies, with the connectivity of these hubs being most heavily related to heritability (Arnatkevičiūtė et al., 2021b). This previous study also leveraged post-mortem gene expression data to show that the connections between these hub nodes span regions with significantly stronger profiles of genetic similarity than elsewhere in the network. We did not replicate this finding, in part because we could not separate out the geometry of the network – the distances that exist within the network – from the gene expression similarity. This is perhaps due to parcellation differences between our study and the original. We did however unearth an interesting result – the PGS effects have a quadratic relationship with gene expression similarity. That is, they appear to be strongest at the mid-range of gene similarity, even when controlling for connection distance. This chimes with a previous finding in **Chapter 5**, that feeder connections are more associated with the PGS and SES*PGS interaction effects.

Our account is that rich-club nodes and their interconnections are indeed likely to be highly genetically programmed, but that PGSs and the early life environment shape *the inputs* to that network, rather than connectivity within the network itself. The rich-club is so crucial a hallmark of connectomes that it is preserved even in the face of relatively severe environmental adversities, such a pre-term or extremely pre-term birth (Gozdas et al., 2018). Instead, the population-level measures we captured with PGSs, and its interaction with SES, seem to be most closely related to feeder connections and connections with a moderate degree of genetic similarity. Why do these PGSs, and the interaction between PGSs and SES, shape these connections? It is possible this has something to do with the variants captured by the PGSs, and that within a broadly normative environment, the effect of these factors is around the *edge* of the rich-club, as opposed to within the rich-club itself. A crucial feature of the human brain is its capacity to adapt to its environmental niche (Johnson et al., 2015; Menary, 2014). One possible route to doing this could be via the variation of these feeder connections. Put simply, some aspects of brain organisation may be more 'free to vary' than others. The rich-club is so fundamental to network function that its connections are highly genetically programmed (Arnatkevičiūtė et al., 2021b) and disruptions are associated with more severe mental illness (Baldi et al., 2022; Zhao et al., 2017). Whereas the connections that feed to and from that network may be within a zone that they can vary according to common variants across the population and environmental experience, allowing the system to adapt without jeopardising overall network functionality. Specifically in our data we found additive PGS and SES interactions with the strength of these feeder connections. In simple terms, they form a positive manifold. Those with a higher PGS also show the biggest effect of SES. This is somewhat different to the under-additive interaction we observed in the cognitive outcome data. But here it is important to remember that we are looking at very different outcomes. The relationship between brain organisation and cognition is itself complex and non-linear. Demonstrating an under-additive interaction with the cognitive data does not preclude the possibility of a different set of gene-environment interactions operating at a brain level, not least because in the case of the ALSPAC the cognitive data were collected when the children were ~8 years old, whereas the neuroimaging data were acquired when participants were ~20 years old.

6.6 LIMITATIONS AND FUTURE DIRECTIONS

6.6.1 SAMPLE

All analyses carried out in this thesis employed data types from the ALSPAC cohort. There were limitations in these analyses on the basis of the ALSPAC sample demographic. These limitations remained a theme throughout the empirical chapters of this thesis. As noted throughout this thesis, the ALSPAC cohort are relatively affluent and predominantly White. For example, of the mothers who participated in the ALSPAC, 79.1% lived in owner-occupier accommodation, 90.8% had a car, 79.4% were married, 2.2% were non-White, and 42.6% of mothers were educated to an A level or above (Fraser et al., 2013). This is problematic, as this sample is not representative of the UK population. Given this thesis' scope to explore the influence of the early life environment by way of the socioeconomic environment on cognition and neural developmental outcomes, this limits the generalisability of the findings discussed. The affluent nature of this sample may have also contributed to the counterintuitive findings that appeared in **Chapter 2**. For example, in **Chapter 2**, we saw SES to be negatively associated with

child mental health, with higher SES being associated with poorer child mental health, and vice versa. We considered why this might be the case by drawing on the literature exploring the manifestation of higher anxiety and depression levels in children from affluent backgrounds due to parental pressures and intensive schedules (Luthar, 2003; Luthar & Becker, 2002; Parenteau et al., 2020). Still, this finding suggests that the population demographic of the ALSPAC cohort may be contributing to the results in ways that are not always anticipated. Obtaining data from a more representative cohort would provide clarification on these results and improve the generalisability of the research findings. One such cohort is that of the Adolescent Brain Cognitive Development (ABCD; https://abcdstudy.org/about/) Study. This ongoing study is currently in the process of obtaining biological and behavioural data from adolescence into early adulthood. Although the ABCD study currently lacks the truly prospective longitudinal nature of the ALPSAC, it would provide a great starting point to follow-up some of the results in this thesis.

6.6.2 RECRUITMENT BIASES IN NEUROIMAGING

There were also limitations by virtue of recruitment biases with neuroimaging data acquisition. The ALSPAC neuroimaging data was acquired as part of three different studies (Björnholm et al., 2017; Fonville et al., 2019; Lancaster et al., 2018) which all varied in scope and aim (see Sharp et al., 2020 for an overview). One of the studies, which comprised the largest neuroimaging sample across the three (n = 513), was a testosterone study that selected for males-only during recruitment (Björnholm et al., 2017). Another of the studies, a psychosis study, had a sample size of n = 252, of which 65% were female (Fonville et al., 2019). This meant that the resulting sample for the neuroimaging data in this thesis was 72.8% male. In addition to this sample imbalance, there were additional unwanted sources of variability we made efforts to account for. For example, whilst scanning protocols were harmonised across the three studies, this is imperfect. We attempted to correct for this by passing our graph theory metrics through the neuroCombat package (Fortin et al., 2017, 2018) before proceeding with the subsequent analyses. As discussed in **Chapter 4**, neuroCombat accounts for potential non-biological variance resulting from variations in MRI scanners and protocols by harmonising values acquired across data sets (Fortin et al., 2018). We further accounted for the sex imbalance by incorporating sex in the models as part of the PLS and GLM analyses in **Chapter 4** and **Chapter 5**, respectively. Even so, this may still have posed residual issues with the analyses. As it stands, there are no good methods for harmonising connectomes to capture unwanted sources of variability. In the future, there is important work to be done on how we harmonise connectomes themselves (rather than via downstream derivative measures, as we did here). The main barrier to doing this is the sparsity within the structural connectomes. If a connection does not exist within a connectome because of differences in scanner protocol, we cannot insert that connection via harmonisation. One possibility that we would like to explore in future work, is whether probabilistic connectomes, which are incredibly dense (e.g., Zalesky et al., 2016), could provide a way of doing this. If we had time, then we would very much like to explore systematically whether probabilistic connectomes, which themselves have limitations (Sarwar et al., 2019), could be used to better harmonise the data early on. This might make downstream analyses far easier.

6.6.3 AVAILABILITY OF MEASURES

Whilst the ALSPAC dataset provides a vast offering of data types and measures, there are additional measures this thesis would have benefited from, but which were not available. For instance, this thesis would have benefitted from more direct economic measures, such as household income. Particularly so given the thesis' focus on the socioeconomic environment for developmental outcomes. In this thesis, I obtained the nearest measures to household income that were available. This led to the inclusion of questionnaire items regarding the level of difficulty affording food and housing. This is potentially problematic, as these measures may not accurately capture household income. As mentioned in **Chapter 4**, these measures are quite subjective compared to the measures obtained for occupation and education aspects of SES (i.e., maternal occupation status and parental education levels), which are more prescriptive. Thus, it is possible the financial difficulty measures of SES are capturing unintended aspects of income, such as the level of support a household receives, which may buffer against the level of difficulty experienced to afford food and housing. If the financial difficulty measures of SES obtained are not accurately capturing household income, this may have had an unintended effect on the results of these analyses. It may also explain why financial difficulty aspects of SES did not overlap with occupation and education aspects of SES in the results seen in **Chapter 4**, when these measures were assessed as individual components as opposed to an aggregated measure of SES, as was done in **Chapter 2**. Future research would gain from accessing a longitudinal cohort data with more specific financial measures.

There are additional environmental aspects that are likely to further influence the associations drawn upon in this thesis, but which could not be captured here on the basis of the availability of measures. One such example is the level of community support a child receives, which may also mediate associations between SES, polygenic propensity, and developmental outcomes. For example, a large portion of the variation in maternal depression scores has been attributable to the level of social support mothers receive (Shalowitz et al., 2006). It is possible social support is an extenuating factor that influences maternal mental health, as well as child development, both directly and indirectly considering the mediating role of maternal mental health on developmental outcomes (**Chapter 2**). Social support may also influence the associations drawn upon in **Chapter 4** through its contribution to perceived financial difficulties. Future research should aim to obtain data from longitudinal studies which measure the wider environmental context, as this may further highlight how environmental and genomic factors interact to influence developmental outcomes.

Data collection for longitudinal studies, such as the ALSPAC, began during a time when the deficit model of adversity was still widely adopted. The deficit model of adversity emphasises risk factors and impairments associated with adversity, with the primary goal being to promote policies and interventions that aim to prevent, reduce, or repair its effects. As such, the data obtained from these cohorts tends to lean towards potential risk factors, as opposed to unforeseen enrichment opportunities and so-called 'hidden talents' that may arise as children in high-adversity contexts adapt to their environments (see Ellis et al., 2017 for a discussion). Whilst the deficit model has been important in establishing a fundamental understanding of how deprivation influences development across the lifespan, it does not provide a comprehensive picture of development, nor does it consider the enhanced stress-adapted skills children may develop. These types of measures do not often find themselves the focus of study, but are very well likely to influence developmental outcomes (Ellis et al., 2017, 2022; Rosen

et al., 2020). As such, future research should aim to consider whether longitudinal cohort studies provide a platform for the consideration of unforeseen enrichment opportunities and hidden talents, in order to provide a more comprehensive assessment of multifactorial influence on development.

6.6.4 LACK OF DEVELOPMENTALLY APPROPRIATE TRANSCRIPTOMIC DATA

Comprehensive transcriptomic data covering the full cortex are not currently available for developing participants. As such, analyses in **Chapter 5** incorporated regional microarray expression data from the AHBA to explore whether the connectome connection types mirrored genetic similarity. Whilst the AHBA has revolutionised genetic neuroimaging, as was discussed in **Chapter 5**, it is limited in some ways. For example, whilst the AHBA comprises a microarray analysis of post-mortem tissue samples, data are only available for adults between the ages of 18 and 68. The AHBA also suffers from a small sampling pool, with only six donors at present. Right hemispheric data are only available for two of these six donors, resulting in only left hemispheric data being incorporated into the analyses in **Chapter 5**. Not having developmentally sensitive transcriptomic data available is problematic, and there is a need for a considerable effort to be made in this area. For example, the Allen Developing Mouse Brain Atlas has mapped gene expression changes during the development of the central nervous system, allowing for the spatio-temporal assessment of the developing mouse brain (see Sunkin et al., 2012 for a review). We further know the topology of the structural connectome to change significantly during development (Bullmore & Sporns, 2012; Di Martino et al., 2014). As such, having human developmentally sensitive transcriptomic data available would provide us with the opportunity to better explore how endogenous and exogenous factors interact to shape this development.

6.7 CONCLUSION

During early development, endogenous and exogenous factors interact to influence developmental outcomes and the structural organisation of the brain. This thesis has explored some of the ways these factors may interact to exert their effects, to better understand these developmental processes. In doing so, it provides new insights made possible by employing a contemporary approach to developmental science combined with the statistical means to model this multifactorial influence. I have drawn attention to the role of compounding environmental factors, namely SES and maternal mental health, in longitudinally shaping key developmental outcomes. I have highlighted the potential to generate valid and functional PGSs within the ALSPAC cohort, and have shown the utility of incorporating PGSs in more complex analyses to unravel genomic influence. Through the combined analysis of environmental, genomic, and connectomic data, I have assessed the ways SES and PGSs for cognitive ability influence local and global features of brain organisation. I have further explored how this interaction operates to influence cognitive ability, and assessed in more detail how the socioeconomic environment and the genome interact to influence specific features of the structural connectome. To that end, the primary take-away is that the first year of life is an incredibly important time for development, whereby environmental factors can have longitudinal implications for child mental health and cognitive ability. Moreover, the early life environment and the genome both influence the structural organisation of the brain, as well as interact to shape structural brain connectivity. Lastly, these findings suggest the need to further assess specific aspects of SES, and consider the

ways the genome may contribute to this commonly perceived ‘purely environmental’ measure, and in turn how apparently genomic effects exert their effects via the environment.

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