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Genetic liability to psychiatric disorders in early childhood; phenotypic effects and differing sensitivity to environmental influences

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” What we see changes what we know. What we know changes what we see.”
— Jean Piaget

To My Family

Abstract

The large genome-wide association studies conducted during the past fifteen years have broadly increased our understanding of the genetic basis of psychiatric disorders. These studies have shown that not only are all psychiatric disorders highly polygenic, but the implicated genetic factors are largely common variation that all of us carry. This raises the question of whether the common genetic liability is also manifested in the unaffected general population, and, whether they have detectable effects, or phenotypic effects, already in childhood, suggesting genetically influenced psychopathological developmental pathways. Furthermore, the genetic factors may have indirect effects by affecting the sensitivity to the environment. Studying these effects may increase our understanding of genetically influenced developmental pathways to mental health problems, which is essential in considering preventive measures and interventions.

The main aim of this thesis was to examine the effect of genetic liability for psychiatric disorders on childhood development and on the sensitivity to environmental influences in the first two years of life. The focus was on the genetic liability for two phenotypes: schizophrenia, a severe mental disorder profoundly affecting the function of neuronal networks and typically manifesting with cognitive impairments, and neuroticism, a trait associated with problems in emotion regulation and general susceptibility to mental health problems. The childhood phenotypes covered a wide range of indicators, from markers of neurophysiological maturation to motor as well as socio-emotional development.

The study utilized three Finnish birth cohorts, the Northern Finland Birth Cohort 1966 (Study I), CHILD-SLEEP (Studies II and III), and FinnBrain (Study III). Additionally, a Finnish schizophrenia family sample was used as a replication sample (Study I). Polysomnography recordings analyzed in Study II were available for a subsample (N = 92) of the CHILD-SLEEP birth cohort. Motor development (Study II) and socio-emotional development measured by internalizing and externalizing symptoms (Study III) were parentally assessed and neurophysiological development was based on sleep-electroencephalogram (EEG) recordings (Study II). Additionally, we used information on schizophrenia diagnosis in adulthood (Study I).

We found the genetic liabilities for schizophrenia and neuroticism to be associated with childhood development, including neurophysiological, motor, and socio-emotional development, and with sensitivity to the environment, in the first two years of life. More specifically, we found higher genetic risk for neuroticism was associated with more externalizing symptoms in two-year-old boys and higher genetic risk for schizophrenia was associated with slower motor development in eight-month-old girls. Both genetic risk scores were associated with sleep-EEG traits, although there were age-dependent differences. Genetic risk for schizophrenia was additionally associated with higher sensitivity to early environmental factors; in women, higher genetic risk together with high

birthweight, reflecting pre- and perinatal environmental factors, were associated with a higher likelihood of schizophrenia diagnosis in adulthood.

In conclusion, this thesis suggests that the genetic risk factors for schizophrenia and neuroticism may already have age- and developmental phase–dependent phenotypic effects in the first two years of life, partially in a gender-specific manner. However, whether this implies that the developmental process leading to an increased risk for mental health problems may already start soon after birth is not yet clear and more research, including longitudinal studies, is needed before we can fully understand the implications. Our study also suggests that genetic liability for psychiatric disorders may affect the child's sensitivity to environmental effects. The role of the environment in shaping the influence of genetic effects on development should be considered more extensively in future studies in order to advance our understanding of the possibly harmful and protective elements of the environment – vital information in considering preventive measures and intervention.

Keywords: Early childhood, electroencephalography, externalizing, gene–environment interaction, infancy, internalizing, motor development, neuroticism, phenotypic effect, polygenic risk score, schizophrenia, gender difference, socio-emotional development

Tiivistelmä

Koko perimän kattavat analyysit ovat viimeisen viidentoista vuoden aikana lisänneet valtavasti ymmärrystämme psykiatristen häiriöiden geneettisestä taustasta. Psykiatristen häiriöiden taustalla on todettu olevan erittäin suuri joukko perinnöllisiä tekijöitä ja lisäksi näiden tekijöiden on todettu olevan pitkälti yleisiä perinnöllisiä muunnelmia, joita meiltä jokaiselta löytyy perimästämme. Tämä herättää kysymyksen, voiko näillä yleisillä, psykiatrisille häiriöille altistavilla perinnöllisillä tekijöillä, olla näkyvää vaikutusta myös terveessä yleisväestössä, jopa jo lapsuudessa. On mahdollista, että nämä perinnölliset tekijät myötävaikuttavat mielenterveyden häiriöihin johtavien kehityspolkujen syntymiseen. Lisäksi perinnöllisten tekijöiden vaikutus voi olla myös epäsuoraa muuttaen yksilön herkkyyttä ympäristön vaikutuksille. Näiden vaikutusten tutkiminen voi auttaa ymmärtämään mielenterveyden ongelmiin mahdollisesti johtavia kehityspolkuja.

Tämän väitöskirjatyön tavoitteena oli tutkia psykiatrisille häiriöille altistavien perinnöllisten tekijöiden suoria ja epäsuoria vaikutuksia lapsuuden kehitykseen kahden ensimmäisen elinvuoden aikana. Tutkimuksessa tarkasteltiin perinnöllistä alttiutta skitsofrenialle ja neuroottisuudelle (ahdistuneisuusherkkyys). Skitsofrenia on vakava, laaja-alaisesti aivojen toimintaan vaikuttava mielenterveyden häiriö, kun taas neuroottisuus on tunne-elämän säätelyn ja mielenterveyden ongelmille altistava persoonallisuuspiirre. Lapsuuden kehityksestä tarkastelun kohteena oli neurofysiologinen kehitys mitattuna unen aikaisella aivosähkökäyrällä, sekä motorinen ja tunteiden säätelyn kehitys.

Tutkimuksessa käytettiin kolmea suomalaista syntymäkohorttia: Pohjois-Suomen syntymäkohortti NFBC1966 (osatyö I), CHILD-SLEEP (osatyöt II ja III) ja FinnBrain (osatyö III). Lisäksi toistoaineistona käytettiin suomalaista skitsofreniaperheaineistoa (osatyö I). Aivosähkökäyrään liittyviä tutkimuskysymyksiä tarkasteltiin CHILD-SLEEP-syntymäkohortista poimitussa alaotoksessa (N = 92), jolle oli tehty unipolygrafiatutkimus. Lapsuuden kehitystä kuvaavina vastemuuttujina käytettiin vanhempien arvioimaa tunteiden säätelyn kehitystä ja motorista kehitystä sekä unen aikana mitattuun aivosähkökäyrään pohjautuvia, unen rakenteesta kertovia muuttujia. Lisäksi osatyössä I oli käytössä joko rekisteripohjainen tai diagnostiseen haastatteluun perustuva tieto skitsofreniadiagnoosista aikuisuudessa.

Skitsofrenialle ja neuroottisuudelle altistavilla perinnöllisillä tekijöillä oli sekä suoria että epäsuoria vaikutuksia kahden ensimmäisen elinvuoden aikana. Perinnöllinen alttius skitsofrenialle ja perinnöllinen alttius neuroottisuudelle olivat yhteydessä varhaislapsuuden neurofysiologiseen, motoriseen ja tunnesäätelyn kehitykseen: Korkea perinnöllinen riski neuroottisuudelle oli yhteydessä ulospäinsuuntautuvaan käyttäytymiseen kaksivuotiailla pojilla ja korkea perinnöllinen alttius skitsofrenialle oli yhteydessä hitaampaan motoriseen kehitykseen kahdeksankuisilla tyttövauvoilla. Lisäksi molemmat perinnölliset alttiudet olivat yhteydessä uni-aivosähkökäyrään perustuviin

muuttujiin, tosin näissä yhteyksissä oli lapsen iästä riippuvia eroavaisuuksia. Skitsofrenian perinnölliset riskitekijät näyttivät lisäksi altistavan suuremmalle herkkyydelle varhaisten ympäristötekijöiden vaikutusten suhteen: naisilla korkea perinnöllinen riski yhdistettynä korkeaan syntymäpainoon, jonka ajatellaan heijastavan raskauden- ja synnytyksen aikaisia ympäristötekijöitä, oli yhteydessä suurempaan skitsofreniariskiin aikuisuudessa.

Yhteenvetona voidaan todeta, että skitsofrenian ja neuroottisuuden perinnölliset riskitekijät voivat olla yhteydessä varhaislapsuuden kehitykseen, tosin vaikutukset ovat todennäköisesti lapsen iästä, kehitysvaiheesta ja mahdollisesti myös sukupuolesta riippuvia. Tulos viittaa siihen, että mielenterveyden häiriöille altistavat kehityspolut saattavat alkaa jo hyvin varhain. Tarvitaan kuitenkin enemmän tutkimusta, erityisesti pitkittäistutkimuksia, ennen kuin näiden tulosten merkitystä voidaan arvioida mielenterveyden ongelmien kehittymisen kannalta. Tässä työssä havaittiin myös, että geneettinen alttius psykiatrisille häiriöille voi vaikuttaa siihen, miten herkästi ympäristötekijät vaikuttavat lapseen. Ympäristötekijöiden merkitystä geneettisten vaikutusten muokkaajana tulisikin tutkia entistä laajemmin seuraavissa tutkimuksissa, sillä mahdollisten suojaavien ja haitallisten ympäristötekijöiden tuntemus olisi keskeistä ehkäisevien toimien kannalta.

Asiasanat: Aivosähkökäyrä, motorinen kehitys, neuroottisuus, perinnöllinen riski, skitsofrenia, sukupuoliero, tunnesäätelyn kehitys, varhaislapsuus

Contents

List of original publications

This thesis is based on the following publications:

I **Liuhanen, J.**, Suvisaari, J., Kajantie, E., Miettunen, J., Sarin, A. P., Järvelin, M. R., Lönnqvist, J., Veijola, J., & Paunio, T. (2018). Interaction between compound genetic risk for schizophrenia and high birth weight contributes to social anhedonia and schizophrenia in women. Psychiatry Research, 259, 148–153. https://doi.org/10.1016/j.psychres.2017.10.020

II **Liuhanen, J.**, Himanen, S.-L., Kärki, A., Satomaa, A.-L., Kylliäinen, A., Kantojärvi, K., Laitinen, P., Saastamoinen, A. E. Paavonen, E.J., Saarenpää-Heikkilä, O., & Paunio, T. (submitted). Polygenic risk score for schizophrenia is associated with sleep electroencephalogram in the first two years of life.

III **Liuhanen, J.**, Kantojärvi, K., Acosta, H., Pietikäinen, J. T., Nolvi, S., Savukoski, M., Kylliäinen, A., Pölkki, P., Karlsson, H., Karlsson, L., Paavonen, E. J., & Paunio, T. (2023). Polygenic risk for neuroticism is associated with externalizing symptoms in 2-year-old boys. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 123, 110720. https://doi.org/10.1016/j.pnpbp.2023.110720

This thesis includes additional unpublished results.

The publications are referred to in the text by their Roman numerals.

List of abbreviations

ADHD	Attention deficit-hyperactivity disorder
AS	Active sleep
BITSEA	Brief Infant-Toddler Social and Emotional Assessment scale
BMI	Body mass index
CES-D	Center for Epidemiological Studies Depression Scale
CI	Confidence interval
CNV	Copy number variation
CS	CHILD-SLEEP birth cohort
C + T	Clumping and thresholding method
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBI	European Bioinformatics Institute
EEG	Electroencephalogram
EPDS	Edinburgh Postnatal Depression Scale
FB	FinnBrain birth cohort study
FSZ	Schizophrenia Family Sample
GEE	General Estimations Equations
gnomAD	Genome Aggregation Database
GO	the Gene Ontology project
GPC	Genetics of Personality Consortium
GWAS	Genome-wide association study
LD	Linkage disequilibrium
MAF	Minor allele frequency
MDD	Major depressive disorder
NEO	Neuroticism-Extraversion-Openness
NFBC1966	Northern Finland Birth Cohort 1966
NHGRI	the US National Human Genome Research Institute
NREM	Non-rapid eye movement
OR	Odds ratio
PGC	Psychiatric Genetics Consortium
PRS	Polygenic risk score
PSG	Polysomnography
QS	Quiet sleep

RDoC	Research Domain Criteria
REM	Rapid eye movement
r_g	Genetic correlation
SCHEMA	Schizophrenia Exome Sequencing Meta-analysis consortium
SD	Standard deviation
SEI	Sleep efficiency index
SNP	Single nucleotide polymorphism
SNV	Single nucleotide variant
SWA	Slow wave activity
SZ	Schizophrenia
TIB	Time in bed
TST	Total nocturnal sleep time

1 Introduction

Our understanding of the genetic basis of psychiatric disorders has been greatly advanced during the past fifteen years – a period that could be called "the GWAS era" of psychiatric genetics – as the advances in microchip technology and efforts in international collaboration have made large genome-wide association studies (GWAS) increasingly possible to conduct. These studies have broadened our understanding of the genetic basis of psychiatric disorders vastly. The main finding of these studies has been that all psychiatric disorders are highly polygenic: there seems to be thousands of genetic variants all over the genome that collectively contribute to the genetic liability, and accordingly, the genetic basis of any psychiatric disorder is not simple, but very complex. Another interesting finding has been that the genetic factors are largely common genetic variation that all of us carry to some extent, some of us more than others. Since it does not seem to be the case that only a few "illness-provoking" genes can be singled out, it raises the question of whether this common genetic liability is also manifested in people without a diagnosis for a psychiatric illness. Additionally, since the genetic factors are present from the very beginning of life, even before birth, it is a valid question to consider whether the genetic factors that contribute to psychiatric disorders have detectable effects, or phenotypic effects, already in childhood.

Many psychiatric disorders, such as schizophrenia, typically manifest during adolescence or adulthood, but the etiological origins often lie at least partly earlier in childhood (Fusar-Poli et al., 2022; Arango et al., 2021; Pine & Fox, 2015; Rutter et al., 2006; Kessler et al., 2005). Twin studies have shown that the continuity of emotional and behavioral problems over time, suggesting underlying psychopathology, is mainly genetically influenced (Hannigan et al., 2017). This implies the possibility of genetically influenced psychopathological developmental pathways that are currently not well known, but genetic factors predisposing to psychiatric disorders are plausible candidates. Moreover, the genetic factors may not only have a direct effect on psychopathological development, but they may influence indirectly via sensitivity to environmental effects (Kendler & Eaves, 1986). Studying the effects of such genetic risk factors in childhood increases our understanding of how the genetic predisposition is manifested in developmental time and may illuminate the genetically influenced developmental pathways to mental health problems. Understanding the etiological pathways is important since

preventive measures and interventions are probably more effective before the onset of a psychiatric disorder.

The phenotypic effects of genetic risk factors for psychiatric disorders have been studied in children aged (two to) four years and older, but less in younger children (Askeland et al. 2022; Costantini et al., 2023). For example, the genetic risk for schizophrenia has been associated with broad psychopathological liability from childhood to adolescence (Hannigan et al., 2021). However, it is not yet clear whether the genetic risk factors for psychiatric disorders already have phenotypic effects in young children. The aim of this thesis was to study the phenotypic effects of genetic risk factors for psychiatric disorders in the first two years of life and examine their possible influence on the varying sensitivity to environmental influences.

2 Literature Review

2.1 Genetic background of psychiatric disorders

Most human traits are influenced by genetic factors, and psychiatric disorders are no exception: psychiatric disorders are influenced by genetic factors, just as are many somatic illnesses and physiological traits, as well as psychological characteristics (Polderman et al., 2015). Twin studies have shown that most psychiatric disorders are moderately to highly heritable, with schizophrenia, bipolar disorder and autism being among the most heritable, with heritability estimates ranging from 60% to 80% (Sullivan et al., 2012; Pettersson et al., 2019; Bienvenu et al., 2011; Smoller & Finn, 2003).

It has been generally noted that psychiatric disorders tend to aggregate by family and by individual: offspring of parents with psychiatric disorders are susceptible to develop a broad range of psychiatric disorders, not just the one the parents are suffering from, and people suffering from psychiatric problems tend to have more than one diagnosis (Grotzinger et al., 2022). This suggests that psychiatric disorders may share a common genetic background and many studies have indeed shown differing amounts of genetic overlap between psychiatric disorders (e.g., Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Grotzinger et al., 2022). Another factor favoring the assumption of a shared genetic background is that while psychiatric disorders have been shown to share a common genetic background, neurological disorders seem to be more genetically distinct from one another, and from the psychiatric disorders (The Brainstorm Consortium et al., 2018). Although a general susceptibility factor “p” for psychiatric disorders has been suggested (Caspi et al., 2014) and supported (e.g., Selzam et al., 2018), no clear genetic or biological evidence for its existence has been found (Grotzinger et al., 2022). Accordingly, although most psychiatric disorders share some genetic background, each disorder seems to have its own distinctive genetic background.

Since it is out of the scope of this thesis to cover all psychiatric disorders, I will focus on one of the most heritable psychiatric disorders, schizophrenia, which is also one of the most intensively studied psychiatric disorders in psychiatric genetics. Schizophrenia is a severe mental disorder profoundly affecting the function of neuronal networks and typically manifesting with cognitive impairments. Furthermore, genetic risk for schizophrenia has been suggested to

reflect general liability to psychiatric disorders (Jones et al., 2018). In addition, I will focus on neuroticism, a personality trait that has been associated with problems in emotion regulation and with almost every psychiatric disorder (The Brainstorm Consortium et al., 2018). Neuroticism has even been suggested to represent a heritable risk for psychiatric disorders (Lo et al., 2017).

2.1.1 Schizophrenia – a highly heritable psychotic disorder

Schizophrenia is a highly heritable, severe mental disorder. It is not a very common disorder, as the lifetime prevalence of the disorder is around 1–1.5% (Perälä et al., 2007; Pedersen et al., 2014; Marder & Cannon, 2019). The typical age of onset for schizophrenia is earlier for men, in their late teens or early twenties, than for women, who typically fall ill with the disorder in their early thirties (Häfner et al., 1994). The symptoms of schizophrenia are usually categorized as positive symptoms, including hallucinations and delusions, negative symptoms, such as lack of motivation or social interest, and symptoms of disorganization, reflecting disorganization of thoughts and behavior (Jauhar et al., 2022). Cognitive deficits, including attention, working memory and verbal learning (Bowie et al., 2006) are also often associated with the disorder. Schizophrenia is highly heritable – it is among the most heritable psychiatric disorders, with heritability estimates from twin and pedigree studies ranging from around 60% to over 80% depending on the type of study (estimates are higher in twin studies than in pedigree studies) (Sullivan et al., 2012; Pettersson et al., 2019; Sullivan et al., 2003; Lichtenstein et al., 2009; Cardno & Gottesman, 2000). The single nucleotide polymorphism (SNP)-based heritability estimate, which indicates the proportion of phenotypic variance explained by all measured genetic variants in a GWAS (Zhu & Zhou, 2020), is considerably lower, around 24% (Trubetskoy et al., 2022), but is among the highest for psychiatric traits. For example, the SNP-based heritability estimates for type I bipolar disorder and for different autism phenotypic subcategories, the psychiatric disorders that are among the most heritable ones, are around 21% (Mullins et al., 2021) and 3–10% (Grove et al., 2019), respectively.

2.1.1.1 Etiology – the neurodevelopmental hypothesis

The etiology of schizophrenia is currently unknown, but hypotheses about the origin of the disorder have been proposed. The neurodevelopmental hypothesis is a widely accepted theory, which states that schizophrenia originates in the early development of the nervous system, and the disorder emerges years or decades later because of abnormalities in this development (Murray & Lewis, 1987; Rapoport et al., 2012). It is widely accepted that schizophrenia is a brain disease, and especially

a disorder related to brain development (Owen et al., 2016). Further support for the neurodevelopmental hypothesis is given by the numerous studies that have shown that environmental factors related to schizophrenia include prenatal incidents and incidents during labor in particular that affect brain development (Walker et al., 2004). These environmental risk factors include obstetric complications during labor (Cannon et al., 2002), maternal nutritional scarcity during pregnancy (St Clair et al., 2005), gestational infections (Suvisaari et al., 1999), severe maternal stress during pregnancy (Khashan et al., 2008), and high and low birthweight (Moilanen et al., 2010). In addition to the factors related to brain development, social experiences and adversities, especially together with the developmental risk factors, have been suggested as important risk factors for developing schizophrenia (Howes & Murray, 2014).

2.1.1.2 Endophenotypes of schizophrenia

Genetic studies of complex phenotypes including psychiatric disorders often benefit from studying endophenotypes, measurable traits or components that exist between genetic liability and a mental disorder (Gottesman & Gould, 2003). These intermediate phenotypes have been largely utilized in the genetic study of schizophrenia, and several endophenotypes for schizophrenia have been proposed (Cannon & Keller, 2006). For example, social anhedonia, a disposition to find social interactions unpleasant, is a trait-like characteristic measurable in the general population that reflects schizophrenia liability (Wang et al., 2014; Cohen et al., 2011; Miettunen et al., 2011; Kwapil, 1998). In patients with schizophrenia, it is regarded as a negative symptom and it seems to be very stable; it has been found to remain stable, even when other symptoms have remitted (Blanchard et al., 2001). Genetic studies suggest that social anhedonia and schizophrenia share a common genetic background (Ortega-Alonso et al., 2017), which further supports the assumption of social anhedonia being an endophenotype for schizophrenia. The endophenotype approach is related to the Research Domain Criteria (RDoC) framework, which was formulated to advance the understanding of psychiatric disorders beyond the clinical diagnosis categories (National Institute of Mental Health, 2023; Insel et al., 2010). The RDoC framework recognizes the continuous nature of the biological and psychological processes that underlie human neurobehavioral functioning, and aims to enhance the prevention, diagnosis, and treatments of psychiatric disorders by fostering the research of these continuous dimensions (National Institute of Mental Health, 2023).

2.1.2 Neuroticism – a personality trait associated with mental health

Neuroticism is a moderately stable, heritable personality trait characterized by a tendency to worry and to experience negative feelings. Neuroticism has been shown to be a robust predictor of a variety of mental health problems and it has even been argued to have notable significance for public health (Lahey, 2009; Widiger & Oltmanns, 2017). The trait neuroticism is clearly related to mental health since in the general population, neuroticism has been shown to significantly correlate with almost every psychiatric disorder (The Brainstorm Consortium et al., 2018).

Neuroticism is one of the most important traits thought to describe human personality. It is included in several main personality theories, and despite slightly differing names, similar contents, including recurrent feelings of anxiety, worrying, emotional instability, and low tolerance of stress, are related to this core trait of human personality (Eysenck & Eysenck, 1969). Neuroticism can be assessed by self-report questionnaires, and there are several measures that have been developed to measure neuroticism. The measures mostly used in genetic studies include the questionnaires based on Eysenck's personality theory (Eysenck et al., 1985) and NEO (Neuroticism-Extraversion-Openness) personality inventories based on the five-factor theory (Costa & McRae, 1992).

2.1.2.1 Heritability of neuroticism

Neuroticism is a moderately heritable trait with heritability estimates around 40–50% (Boomsma et al., 2018; Vukasović & Bratko, 2015), depending on research design (twin studies showing the highest estimates) but not significantly differing regarding which personality theory the measurement is based on (Vukasović & Bratko, 2015). The SNP-based heritability of neuroticism is considerably lower, ranging from 10% to 15% (Realo et al., 2017; de Moor et al., 2015; Power & Pluess, 2015; Smith et al., 2016; Zeng et al., 2018; Docherty et al., 2016; LifeLines Cohort Study et al., 2016). A further 1.5% of the variation has been shown to be explained by the X chromosomal variants (Luciano et al., 2021).

2.1.2.2 Negative emotionality – a temperament trait related to later neuroticism

Neuroticism as a trait is not yet present or measurable in children. However, negative emotionality is a temperament trait that has been argued to closely resemble neuroticism in young children (Muris & Ollendick, 2005). Negative emotionality shares many aspects in common with neuroticism, including the tendency to easily experience negative affect, anxiety, and sadness. Negative emotionality has been shown to be associated with problems and vulnerability to

psychopathology in childhood, and to play an important role in the etiology and maintenance of internalizing and externalizing problems in childhood and adolescence (Muris & Ollendick, 2005). Internalizing problems (e.g., anxiety, depression and withdrawal) and externalizing problems (e.g., aggression, impulsivity and rule-breaking behavior) in childhood have been associated with later psychopathologies throughout the lifespan (Weeks et al., 2016).

2.2 Genetic underpinnings of schizophrenia and neuroticism

2.2.1 Genetic variation in the human genome

The genetic information of all living organisms is contained in DNA, deoxyribonucleic acid, a long molecule comprised of two polynucleotide chains, or DNA strands, that are composed of four nucleotides (adenine, thymine, cytosine and guanine). The human genome includes 23 chromosome pairs, 22 autosomal chromosome pairs and the sex chromosomes, XX in women and XY in men, and a small amount of mitochondrial DNA. Any two random individuals differ approximately 0.1% in their DNA sequence (Przeworski et al., 2000). This small difference is enough to produce the uniqueness of individuals in their phenotypic appearance. The most common type of genetic variation is a single nucleotide polymorphism (SNP), in which a single base (adenine, thymine, cytosine or guanine) – the building blocks of the genetic code – has been substituted with another base. By definition, a base-pair substitution is called a SNP, if it has at least 1% prevalence in the population, while rarer base-pair substitutions are called single nucleotide variants (SNV).

In addition to base-pair substitutions, the human genome contains structural variation including copy number variations (CNV), inversions and translocations (Feuk et al., 2006). CNVs are segments of the DNA, larger than 1 kb in size (typically ranging from 1 kb to several megabases) that are either inserted, deleted, or duplicated. Segments of DNA that are in reverse order compared with a reference genome, are called inversions, while translocations refer to segments of DNA that have translocated, either within the same chromosome or to another chromosome compared with the usual position in the reference genome. In addition, structural variation includes smaller insertions and deletions (less than 1 kb) that are usually called indels (Feuk et al., 2006). Indels and CNVs are very common; on average, every person has a total CNV burden of 655 kb in their genome (Li et al., 2020). Although CNVs are found all over the genome, there seem to be regions in the genome that harbor more CNVs (Li et al., 2020). The variation and common patterns in the human genome across different populations have been investigated in international collaborative projects including the 1000 Genomes Project (1000

Genomes Project Consortium, 2015) and the International HapMap Project (The International HapMap Consortium, 2003). The information is constantly increasing and the knowledge is compiled in public databases, for example the International Genome Sample Resource, which is based on the results of the 1000 Genomes Project (https://www.internationalgenome.org/) and the Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org/). As an example, there are currently almost 800 million SNVs, over 120 million indels and over 1 million structural variations reported in the gnomAD (gnomAD, 2023).

The alternative forms of genetic variants, called alleles, at different loci are not randomly associated with each other. This nonrandom association of alleles at two or more loci is called linkage disequilibrium (LD) and it arises from the basic laws of passing down genetic material: during meiosis, the cell division of the germ cells, homologous chromosomes exchange genetic material and create new combinations of the genetic material. However, DNA segments close to each other are more often inherited together, since recombination is less likely to occur between closely located areas. This results in linkage between closely located variants and in haplotypes – groupings of alleles that are typically inherited together. Due to the shared ancestry of contemporary chromosomes, many regions in the human genome can be parsed into haplotype blocks, which are genomic regions with a limited number of existing haplotypes and little evidence of a history of genetic recombination (Gabriel et al., 2002). The haplotype structure of the human genome can be utilized in genetic association analyses, for example by using tagging variants for entire haplotypes (The International HapMap Consortium, 2005). However, because of differing population histories, the haplotype structures vary between different populations. For example, the haplotype blocks are shown to be longer and with fewer alternative haplotypes in European and Asian populations compared to African populations (Gabriel et al., 2002). Since there is variability in the haplotypes between populations, findings in genetic association analysis on one population do not necessarily apply to another population.

There is wide variation in the frequency of genetic variants in the human population, ranging from ultra-rare singletons to common variants with a minor allele frequency (MAF) – the percentage of the rarer form of the variant – of 50%. Variants with an MAF equal to or greater than 5% in the population are generally defined as common variation, while variants with an MAF lower than 1% or an MAF in between (1–5%) are usually called rare and low-frequency variants, respectively (UK10K Consortium et al., 2015). However, these definitions, especially for rare and low-frequency variants, slightly vary between studies, for example, in some studies rare variants are defined as variants with an MAF < 0.5% (e.g., Gazal et al., 2018). It is assumed that most of the heritability of polygenic traits is explained by common variation (Schoech et al., 2019; Gazal et al., 2018). Common variants are expected to have smaller effect sizes (Manolio et al., 2009), and the relationship between a

variant's effect size and the MAF has been shown to be negative in most polygenic traits (Zeng et al., 2018). Common variation associated with polygenic traits is analyzed in GWASes, while rare variation requires sequencing, the untangling of the exact sequence of the bases of DNA – either whole-exome sequencing, in which only the coding regions (approximately 2%) of the genome are sequenced, or whole-genome sequencing, in which the entire nuclear DNA sequence is determined (Whole Genome Sequencing for Psychiatric Disorders (WGSPD) et al., 2017).

2.2.2 Genome-wide association studies

For more than a decade, the prevailing method for studying the genetic background of complex traits, including psychiatric disorders and personality, has been the GWAS, which is a hypothesis-free method covering the whole genome (or the 22 autosomal chromosomes) and can be implemented with large datasets containing unrelated individuals (Uffelmann et al., 2021). The basic idea of a GWAS is to test the statistical association between a phenotype and the allele frequency of a genetic variant, usually a SNP, in a large sample of unrelated individuals, and determine whether the genetic variant is statistically significantly associated with the phenotype. GWASes utilize microarrays, a relatively cheap genotyping method that allows the genotyping of hundreds of thousands (or even a couple of million) genetic variants for a person simultaneously. Using imputation, a method that exploits the knowledge of the human genome sequence and associations between genetic loci (Marchini & Howie, 2010), GWASes can test the association between millions of genetic variants all over the genome and the phenotype in one study. SNPs selected for microarrays typically correlate highly with neighboring SNPs and accordingly the SNPs analyzed in a GWAS serve as tagging SNPs for larger genomic areas containing unmeasured genetic variation (Ding & Kullo, 2007). However, rare variants and structural variation are not well tagged by the common SNPs, and accordingly GWASes capture mostly common variation. GWASes have been successful in discovering genetic loci for numerous complex traits and diseases and the accumulating results are compiled in public databases, for example the US National Human Genome Research Institute (NHGRI)–European Bioinformatics Institute (EBI) GWAS Catalog (https://www.ebi.ac.uk/gwas/), which currently contains variant–trait associations for over 5000 human traits (Sollis et al., 2023).

GWASes have proven to be useful in discovering genetic loci related to traits and disorders, but locating the actual causal variants has not been straightforward. Due to LD and the haplotype structure of the genome, there are typically many significant hits within a genomic region, and it is not straightforward to define which of the variants are the causal ones, or in LD with the actual causal variant, since the causal variant might not be included in the GWAS. Furthermore, the implicated genomic regions may include several genes, and accordingly it is not

necessarily even clear which genes are implicated. Several methods have been developed to assist in the interpretation of GWAS results. Fine-mapping is a general term for a group of in silico methods developed to define the most credible causal variants in a genomic region indicated in a GWAS that most parsimoniously explain the regional signal (Uffelmann et al., 2021). In general, fine-mapping integrates information of the genomic region's LD structure and functional annotations of the SNPs from databases, in defining the variants that are most likely the causal – and functional – variants (Schaid et al., 2018). There are several programs available for fine-mapping, for example FINEMAP (Benner et al., 2016) and SuSiE (Wang et al., 2020), which are both based on Bayesian models. In addition to fine-mapping, methods focusing on genes and gene sets have been developed to help in aggregating GWAS results in a biologically meaningful way (Wang et al., 2011). The general idea of a gene-set analysis is to test whether the phenotype is associated with gene sets grouped in a biologically or functionally meaningful way to obtain insight into the biological pathways involved with the phenotype (de Leeuw et al., 2015). Information on gene ontologies is provided by international collaborative efforts, for example the Gene Ontology project (GO) (Gene Ontology Consortium, 2015). There are several programs available for gene-set analyses, including MAGMA (de Leeuw et al., 2015).

2.2.3 Genetic background of schizophrenia

2.2.3.1 Findings from large genome-wide association studies

The genetic background of schizophrenia has been studied intensively over the past few decades. Before the era of GWASes, linkage studies, which utilized pedigrees to find chromosomal segments co-segregating with schizophrenia, and a candidate gene approach, analyzing the association between one or a few specific genomic loci and schizophrenia based on a pre-determined hypothesis, prevailed. However, these studies suffered from inconclusive findings and lack of replication (Risch & Merikangas, 1996; Farrell et al., 2015). The first GWASes of schizophrenia were conducted in 2008 with a few hundred cases and controls (Molecular Genetics of Schizophrenia Collaboration et al., 2008; Sullivan et al., 2008). Since the findings in these studies were modest, it was soon realized that GWASes require larger sample sizes. In fact, the most coherent finding from GWASes has been that schizophrenia, like all complex traits, is highly polygenic (as was postulated already by Gottesman in 1967 (Gottesman & Shields, 1967)), implying that there are a lot of genetic variants that all have a minor effect; finding these variants requires very large sample sizes. Accordingly, international collaboration between research groups was established, and the Psychiatric Genomics Consortium (PGC) was founded to advance the genetic study of psychiatric disorders. The Schizophrenia

Working Group of the PGC aims to combine all available schizophrenia samples with GWAS genotypes into one analysis. The PGC has thus far published three waves of GWASes of schizophrenia with increasing sample sizes (Table 1). The latest and largest schizophrenia GWAS published included more than 90 study cohorts from several countries and analyzed over 76,000 schizophrenia cases and more than 240,000 controls and reported over 280 genomic loci associated with schizophrenia (Trubetskoy et al., 2022).

Table 1 The three waves of genome-wide association studies of schizophrenia by the Psychiatric Genomics Consortium.

Reference	N Cases	N Controls	N Genome-wide significant loci	Main Findings
The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011	17,836	33,859	7	6p21.32-22.1 MHC region; 18q21.2 *TCF4*; 1p21.3 *MIR137*; 2q32.3 *PCGEM1*; 8p23.2 *CSMD1*; 8q21.3 *MMP16*; 10q24.32-q24.33 *CNNM2*, *NT5C2*
Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014	36,989	113,075	108	Genes expressed in the brain and in tissues important for immunity. Reinforcement for several earlier hypotheses, including glutamatergic neurotransmission, synaptic plasticity and voltage-gated calcium channels. Role of the immune system strongly implicated. Also, novel biological pathways suggested.
Trubetskoy et al., 2022	76,755	243,649	287	Genes expressed in CNS neurons. Refined set of 120 genes potentially related to SZ. Genes related to synaptic differentiation, organization and transmission, especially postsynaptic processes implicated.

CNS = Central nervous system, MHC = Major histocompatibility complex, SZ = Schizophrenia

In the latest and largest GWAS of schizophrenia, common genetic variation explained approximately 24% of schizophrenia liability (Trubetskoy et al., 2022). Since the twin heritability estimates of schizophrenia are much higher, around 60–80% (Sullivan et al., 2012; Lichtenstein et al., 2009; Cardno & Gottesman, 2000), the common genetic variation captured by GWASes is clearly not explaining the whole genetic background of schizophrenia. This phenomenon, called “missing

heritability", has been seen in basically all studies of complex traits, and several hypotheses to explain the missing heritability have been proposed, including the effect of rare genetic variation, epistasis (gene x gene interactions), gene–environment interactions, incomplete LD between tag SNPs and the causal variants, and a failure to properly take the common environment into account in twin studies leading to inflated heritability estimates (Manolio et al., 2009; van Dongen & Boomsma, 2013; Matthews & Turkheimer, 2022). In addition, investigation of structural variants has been called for, since for example CNVs are not well-tagged by common SNPs, and notable overlap between CNV regions and GWAS signals suggests that rare CNVs may have a significant role in polygenic diseases (Li et al., 2020). The explanation for the missing heritability presumably depends on the genetic architecture of the studied trait and accordingly a general solution might not be broadly applicable (Eichler et al., 2010). In the case of schizophrenia, the two main suggestions to resolve the missing heritability problem have been to search for more common variation with even smaller effects and to look for rare variation (Trubetskoy et al., 2022), although a role for gene–environment interactions has also been suggested (van Dongen & Boomsma, 2013). Finding more common variation with smaller effect sizes requires even larger sample sizes and better tagged SNPs in GWASes, while the detection of rare variants and CNVs require exome or whole-genome sequencing.

2.2.3.2 Rare variants and CNVs in schizophrenia

Searching for rare variants and CNVs for schizophrenia has also called for global cooperation: the CNV Analysis Group of the PGC published the largest study so far on CNVs in schizophrenia in 2017 (Psychosis Endophenotypes International Consortium et al., 2017), and in the same year the Schizophrenia Exome Sequencing Meta-analysis (SCHEMA) consortium was established to advance the analysis of sequencing data of schizophrenia patients. In 2022, the SCHEMA consortium published the largest study on rare variation in schizophrenia (Singh et al., 2022).

Studies on CNVs and rare variation are clearly showing an elevated burden of rare variation, especially in the coding regions of genes, in schizophrenia cases vs. controls, including CNVs (Walsh et al., 2008; The International Schizophrenia Consortium, 2008; Psychosis Endophenotypes International Consortium et al., 2017), rare disruptive mutations (Purcell et al., 2014; Genovese et al., 2016), and ultra-rare variants (Singh et al., 2022). The same result has also been found in populations of different ancestries (Liu et al., 2023). In addition to a general excess burden of rare variants and CNVs, there are also single rare CNVs that have reached genome-wide significance, including copy number losses at 22q11.2, 16p11.2, 2p16.3 (*NRXN1*), 1q21.1, 15q13.3, 3q29, and gains at 7q11.23 and 16p11.2 (Psychosis Endophenotypes International Consortium et al., 2017; The International

Schizophrenia Consortium, 2008). These rare CNVs have significantly higher effect sizes than common SNPs in GWASes, with odds ratios ranging from 2 to 60 (Singh et al., 2022), but they are typically found in only a very small proportion of schizophrenia cases, and accordingly explain only a small fraction of the phenotypic variance. For example, the deletion in 22q11.2 is found in approximately 0.5–1% of schizophrenia cases (Van et al., 2017). Although there is strong support for rare structural variants being influential in schizophrenia pathogenesis, it is not known how much of the total schizophrenia risk rare variation will explain. For example, the Psychosis Endophenotypes International Consortium and colleagues (2017) estimated that the rare variants found in their study explained only 0.85% of the phenotypic variance of schizophrenia. However, it is suggested that a majority of rare risk variants are still to be discovered (Singh et al., 2022), and exome and whole-genome sequencing is the way to find them.

2.2.3.3 Genes related to schizophrenia are important in early brain development

Most of the genetic variation in schizophrenia is currently explained by common variation, but studies exploring rare variation and CNVs is ongoing. The findings from GWASes and rare variant studies converge, since the same biological pathways are implicated by both types of studies. GWASes show clear accumulating evidence for the role of synaptic processes in the etiology of schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Trubetskoy et al., 2022, Pardiñas et al., 2018). The most recent GWAS (Trubetskoy et al., 2022) suggests postsynaptic processes in particular, but also presynaptic processes, synaptic organization and synaptic signaling (Trubetskoy et al., 2022). Genes related to neuronal maturation and differentiation are also implicated (Trubetskoy et al., 2022; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Currently, it seems that the associations found in GWASes are related to genes that are expressed all over the brain and not restricted to certain brain regions. However, it seems that schizophrenia is a disorder of the neurons, since genes expressed in glia or microglia are not currently showing significant associations. Calcium signaling is implicated in both GWASes and studies on rare variation, including accumulating evidence for voltage-gated calcium channels (Trubetskoy et al., 2022; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Pardiñas et al., 2018; Purcell et al., 2014), calcium metabolism (Trubetskoy et al., 2022), and calcium ion import (Pardiñas et al., 2018). The evidence for glutamatergic neurotransmission is also accumulating, with several genes implicated (e.g., *DRD2*, *GRIN2A*) in both GWASes (Trubetskoy et al., 2022; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and rare variant studies (Singh et al., 2022). Studies

also support a role for the immune system (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). In summary, the genetic background of schizophrenia seems to strongly involve genes related with synaptic processes. Additionally, genes related to neuronal maturation and differentiation are implicated, supporting the hypothesis that genetic risk for schizophrenia involves early brain development.

2.2.4 Genetic background of neuroticism

2.2.4.1 Genome-wide association studies of neuroticism

The genetic basis of neuroticism has been studied since the 1990s, and at first, the genetic structure was assumed to be simple, at least simpler than for psychiatric disorders. Since personality theories suggested specific biological correlates for the traits (e.g., Lester, 1989), candidate gene studies of neuroticism were performed quite intensively for a couple of decades after the classical study of Lesch and colleagues (1996), which showed that a polymorphic site (5-HTTLPR) near the serotonin transporter coding sequence was associated with neuroticism. In particular, genes related to serotonergic neurotransmission were supposed to be associated with neuroticism, and several candidate gene studies and following meta-analyses have examined the role of the serotonergic system in neuroticism (Sen et al., 2004; Munafò et al., 2003). However, the results have been inconclusive (Munafò et al., 2003), and the utility of candidate gene studies has been questioned (as it has been for other polygenic traits as well) (Munafò & Flint, 2011). The GWASes of neuroticism have convincingly shown that the genetic basis of neuroticism is highly polygenic and includes numerous genetic loci with minor effect sizes (de Moor et al., 2015; Nagel et al., 2018a; Zeng et al., 2018). The studies have required very large sample sizes, and international collaboration between research groups has been called for to achieve enough power for the genetic association studies. Accordingly, the Genetics of Personality Consortium (GPC) has been established to advance the genetic studies of neuroticism and other personality traits. Examples of genome-wide association analyses studying the genetic background of neuroticism are presented in Table 2.

The largest GWAS of neuroticism conducted so far included almost 450,000 individuals and reported 136 genomic loci associated with neuroticism (Nagel et al., 2018a). Together, all common variants explained 10% of the variability in neuroticism (Nagel et al., 2018a). Since this percentage is considerably lower than the 40–50% heritability estimates from twin studies, the “missing heritability” problem is also encountered in the study of neuroticism. Possible explanations suggested for the missing heritability of neuroticism include rare variants, gene–gene interactions and biased heritability estimates of twin studies due to improper

accounting of nonadditive genetic effects and environmental factors (Nagel et al., 2018a; Vinkhuyzen et al., 2012). However, so far no rare or structural variation associated with neuroticism has been found (Luciano et al., 2012b), and some studies have even suggested that rare variation might not be important in neuroticism (Hill et al., 2018). The possibility of finding more common variants with even smaller effects has also been proposed, and very large sample sizes have been called for to find the common genetic variation, due to the presumably highly polygenic nature of neuroticism (Nagel et al., 2018a).

Table 2 Examples of genome-wide association analyses of neuroticism.

Reference	**N**	**N Genome-wide significant loci**	**Main findings**
Terracciano et al., 2010	3,972	0	
Luciano et al., 2012a	6,268	0	
de Moor et al., 2012	17,375	0	
de Moor et al., 2015	63,661	1	3p14.1 (*MAGI1*)
Smith et al., 2016	91,370	9	8p23.1(4 Mb LD block including an inversion polymorphism and genes related to innate immunity and the nervous system); 1p34.3 (*GRIK3*); 1q42.12; 3q13.13; 4q32.3 (*KLHL2*); 9p21.3; 9p23; 17q21.31 (*CRHR1*, *MAPT*); 18q12.2 (*CELF4*)
LifeLines Cohort Study et al., 2016	170,910	11	8p23.1 (inversion polymorphism, see Smith et al., 2016); 3p22.3; 9p21.3; 9p23; 11p15.4 (*SBF2*); 11q23.3; 15q24.3; 17p13.3 (*PAFAH1B1*); 17q21.31 (*KANSL1*); 18q12.2 (*CELF4*)
Lo et al., 2017	122,867	2	8p23.1 (4 Mb LD block, see Smith et al., 2016) and 22q13.2 (*L3MBTL2*)
Luciano et al., 2018	329,821	116	Genes related to neuronal genesis and differentiation, and cell adhesion. Reinforcement for earlier findings (including the inversion polymorphism on 8p23.1, *CRHR1*, and *CELF4*)
Nagel et al., 2018a	449,484	136	Genes expressed in the brain. 599 genes implicated: related to neurogenesis, behavioral response to cocaine, axon part (and neuron differentiation); reinforcement for earlier findings including the inversion polymorphism on chr 8 and serotonergic hypothesis (serotonergic neurons involved)

LD = Linkage disequilibrium

2.2.4.2 Genes related to neuroticism

GWASes of neuroticism are showing accumulating evidence that genes related to neuroticism are mostly expressed in the brain and involve the biological mechanisms related to neurogenesis and neuronal differentiation (Nagel et al., 2018a; Luciano et al., 2018; Belonogova et al., 2021). Other suggested mechanisms include processes related to axons, synapses, and synaptic function (Nagel et al., 2018a; Luciano et al., 2018; Belonogova et al., 2021; Kim et al., 2023). The SNPs associated with neuroticism have mostly been intronic or located between genes, especially in regions associated with chromatin interactions, namely trimethylated Lys4 on histone H3 (H3K4me3) and acetylated Lys9 on histone H3 (H3K9ac) regions (Nagel et al., 2018a). Since chromatin interactions regulate gene expression, and for example H3K4me3 is typically associated with more actively transcribed genes in the area (Barski et al., 2007), it implies that the genetic variation related to neuroticism may be mostly regulatory and not for example involving changes in protein structure or function. However, the importance of protein-coding variants in neuroticism has also been suggested (Belonogova et al., 2021). Other biological mechanisms implicated by GWASes include a stress-related mechanism, since the *CRHR1* gene involved in hormonal response to stress has been associated with neuroticism in several studies (Nagel et al., 2018a; LifeLines Cohort Study et al., 2016; Smith et al., 2016). Neuroticism as a trait has been traditionally associated with the stress response (Lahey, 2009). Immune functions are also suggested by some studies (Luciano et al., 2018), which supports the idea of a link between the immune system and neuroticism that has been suggested by several researchers and studies (e.g., Lahey, 2009).

2.2.4.3 Two genetically distinct subscores of neuroticism – worry and depressed affect

Neuroticism has been suggested to be a genetically heterogeneous trait that contains two genetically distinct, homogenous sets of questions, reflecting worry and depressed affect, although there is some disagreement on which questions should comprise the two subscores (Nagel et al., 2018a,b; Hill et al., 2020). Nagel and colleagues (2018a) argue that worry and depressed affect reflect different aspects of neuroticism because their genetic correlations with other traits differ markedly: the worry subscore is genetically linked with schizophrenia, bipolar disorder, and anorexia, while depressed affect is more related to depression (Nagel et al., 2018a).

2.2.5 Genetic correlation of schizophrenia and neuroticism

Genetic correlation (r_g) is an estimation of heritable overlap between traits and accordingly it reflects their genetic similarity and shared genetic background. Genetic correlation implies some form of pleiotropy – a single genetic locus affecting more than one phenotype – the main forms of which include horizontal (genetic variant has an independent influence on both traits, or there is a shared intermediate phenotype) and vertical pleiotropy (there is a causal relationship between the traits) (van Rheenen et al., 2019). Genetic correlation between schizophrenia and neuroticism is modest, around 0.2 (Smith et al., 2016: 0.22; Duncan et al. 2018: 0.18; Luciano et al., 2018: 0.21; Nagel et al., 2018a: 0.20), although lower estimates have also been reported (Lo et al., 2017: 0.14). Interestingly, the genetic correlation between schizophrenia and neuroticism has been suggested to relate to brain functional networks (Moreau et al., 2023). Schizophrenia has been shown to have the highest genetic correlations with bipolar disorder, r_g ranging from 0.65 to 0.83 (Duncan et al., 2018; Lo et al., 2017), and moderate genetic correlations with Major Depressive Disorder (MDD), r_g = 0.47 (Duncan et al., 2018; Lo et al., 2017), autism spectrum disorders, r_g = 0.19 (Duncan et al., 2018), and anorexia nervosa, r_g = 0.19 (Duncan et al., 2018). Some genetic overlap has also been reported with immune phenotypes with an r_g around 0.10 (Duncan et al., 2018). Furthermore, some of the rare risk variants associated with schizophrenia are shared with other neurodevelopmental disorders, including autism and intellectual disability and thus indicate shared genetic etiology (Singh et al., 2022; Rees et al., 2021).

Neuroticism shows high genetic correlations with anxiety disorders, r_g = 0.82 (Nagel et al., 2018a), depressive symptoms, r_g = 0.82 (Luciano et al., 2018), and MDD, r_g ranging from 0.56 to 0.69 (Luciano et al., 2018; Nagel et al., 2018a; Smith et al., 2016; Lo et al., 2017), and modest genetic correlations with anorexia nervosa, r_g ranging from 0.15 to 0.29 (Nagel et al., 2018a; Luciano et al., 2018; Lo et al., 2017), and attention deficit-hyperactivity disorder (ADHD), with an r_g around 0.23 (Nagel et al., 2018a; Luciano et al., 2018).

2.3 Estimation of genetic risk in the general population – polygenic risk scores

The large GWASes have provided an opportunity to estimate individual genetic risk for a polygenic trait or disorder by utilizing the results of the genome-wide association analyses. These liability estimates, called polygenic risk scores (PRS), summarize the wealth of information of a GWAS into one continuous score that indicates the cumulative effect of thousands of risk alleles (Wray et al., 2021). The idea of calculating PRSes was partly based on the notion that the genome-wide

significant hits found in early GWASes accounted for only a fraction of the phenotypic variance, but, if a larger number of genetic variants were used in prediction, the proportion of explained phenotypic variance was improved (Martin et al., 2019). However, the concept of the PRS has also been criticized: the biological plausibility behind the scores is not clear, and a large proportion of the variants included have an effect size very close to zero, which calls into question the relevance of the variant's influence on the phenotype (Janssens, 2019). These are valid arguments and can only be resolved with further research.

2.3.1 Calculation of polygenic risk scores

The idea of the polygenic model dates to Fisher's seminal paper in 1919, in which he introduced the infinitesimal model stating that a large number of discrete inherited elements each with a small effect may underlie heritable quantitative traits (Crouch & Bodmer, 2020). The inherited elements, or at least a part of them, and their effect sizes are now possible to estimate in GWASes. The effect sizes are estimated in a discovery GWA sample and a PRS is calculated in the target sample basically as a weighed sum of a person's risk alleles, with reported effect sizes from the discovery GWAS used as weights. The PRS can be calculated as:

$$PRS = \sum_{i}^{k} \beta_i \left(\sum_{j=0}^{2} p_{ij} \times j \right)$$

where k is the number of SNPs to be included in the score, β_i is the effect size of the ith SNP in the discovery sample, p_{ij} is the probability of genotype j, and j is the number of risk alleles (0, 1 or 2) of the ith SNP (Choi & O'Reilly, 2019). There are several issues that impact the accuracy and validity of the calculated scores, including the SNP heritability and the genetic architecture of the trait (Martin et al., 2019). In addition, aspects of both the original discovery GWAS sample and the target sample may affect the generalizability of the effect size estimates in the target sample, which has an impact on the accuracy of the calculated scores (Martin et al., 2019). A key element is the optimal similarity of the two samples; the discovery and target samples should preferably have no overlapping individuals or close relatives, but they should otherwise be as similar as possible: differences in population structure, allele frequencies, LD patterns, genotype effect sizes or the environment between the two samples may reduce the accuracy and validity of a PRS (Choi et al., 2020). The sample size of the discovery sample is also of importance: estimating small effect sizes accurately requires large sample sizes and this is especially true with highly polygenic traits with minor effect sizes for most of the variants (Martin et al., 2019). However, large sample sizes accomplished by pooling results across

several study populations may also pose problems. The effect sizes may not represent any of the study populations well and pooling several samples may require compromises to be made in the definition and criteria for the phenotype, which may further undermine the accuracy and generalizability of the estimates (Janssens, 2019).

The conventional method for calculating a PRS, the "clumping and thresholding" method (C+T), includes pruning genetic variants based on their LD pattern and setting a p-value threshold determining which of the variants to include in the score. The LD structure between SNPs results in correlated signals within genomic regions. The purpose of clumping is to discard correlated SNPs so that only independent and presumably additive signals remain and are included in the PRS. Selecting the p-value threshold implies that all the variants that reached the selected or lower p-value (for example 0.5) in the discovery GWAS are included in the score. Since the weights are based on the reported effect sizes, the variants with greater p-values have smaller effect sizes and contribute less to the total score. More permissive p-value thresholds that allow taking tens of thousands or hundreds of thousands of SNPs into account in a PRS usually yield better predictive power than PRSes calculated with more stringent p-values (Martin et al., 2019). This is understandable since a single common variant explains at the most only about 0.1% of the phenotypic variance, aggregating many variants will result in more variance explained. However, there is no simple solution to selecting an optimal p-value threshold, and it is affected by several factors including the genetic architecture of the trait and aspects of the discovery and target samples. Preferentially, the selection of the p-value threshold is based on a tuning sample, a sample independent of the discovery and target samples, in which the optimal p-value threshold for a maximal predictive power for the PRS can be determined (Ni et al., 2021). There are several programs available for the calculation of PRSes in the conventional way, including PLINK (Purcell et al., 2007), PRSice (Euesden et al., 2015), and PRSice2 (Choi & O'Reilly, 2019).

The conventional C+T method has been criticized for not properly taking into account the LD structure, which has been shown to lead to less predictive power of the PRSes (Vilhjálmsson et al., 2015). In addition, since the selection of a p-value threshold is not straightforward, this step has also been questioned. Accordingly, newer techniques utilizing a Bayesian regression framework have been developed, and these methods resolve some of the problematic issues in the conventional C+T method. In these techniques, all the genetic information is fully used while accounting for the LD pattern with external reference panels. Following a Bayesian framework, the estimated parameter distributions are based on both the discovery data and prior knowledge; posterior mean effect sizes for the SNPs are estimated from a discovery GWAS by assuming a prior for the genetic architecture. Depending on the program used, the prior distributions may vary from discrete to continuous.

Programs to calculate PRSes that utilize the Bayesian approach include for example LDPred (Vilhjálmsson et al., 2015), PRS-cs (Ge et al., 2019), and SBayes (Lloyd-Jones et al., 2019).

2.3.2 Predictive accuracy of polygenic risk scores

PRSes offer a way to estimate genetic liability to polygenic traits, including psychiatric disorders and neuroticism, that was not possible before the era of GWASes. Basically, a PRS is an estimate of genetic liability for a trait on an individual level and optimally it indicates the individual's location on a continuum of low versus high genetic risk for a disorder. Currently, the clinical utility of PRSes for psychiatric disorders or personality traits is still low and they cannot be used for disease prediction. However, although the clinical utility is low, PRSes are informative of the genetic risk and are usable for research purposes.

The predictive power of PRSes is quite low; PRSes typically explain only a few percent of the trait variability, depending on the trait in question. The heritability, and especially the SNP-based heritability, of a trait or disorder determines the theoretical upper limit for the phenotypic variance that can be explained by the PRS (Wang et al., 2022). In schizophrenia, the SNP-based heritability is 24% (Trubetskoy et al., 2022) and the PRS based on the latest and largest GWAS (SNPs with $p < 0.05$) explained 7.3% of the variance in schizophrenia liability, while genome-wide significant SNPs explained only 2.4% (Trubetskoy et al., 2022). The percentage was slightly higher, 8.2%, when only European samples were used in the prediction, which is understandable since most of the datasets in the discovery samples were European. The predictive power was also increased in samples with the most severe cases (Trubetskoy et al., 2022). Although the predictive power of schizophrenia PRSes is not very high, there is a considerable difference in schizophrenia risk between the high and low end of the schizophrenia PRS continuum: the highest PRS centile has been shown to have a much higher risk for schizophrenia diagnosis than the lowest centile, odds ratio (OR) = 39 (95% confidence interval (CI) 29–53), and also a clearly higher risk when compared with the remaining 99% of individuals, OR = 5.6 (95% CI 4.9–6.5) (Trubetskoy et al., 2022).

The predictive power of neuroticism PRSes is considerably lower, as is expected based on the lower SNP-based heritability, 10–15% (Realo et al., 2017). The neuroticism PRS based on the latest and largest neuroticism GWAS explained 4.2% of the variance in neuroticism (Nagel et al. 2018a), and the percentages of variances explained have ranged from 1% to 3% in earlier studies (Luciano et al., 2018: 2.8%; Lehto et al., 2019: 1.7%; Smith et al., 2016: ~1%).

2.3.3 Limitations of polygenic risk scores

PRSes for psychiatric disorders have limitations that need to be accounted for. One of the main limitations currently is the low predictive power of the scores, which raises the question of overall validity. Another clear limitation is the lack of understanding of the biological mechanisms behind the scores. Furthermore, the possibility of pleiotropy limits the causal inferences that can be made with the scores, which needs to be accounted for in research.

One of the likely reasons for the low predictive power of PRSes is that they do not cover all genetic variation, but mostly common genetic variation, while rare and structural variation are missing from the scores. Rare variation and CNVs have been shown to be important at least in schizophrenia (Purcell et al., 2014). However, the currently-known rare variants explain only a small amount of the total liability for schizophrenia (Psychosis Endophenotypes International Consortium, 2017), although they may have large effect sizes. Another reason for the low predictive power of the scores is that the detection of true causal variants is challenging, which complicates the estimation of true genetic risk. Since ethnicity and population history impacts the genetic haplotypes present in a population, a PRS based on a GWAS performed with people of different genetic backgrounds may not be properly tagging the genetic liability of the disorder. Accordingly, careful attention needs to be paid to the characteristics of the discovery GWAS. The phenotypic definition is also crucial since the more heterogeneity there is in the phenotype, the more heterogeneity there is in the genetic signals in a GWAS.

As previously mentioned, PRSes have been criticized for the ambiguity of the biological mechanisms behind the scores (Janssens, 2019). The biological plausibility of the PRSes is not yet clear and needs further elaboration. The genetic backgrounds of schizophrenia and neuroticism are highly polygenic and there are many biological mechanisms supposedly involved. Whether these mechanisms operate together or are alternative routes to schizophrenia (or to higher levels of neuroticism) is not known. Thus, having high or low genetic risk for a trait does not inform about the biological mechanisms, but is only a theoretical estimate of the genetic risk.

Since PRSes are calculated using numerous SNPs, the phenomenon of pleiotropy is likely to occur. In other words, the SNPs used in calculation of a PRS are not solely affecting the trait in question, but they have pleiotropic effects which may influence the outcome. SNPs in PRSes typically influence two or more biological processes. Accordingly, PRSes cannot be used as proof of causality.

2.4 Phenotypic effects of schizophrenia PRS and neuroticism PRS in the general population

The phenotypic effects of the genetic risk factors for schizophrenia and neuroticism have been studied in adults and children in the general population. Basically, genetic risk for schizophrenia has been associated with psychopathological liability in childhood and later in adolescence and adulthood (Hannigan et al., 2021; Jones et al., 2018; Marsman et al., 2020), and genetic risk for neuroticism has been associated with a higher likelihood of childhood psychopathology (Neumann et al., 2022; Nivard et al., 2017) and an increased risk for a psychiatric diagnosis in adulthood, including MDD, anxiety-related disorders and phobias (Docherty et al., 2018; de Moor et al., 2015; Verhoeven et al., 2019).

Table 3 Phenotypic associations of schizophrenia PRS in childhood.

Phenotype	Age of children	Reference
Negative mood (temperament)	2 years	Riglin et al., 2022
Internalizing problems	3, 6, 10 years	Jansen et al., 2018
Externalizing problems	3, 6 years	Jansen et al., 2018
Emotional problems	4–8 years (follow-up 12–17 years)	Riglin et al., 2019
Externalizing problems	5–6 years	Ensink et al., 2020
Child psychopathology (and internalizing psychopathology)	5–7 years	Neumann et al., 2022
Performance IQ, social and communication difficulties, emotion and mood dysregulation, behavior problems	7–9 years	Riglin et al., 2017
General psychopathology (factor “p”)	7–8 years, 13 years	Riglin et al., 2020
Emotional problems	7, 11, 16, 23, 33, 42 years (longitudinal study)	Riglin et al., 2018
Childhood psychopathology	7–16 years	Nivard et al., 2017
Cognitive functions	9–10 years	Gui et al., 2022
Learning problems and inattention	9, 12 years	Chen et al., 2022
School performance*	12 years	Koch et al., 2021

IQ = Intelligence quotient, PRS = Polygenic risk score

*Found only in boys

2.4.1 Schizophrenia PRS – phenotypic effects in childhood

Studies that have examined the phenotypic effects of the PRS for schizophrenia in childhood are presented in Table 3. Genetic risk for schizophrenia has been associated with a range of problems in children aged two years and older, including emotion and mood dysregulation, social and communication difficulties, behavior problems, poorer cognitive functions, and psychopathology (Riglin et al., 2017; Riglin et al. 2020; Neumann et al., 2022; Ensink et al., 2020; Jansen et al., 2018; Gui et al., 2022). However, there are also studies that have not found phenotypic effects for the genetic risk for schizophrenia. For example, Askeland and colleagues (2022) did not find genetic risk for schizophrenia to be associated with language or motor difficulties, inattention, or social communication at the ages of 6 or 8 months, or 3, 5, or 8 years, while Riglin and colleagues (2022) did not find associations between schizophrenia PRS and motor or language development at the ages of 18 and 24 months, respectively. Furthermore, many of the studies reported in Table 3 found associations at one age, but not necessarily at another.

2.4.2 Phenotypic effects of neuroticism PRS in childhood

Studies reporting childhood phenotypic effects for the PRS for neuroticism are presented in Table 4. In children aged two and older, genetic risk for neuroticism has been associated with varying phenotypes ranging from temperament and socio-emotional development to psychopathology (see Table 4). However, there are also studies that have not found phenotypic associations. For example, the neuroticism PRS was not associated with a child's internalizing or externalizing problems at the age of 5 to 6 years or 11 to 12 years (Ensink et al., 2020), nor with ADHD symptoms or social problems at the age of 9 to 10 years (Akingbuwa et al., 2023). Additionally, many of the studies reported in Table 4 did find associations at some ages, but not necessarily at others.

2.4.3 Role of the environment

Genes do not operate in isolation and the environmental circumstances in a child's life may influence the effect genetic factors have on a phenotype. This interplay between genes and environment may also be interpreted as a differential sensitivity to environmental effects; genetic propensities may affect how the environment affects the individual (Kendler & Eaves, 1986). Earlier studies have shown that children with a genetic propensity to psychiatric disorders may be especially vulnerable to disturbing child-rearing environments (Tienari et al., 1987). With respect to psychopathology, gene–environment interactions, or GxE, have been studied intensively within the candidate gene approach, however, the studies have

Table 4 Phenotypic effects of neuroticism PRS in childhood.

Phenotype	Age of children	Reference
Temperament	2 years	Costantini et al., 2023
Internalizing problems	2–16 years (cross-age composite)	Gidziela et al., 2022
Emotional and behavioral problems, internalizing problems	4, 6, 8, 9, 11 years	Costantini et al., 2023
Child psychopathology and internalizing psychopathology	5–7 years	Neumann et al., 2022
Anxiety-related disorder, depressive disorder (10 years)	7, 10 years	Costantini et al., 2023
Emotional problems	7, 9, 12 years	Plomin et al., 2022
Locus of control, self-esteem, IQ	8 years	Costantini et al., 2023
Internalizing problems	9–10 years	Akingbuwa et al., 2023
Anxiety in childhood	9, 12 years	Chen et al., 2022
Childhood psychopathology	1–20 years (mean age 10 years)	Jansen et al., 2021
Depressive symptoms and steeper trajectories of depressive symptoms	10 years and older	Kwong et al., 2021

IQ = Intelligence quotient, PRS = Polygenic risk score

largely been underpowered since a single GxE finding is expected to explain only a very small proportion of the total variance of the phenotype (Duncan & Keller, 2011). Fewer studies have examined GxE using PRSes, and the studies have mostly focused on adults (Plomin et al., 2022). However, in a recent study, it was suggested that GxE contributes substantially to mental health symptoms in youth (Choi et al., 2022). Studies examining schizophrenia PRS or neuroticism PRS regarding childhood development and psychopathology are scarce. For example, Plomin and colleagues (2022) did not find the neuroticism PRS to interact with childhood environmental factors in predicting childhood behavior problems. However, although there are not yet robust gene–environment interaction findings regarding childhood development or psychopathology, it is acknowledged that gene–environment interactions may prove to be important and merit further investigation (Plomin et al., 2022).

2.4.4 Studies in the first two years of life are scarce

Previous studies have shown that schizophrenia PRS and neuroticism PRS have various phenotypic effects in childhood. However, studies covering the first two years of life are scarce. To our knowledge, there are only a few studies that have examined the phenotypic effects of schizophrenia PRS (Askeland et al. 2022; Riglin et al., 2022) and neuroticism PRS (Costantini et al., 2023) in children aged 0 to 2 years. Askeland and colleagues (2022) studied social communication, language and motor difficulties, hyperactivity, and inattention reported by the mother at the ages of 6 and 18 months (and 3, 5, and 8 years), but did not find any robust associations between schizophrenia PRS and these phenotypes. Motor skills at 18 months were also studied by Riglin and collegues (2022), but they also did not find evidence of schizophrenia PRS to be associated with these phenotypes. Riglin and colleagues (2022) also studied parentally assessed temperament at the age of two years and found schizophrenia PRS to be associated with higher negative mood. Costantini and colleagues (2023) examined the association between neuroticism PRS and temperament assessed by mothers at their child's ages of six months and two years and found suggestive evidence for an association between neuroticism PRS and a more difficult temperament at the age of two years.

2.5 Development in infancy and toddlerhood – the first two years of life

The development of a child during the first two years of life is remarkable, as the child develops from a newborn to a capable toddler with a variety of acquired abilities ranging from motor skills to communicating and self-aware perceptions of the world. The maturation and development are comprehensive and include several areas that may be broadly categorized as physical (including e.g., growth, motor development, sensation, and perception), cognitive (including e.g., sensorimotor reasoning, attention, memory, and language), and socio-emotional development (including e.g., psychosocial and emotional development, and social interaction skills) (Kuther, 2023).

This thesis focuses on three aspects of early development: neurophysiological, motor, and socio-emotional development.

2.5.1 Neurophysiological development and sleep EEG

Rapid brain maturation and development are defining features of the first years of life, and it is coupled with the developmental attainments of the child. Sleep has an important role in brain development and during the first weeks the child is asleep most of the day, while the amount of sleep gradually decreases as the child matures

(Knoop et al., 2021). The continuing changes in the structure, amount, and topographical variation of sleep have been suggested to relate to the progress of brain maturation (Knoop et al., 2021; Page et al., 2021; Dan & Boyd, 2006) and thereby can be considered as neurophysiological markers of brain development. Newborns already have sleep stages, including active and quiet sleep, that are distinguishable in electroencephalogram (EEG) measurements. During the first months of life, active and quiet sleep gradually mature into rapid eye movement (REM) and non-rapid eye movement (NREM) sleep stages, respectively (Grigg-Damberger et al., 2007). Both active/REM sleep and quiet/NREM sleep have been shown to be essential for normal brain maturation and development (Page et al., 2021; Dan & Boyd, 2006): REM sleep has been suggested to play a role in selective pruning and maintenance of new synapses during development (Page et al., 2021), and alterations in REM sleep in infancy have been shown to be temporally connected to brain development (Mirmiran et al. 2003), while NREM sleep, including the two hallmark phenomena of NREM sleep, the slow wave activity (SWA) and sleep spindles, is suggested to regulate synaptic homeostasis and to stimulate synaptic and cortical maturation (Knoop et al., 2021; Kurth et al., 2012). In addition, the characteristics of sleep have been associated with many aspects of learning and development; for example, NREM sleep is suggested to play an important role in the development of episodic memory and in verbal and motor learning (Page et al., 2021; Page et al., 2018; Dan & Boyd, 2006).

Since the genetic risk factors for schizophrenia and neuroticism are involved with gene pathways related to brain development, it is plausible that genetic liabilities to schizophrenia or neuroticism might have phenotypic effects in terms of EEG-measured sleep in infancy. Studies in adults have shown that the genetic underpinnings of both schizophrenia and neuroticism are associated with sleep. Schizophrenia and sleep, including sleep duration in childhood, have been suggested to share genetic liability (O'Connell et al., 2021) and schizophrenia PRS has been associated with higher spindle activity in adults (Merikanto et al., 2019). However, this is contrary to the lower spindle activity seen in chronic schizophrenia patients (Ferrarelli et al., 2021). Furthermore, some sleep measures, such as spindle activity, have been proposed as endophenotypes of schizophrenia (Merikanto et al., 2019). Neuroticism PRS has been associated with lower sleep quality in adults (Stephan et al., 2020), and neuroticism as a trait has been associated with many aspects of poor sleep (Calkins et al., 2013; van de Laar et al., 2010; Vincent et al., 2009; Williams & Moroz, 2009; Gray et al., 2002). Since negative emotionality in children has been associated with EEG-measured sleep characteristics (Weisman et al., 2011) and sleep problems (Morales-Muñoz et al., 2020), the study of neuroticism PRS and sleep in early childhood becomes even more intriguing.

In this thesis, we studied whether schizophrenia PRS and neuroticism PRS, including the two subscores, worry PRS and depressed affect PRS, were associated

with neurophysiological development measured by sleep EEG. Our hypothesis was that the PRSes studied are associated with neurophysiological development and accordingly show an association with sleep EEG–based phenotypes.

2.5.2 Socio-emotional development in childhood – internalizing and externalizing symptoms

Early emotional and behavioral problems have been shown to be a significant risk factor for future mental health problems (Hannigan et al., 2017). In young children, socio-emotional and behavioral problems are usually understood by the two broad classes of internalizing (e.g., depression, withdrawal, anxiety and somatic complaints) and externalizing (e.g., impulsivity, aggression and rule-breaking behavior) symptoms (Achenbach, 1966). In young children, negative emotionality has been suggested to play an important role in the etiology and maintenance of internalizing and externalizing problems (Muris & Ollendick, 2005). Furthermore, since genetic factors have been shown to explain approximately half of the variability in internalizing and externalizing symptoms (van der Valk et al., 2003), it becomes plausible to assume that neuroticism PRS is associated with these symptoms. Neuroticism PRS has been associated with internalizing and externalizing problems in children aged four years and older (Akingbuwa et al., 2023; Costantini et al., 2023; Neumann et al., 2022; Akingbuwa et al., 2020), but it has not been explicitly studied in younger children. In this study, we examine the association between neuroticism PRS and socio-emotional development measured by internalizing and externalizing symptoms at the age of two years, and hypothesize that a higher neuroticism PRS is associated with higher internalizing and externalizing symptoms.

2.5.3 Motor development

Motor development in early childhood progresses from automatic responses of the neonate to self-controlled motor skills of a toddler in a predictable sequence. The motor skills are typically acquired within certain time frames, although there is great variation in timing on the individual level. Several studies have shown that people diagnosed with schizophrenia in adulthood have had a slower motor development in infancy (Filatova et al., 2017; Dickson et al., 2012; Sørensen et al., 2010; Isohanni et al., 2001). Based on these results, the association between genetic risk for schizophrenia and motor development seems plausible. However, earlier studies have not found associations between PRS for schizophrenia and motor skills or difficulties at the ages of 6 or 18 months (Askeland et al., 2022; Riglin et al., 2022). Earlier studies on patients with schizophrenia have found a slower attainment of certain motor skills. For example, in the review conducted by Filatova

and colleagues (2017), walking unsupported, standing unsupported and sitting unsupported were associated with adulthood-onset schizophrenia, while Sørensen and colleagues (2010) found slower attainment of the motor skills of sitting, crawling, and walking in schizophrenia patients compared to healthy controls. These skills develop within certain time frames, and accordingly, finding an association between motor development and genetic risk for schizophrenia might be dependent on the age and developmental phase studied. In this study, we examined the association between motor development and schizophrenia PRS at the age of eight months and expected to find a negative association between schizophrenia PRS and motor development.

2.5.4 Differences between boys and girls

There is accumulating evidence that girls and boys might differ in their development, and in how genetic and environmental factors contribute to their development (Bernabeu et al., 2021; DiPietro & Voegtline, 2017). For example, Bernabeu and colleagues (2021) showed in their study performed with UK Biobank data that there might be sex differences in the genetic architecture of traits. They argued that sex-specific molecular mechanisms are possible and that sex-aware analyses should be considered. Several studies additionally show that boys and girls might have different sensitivity to environmental exposures. For example, maternal stress (O'Connor et al., 2002) and depression (Gerardin et al., 2011) during pregnancy, and stress in early childhood (Andiarena et al., 2017) have been shown to have differing effects on girls and boys, with mostly boys showing more sensitivity (DiPietro & Voegtline, 2017). There are also studies that have shown differing effects for PRSes in the two genders, for example, a higher schizophrenia PRS was associated with lower cognitive performance in boys, but not in girls (Koch et al., 2021). We decided to take the possibility of gender differences in the genetic and environmental effects into account in this study and analyze girls and boys separately (whenever the sample size was large enough for separate analyses).

3 Aims

The main aim of this study is to examine the effect of genetic liability to psychiatric disorders on child development and on the sensitivity to environmental influences in early childhood. We focus on the genetic liabilities of two phenotypes: schizophrenia, a highly heritable and severe mental disorder profoundly affecting the function of neuronal networks and typically manifesting with cognitive impairments, and neuroticism, a trait associated with problems in emotion regulation and general susceptibility to psychiatric disorders, such as mood and anxiety disorders. First, we will examine whether the genetic risk factors for schizophrenia are already relevant in early childhood via interaction with the pre- and perinatal environment, and thereby affecting later schizophrenia liability. Next, we will examine the phenotypic effects of genetic liabilities of schizophrenia and neuroticism in the first two years of life of healthy children on neurophysiological, motor and socio-emotional development. The time points of the study are presented in Figure 1.

The three specific aims of the study are:

1) Does genetic liability to schizophrenia interact with early environmental factors and affect later liability to schizophrenia or related phenotypes? (Study I)
2) Are genetic risk factors for schizophrenia and neuroticism associated with characteristics of sleep EEGs and motor development in the first two years of life? (Study II)
3) Is genetic liability to neuroticism associated with internalizing and externalizing symptoms at the age of two years? (Study III)

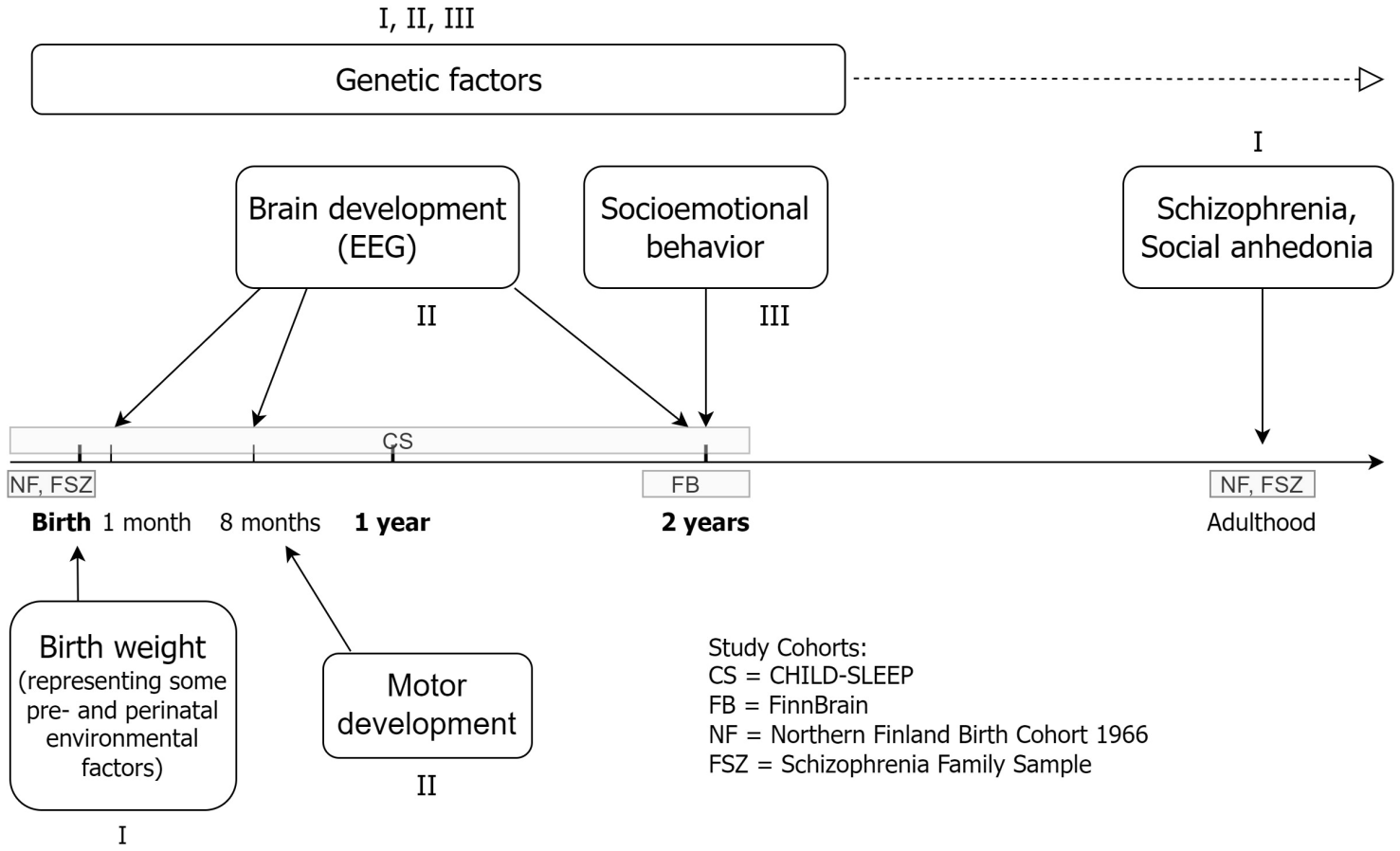

Figure 1 Time points of the study.

4 Materials & Methods

4.1 Study samples

4.1.1 Northern Finland Birth Cohort 1966

The Northern Finland Birth Cohort 1966 (NFBC1966) is an unselected birth cohort including N = 12,058 live births in Northern Finland, covering 96.3% of all births in the provinces of Oulu and Lapland during 1966 (Rantakallio, 1969). All pregnant women with an expected delivery date in 1966 in the provinces of Oulu and Lapland were invited to the study in 1965. The cohort has been followed prospectively since the 16th gestational week at several time points, including delivery, 28 days, 1, 14, 31, and 46 years of the child's age. The Ethics Committee of the Northern Ostrobothnia Hospital District has approved the study protocol and all participants have given written consent.

The NFBC1966 cohort was analyzed in Study I and participants were selected based on the data availability of the 31-year follow-up. The 31-year follow-up included 3 phases: a postal questionnaire, clinical examination and questionnaire containing psychometric assessments handed out in the clinical examination (Haapea et al., 2008). A total of 8365 participants were invited to the clinical examination (only cohort members living in northern Finland or the Helsinki area in 1997). Of these, 5960 participated in the clinical examination and 5084 returned the questionnaire. In addition, information on psychiatric diagnoses was collected for all participants from healthcare registers. Attrition analysis of the 31-year follow-up has been previously analyzed (Haapea et al., 2008). From the 31-year follow-up, we utilized data from the clinical examination (blood samples, needed for DNA extraction), the questionnaire handed out in the clinical examination (containing the social anhedonia scale) and psychiatric diagnoses collected from registers. We included all participants who had the following data available: successful genotyping, birthweight, covariate information, and either the social anhedonia scale or information on schizophrenia diagnosis. Accordingly, we had two datasets in our analysis; the Ns of the datasets were N = 4223 for the social anhedonia analysis and N = 5033 for the schizophrenia analysis, of which N = 4182 were included in both datasets.

4.1.2 Schizophrenia Family Sample

The Schizophrenia Family Sample (FSZ) is a systematically collected sample of Finnish schizophrenia families (Finnish Institute for Health and Welfare, 2024). The families were identified from nationwide registries including the Hospital Discharge Register (screened for hospitalization due to schizophrenia, schizoaffective disorder, or schizophreniform disorder between 1969 and 1998), Medication Reimbursement Register (screened for use of free outpatient antipsychotic medication), and Pension Register (screened for disability pension due to schizophrenia, schizoaffective disorder, or schizophreniform disorder). All individuals born in Finland between 1940 and 1976 were screened for in these three registers. Information on the pedigrees were derived from the Population Register Center based on the personal identification numbers of the affected individuals. Two samples were collected: 1) Families with at least two affected siblings with schizophrenia and all their first-degree relatives from the whole geographical area of Finland and 2) Families that had at least one member with schizophrenia from Kuusamo, a historically isolated area in northeastern Finland with an exceptionally high risk of schizophrenia (Hovatta et al., 1999). Data collected from these two samples included for example DNA samples, family structures and genealogy, and best-estimate lifetime psychiatric diagnoses according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). The study has been approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa, and all participants gave written informed consent.

The FSZ was used as a replication sample in Study I. The total FSZ sample included 3335 individuals with DNA samples, but availability of birthweight and social anhedonia data considerably limited the number of participants, resulting in N = 256 for the analysis of schizophrenia diagnosis and N = 133 for the analysis of social anhedonia.

4.1.3 CHILD-SLEEP Birth Cohort

The CHILD-SLEEP (CS) birth cohort is a systematically recruited birth cohort collected from the Pirkanmaa hospital district. It includes children born between April 2011 and January 2013 and their families (Paavonen et al., 2017). Initially, 1673 families (out of the 2244 families informed of the study) participated in the study. Families were recruited during pregnancy at the 32nd gestational week. Follow-ups were arranged at birth, 3, 8, 18, 24 months and 5 years. The study is still ongoing and the 10-year follow-up has recently been completed. The data includes several questionnaires filled in by both mothers and fathers, and blood samples collected from mothers, fathers, and from the umbilical cord. In addition, records from maternity hospitals and clinics were gathered. The study protocol was approved by the Ethics Committee of Pirkanmaa Hospital District, and the study

was conducted in accordance with the Declaration of Helsinki. All parents gave written informed consent.

The cohort also includes several smaller subsamples, including a polysomnography (PSG) study of 92 participants. The participants for the PSG study were recruited after birth as the mothers were staying in the maternity ward. All families willing to participate and fulfilling the inclusion criteria were included in the study. The inclusion criteria included an uneventful birth, full-term pregnancy, birthweight ≥ 2.5 kg, Apgar score at 1 min ≥ 8, no long-term severe illnesses of the child, and no medication affecting the central nervous system during the pregnancy. The PSG recordings were conducted at the ages of 1 month, 8 months, 24 months and 5 years. In this study, we used data on the time points of 1 month, 8 months and 24 months. The number of participants at these time points were N = 79 at 1 month, N = 68 at 8 months, and N = 63 at 24 months, and N = 50 participants had PSG measurements at all three time points. Out of the 92 families included in the study, 13 (1 discontinued, 3 could not participate, 3 recording failures, 4 were missing genotype data and 2 were missing data on covariates), 24 (16 discontinued, 4 recording failures, 2 were too old at the time of recording, and 2 were missing data on covariates), and 29 (27 discontinued, and 2 recording failures) participants were excluded at the ages of 1 month, 8 months and 24 months, respectively.

The CS cohort data was used in Studies II and III. In Study II, the PSG subsample was the main study sample, but one study question (motor development) was analyzed in the whole cohort. Of the 1117 participants having data on motor development and genotypes, we excluded 72 children due to possible errors in genetic data (N = 11), age ≥ 9 months at the time of assessing motor development (N = 39), and missing covariates (N = 22), resulting in N = 1045. In Study III, we included all the CS participants that had information on study variables and genotypic information: of the 942 children having questionnaire data on externalizing symptoms (N = 938 for internalizing symptoms), we excluded 136 children, based on missing genotype data (N = 121) and missing data on maternal depressive symptoms (N = 15), resulting in N = 806 for the study of externalizing symptoms (N = 803 for internalizing symptoms).

4.1.4 FinnBrain Birth Cohort Study

The FinnBrain Birth Cohort Study (FB) is a systematically recruited birth cohort collected from southwestern Finland and the Åland Islands (Karlsson et al., 2018). The sample includes children born between December 2011 and April 2015. Initially, 3808 mothers (out of 5790 pregnant women who were contacted) and 2623 fathers or partners agreed to participate in the study. Enrollment for the study was at the 12th gestational week and there have been several follow-ups during

pregnancy and after birth (e.g., at the child's age of 3 months, 6 months, 1 year, 2 years, 4 years, and 5 years). The study is still ongoing, with the 9-year follow-up in progress. The gathered information and measurements include several questionnaires, register data, biological samples, and medical and psychological assessments over the years. The ethics committee of the Hospital District of Southwest Finland approved the study protocol, and written informed consent was obtained from all the parents. The study was conducted in accordance with the Declaration of Helsinki.

The FB cohort was used in Study III, and data utilized included DNA extracted from umbilical blood sample (collected from 2063 infants) and questionnaire data from the 2-year follow-up. In the analyses, we included all children that had the required genotype and questionnaire information available. Of the 1444 children having questionnaire data on internalizing symptoms (N = 1443 for externalizing symptoms), we excluded 457 children due to missing genotypes (N = 398) and missing maternal depressive symptoms (N = 59), resulting in N = 987 for the study of internalizing symptoms (N = 986 for externalizing symptoms).

4.2 Measures

4.2.1 Measures in early childhood

The main outcome measures in childhood were EEG-measured sleep (0–2 years), motor development (8 months), and internalizing and externalizing symptoms (2 years). In addition, birthweight was used as a proxy for environmental factors in Study I.

4.2.1.1 EEG-measured sleep (0–2 years; Study II)

The EEG-based sleep measures analyzed in Study II included sleep architecture measures and power spectrum density variables on SWA and sigma frequencies. The measures were based on PSG recordings that were carried out as ambulatory overnight home recordings between 2011–2013. The home PSG protocol comprised six channels of EEG including left and right frontal, central and occipital channels (F3-, F4-, C3-, C4-, O1-, and O2-, respectively), bilateral electro-oculography, and submental electromyography for sleep stage scoring, in addition to respiratory signals to exclude, for example, obstructive sleep apnea. The sleep stages of 1-month-old infants were visually scored according to modified scoring criteria of young infants (Satomaa et al., 2016), while the contemporary recommendations (Berry et al., 2012) were used to score the sleep stages of 8- and 24-month-olds. Cortical arousals were scored according to contemporary guidelines (Berry et al., 2012, The International Paediatric Work Group On Arousals, 2005).

The sleep architecture measures used in the analyses included the total nocturnal sleep time (TST), sleep efficiency index (SEI = TST/TIB (time in bed)), arousal index (the number of cortical arousals and awakenings divided by TST), and percentages of active/REM sleep and quiet/NREM sleep. In one-month-olds, we calculated the percentages of active (AS%) and quiet sleep (QS%) during TST. Indeterminate (transitional) sleep was excluded from the analyses. In the 8- and 24-month-olds, we calculated the percentages of REM (REM%) and NREM sleep (NREM%) during TST. NREM% comprised all NREM sleep stages (N1, N2 and N3). Since the variables QS% (at 1 month) and arousal index (at 24 months) were not normally distributed, we used ln-transformations for these variables.

Spectral analyses of the SWA (1–4 Hz) and sigma (10–15 Hz) frequencies were performed on sleep stages N2 and N3. Power spectral densities on each of the six EEG derivations (F3, F4, C3, C4, O1, O2) were estimated separately by applying the built-in spectrogram tool of Embla Remlogic 4 PSG software for consecutive, non-overlapping epochs of 512 samples throughout the night. The EEG artifacts and arousals were first carefully inspected manually and erased from the analyses. In addition, epochs that had more than 10% of the total power at frequencies above the beta band were excluded.

4.2.1.2 Motor development (8 months; Study III)

As a part of the 8-month follow-up of the CS cohort, parents rated their child's motor development with a 12-item Finnish questionnaire modified for the CS study (Lyytinen et al., 2000). The questions described typical motor skills that are acquired during the first year of life and included items such as "The child can sit up without help", "The child can crawl on all fours", and "The child can move around using furniture as support". Parents rated each item on a three-point rating scale: "Not observed" (0), "Observed once" (1) or "Observed several times" (2). A continuous score ranging from 0 to 24 was calculated by summarizing the scores. Higher scores reflected better motor skills.

4.2.1.3 Internalizing and Externalizing symptoms (2 years; Study II)

Internalizing and externalizing symptoms were assessed by parents at the age of two years by the Brief Infant-Toddler Social and Emotional Assessment (BITSEA) (Briggs-Gowan et al., 2004). The questionnaire was included in the two-year follow-up questionnaire pattern in both the CS and FB cohorts. The BITSEA includes 42 items that were evaluated on a 3-level rating scale: "Not true / rarely" (0), "True to some extent / sometimes" (1) and "Very true / often" (2). A fourth level "Is not involved with other children" was used with two of the questions. Externalizing problems were assessed with 7 items, such as "Is restless and can't sit still" or "Hits,

shoves, kicks or bites children (not including brother/sister)", and internalizing problems with 14 items, such as "Seems nervous, tense or fearful" or "Often gets very upset". The ratings for the scales were summarized into continuous scores ranging from 0–14 (externalizing symptoms) and 0–28 (internalizing symptoms). Higher scores reflected more symptoms.

4.2.1.4 Birthweight (Study I)

In the NFBC1966, birthweight data were obtained from obstetric records and from questionnaires filled in by mothers shortly after the child was born. In the FSZ, information on birthweight was collected from birth reports. In the NFBC1966, birthweight was dichotomized as "high" (more than 4 kg) or "normal/low" (4 kg or less). The cut-off point for high birthweight was set at 4 kg and it was based on earlier findings on the association between birthweight and schizophrenia in the FSZ sample: high birthweight, defined as > 4 kg, was found to increase the risk for schizophrenia by 1.68-fold (Wegelius et al., 2011). In addition, both samples in Study I are rather old (all the participants in the NFBC1966 were born in 1966 and the participants in the FSZ were born in 1927–1976, out of which more than 90% were before 1967). The mean birthweight for gestational week 40 in the total NFBC1966 cohort was 3460 g (Rantakallio, 1973), while the reference values for birthweight at gestational age of 40 weeks have been higher in more recent cohorts in Finland, for example 3766 g for boys and 3642 g for girls in children born between 1996 and 2008 (Sankilampi et al., 2013). Accordingly, the cut-off of > 4kg is reasonable in older samples, while a higher cut-off for high birthweight might be more valid in younger cohorts. In the FSZ, we did not dichotomize the birthweight because of the limited number of participants in the analysis.

4.2.2 Measures in adulthood

Adulthood measures were analyzed in Study I. The two outcome measures were schizophrenia diagnosis and social anhedonia (Cohen et al., 2011; Kwapil, 1998).

4.2.2.1 Schizophrenia diagnosis (Study I)

In the NFBC1966, schizophrenia diagnosis was based on national register data (the Finnish Hospital Discharge Register and national registers of the Finnish Social Insurance Institute) and clinical interviews using the criteria of the DSM revised 3rd edition (DSM-III-R). In the FSZ, the diagnoses were based on patient records (Hospital Discharge Register, Medication Reimbursement Register, and Pension Register) and one-third of the participants were also interviewed with the Structured Clinical Interview, using the criteria of the DSM-IV.

4.2.2.2 Social anhedonia (Study I)

Participants self-rated social anhedonia with the revised Social Anhedonia Scale (Chapman et al., 1976). The measure includes 40 questions, which assess whether the person is interested in social interactions and finds pleasure in them. Each item (e.g., "Having close friends is not as important as many people say." and "People sometimes think I am shy when I really just want to be left alone.") were rated as either true (1) or false (0). The ratings were summarized into a continuous score ranging from 0 to 40, with higher scores reflecting more social anhedonia. In both samples, the NFBC1966 and FSZ, the distribution of scores was positively skewed, and we used square-root transformations in the analyses.

4.2.3 Covariates

Several covariates appropriate for the study designs were used in the analyses. The covariates used in all three Studies I–III, included gender (unless the genders were studied separately, as in Study III), age (unless the outcome measures were assessed in the same age for all participants, as in the birth cohorts), and three principal components calculated from genome-wide data to control for possible population stratification (Price et al., 2006) (except for the FSZ data, in which there were no genome-wide data available at the time the study was completed).

Other covariates included gestational age at birth and mother's body mass index (BMI) in Study I, as these might be associated with child's birthweight. In Studies II and III, maternal depressive symptoms were used as a covariate since mother's depression has been shown to affect her child's sleep (Sadeh et al., 2010) and to be associated with the child's internalizing and externalizing symptoms (Pietikäinen et al., 2020). In the EEG study (Study II), we further controlled for the age and season at the PSG measurement, because both the age of the child (Knoop et al., 2021) and season (Kärki et al., 2019) are shown to affect PSG measurements.

Maternal depressive symptoms were measured with two different scales in the CS and FB cohorts: the Finnish, shortened 10-item version (Kohout et al., 1993) of the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977) was used in the CS, and the Finnish version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) was used in the FB. Both measures contain 10 items, which are rated on a 4-level rating scale: "Rarely / not at all (0)", "A few times / for a while (1)", "Often / for a reasonable amount of time (2)", "All the time (3)". A continuous total score ranging from 0 to 30 (higher scores reflecting more depressive symptoms) was calculated by summarizing the ratings. We used the continuous score in the following analyses: Study III FB cohort (measured at the 2-year follow-up), Study II CS cohort in the analysis of 1-month data (measured prenatally). A dichotomous trajectory variable indicating continuously high or low depressive symptoms over 2 years (measurements at the prenatal phase, 3 months,

8 months, and 2 years of the child's age; see details Kiviruusu et al., 2020) was used in the following analyses: Study III CS cohort, Study II in the analysis of 8- and 24-month data. The validities of both the CES-D scale (Gonzáles et al., 2017) and the EPDS scale (Gibson et al., 2009) have shown to be acceptable.

Season was based on the daily light variation in the Tampere region in Finland, and four seasons were defined: winter Nov 7–Feb 4, spring Feb 5–May 5, summer May 6–Aug 5, and autumn Aug 6–Nov 6.

4.2.4 Genotyping

NFBC1966. DNA samples extracted from whole blood were genotyped with the Illumina Infinium 370cnvDuo platform at the Broad Institute, Cambridge, MA, USA. Genetic markers were checked for call rate (> 95%), Hardy–Weinberg equilibrium (p-value > 5.7× 10−7) and MAF (> 1%). Individuals were checked for missing genotypes (> 5%), sex discrepancy between reported and chromosomal sex, relatedness (identity by descent), sample duplication, ancestry outliers and heterozygosity outliers. Genotype data was imputed at two different time points with Impute2 using the HapMap2 or the 1000 Genomes project (March 2012 version 3 release) as the reference panels. The variants imputed with HapMap2 were used in the schizophrenia PRS of 8 variants (SZ PRS_8), and the variants imputed with the 1000 Genomes project were used in the schizophrenia PRS of 127 variants (SZ PRS_{127}).

FSZ. DNA samples extracted from whole blood were genotyped with homogeneous mass extension using the MassARRAY System (Sequenom, San Diego, CA, USA) in the Institute for Molecular Medicine, Finland. The following eight SNPs associated with schizophrenia (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011) were genotyped: rs10503253, rs7004633, rs1625579, rs17662626, rs2021722, rs7914558, rs11191580, and rs548181.

CS & FB. DNA samples extracted from umbilical blood were genotyped with the Illumina Infinium PsychArray (CS, FB) and Illumina Infinium Global Screening Array (FB) at the Estonian Genome Center. Individuals were checked for missing genotypes (> 5%), relatedness (identical by descent) and ancestry outliers (multidimensional scaling). Markers were removed for missingness (> 5%) and Hardy–Weinberg equilibrium (p-value < 1×10^{-6}). Genotyped data of both cohorts were pre-phased with Eagle 2.3.5 (Loh et al., 2016) and imputed with Beagle 4.1 (Browning and Browning, 2016) using the Finnish population-specific SISu v2 as the reference panel.

4.2.5 Calculating polygenic risk scores

4.2.5.1 Polygenic risk scores for schizophrenia

Three different PRSes for schizophrenia were used in the studies. Two of the scores, SZ PRS_8 and SZ PRS_{127} (Study I), were calculated using genome-wide significant variants and they were based on earlier schizophrenia GWASes. The third score, SZ PRS (Study II), included a considerably larger set of variants and was based on a more recent GWAS of schizophrenia (Trubetskoy et al., 2022).

Polygenic risk scores for schizophrenia calculated with genome-wide significant variants (Study I). In Study I, we calculated two PRSes, SZ PRS_8 and SZ PRS_{127}, that included only genome-wide significant variants. The scores were based on the findings of two large genome-wide association analyses of schizophrenia. The genome-wide meta-analysis of schizophrenia performed in 2011 reported ten independent SNPs that represented eight physically distinct genomic loci (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). Of these ten SNPs, eight passed the quality control of the NFBC1966 cohort and were included in the SZ PRS_8 score: rs1625579, rs17662626, rs2021722, rs7914558, rs11191580, rs548181, rs10503253, and rs7004633. Two of these SNPs were genotyped and six were imputed in the NFBC1966 cohort (in the FSZ, all the variants were genotyped). The score was calculated in both samples, the NFBC1966 and FSZ, as a weighed sum of the risk allele count at each locus using reported ORs for each SNP as weights:

$$Genetic\ Risk\ Score\ SZ\ PRS_8 = \sum_{i=1}^{8} OR_i x_i$$

where OR = odds ratio for the risk allele and x = the number of risk alleles (0, 1, 2) at a locus.

The SZ PRS_{127} score was based on a larger genome-wide meta-analysis of schizophrenia, which reported 128 genome-wide significant variants associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The SZ PRS_{127} score was calculated only in the NFBC1966 sample since we did not have genome-wide data for the FSZ cohort (at the time). Of the 128 variants, one variant, rs77149735 on chromosome 1, did not pass the quality control of imputed variants, and was therefore excluded from the score. Accordingly, we calculated the PRS with 127 variants (15 genotyped and 113 imputed) using the following formula:

$$Genetic\ Risk\ Score\ SZ\ PRS_{127} = \sum_{i=1}^{127} [2 \times p(A_i A_i) + p(A_i B)] \times log(OR_i)$$

where OR = reported odds ratio for the reference allele, p = probability for the genotype, A_i = the reference allele of the variant, and B = the alternative allele of the variant.

Polygenic risk score for schizophrenia (Study II). In Study II, we calculated a PRS for schizophrenia, SZ PRS, using the C + T method. Clumping was performed in a 500 kb window with a cutoff of $r^2 = 0.25$, and p-value = 1 was used as the threshold. The score included N = 364,724 variants in total. We used European samples (including several datasets from Finland) of the most recent and largest GWAS of schizophrenia (Trubetskoy et al., 2022) as the discovery sample and calculated the SZ PRS with the PRSice program (Euesden et al., 2015).

4.2.5.2 Polygenic risk scores for neuroticism (Studies II and III)

We calculated three PRSes for neuroticism, one score for a total neuroticism scale and two scores for the subscores of worry and depressed affect, using the C + T method. We accounted for LD by implementing clumping in a 500 kb window with a cutoff of $r^2 = 0.25$. The p-value of 0.1 was used as the threshold, which resulted in N = 113,522 variants for the neuroticism PRS, N = 100,771 variants for the worry PRS and N = 101,466 variants for the depressed affect PRS. We based the PRSes on published GWAS summary statistics (Nagel et al., 2018a) using the results of the UK Biobank only, and calculated the scores with PRSice (Euesden et al., 2015).

4.3 Statistical analysis

Study I. Our main aim was to analyze gene–environment interactions (genetic risk for schizophrenia × early environment represented by birthweight) on schizophrenia diagnosis and social anhedonia in adulthood. We ran the analyses first in our main sample, the NFBC1966, and used the FSZ as a replication sample. We used logistic and linear regression models for analyzing schizophrenia diagnosis and social anhedonia, respectively. We ran the regression models with gender, gestational age, mother's BMI, and three principal components calculated from the genetic data to control for population stratification as covariates. Age was not used as a covariate because all the participants were of the same age. The gene–environment interaction was studied by adding the interaction term of genetic risk for schizophrenia × birthweight into the regression model. We used "normal/low birthweight" as the reference category for birthweight in the models. In the analysis of schizophrenia diagnosis, we excluded participants who had a diagnosis of

psychoses other than schizophrenia spectrum disorder (N = 63). We ran the analyses in the whole cohort, and separately for men and women. We ran the analyses separately for the two PRSes, SZ PRS_8 and SZ PRS_{127}.

In the replication sample, the FSZ, we ran similar analyses with the following modifications: since the data were a family sample, we used a General Estimations Equations (GEE) model to adjust for the within-family correlations (Liang and Zeger, 1986). In addition, since the number of available participants for this study was restricted, we did not dichotomize the birthweight variable but used it as a continuous variable in the analyses. Since the effect of birthweight on schizophrenia is presumably U-shaped (e.g., Moilanen et al., 2010, an earlier study in the NFBC1966), we excluded participants with low birthweight (< 2.5 kg) from the analyses. The covariates included gender, age and a variable indicating whether the participant belonged to the internal isolate (Kuusamo) sample. We did not have data on mother's BMI, gestational age, or genome-wide data to calculate principal components, and accordingly these variables were not used as covariates in the FSZ sample.

Study II. Our main aim was to analyze whether the PRSes for schizophrenia and the two subscores of neuroticism, worry and depressed affect, were associated with infant sleep, including EEG-based sleep architecture variables and EEG power spectral densities of SWA (1–4 Hz) and sigma (10–15 Hz). We analyzed the study questions in the PSG subsample of the CS birth cohort. Since the sample size of the PSG subsample was small, we did not study boys and girls separately. To analyze the association between the PRSes and the sleep architecture variables, we ran separate linear regression models for each dependent variable (active/REM sleep %, quiet/NREM sleep %, TST, SEI, arousal index) at each time point (1, 8, and 24 months) and for each PRS (SZ PRS, worry PRS and depressed affect PRS). The following variables were included as covariates in the regression models: gender, age (postmenstrual age in weeks at the 1-month recording, and chronological age at 8- and 24-month recordings), season at the recording, maternal depressive symptoms, and the first three principal components calculated from genome-wide data to control for population stratification. The associations between PRSes and EEG power spectral densities were analyzed with Spearman correlations because the power distributions were non-normal. The analysis was exploratory in nature, and we did not add covariates in the analyses.

As an additional study question, we analyzed whether the SZ PRS was associated with motor development at the age of eight months in the larger CS cohort. We analyzed the association by running a linear regression model on motor development using the SZ PRS as the independent variable and gender, age, gestational age at birth, maternal depressive symptoms and the first three principal components calculated from genetic data as covariates. To analyze individual items of the motor development scale, we calculated Kendall's coefficient of rank

correlation (τ_b) between SZ PRS and the 12 individual items. We ran the analysis for the whole data and separately for boys and girls.

Study III. Our main aim was to analyze whether the PRS for neuroticism was associated with externalizing and internalizing symptoms at the age of two years, and, in case of significant findings, to analyze which of the two subscores of neuroticism PRS, worry PRS or depressed affect PRS, or both, were associated with the dependent variable. We analyzed the study questions in two Finnish birth cohorts, CS and FB. Since the ethical permissions prohibited us to combine the two samples, we ran the analyses separately in the two datasets and used meta-analysis to combine the results. We interpreted only the results of the meta-analyses. We analyzed the study questions with linear regression models using internalizing and externalizing symptoms as dependent variables in separate models, neuroticism PRS as an independent variable and the first three principal components calculated from genetic data to control for population stratification and maternal depressive symptoms as covariates. Age was not used as a covariate since all the participants were two-year-olds. Because of the emerging evidence of differential associations in genetic and environmental effects by a child's gender (Bernabeu et al., 2021; DiPietro & Voegtline, 2017), we analyzed boys and girls separately.

We used IBM SPSS Statistics for Windows, versions 20, 22, 26 and 28 (Studies I and III), and R versions 4.1.1. and 4.2.2. (Studies II and III) in the statistical analyses. The meta-analysis in Study III was performed with the R package "meta" (version 4.12–0). Results of Studies II and III were illustrated using a sliding window technique: we ranked participants according to their score on the PRS and calculated a mean value of the dependent variable (EEG power in Study II and externalizing symptoms in Study III) using a sliding window (width = 10 in Study II; width = 100 in Study III) for the PRS to smooth the data.

4.3.1 Correction for multiple testing

In Studies I and III, and in Study II regarding the analyses of sleep architecture and motor development, we tested predetermined research hypotheses, and we did not correct the p-values for multiple testing. Furthermore, in Study III, we interpreted only the results of the meta-analyses, which limited the number of associations tested. In these analyses, p-values < 0.05 were interpreted as statistically significant. In Study II, the analyses between PRSes and EEG power spectrum densities were exploratory in nature, and we used a Bonferroni-corrected p-value threshold of $p = 0.0014$ to indicate significant findings ($0.05/36$ (3 PRSes × 2 frequency ranges × 3 channel positions × 2 points of measurement) = 0.0014).

4.3.2 Power calculations

In Study II, we had a limited number of participants in the PSG study, and we performed power calculations before running the analyses. In the sleep-stage analyses, we had 79, 68 and 63 children at the time points of 1 month, 8 months and 24 months, respectively. With these sample sizes, we had more than 90% power to detect a multiple partial correlation of magnitude 0.4, and 79%, 72% and 69% power to detect a multiple partial correlation of magnitude 0.3, respectively. In the EEG power spectrum analyses, the sample sizes were 57 and 52 at the time points of 8 and 24 months, respectively, and we had over 80% power to detect a correlation of 0.4, and 60% and 56% power to detect a correlation of 0.3, respectively, with a p-value threshold of 0.05. However, with a Bonferroni-corrected p-value threshold of 0.0014, the power to detect significant associations was more limited, with the sample sizes of 57 and 52 at the time points of 8 and 24 months, respectively, we had 42% and 37% power to detect a correlation of 0.4, and 17% and 14% power to detect a correlation of 0.3, respectively.

5 Results

5.1 Genetic risk for schizophrenia, early environment, and schizophrenia diagnosis in adulthood (Study I)

The study questions were analyzed in the NFBC1966 birth cohort, and the FSZ sample was used as a replication sample in the analyses. Characteristics of the study samples and study variables are presented in Table 5.

Table 5 Characteristics of the NFBC1966 (N = 4223) and FSZ (N = 282) study samples (Study I).

	Study sample NFBC1966		**Replication sample FSZ**		
Variable	Mean (SD)/ %(N)	Range	Mean (SD)/ %(N)	Range	p*
Gender (men)	45.0% (1902)	-	46.8% (132)	-	0.61
Age	31.0 (0)	-	45.6 (9.2)	25 – 73	-
Birthweight (kg)	3.47 (0.5)	1.5 – 6.0	3.40 (0.8)	1.1 – 5.5	0.12
High birthweight	11.5% (487)	-	16.7% (47)	-	0.01
Gestational age (weeks)	40.1 (1.9)	26 – 46	-	-	-
Social anhedonia	9.5 (5.6)	0 – 36	11.6 (7.1)	0 – 30	< 0.001
Schizophrenia diagnosis	1.6% (81)	-	31.2% (88)	-	< 0.001
SZ PRS_8	11.4 (1.8)	4.5 – 17.0	12.8 (1.6)	8.0 – 17.0	< 0.001
SZ PRS_{127}	-0.50 (0.5)	-2.5 – 1.8	-	-	-

Modified from Liuhanen et al., 2018.

Note. In the NFBC1966, N for the analysis of schizophrenia diagnosis is 5033, and schizophrenia diagnosis also includes schizophrenia spectrum diagnoses (schizoaffective, schizophreniform, delusional disorder). In the FSZ, descriptives are presented for all participants that had data on the study variables, N = 282. Participants with birthweight < 2.5 kg (N = 26) were excluded from the analysis, resulting in N = 256. Social anhedonia is only from N = 144 participants.

FSZ = Schizophrenia Family Sample, NFBC1966 = Northern Finland Birth Cohort 1966, PRS = Polygenic risk score, SD = Standard deviation, SZ = Schizophrenia

*p-value for the test of statistical difference between the two samples (t-test for continuous variables, X^2 test for categorical variables).

The two samples used in Study I were of different types: the NFBC1966 is an unselected birth cohort, while the FSZ is a systematically collected sample of schizophrenia families. Accordingly, the main difference between these two samples was the prevalence of schizophrenia diagnosis. In the NFBC1966, 1.6% of the participants were diagnosed as having a schizophrenia spectrum disorder (including schizophrenia, schizoaffective disorder, schizophreniform disorder, and delusional disorder), while 31.2% of the participants of the FSZ sample had a diagnosis of schizophrenia. The two samples also differed in terms of social anhedonia, PRSes for schizophrenia and proportion of participants having high birthweight, so that participants in the FSZ had higher scores or higher percentage on all these variables (Table 5). In the NFBC1966, we calculated two PRSes for schizophrenia, SZ PRS_8 and SZ PRS_{127}. The correlation between the two genetic risk scores, PRS_8 and PRS_{127}, was low, $r = 0.03$, $p = 0.03$. Of the two scores, only PRS_{127} was directly associated with schizophrenia diagnosis (OR = 1.8, 95% CI: 1.2–2.7, $p = 0.005$) so that having a higher genetic risk score increased the risk for schizophrenia. In the replication sample, the FSZ, we calculated only one PRS for schizophrenia, SZ PRS_8, which was not significantly associated with schizophrenia diagnosis (OR = 1.02, 95% CI: 0.97–1.08, $p = 0.37$). The SZ PRSes were not directly associated with social anhedonia, neither in the main sample nor in the replication sample.

5.1.1 Genetic risk for schizophrenia × early environment interaction is associated with social anhedonia and schizophrenia in adulthood

In a fully adjusted regression model, with gender, gestational age and the three main genetic principal components as covariates, we found the interaction term of SZ PRS_8 × birthweight was significantly associated with social anhedonia in adulthood ($\beta = 0.20$, $p = 0.05$), so that having both high birthweight and higher genetic liability to schizophrenia was associated with higher scores on social anhedonia. However, after adding mother's BMI as a covariate to the model, the interaction term was no longer statistically significant, although the beta was of similar magnitude ($\beta = 0.19$, $p = 0.08$). The interaction term of SZ PRS_8 × birthweight was not significantly associated with schizophrenia diagnosis in a fully adjusted regression model (OR = 1.3, 95% CI: 0.9–1.9, $p = 0.10$), although the direction of the association was as hypothesized. However, the number of schizophrenia cases in the sample was low (N = 81), due to the low prevalence of the disorder (1.6%). In the replication sample, the SZ PRS_8 × birthweight interaction term was significantly associated with schizophrenia diagnosis (OR = 1.5, 95% CI: 1.1–2.1, $p = 0.02$), but not with social anhedonia (OR = 1.1, 95% CI:

1.0–1.3, p = 0.09), although the OR was in the same direction as in the discovery sample. Having higher genetic risk for schizophrenia together with higher birthweight was associated with more schizophrenia diagnosis in the replication sample.

We did not obtain similar results with the SZ PRS_{127} score. In the main NFBC1966 sample (the score was not calculated in the replication sample), the interaction term of SZ PRS_{127} × high birthweight was not significantly associated with schizophrenia diagnosis (p = 0.24) or with social anhedonia (p = 0.61).

5.1.2 Differences between men and women

In the main sample, the NFBC1966, men and women differed in terms of birthweight (p < 0.001), social anhedonia (p < 0.001), and schizophrenia diagnosis (p = 0.02), so that men had higher scores or more diagnoses in all these variables compared to women as described earlier for this cohort (Miettunen et al., 2010). There were no differences between the genders in the genetic risk scores.

The SZ PRS_8 × birthweight interaction term was similarly associated with social anhedonia in men and women (β = 0.21, p = 0.20 and β = 0.18, p = 0.25 for men and women, respectively), although the associations were not statistically significant. However, in women, the SZ PRS_8 × birthweight interaction term was significantly associated with schizophrenia diagnosis (OR = 7.6, 95% CI: 2.8–20.5, p < 0.001), but the same was not true for men (p = 0.51). In the replication sample, the finding was similar, the SZ PRS_8 × birthweight interaction term was significantly associated with schizophrenia diagnosis particularly in women (OR = 2.0, 95% CI: 1.4–2.9, p < 0.001), while it was non-significant in men (p = 0.93).

5.2 Phenotypic effects of genetic liability to schizophrenia and neuroticism in the first two years of life – Sleep EEG and motor development (Study II & Unpublished results)

The study questions considering sleep EEG were analyzed in the PSG subsample (N = 92) of the CS birth cohort, while the analysis on motor development was performed in the whole CS cohort. Characteristics of the study samples are presented in Table 6. The PSG subsample did not differ from the larger CS cohort in any of the variables studied, except for the PRS for depressive affect: children in the PSG sample had significantly lower scores of the depressive affect PRS (mean = -0.23, standard deviation (sd) = 0.86) compared to the larger CS cohort (mean = 0.01, sd =1.01, t(1423) = 2.25, p = 0.02). The correlations between the PRSes are presented in Table 7.

Table 6 Characteristics of the CHILD-SLEEP birth cohort and the polysomnography (PSG) sub-group of the CHILD-SLEEP birth cohort (Study II).

Variable	CHILD-SLEEP (N = 1669)			CHILD-SLEEP PSG (N = 92)		p*
	N	Mean (SD)/ % (N)	Range	Mean (SD)/ % (N)	Range	
Gender (Boys)		52.8% (882)	-	50% (46)	-	0.67
Gestational age at birth (weeks)	1429	39.6 (1.3)	33 – 42	39.6 (1.1)	36 – 42	0.67
Maternal depressive symptoms profile over 0–2 years, high	1467	17% (249)	-	10.9% (10)	-	0.37
Maternal depressive symptoms at 2-year follow-up	1022	5.55 (4.0)	0 – 23	-	-	-
Schizophrenia PRS	1438	0.00 (1.0)	-3.6 – 3.8	-0.08 (1.1)	-3.6 – 2.6	0.45
Neuroticism PRS	1438	0.00 (1.0)	-3.4 – 3.4	-0.13 (1.0)	-2.5 – 2.7	0.20
Worry PRS	1438	0.00 (1.0)	-3.4 – 3.1	-0.16 (1.2)	-2.7 – 2.4	0.18
Depressed affect PRS	1438	0.00 (1.0)	-3.7 – 3.1	-0.22 (0.9)	-2.1 – 2.0	0.03
Internalizing symptoms at 2 years	803	3.74 (2.9)	0 – 17.2	-	-	-
Externalizing symptoms at 2 years	806	3.11 (2.2)	0 – 11	-	-	-
Motor development at 8 months	1045	15.1 (4.1)	5 – 24	-	-	-

PRS = Polygenic risk score, SD = Standard deviation

*p-value for the test of statistical difference between the CHILD-SLEEP cohort and the PSG subsample (t-test for continuous variables, X2 test for categorical variables).

Table 7 Pearson correlation coefficients between the polygenic risk scores in the PSG sample (N = 92).

Variables	Schizophrenia PRS	Neuroticism PRS	Worry PRS
Neuroticism PRS	0.07		
Worry PRS	0.22*	0.57***	
Depressed affect PRS	0.08	0.43***	0.40***

PRS = Polygenic risk score, PSG = Polysomnography

* p < 0.05, ** p < 0.01, *** p < 0.001

5.2.1 The phenotypic effects of genetic risk for schizophrenia

5.2.1.1 EEG-based sleep architecture variables

We analyzed the association between the SZ PRS and sleep architecture variables at the ages of 1, 8 and 24 months. The SZ PRS was negatively associated with quiet sleep % in 1-month-olds, β = -0.26, p = 0.005 (Figure 2), and with NREM sleep % in 24-month-olds, β = -0.27, p = 0.02, and positively associated with active sleep % in 1-month-olds, β = 0.22, p = 0.007, and with REM % in 24-month-olds, β = 0.27, p = 0.03. The SZ PRS was not associated with sleep length, sleep efficiency or arousal at any of these ages, nor it was associated with NREM% or REM% at the age of 8 months.

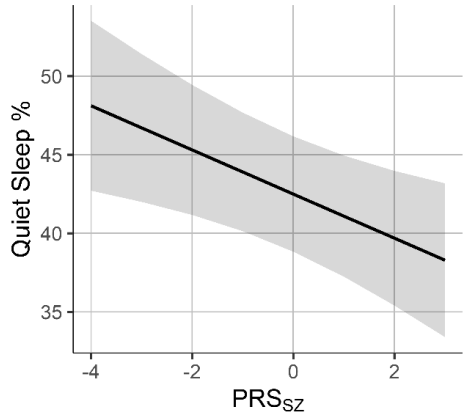

Figure 2 Predicted values of quiet sleep % as a function of schizophrenia PRS (PRS_{SZ}) at the age of one month with 95% confidence intervals.

5.2.1.2 EEG power spectrum

The associations between the SZ PRS and EEG power spectrum density values of SWA (1–4 Hz) and sigma (10–15 Hz) were analyzed at the ages of 8 and 24 months. We had limited power to detect significant associations in this exploratory analysis, but we found two correlations that were of nominal significance: the SZ PRS was negatively associated with right frontal SWA at the age of 8 months, ρ = -0.33, p = 0.02, and positively associated with left central sigma at the age of 24 months, ρ = 0.30, p = 0.04. In addition, the correlations between the SZ PRS and sigma power values were consistently positive at the age of 24 months (correlation coefficients ranging from 0.14 to 0.20, except for the right occipital electrode, r = 0.03).

5.2.1.3 Motor development at 8 months

As an additional study question, followed by the nominally significant negative correlation between the SZ PRS and SWA in eight-month-olds, we further studied whether the SZ PRS was associated with motor development at the same age. We examined the association between motor development and the SZ PRS in the whole CS cohort (N = 1045).

As hypothesized, the SZ PRS was negatively associated with motor development at the age of 8 months, $\beta = -0.07$, $p = 0.02$, so that having a higher genetic risk for schizophrenia was associated with slower motor development. We also analyzed boys and girls separately, and found a negative association in both genders, although a significant one only in girls, $\beta = -0.10$, $p = 0.02$, N = 513 (in boys: $\beta = -0.04$, $p = 0.34$, N = 532). We further analyzed the motor development scale in more detail and found three items that were negatively associated with the SZ PRS in girls: "The child can sit up without help", $\tau = -0.09$, $p = 0.01$; "The child can crawl on all fours", $\tau = -0.07$, $p = 0.04$, and "The child can move around using furniture as support", $\tau = -0.08$, $p = 0.02$ (Figure 3). Accordingly, we found these associations only in girls, but we did not find any significant differences between boys and girls in the proportions of having acquired these motor skills at eight months ($p > 0.1$ for all three comparisons, although the percentages were higher in boys compared to girls), in gestational age ($p = 0.37$) or in the exact age the motor skills were assessed ($p = 0.08$).

Figure 3 Polygenic risk score (PRS) for schizophrenia and motor skills. Mean scores of the schizophrenia PRS (PRS_{SZ}) with 95% confidence intervals separately for eight-month-old boys and girls who have or have not acquired the motor skills of a. "Sitting without help", b. "Crawling on all fours", and c. "Moving around using furniture as support". In girls, the differences between the two groups are significant in all three skills, $p = 0.01$.

5.2.1.4 Replicating the findings with SZ PRS_8

We further analyzed whether the findings in this study replicated with the SZ PRS_8, the PRS for schizophrenia calculated in Study I. The SZ PRS_8 included eight genome-wide significant SNPs based on the schizophrenia GWAS conducted in 2011 (The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). Of these 8 SNPs, 2 (rs1625579 and rs2021722) are within the genome-wide significant genomic areas reported in the latest schizophrenia GWAS (Trubetskoy et al., 2022), used in the calculation of the SZ PRS, and 6 of the SNPs are within 1000 kb, at most, of a genome-wide significant genomic region. Since the SZ PRS is calculated with the p-value threshold of 1, all the SNP information is included in the PRS. The correlation between the SZ PRS and the SZ PRS_8 in the CS cohort was low, $r = 0.09$, $p < 0.001$, $N = 1425$. (The correlation is stronger the more stringent the p-value threshold for the SZ PRS is used, for example with a p-value threshold of 0.0001, $r = 0.22$, $p < 0.001$.)

The significant findings found in the sleep architecture analyses were not replicated with the SZ PRS_8, but the associations between the SZ PRS_8 and EEG power spectrum values were similar: the SZ PRS_8 was almost significantly associated with right frontal SWA at 8 months (Spearman $\rho = -0.25$, $p = 0.07$) and significantly associated with sigma power at several electrode positions at 24 months. While the SZ PRS was positively associated with left central sigma power at 24 months, and also consistently positively associated with other electrode positions, the SZ PRS_8 was positively associated with frontal right, $\rho = 0.43$, $p = 0.001$, and left $\rho = 0.41$, $p = 0.01$, central right, $\rho = 0.29$, $p = 0.03$, and occipital right, $\rho = 0.28$, $p = 0.04$, sigma powers. The association between the SZ PRS and motor development was not replicated with the SZ PRS_8, although the association was also negative. (Liuhanen et al., unpublished results)

5.2.2 The phenotypic effects of genetic risk for neuroticism

5.2.2.1 EEG-based sleep architecture variables

We analyzed the association of the neuroticism PRS and the two subscores, worry PRS and depressive affect PRS, with sleep architecture variables at the ages of 1, 8 and 24 months. The neuroticism PRS, worry PRS and depressed affect PRS were associated with sleep variables at the age of eight months, but not at other ages. A higher depressed affect PRS was associated with a lower proportion of REM sleep ($\beta = -0.48$, $p = 7.9\times10^{-4}$) and with a higher proportion of NREM sleep ($\beta = 0.51$, $p = 2.7\times10^{-4}$), see Figure 4. The neuroticism PRS and worry PRS were associated with total nocturnal sleep time ($\beta = -0.26$, $p = 0.02$ and $\beta = -0.25$, $p = 0.01$ for the neuroticism PRS and worry PRS, respectively), with every 1 SD increase in

neuroticism PRS or worry PRS shortening the sleep time by approximately 15 minutes (Liuhanen et al., unpublished results).

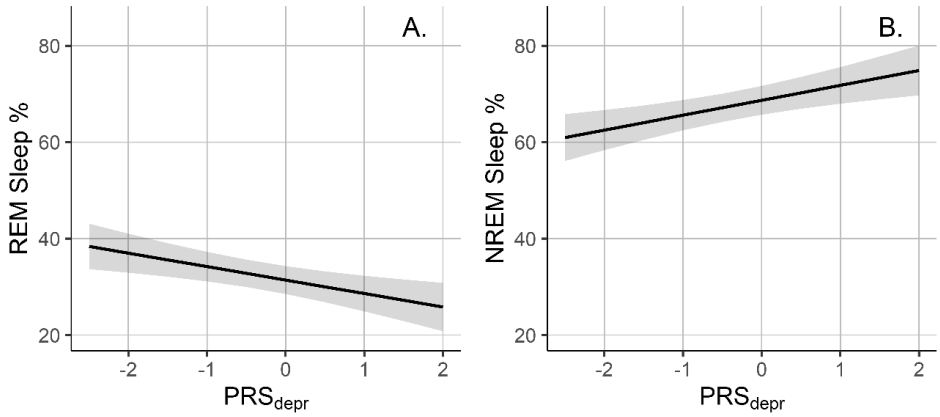

Figure 4 Predicted values of a. REM sleep % and b. NREM sleep % as a function of depressed affect PRS (PRSdepr) in 8-month-olds with 95% confidence intervals.

5.2.2.2 EEG power spectrum

The associations between the PRSes and EEG power spectrum density values of SWA (1–4 Hz) and sigma (10–15 Hz) were analyzed at the ages of 8 and 24 months. There were no significant associations between the PRSes and EEG power spectral density values of SWA or sigma at the ages of 8 and 24 months in this analysis of limited power. However, there was one nominally significant correlation between the neuroticism PRS and left frontal sigma power at the age of 8 months, $\rho = 0.30$, $p = 0.03$. Additionally, there were consistent patterns in the results; the worry PRS was consistently positively correlated with sigma at the age of 24 months (Spearman correlation coefficients ranging from 0.19 to 0.24 through all the electrode positions except for the left occipital electrode). The neuroticism PRS was consistently negatively associated with SWA at the age of 24 months (correlation coefficients ranging from -0.07 to -0.18) and the depressed affect PRS was consistently negatively associated with SWA at the age of 8 and 24 months, except for the right occipital electrode at 24 months (correlation coefficients ranging from -0.07 to -0.14 and from -0.06 to -0.18 at the ages of 8 and 24 months, respectively) (Liuhanen et al., unpublished results).

Table 8 Descriptive statistics of the study variables of the CHILD-SLEEP cohort (CS) and the FinnBrain cohort (FB) by gender (Study III).

	CHILD-SLEEP N = 940							**FinnBrain N = 1444**						
	Girls N = 446			Boys N =494				Girls N = 671			Boys N = 773			
Variable	N	Mean	SD	N	Mean	SD	p*	N	Mean	SD	N	Mean	SD	p*
Internalizing symptoms	445	3.9	2.9	491	3.6	2.9	0.07	671	3.4	2.6	773	3.4	2.4	0.52
Externalizing symptoms	446	2.8	2.1	494	3.3	2.2	<0.001	671	2.2	1.8	772	2.9	2.1	<0.001
Maternal depressive symptoms	431	5.8	4.0	460	5.4	4.0	0.13	630	4.6	4.3	737	4.6	4.3	0.98
Maternal depressive symptoms profile over 0-2 years, high	442	17.2%	-	481	13.7%	-	0.29	-	-	-	-	-	-	-

Modified from Liuhanen et al., 2023

Note. Descriptive statistics are presented for all participants having data on internalizing and externalizing symptoms. Genetic data were available for N = 820 (CS) and N = 1046 (FB) participants, and N for having all the study variables was 806 in CS and 987 in FB. Maternal depressive symptoms were measured by the Center for Epidemiological Studies Depression Scale (CES-D) in CS and the Edinburgh Postnatal Depression Scale (EPDS) in FB.

SD = Standard deviation

*p-value for testing the statistical difference between boys and girls (t-test for continuous variables, X^2 test for categorical variables).

5.3 Genetic liability to neuroticism and internalizing and externalizing symptoms at the age of two years (Study III)

The study questions were analyzed in the CS and FB birth cohorts. The descriptive statistics of the study variables are presented in Table 8. In both samples, boys had higher scores on externalizing symptoms than girls ($p < 0.001$). We analyzed whether children having missing data on externalizing and internalizing symptoms differed from children with non-missing data on the neuroticism PRS with t-tests for independent samples and found that participants with missing data had higher neuroticism PRS scores compared to participants with non-missing data in both datasets ($p = 0.01$ for all t-tests).

We first analyzed whether the neuroticism PRS was associated with internalizing or externalizing symptoms and found it to be significantly associated with externalizing symptoms in boys ($\beta = 0.08$, $p = 0.01$). The neuroticism PRS was not associated with internalizing symptoms in boys ($\beta = 0.02$, $p = 0.58$), and in girls, there were no significant associations at all ($\beta = -0.02$, $p = 0.53$ and $\beta = -0.02$, $p = 0.62$ for externalizing and internalizing symptoms, respectively).

Upon closer examination, we found that the subscore worry PRS ($\beta = 0.09$, $p = 0.01$), but not depressed affect PRS ($\beta = 0.02$, $p = 0.54$) was associated with externalizing symptoms in boys. If analyzed with different (more liberal) p-value thresholds for the PRSes, the results were even stronger (Tables 9 and 10 for the results of the neuroticism PRS and worry PRS, respectively). Plots representing the association between the neuroticism PRS or worry PRS and externalizing symptoms in boys are presented in Figure 5.

Table 9 Results of regression analyses using different p-value thresholds for the neuroticism PRS. Each row represents a separate regression model analyzing the association between the neuroticism PRS and externalizing problems in boys with maternal depressive symptoms and the first three genetic principal components as covariates. Reproduced with permission from Elsevier (Liuhanen et al., 2023).

Neuroticism PRS p-value threshold	**CS (N = 416 boys)**			**FB (N = 528 boys)**			**Meta-analysis**		
	β	s.e.	p	β	s.e.	p	β	95% CI	p
1	0.13	0.05	0.01	0.05	0.04	0.26	0.08	0.02; 0.15	0.01
0.5	0.13	0.05	0.01	0.05	0.04	0.27	0.09	0.02; 0.15	0.01
0.3	0.13	0.05	0.01	0.05	0.04	0.23	0.09	0.02; 0.15	0.01
0.1	0.12	0.05	0.01	0.05	0.04	0.21	0.08	0.02; 0.15	0.01
0.05	0.12	0.05	0.02	0.06	0.04	0.21	0.08	0.02; 0.15	0.01
0.001	0.08	0.05	0.13	0.03	0.05	0.59	0.05	-0.02; 0.11	0.16

CI = Confidence interval, CS = CHILD-SLEEP birth cohort, FB = FinnBrain birth cohort study, PRS = Polygenic risk score, s.e.= standard error

Table 10 Results of regression analyses using different p-value thresholds for the worry PRS. Each row represents a separate regression model analyzing the association between the worry PRS and externalizing problems in boys with maternal depressive symptoms and the first three genetic principal components as covariates. Reproduced with permission from Elsevier (Liuhanen et al., 2023).

Worry PRS p-value threshold	**CS (N = 416 boys)**			**FB (N = 528 boys)**			**Meta-analysis**		
	β	s.e.	p	β	s.e.	p	β	95% CI	p
1	0.12	0.05	0.02	0.10	0.05	0.03	0.11	0.04; 0.17	0.001
0.5	0.11	0.05	0.03	0.10	0.05	0.03	0.11	0.04; 0.17	0.002
0.3	0.12	0.05	0.01	0.10	0.05	0.03	0.11	0.04; 0.18	0.001
0.1	0.11	0.05	0.03	0.08	0.05	0.10	0.09	0.02; 0.15	0.01
0.05	0.11	0.05	0.03	0.04	0.05	0.36	0.07	0.01; 0.14	0.03
0.001	0.07	0.05	0.19	-0.00	0.04	0.96	0.03	-0.04; 0.09	0.40

CI = Confidence interval, CS = CHILD-SLEEP birth cohort, FB = FinnBrain birth cohort study, PRS = Polygenic risk score, s.e.= standard error

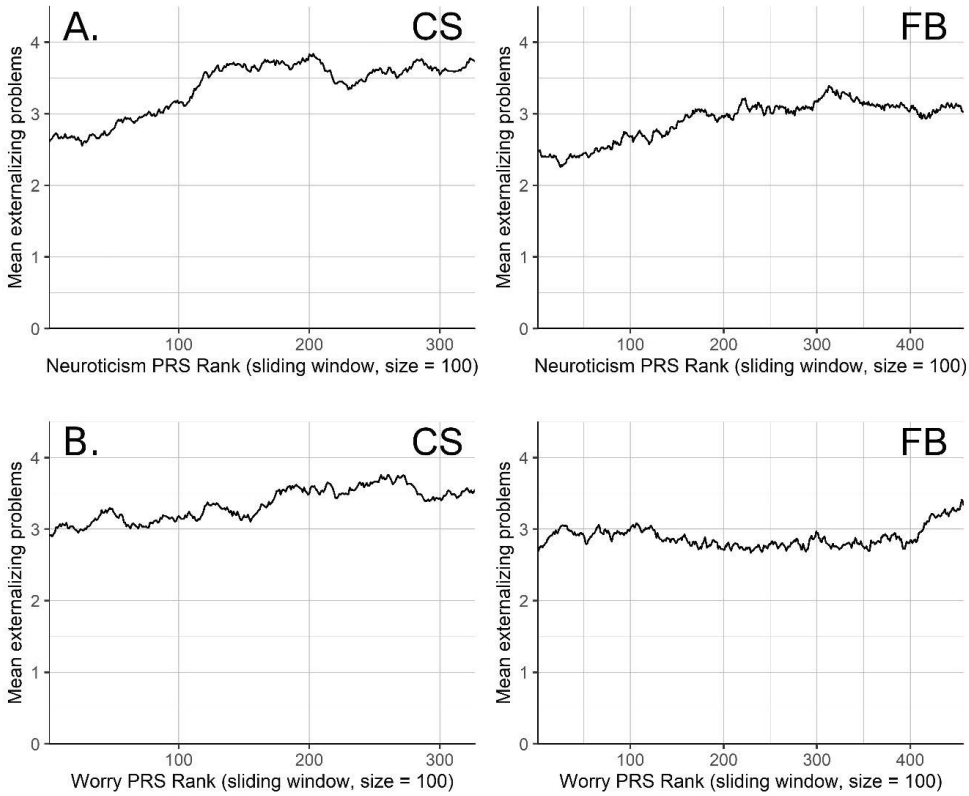

Figure 5 Externalizing symptoms in boys as a function of a. neuroticism polygenic risk score (PRS) and b. worry PRS using a sliding window of size = 100 in CHILD-SLEEP birth cohort (CS) and Finnbrain birth cohort study (FB). Reproduced with permission from Elsevier (Liuhanen et al., 2023).

6 Discussion

The main aim of this study was to examine the effect of genetic liabilities for schizophrenia and neuroticism on childhood development and on the sensitivity to environmental influences in the first two years of life in healthy children. First, we examined whether the genetic risk for schizophrenia affected sensitivity to the early environment and, together with an unfavorable environment, increased the risk for schizophrenia diagnosis and social anhedonia later in adulthood. Next, we analyzed whether genetic risk scores for schizophrenia and neuroticism were associated with neurophysiological development and motor development in the first two years of life. Last, we studied whether genetic risk for neuroticism was associated with socio-emotional development at the age of two years.

We found the genetic liabilities for schizophrenia and neuroticism were associated with childhood development ranging from neurophysiological maturation to motor and socio-emotional development, and the genetic risk for schizophrenia was also associated with sensitivity to the early environment. Accordingly, our results suggest that the genetic liabilities to schizophrenia and neuroticism may already have phenotypic effects in the first two years of life in healthy children. However, the effects might be dependent on the age and developmental phase of the child and there may be gender differences.

6.1 Genetic risk for schizophrenia, sensitivity to early environmental factors and schizophrenia diagnosis in adulthood

We found genetic risk factors for schizophrenia to affect sensitivity to early environmental factors: High birthweight, representing early environmental factors, together with a higher genetic risk for schizophrenia was associated with higher scores of social anhedonia, a characteristic related to negative symptoms in schizophrenia, and with a higher risk for schizophrenia diagnosis 31 years later in adulthood, although the latter result was found only in women. The results were found in two different sample types, a population-based sample, and a schizophrenia family sample with high rate of schizophrenia patients, thus suggesting a robust finding. The result was in line with previous studies showing that high birthweight increases the risk for schizophrenia in individuals with a high

familial risk for schizophrenia, presumably reflecting high genetic risk (Keskinen et al., 2013; Wegelius et al., 2011). High birthweight is assumed to be a proxy for early environmental circumstances mostly related to gestation and labor, including gestational diabetes and maternal hyperglycemia, prolonged labor, and obstetric complications, all of which are risk factors for the child for developing schizophrenia later in adulthood (Van Lieshout et al., 2008; Cannon et al., 2002). It must be noted, however, that the relevance of high birthweight as a risk factor in younger cohorts, at least with the cut-off of 4 kg used here, might not be similar to the risk in the older cohorts used in this study since the follow-up of pregnancies by healthcare professionals and for example screening for maternal diabetes has progressed vastly during recent decades. However, our results suggest that infants with higher genetic liability to schizophrenia might be more susceptible to the harmful effects of the early environmental risk factors. Similar results have been found in other studies (Ursini et al., 2018), although there are also studies that report no significant interaction between obstetric complications and genetic risk for schizophrenia in predicting later schizophrenia status (Valli et al., 2023; Vassos et al., 2022). Neither the nature of the interaction nor the actual operating mechanism is currently known, although a hypothesis of a placenta-mediated effect has been proposed (Ursini et al., 2018). In their study, Ursini and colleagues (2018) found that the schizophrenia liability genes that interacted with obstetric complications were highly expressed in the placenta and suggested a role for a placental cellular stress response. Another hypothesis might be that people with higher genetic risk for schizophrenia have less resilience in their developing brain so that for example a lack of oxygen during labor would have more detrimental effects than for a person with more resilience. However, the current study cannot say anything about the possible mechanisms. It must also be noted that the interaction found here is in a statistical sense. Based on this study, there is no proof of an actual interaction between genetic factors and the early environment.

We calculated two genetic risk scores for schizophrenia, which differed from each other by the GWAS they were based on and by the number of genetic variants included in the scores. We would have expected to obtain similar findings with both scores, but found differing results. We found the results described above only with the score with fewer genetic variants, the SZ PRS_8, but not with the SZ PRS_{127}. In addition, we found that, of the two scores, only SZ PRS_{127} was directly associated with schizophrenia diagnosis. However, this might be because SZ PRS_8 is capturing only a limited amount of genetic information. Although the broader score, SZ PRS_{127}, would be expected to represent a broader genetic liability to schizophrenia and correlate with the narrower score, the correlation between the scores was very low, only $r = 0.03$, which suggests that the two scores are probably measuring different aspects of genetic liability to schizophrenia. In fact, the scores do not have any genetic variants in common, although five of the genetic variants in SZ PRS_8

are near the genomic loci found in the GWAS that the SZ PRS_{127} was based on (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Furthermore, the scores were based on variants imputed with differing reference panels at different time points, which could have affected the low correlation to some extent. Schizophrenia has been shown to be a very polygenic disorder, with hundreds of genes currently associated with the disorder. It is not known how the genes are involved in the etiology of schizophrenia, but it is highly possible that there are several differing genetic pathways that contribute to the disease. The two genetic risk scores in this study might not reflect the same genetic pathways, which may result in differences in the findings.

We found differing results for men and women: the interaction between genetic risk for schizophrenia and birthweight was significantly associated with schizophrenia diagnosis only in women in both study samples. Although there is plenty of literature showing gender differences in the prevalence, onset, symptom patterns or cognitive functions in schizophrenia (Pedersen et al., 2014; Abel et al., 2010), though not all studies report similar findings (e.g., Saha et al., 2005), the possible differential developmental pathways for schizophrenia in the two genders have not been studied intensively. "A female protective model" in neurodevelopmental disorders has been proposed (Jacquemont et al., 2014), suggesting that women might tolerate more deleterious mutations before becoming ill, as has been shown regarding autism. Whether this is true for schizophrenia or applicable to environmental insults as well, is, to our knowledge, currently unknown. It must be noted that the cut-off point for high birthweight in our study was more extreme for women than for men, since it deviated more from girls' mean birthweight than from boys' mean birthweight (Rantakallio, 1968).

6.2 Genetic risks for schizophrenia and neuroticism and neurophysiological and motor development in early childhood

6.2.1 Genetic risk for schizophrenia and neurophysiological development

Neurophysiological development in the first two years of life was measured with sleep EEG, and the studied phenotypes covered sleep architecture variables and power spectrum density values. We found the genetic risk for schizophrenia to be associated with the sleep-EEG phenotypes in infancy: a higher genetic risk for schizophrenia was associated with a lower percentage of quiet or NREM sleep and a higher percentage of active or REM sleep at the ages of 1 and 24 months. In addition, the genetic risk for schizophrenia was nominally significantly associated

with EEG power spectrum values of SWA and sigma, so that higher genetic risk for schizophrenia was associated with lower values of right frontal SWA at the age of 8 months and a higher value of left central sigma at the age of 24 months.

The results are in line with our hypothesis that genetic risk for schizophrenia is associated with EEG-measured sleep phenotypes in infancy and suggest an influence on early brain development. There are no previous studies, however, at least to our knowledge, that have examined the association between the PRS for schizophrenia and EEG-measured sleep in infants. However, there is a study that suggests that genetic risk for schizophrenia is involved with early brain growth: Le and colleagues (2023) examined the association between a PRS for schizophrenia and brain volumes in small infants and found higher genetic risk for schizophrenia was associated with smaller volumes of white matter in the whole brain and specifically in the frontal lobe, and with smaller volumes of grey matter in specific brain areas.

NREM sleep is proposed to have an important role in stimulating synaptic and cortical maturation, although it is dependent on the age and developmental phase of the child (Knoop et al., 2021). The association between the genetic risk for schizophrenia and the percentage of quiet/NREM sleep might reflect an altered developmental process in which high genetic risk for schizophrenia is predisposing to alterations of synaptic processes during brain development. On the other hand, high genetic risk was also associated with the percentage of active/REM sleep, which has been shown to diminish as the baby matures (Knoop et al., 2021). Active/REM sleep has been suggested to reflect the maturational level of the brain (Mirmiran et al., 2003), and accordingly our results might suggest that the genetic risk factors for schizophrenia are associated with altered proportions of the sleep stages reflected in the brain development of babies. Since the proportions of REM and NREM sleep are inversely associated, it is impossible to tell whether genetic risk for schizophrenia was associated with the percentage of NREM or REM or both.

We found genetic risk for schizophrenia to be associated with nominal significance to EEG power spectrum values of SWA and sigma at the ages of 8 and 24 months. The analysis was exploratory in nature and gave us suggestive evidence of the phenotypic effects of genetic risk factors of schizophrenia in early childhood. We found higher genetic risk for schizophrenia to be associated with lower right frontal SWA at the age of eight months. This result could be thought of as being in line with studies of adult unmedicated schizophrenia patients, which have shown reduced SWA (Keshavan et al., 1998; Ganguli et al., 1987). Frontal SWA has been associated with fine motor and language development in eight-month-old babies in this same study cohort (Satomaa et al., 2020) and with cognitive performance and learning in healthy adults (Huber et al., 2004; Simon et al., 2017; Göder et al., 2006). Accordingly, our result suggests that genetic risk for schizophrenia may have phenotypic effects on sleep that are associated with cognitive and motor

development in infancy and cognitive performance in adulthood, and that these phenotypic effects are already detectable in the first months of life.

Genetic risk for schizophrenia was also associated with higher left central sigma at the age of 24 months, and the correlation coefficients were quite consistently positive on all electrode positions bilaterally in this exploratory analysis of limited power. Sigma power reflects spindle activity, and here higher genetic risk was associated with higher sigma, indicating more spindle activity. This is not in line with earlier studies on schizophrenic patients and their healthy relatives, which have quite consistently shown reduced spindle activity in both patients and their healthy relatives (Lai et al., 2022; Ferrarelli, 2021). Furthermore, higher spindle activity and sigma power have been consistently associated with better cognitive performance, memory and learning in children and in adults (Friedrich et al., 2019; Bestmann et al., 2019; Friedrich et al., 2015; Schabus et al., 2006; Satomaa et al., 2020). Interestingly, however, a PRS for schizophrenia has earlier been associated with higher spindle activity in both healthy adults and adolescents (Schilling et al., 2022; Merikanto et al., 2019). Accordingly, our results are in line with earlier studies on healthy individuals. However, the associations between spindles, cognition and genetic risk for schizophrenia clearly require further studies.

6.2.2 Genetic risk for neuroticism and neurophysiological development

We studied the association between genetic risk for neuroticism, including the two subscores, worry and depressed affect, and the sleep-EEG phenotypes at the ages of 1, 8 and 24 months. We found associations at the age of eight months, but not at other ages: higher genetic risk for depressed affect was associated with a higher percentage of NREM sleep and a lower percentage of REM sleep, while the genetic risk scores for neuroticism and worry were associated with shorter total sleep time at night. (Of note, the association between genetic risk for depressed affect and total sleep time at night was in the same direction, but not significant.) We further found a nominally significant association between genetic risk for neuroticism and frontal sigma power at the age of eight months.

The results are in line with our hypothesis that the genetic risk for neuroticism, and its subscores, are associated with EEG-measured sleep phenotypes. The association between genetic risk for neuroticism or worry and shorter total sleep time at night is in line with a previous study in adults regarding the neuroticism trait, in which neuroticism was associated with shorter sleep (Vincent et al., 2009). The reason why the effects are found at the age of eight months might relate to the new phases of development babies are going through at that age. For example, motor development is advancing rapidly and separation anxiety, a part of normal socio-emotional development, is typically emerging at this age. These

developmental challenges have been shown to affect babies' sleep (Atun-Einy & Scher, 2016). REM sleep has been hypothesized to be involved in emotional processing and emotion regulation in adults (Deliens et al., 2014; Genzel et al., 2015), and adults high in neuroticism are suggested to be particularly vulnerable to stress-related sleep disruption (Williams & Moroz, 2009). In young children, negative emotionality has been associated with more sleeping problems (Touchette et al., 2005), and night awakenings in eight-month-olds have been associated with socio-emotional behavior and self-regulatory abilities (Mäkelä et al., 2021). Consequently, our findings may suggest that genetic liability to depressed affect may relate to an impaired capacity of the infant's brain to regulate emotions, which is reflected in the REM sleep at eight months. However, important environmental aspects that play a role in the development of emotion regulation, including parent–child interaction, were not studied, or controlled for in this study.

Higher genetic risk for neuroticism was nominally significantly associated with higher sigma power, reflecting higher spindle activity, at the age of eight months. The association between polygenic risk for neuroticism and spindles has not been studied before, to our knowledge, and only a limited number of studies have examined the association between neuroticism as a trait and spindles with differing results. In a study by Benbir Şenel and colleagues (2021), neuroticism as a trait was not associated with spindles in a sample of 20 patients with paradoxical insomnia and 20 healthy controls. However, Becske and colleagues (2023) found preliminary indications that neuroticism as a trait might be associated with sleep spindles, as they found an association between neuroticism trait and left lateralization of slow sleep spindles (Becske et al., 2023).

The finding that the genetic liabilities for schizophrenia and neuroticism were differentially associated with EEG-measured sleep phenotypes depending on the age of measurement was not a result we anticipated. However, due to the scarcity of previous studies, setting down specific hypotheses based on earlier knowledge was not possible. We did find associations between genetic risk for schizophrenia and EEG-measured sleep phenotypes at all the ages studied, but, at the age of eight months there were no associations at the level of sleep stages. The lack of an association at the age of 8 months, as contrary to 1 and 24 months, could indicate that the effects of the genetic risk factors for schizophrenia on sleep architecture are overridden by other emotional and developmental factors more relevant to this developmental period. However, it should be noted that the results found in this study are not yet replicated and are as such, only suggestive, but they raise interesting hypotheses about age-dependent effects of different genetic liabilities. More studies to understand the findings, however, are needed.

6.2.3 Genetic risk for schizophrenia and motor development

The association between genetic risk for schizophrenia and motor development was studied at the age of eight months. The idea for examining this association was partly based on the nominally significant finding between genetic risk for schizophrenia and frontal SWA at the same age, since SWA has been argued to have an important role in learning motor skills (Huber et al., 2004). As hypothesized, genetic risk for schizophrenia was associated with motor development, so that higher genetic risk was associated with slower motor development, although the association was only significant in girls. The finding is in accordance with previous research reporting slower motor development in childhood in schizophrenia patients (Filatova et al., 2017). However, the result is not in line with earlier studies, which have not found association between polygenic risk for schizophrenia and motor difficulties at ages 6 and 18 months, and 3, 5 and 8 years (Asekland et al., 2022) or motor skills at the age of 18 months (Riglin et al., 2022). However, the ages in these previous studies differed from the age of eight months examined in our study, and it is possible that the associations we found are age specific and related to specific developmental phases of the child. Earlier studies on schizophrenia patients have shown that the motor skills of sitting, crawling, standing, and walking are among the developmental milestones that have been shown to differ between schizophrenia patients and healthy controls (Sørensen et al., 2010; Filatova et al., 2017). These skills develop within a limited time range, and the developmental process may not be captured at other ages. It is possible that at the age of around eight months the differences in motor development are more discernible, however proof of this requires further studies. In all, our results together with these earlier studies suggest that slower motor development might indicate a genetically influenced process that might relate to later vulnerability to schizophrenia.

The association between genetic risk for schizophrenia and motor development was found to be significant only in girls. In earlier studies, slower motor development has been associated with schizophrenia diagnosis in adulthood in both genders (e.g., Sørensen et al., 2010; Isohanni et al., 2001). A possible limitation is that we had information on motor development from a single time point, and not over a longer period. It is possible that the age of eight months was not the optimal time point considering motor development in boys, although there is no clear evidence that girls and boys would differ in their pace of development (WHO Multicentre Growth Reference Study Group, 2006). However, earlier literature shows that girls and boys may have different developmental pathways in terms of motor development (Grace et al., 2016). Accordingly, boys and girls may be influenced differently by early risk factors, but this naturally requires further studies.

6.3 Genetic risk for neuroticism and socio-emotional development

We studied the association between genetic risk for neuroticism and socio-emotional development, measured by internalizing and externalizing symptoms, at the age of two years. We found the genetic risk for neuroticism to be associated with externalizing symptoms in boys, so that lower genetic risk for neuroticism was associated with less burden of externalizing symptoms. The effect seemed robust: the result was based on data from two independent Finnish birth cohorts, and it was independent of the choice of the PRS p-value threshold. Of the two subscores of neuroticism, worry and depressed affect, only genetic risk for worry was associated with externalizing symptoms in boys. It seemed that particularly low genetic risk for neuroticism or worry was associated with less burden of externalizing symptoms, while the association flattened at the high end of the polygenic score. However, children having missing data and accordingly excluded from the study had significantly higher scores on the genetic risk score for neuroticism than included children, suggesting that the higher end of the PRS scale may have not been properly represented in this study.

The finding was according to our hypothesis: lower genetic risk for neuroticism or worry was associated with less burden of externalizing symptoms. However, we would have also expected a similar finding regarding internalizing symptoms. In earlier literature, neuroticism (as a trait) has been suggested to be a common factor underlying both internalizing and externalizing behavior (Muris & Ollendick, 2005) and internalizing and externalizing disorders (Hink et al., 2013), and, earlier studies have reported associations between polygenic risk for neuroticism and internalizing problems and psychopathology in children aged four years and older (Neumann et al., 2022; Akingbuwa et al., 2020), although not all studies have found associations (Ensink et al., 2020). In fact, earlier studies have found genetic risk for neuroticism to be associated particularly with internalizing problems, and associations to externalizing problems have been reported less: Costantini and colleagues (2023) found polygenic risk for neuroticism to be associated with an overall increase of externalizing problems between 4 and 11 years of age, but, the association between the neuroticism PRS and increase in internalizing problems was stronger. In our study, we had two-year-old children, who are considerably younger than the study participants in earlier studies. It is possible that internalizing and externalizing symptoms are not clearly distinguishable at such a young age. The cognitive and speech development required for the full expression of internalizing symptoms is not yet achieved at that age and internalizing symptoms, like fear or nervousness, might be expressed with externalizing behavior. Furthermore, externalizing symptoms are easier for parents to observe and assess, and studies show that they might also be over reported (Clarke-Stewart et al., 2003). Furthermore, studies are

also showing that internalizing and externalizing symptoms frequently co-occur (Pesenti-Gritti et al., 2008), and that externalizing symptoms predict later internalizing problems as well (Speranza et al., 2023). In summary, our finding suggests that genetic risk for neuroticism is already associated with socio-emotional development at the age of two years.

We found an association between genetic risk for neuroticism and externalizing symptoms only in boys. Although we expected to find differences between the genders, we cannot explain why we did not find any associations in girls. In our study, boys had more externalizing symptoms than girls in both samples, which is in line with earlier studies (Rescorla et al., 2012). Possible association with genetic risk for neuroticism and internalizing symptoms might not be detectable at such a young age. Earlier studies have mostly analyzed girls and boys together, and accordingly possible gender differences regarding the association between genetic risk for neuroticism and internalizing problems later in childhood might not have been fully explored. Another possible explanation is that there are differences between the genders on how genetic influences affect behavior. Earlier studies have suggested a higher genetic influence for boys than girls in externalizing and internalizing behavior (Rhee et al., 2007). Gender differences have also been reported with other PRSes (Koch et al., 2021; Acosta et al., 2020). The possibility of differences in genetic influences between the genders requires further research.

6.4 Causality and mechanisms

Our results suggest that genetic risk for psychiatric disorders may already have phenotypic effects in the very beginning of life in healthy children. However, our results do not signify causality since our results represent statistically discovered associations between study variables, and neither do they inform us about the mechanisms behind the associations. Although there is no uncertainty about the direction of possible causality, we still cannot be sure of whether the genetic factors have a causal effect on the studied outcomes. Pleiotropy, for example, poses a potential problem for the interpretation of causality: the PRSes are calculated over thousands of genetic variants, and the genetic variants may influence several biological processes, which may be indirectly associated with the phenotypes studied (Martin et al., 2019). In addition, the mechanisms and routes from genes to the phenotypes studied are not simple or straightforward, but may include many functional levels and perhaps even the environment. Since the genetic risk factors for schizophrenia and neuroticism have been related with genes involved with brain development and especially synaptic processes, a reasonable explanation would be that the genetic factors exert their effects on these phenotypes through differences in the developing brain. What the actual biological mechanisms are, how they operate and how are they connected with other mechanisms responsible for the

development and maturation of the brain, are not known. Although genome-wide association analyses have provided us with a wealth of knowledge about the possible genes and genetic variants related to schizophrenia and neuroticism, the actual etiological or biological mechanisms behind these phenotypes are not currently known.

It is also possible that the phenotypic effects observed for the genetic liabilities of schizophrenia and neuroticism in this study reflect more complicated mechanisms, including gene–environment correlations and interactions. The genetic risk scores of both schizophrenia and neuroticism have been associated with environmental factors in earlier studies (Ensink et al., 2020; Bolhuis et al., 2022), suggesting that a gene–environment correlation might also play a role. The environmental measures associated with the genetic risk factors for schizophrenia include for example single parenthood, lack of the father's involvement in childcare, mother's alcohol intake during pregnancy and higher overall burden of childhood adversities before the age of five (Bolhuis et al., 2022; Machlitt-Northen et al., 2022; Ratanatharathorn et al., 2021; Ensink et al., 2020), while genetic risk for neuroticism has been associated for example with mother's anxiety and alcohol intake during pregnancy (Ensink et al., 2020). These factors that are considered as environmental for the child might have influenced the child's development, and accordingly demonstrate more of a passive gene–environment correlation than a direct genetic effect. This might be especially true for children with a genetic propensity to psychopathology, since they seem to be susceptible to disadvantageous environments (Tienari et al., 1987). Furthermore, regarding the sleep-EEG findings, parental emotions (e.g., depression and anxiety) and behaviors have been shown to affect a child's sleep (Sadeh et al., 2010), and sleep disturbances in childhood are suggested to be related to negative maternal perceptions of child temperament (Sadeh et al., 1994). A parent's genetic disposition to neuroticism might have affected their baby's sleep through parental negative emotions, behaviors, or perceptions of the child, which all are important aspects of the child's environment, but this was not addressed in the current study. It is also possible that parental genetic liability to neuroticism or schizophrenia affects the way they assess their child. Since the measures of motor and socio-emotional development were based on parental assessments, it is possible that the associations found between genetic risk scores and the phenotypes reflect a gene–environment correlation, indicative of a relationship between parental genetic liability and their perception of the child rather than a true association between the child's genetic dispositions and their behavior. Additionally, a gene–environment correlation might be combined with a gene–environment interaction as a possible explanation for the phenotypic associations observed: for example, maternal alcohol intake during pregnancy is associated with the genetic risk of both schizophrenia and neuroticism (Ensink et al., 2020). If fetuses who have a high genetic risk for schizophrenia or

neuroticism were more sensitive to the effects of alcohol, and if this sensitivity led to alterations in the sleep EEG, this might result in an apparently direct association between genetic risk score and sleep EEG, while the alcohol would be the actual causal factor.

6.5 Differences between boys and girls

We found several gender-specific results in this study: genetic risk for schizophrenia was only associated with slower motor development in girls, genetic risk for neuroticism was only associated with externalizing symptoms in boys, and genetic risk factors for schizophrenia together with an early unfavorable environment was only associated with schizophrenia diagnosis in adulthood in women. Accordingly, our results suggest that the genetic risk factors for both schizophrenia and neuroticism may have differing effects for boys and girls, which is in line with earlier results showing emerging evidence of differing genetic influences (Bernabeu et al., 2021) and sensitivity to environmental exposures (DiPietro & Voegtline, 2017) for boys and girls. Earlier studies do not show clear evidence that the genetic background for schizophrenia or neuroticism are different for men and women (Trubetskoy et al., 2022; Smith et al., 2016), although differences between men and women regarding heritability and non-additive genetic effects in neuroticism have been proposed (Weinschenk et al., 2022; Eaves et al., 2012; Viken et al., 1994). Nevertheless, it is still possible that the effects of the genetic risk factors for schizophrenia and neuroticism are different for boys and girls. Furthermore, differential sensitivity to environmental effects may also play a role since boys have been shown to be more vulnerable to disadvantageous environments (DiPietro & Voegtline, 2017; Schore, 2017). These are important considerations that should be emphasized in future studies since it might be difficult to properly disentangle the genetic effects, if all possible sources of variation are not considered.

6.6 Strengths

One of the main strengths of this thesis is the samples: we utilized three relatively large and presumably representative samples of the Finnish population in the main analyses of this study. In addition, the replication sample in Study I was a systematically collected sample of Finnish schizophrenia families. The findings in Studies I and III were based on two samples, which increases the robustness of the findings: the results of Study I were replicated in a different sample type and the analyses in Study III were based on two birth cohorts with no overlapping individuals. Furthermore, the sample sizes were large enough to allow separate analyses for the two genders, enabling the consideration of gender differences.

However, this was not possible in the analyses of EEG-based sleep phenotypes. Finally, our measures for child development included different types of data ranging from parentally assessed phenotypes to measures based on PSG recordings.

6.7 Limitations

The main limitation of this study was the lack of replication sample in Study II, and accordingly the results of Study II should be regarded as tentative until replicated in subsequent studies. Another considerable limitation in Study II was the small sample sizes, although they were relatively large for an EEG study. Accordingly, our power in Study II was limited and we cannot for example conclude that the non-significant findings are an indication of a lack of an association. It is highly possible that the PRSes have only small effects on the variables measured, and that these small effects can only be detected with larger sample sizes. Small sample sizes may also result in smaller variances and non-normal distributions of the variables studied.

The childhood environmental factors were only considered to a limited extent. Several important environmental factors that have a substantial impact on the developing child, including the parent–child interaction, were not assessed or considered in this study.

In Study I, since the main sample was a population-based sample, there was a limited number of schizophrenia patients. This resulted in a small number of affected participants in some of the analyzed groups, especially in the high birthweight group. However, the results were replicated in a schizophrenia family sample with a large proportion of affected individuals. Another limitation of Study I was the small sample size of the replication sample, which followed from the limited availability of birthweight information. In addition, we lacked some of the covariates used in the main sample.

In Study III, the maternal depressive symptoms were assessed with different questionnaires in the two samples (CES-D and EPDS). However, both scales have been shown to be valid measures of depressive symptoms (Gonzáles et al., 2017; Cox et al., 1996). Furthermore, we only had longitudinal trajectory data on maternal depressive symptoms available for the CS cohort.

6.7.1 Representativeness of the samples

Although the main study cohorts in all three studies were population-based samples, they might not have represented the population well in terms of the genetic risk scores. Having high genetic risk for schizophrenia or neuroticism might be related to a higher drop-out rate from a study and accordingly, all these studies might suffer from a lack of participants from the higher end of the PRS scale. For

example, in Study III, participants with missing data on socio-emotional development had significantly higher genetic risk scores for neuroticism than the participants with non-missing data. However, it is likely that the lack of the higher end of the polygenic risk scale mostly attenuates the associations rather than produces spurious associations. In that sense, it is noteworthy that we found significant associations despite our samples possibly lacking proper representativeness of the high end of the genetic risk scale, at least in Study III.

In Study II, the PSG sample might not have represented the general population well, although it was recruited from a birth cohort, since there were requirements considering the health of the participants and their mothers. For example, participants of the PSG sample had lower scores on the genetic risk score for depressive affect than the participants in the larger CS cohort, possibly due to the exclusion criteria of maternal depression medication use. However, the PSG sample did not differ on the other genetic risk scores from the larger CS cohort.

6.7.2 Validity of the polygenic risk scores

There are several aspects regarding the PRSes that might limit their validity. The genetic risk score for neuroticism and its subscores of worry and depressed affect used in Studies II and III were not based on a Finnish sample, but on a UK Biobank sample, and they were not validated on a Finnish sample. This may limit the validity of the scores in a Finnish sample since Finns differ genetically from other Europeans (Nelis et al., 2009). The same limitation does not apply to the genetic risk scores for schizophrenia since the GWASes the scores were based on also included Finnish samples (Trubetskoy et al., 2022; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014; The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). However, the PRS for neuroticism based on the UK Biobank sample has been successfully used in other non-British European samples (Ahrens et al., 2022; Jansen et al., 2021), and other PRSes based on the UK Biobank have been successfully used in Finnish samples (Ripatti et al., 2020).

This study relies strongly on the assumption that PRSes are valid indicators of genetic liability. However, PRSes do not have high predictive accuracy, in fact it is rather low, and accordingly implications based on studies performed with PRSes should be interpreted with this shortcoming in mind. One of the problems presumably leading to low predictive accuracy is that PRSes include mainly common genetic variation, and mostly exclude other types of variation, including rare variation and CNVs, which have been shown to be associated with schizophrenia, for example (Singh et al., 2022). However, it has been estimated that neither rare variants nor CNVs explain a notable portion of the variation in schizophrenia. However, incorporating all the genetic variation that is known to

affect schizophrenia liability would be desirable. Another problem, which may also pertain to the low predictive accuracy, is that PRSes are not currently biologically coherent entities, but represent a wide variation of biological pathways. How these pathways are related to the etiology of the phenotype or how they are related to each other is currently not known. Accordingly, a PRS is currently a rough measure of genetic liability, which is calculated without biological understanding of the operating mechanisms. This also poses a potential problem for the interaction analyses: since the risk score does not represent a unified biological mechanism, can we assume that the interaction of all these variants and pathways with the environment is similar? Furthermore, the genetic factors included in the PRSes may also be differentially expressed in developmental time. Studies are emerging that show differential expression of the genes implicated in schizophrenia during developmental time (van de Meer et al., 2023). Understanding the biological and etiological meaning of the PRSes is clearly still at an early phase, but this will hopefully be resolved with future research.

7 Conclusions

This study suggests that the genetic risks for schizophrenia and neuroticism may already have age- and developmental phase–dependent phenotypic effects in the first two years of life. These results complement earlier studies that have shown a wide range of phenotypic effects of the genetic risks of schizophrenia and neuroticism in children aged two years and older (Riglin et al., 2017; Costantini et al., 2023). Accordingly, together with earlier research, our results suggest that the genetic risk factors for schizophrenia and neuroticism may have phenotypic effects throughout childhood, starting from the very beginning of life.

Many psychiatric disorders have etiological roots in childhood (Rutter et al., 2006). Whether the results of this study imply that the developmental process toward a mental health disorder may already start after birth is not yet clear. In this study, we examined normal healthy children in population-based settings, and most of the children will not be diagnosed with for example schizophrenia later in their life. Since the associations in this and many other studies have been dependent on the age and developmental phase of the child, both the continuity of these effects throughout childhood and the implications for the risk for mental health problems are not yet fully understood. It is possible that the phenotypic effects found are specific to certain ages and developmental phases and merely reflect passing variation in the normal phenotypic range. More research, including longitudinal studies, is needed to understand the implications of these findings and before we can fully understand the developmental pathways that lead to increased risk for mental health problems.

The role of the environment should be considered more extensively in future studies, comprising both the amount and precision of the data and including different age and developmental phases. Based on the results of Study I, it is plausible to assume that the genetic risk factors for schizophrenia may have different effects depending on the environment. If the environment has a clear role in shaping the result of genetic effects, it would be valuable information in considering possible interventions. It is possible that high genetic risk for schizophrenia reflects higher vulnerability or lower resiliency to environmental insults, and understanding the possibly harmful and protective elements of the environment would be important. The role of gene–environment interactions in

relation to other genetic liabilities, including the genetic risk for neuroticism, is also worth further investigation.

This study focused on the genetic liabilities of schizophrenia and neuroticism, which were thought to reflect different aspects of general risk for mental health problems. How these findings relate to genetic liabilities of other psychiatric disorders would be worth studying. For example, an autism PRS has been associated with language difficulties at 18 months, and an ADHD PRS has been associated with hyperactivity and inattention before the age of two (Askeland et al., 2022), and in particular among children with short sleep (Morales-Munoz et al.,2023). In future studies, it would be interesting not only to broaden the perspective to the genetic risk factors for other psychiatric disorders and traits, but to study multiple genetic liabilities jointly, allowing us to see whether the phenotypic effects are specific for different psychiatric disorders or whether multiple genetic liabilities have cumulative effects.

Our results suggest that differences between boys and girls need to be considered in future studies. There is accumulating evidence that the developmental pathways in boys and girls may differ, as may also the factors that contribute to this development (Schore, 2017; DiPietro & Voegtline, 2017). If these differences are ignored, it might be difficult to fully understand the role of genetics and the environment in the development of boys and girls.

In summary, this thesis showed that the genetic risk factors for psychiatric disorders may already have phenotypic effects in the first two years of life and varying sensitivity to environmental influences. Studying these effects further may increase our understanding of the early roots and developmental pathways of psychiatric disorders.

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