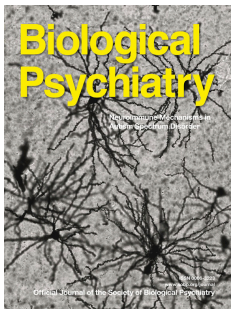
Journal Pre-proof



Genetic Influences on the Developing Young Brain and Risk for Neuropsychiatric Disorders

Ann M. Alex, Claudia Buss, Elysia Poggi Davis, Gustavo de los Campos, Kirsten A. Donald, Damien A. Fair, Nadine Gaab, Wei Gao, John H. Gilmore, Jessica B. Girault, Karen Grewen, Nynke A. Groenewold, Benjamin L. Hankin, Jonathan Ipser, Shreya Kapoor, Pilyoung Kim, Weili Lin, Shan Luo, Elizabeth S. Norton, Thomas G. O'Connor, Joseph Piven, Anqi Qiu, Jerod M. Rasmussen, Michael A. Skeide, Dan J. Stein, Martin A. Styner, Paul M. Thompson, Laurie Wakschlag, Rebecca Knickmeyer, for the ENIGMA ORIGINs group

PII: S0006-3223(23)00040-9

DOI: https://doi.org/10.1016/j.biopsych.2023.01.013

Reference: BPS 15097

To appear in: *Biological Psychiatry*

Received Date: 15 July 2022

Revised Date: 9 January 2023

Accepted Date: 11 January 2023

Please cite this article as: Alex A.M., Buss C., Davis E.P., Campos G.d.l., Donald K.A., Fair D.A., Gaab N., Gao W., Gilmore J.H., Girault J.B., Grewen K., Groenewold N.A., Hankin B.L., Ipser J., Kapoor S., Kim P., Lin W., Luo S., Norton E.S., O'Connor T.G., Piven J., Qiu A., Rasmussen J.M., Skeide M.A., Stein D.J., Styner M.A., Thompson P.M., Wakschlag L., Knickmeyer R. & for the ENIGMA ORIGINs group, Genetic Influences on the Developing Young Brain and Risk for Neuropsychiatric Disorders, *Biological Psychiatry* (2023), doi: https://doi.org/10.1016/j.biopsych.2023.01.013.

Genetic Influences on the Developing Young Brain and Risk for Neuropsychiatric Disorders

Running Head: Genetic Influences on Young Brain

Ann M. Alex 1, Claudia Buss 2,3,4, Elysia Poggi Davis 3,5, Gustavo de los Campos 1,6,7, Kirsten A. Donald 8,9, Damien A. Fair 10,11,12, Nadine Gaab 13, Wei Gao 14,15, John H. Gilmore 16, Jessica B. Girault 16,17, Karen Grewen 16, Nynke A. Groenewold 9,18,19, Benjamin L. Hankin 20, Jonathan Ipser 9, Shreya Kapoor 21, Pilyoung Kim 22, Weili Lin 23, Shan Luo 24,25,26, Elizabeth S. Norton 27,28, Thomas G. O'Connor 29, Joseph Piven 16,17, Anqi Qiu 30,31,32,33,34,35, Jerod M. Rasmussen 3,4, Michael A. Skeide 21, Dan J. Stein 9,36, Martin A. Styner 16,37, Paul M. Thompson 38, Laurie Wakschlag 28, Rebecca Knickmeyer 1,39, for the ENIGMA ORIGINs group.

1. Institute for Quantitative Health Sciences and Engineering, Michigan State University, East Lansing, MI, USA
2. Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Medical Psychology, Berlin, Germany
3. Department of Pediatrics, University of California Irvine, Irvine, CA, USA
4. Development, Health and Disease Research Program, University of California Irvine, Irvine, CA, USA
5. Department of Psychology, University of Denver, Denver, CO, USA
6. Departments of Epidemiology & Biostatistics, Michigan State University, East Lansing, MI, USA
7. Department of Statistics & Probability, Michigan State University, East Lansing, MI, USA

8. Division of Developmental Paediatrics, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa
9. Neuroscience Institute, University of Cape Town, Cape Town, South Africa
10. Masonic Institute for the Developing Brain, University of Minnesota Medical School, Minneapolis, MN, USA
11. Institute of Child Development, College of Education and Human Development, University of Minnesota, Minneapolis, MN, USA
12. Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN, USA
13. Harvard Graduate School of Education, Harvard University, Cambridge, MA, USA
14. Cedars–Sinai Biomedical Imaging Research Institute, Los Angeles, CA, USA
15. Departments of Biomedical Sciences and Imaging, Cedars-Sinai Medical Center, Los Angeles, CA, USA
16. Department of Psychiatry, UNC- Chapel Hill, Chapel Hill, NC, USA
17. Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill, Carrboro, NC, USA
18. South African Medical Research Council (SA-MRC) Unit on Child & Adolescent Health, University of Cape Town, Cape Town, South Africa
19. Department of Paediatrics and Child Health, University of Cape Town, Faculty of Health Sciences, Cape Town, South Africa
20. Psychology Department, University of Illinois-Urbana Champaign, IL, USA
21. Research Group Learning in Early Childhood, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
22. Department of Psychology, University of Denver, Denver, CO, USA
23. Department of Radiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
24. Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, United States
25. Department of Psychology, University of Southern California, Los Angeles, CA, United States

26. Center for Endocrinology, Diabetes and Metabolism, Children's Hospital Los Angeles, Los Angeles, CA, USA
27. Roxelyn and Richard Pepper Department of Communication Sciences and Disorders, Northwestern University, Evanston, IL, USA
28. Department of Medical Social Sciences and Institute for Innovations in Developmental Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
29. Departments of Psychiatry, Psychology, Neuroscience, Obstetrics and Gynecology, University of Rochester, Rochester, NY, USA
30. Department of Biomedical Engineering, National University of Singapore, Singapore
31. NUS (Suzhou) Research Institute, National University of Singapore, China
32. The N.1 Institute for Health, National University of Singapore, Singapore
33. School of Computer Engineering and Science, Shanghai University, China
34. Institute of Data Science, National University of Singapore, Singapore
35. Department of Biomedical Engineering, the Johns Hopkins University, USA
36. SAMRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry, University of Cape Town, Cape Town, South Africa
37. Department of Computer Science, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
38. Imaging Genetics Center, Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of USC, Marina del Rey, CA, USA
39. Department of Pediatrics and Human Development, Michigan State University, East Lansing, MI, USA

Corresponding author:

Rebecca Knickmeyer

Associate Professor, Pediatrics and Human Development

Michigan State University,

East Lansing, MI, USA

Phone: 517-355-3977

Email: knickmey@msu.edu

Keywords: imaging; genetics; infant; childhood, pediatric, magnetic resonance imaging

Abstract

Imaging genetics provides an opportunity to discern associations between genetic variants and brain imaging phenotypes. Historically, the field has focused on adults and adolescents; very few imaging genetics studies have focused on brain development in infancy and early childhood (from birth to age six). This is an important knowledge gap as developmental changes in brain during the prenatal and early postnatal period are regulated by dynamic gene expression patterns that likely play an important role in establishing an individual's risk for later psychiatric illness and neurodevelopmental disabilities. In this review, we summarize findings from imaging genetics studies spanning from early infancy to early childhood with a focus on studies examining genetic risk for neuropsychiatric disorders. We also introduce the Organization for Imaging Genomics in Infancy (ORIGINs), a working group of the ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) consortium, which was established to facilitate large-scale imaging-genetics studies in infancy and early childhood.

Introduction

Imaging genetics reveals considerable information about genetic influences on structural and functional imaging phenotypes(1–3), but until recently largely focused on adolescent or adult human brain(4,5). This is an important limitation as the most dynamic phase of human brain development is from embryonic life through early childhood(6) (Figure 1). Disrupted gene expression in this period can produce life-long changes in brain morphology and function. Even common genetic variations may affect early neurodevelopmental processes, thereby increasing

risk for psychiatric conditions later in life(7). These effects may be detectable in early life via neuroimaging, providing opportunities for identifying at-risk populations in infancy for primary prevention, and developing interventions to adjust adverse trajectories earlier in the clinical sequence. This paper reviews empirical evidence underlying this hypothesis focusing on magnetic resonance imaging (MRI). Studies using ultrasound(8,9) and studies integrating imaging and epigenetic data(10–13) also provide insights into how genes influence the developing young brain but are beyond the scope of this review. First, we describe heritability of brain imaging phenotypes in early life. We then discuss candidate gene studies of brain structure, function, and connectivity. Next, we review studies characterizing associations between psychiatric risk genes and brain phenotypes in early life using polygenic scores. We then discuss genome-wide studies on brain imaging phenotypes in early childhood. Finally, we introduce the Organization for Imaging Genomics of Infancy (ORIGINs), a working group of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium, which was established to facilitate large-scale imaging-genetics studies in infancy and early childhood.

Insert Figure 1 around Here

Heritability

Twin studies reveal that many brain phenotypes are heritable in early infancy. Genetic effects explain around 85% of variance in global white-matter volumes (WMV) and 56% variance in global gray-matter volumes (GMV), around 1 month of age(14), while heritability of head size is negligible(15). This contrasts with studies of older children and adults where heritabilities greater than 80% are reported for all three phenotypes (global WMV, GMV, and head size)(16–18). Heritability estimates for global cortical surface area (SA) are high in early infancy (78%), while estimates for global cortical thickness (CT) are lower (29%) with significant genetic overlap

between the two(19). This differs from adults where SA and CT are both highly heritable (89% and 81% respectively) with distinct genetic factors contributing to each measure(20–22). White matter microstructure is moderately heritable in early life with 30-60% of variability in mean fractional anisotropy (FA) linked to genetic variation, and similar estimates for other diffusivity indices (23,24). In adults estimates for FA range from 72%-88%(25). Despite large variations in heritability estimates across individual tracts, a single latent measure of white matter microstructure accounts for much heritable variation in neonates (50%)(26). Similarly, individual differences in regional CT and SA appear to be driven by a common set of genetic factors influencing cortical structure at the global level(19). In both cases, the pattern of results mirrors temporal changes in gene expression which show strong spatial differences in fetal, but not postnatal development(27,28). Finally, genetic effects on resting state functional magnetic resonance imaging (rsfMRI) phenotypes, have been observed in the first two years of life. Gao and colleagues(29) reported modest genetic effects on within network connectivity in neonates with three visual networks and the right frontoparietal network demonstrating above-average effects. At one year, the most heritable networks were bilateral frontoparietal networks, the salience network, and two visual networks. At two years, genetic effects were strongest for the auditory network. However, genetic effects were not as strong as those reported in adolescents and adults(30–32). Genetic effects on between network connectivity are also minimal in neonates(33). Intergenerational transmission of imaging phenotypes has been reported and likely reflects a combination of genetic, epigenetic, and environmental effects(34–36) . One such study examined the intergenerational transmission from mothers to their five-year-old children and reported significant effects on sulcal phenotypes in right frontal and parietal cortex(35).

A recurring theme across studies is that heritability is higher in adulthood compared to infancy. This might appear paradoxical as interindividual variation in environmental exposures increases with age, but similar patterns are observed for IQ, where increasing heritability during development is called the Wilson effect(37). The Wilson effect is thought to arise from gene–environment correlations that increase with age. In other words, babies and young children have environments thrust upon them, but as they age, they select, modify, and create environments correlated with their genetic predispositions(38). Alternatively, higher heritability observed at later ages could reflect stronger heritability of postnatal processes such as myelination and shifts in proportions of white versus gray matter across development. Determining whether a genetic amplification model applies to neuroimaging phenotypes will require large scale longitudinal studies addressing gene-environment interplay across lifespan. The ENIGMA plasticity working group has begun tackling this question. Using five longitudinal twin cohorts, they demonstrated that rates of brain change are heritable and heritability estimates of change rates were higher in adults than children(39). They subsequently identified variants involved in structural brain changes via a genome-wide association study (GWAS)(40). However, their studies did not include infants or toddlers.

Candidate gene approaches

Traditional candidate gene studies test for associations between phenotypic outcomes and variation within specific genes, selected for suspected roles in organ development or physiology. In imaging genetics, selection is often based on hypothesized involvement in psychiatric disease. The first candidate gene study of brain imaging phenotypes in neonates focused on global and local brain tissue volumes and several genes with known roles in brain development and putative links to psychiatric disease including *DISC1*, *COMT*, *NRG1*, *ESR1*, and *BDNF*(41). Many reported effects

mirrored findings in adults; others were unique to infancy. For the *BDNF* Val/Met polymorphism, Met+ neonates had decreased volumes in regions of right occipital cortex, left hippocampus, parahippocampus, fusiform gyrus, and inferior temporal gyrus and increased volumes in motor and somatosensory cortex(41). We highlight this result as a recent study partially replicated the original findings. Specifically, Kawasaki et al. (2021) reported that Met+ neonates had significantly smaller relative hippocampal volumes(42).

The largest traditional candidate gene study to include children under 6 years of age focused on Klotho, a gene linked to age-related decline. A significant interaction between Klotho allele status (rs9536314) and age was observed for total brain volume (TBV) and total GMV with KLS-VS heterozygotes having larger volumes in early childhood, but not in later childhood/adolescence. Among girls, KL-VS heterozygotes had smaller WMV than non-carriers whereas among boys, heterozygotes had greater WMV than non-carriers. No effects were significant in a replication cohort that did not include children below 6 years of age(43), supporting the importance of conducting imaging genetics studies in early life to unveil effects absent in older cohorts.

In addition to age, genetic effects on neurodevelopment may vary based on factors such as prematurity and family history. For example, Krishnan et al. 2017(44) hypothesized that polymorphisms in *DLG4*, would moderate responses to perinatal inflammation and their impact on white matter microstructure based on gene network analysis of the microglial transcriptomic response to injury in mouse models and complementary, data-driven analysis of protein-protein interactions, transcription factors and human brain gene expression. The team discovered a specific variant in *DLG4* (rs17203281) associated with FA in preterm individuals in two independent cohorts. Van Steenwinckel et al. (2019) adopted a similar approach, identifying key genes and gene networks in animal models of neuroinflammation-induced hypomyelination and then testing

for associations in preterm infants. The researchers revealed that Wnt pathway genes were collectively associated with cerebral structural connectivity(45). In addition, a study of 13 candidate genes revealed *ARVCF*, previously linked to schizophrenia, and *FADS2*, previously linked to intelligence, were associated with white matter FA in preterm infants(46). These studies highlight the importance of considering potential interactions between genetic variation and early life environmental exposures as neither *DLG4* nor the Wnt pathway genes would be expected to impact DTI phenotypes in the absence of perinatal inflammation. With regard to family history, Douet et al. (2015) reported that the effects of variants in *ERBB4* differed in children with and without a family history of schizophrenia and/or bipolar disorder. The TT variant for rs7598440 had more pronounced effects on age-related changes (3-20 years) in CT and SA in children with a family history; these children showed steeper increases in frontal and temporal SA in both early and late childhood(47).

Several studies explicitly tested for gene-environment interactions using the candidate gene approach. *COMT* SNPs moderated the association between antenatal maternal anxiety and prefrontal and parietal CT in neonates(48). *BDNF* genotype (Val66Met) moderates associations between methylation patterns and neonatal hippocampus and amygdala volumes(49). *FKBP5*, which regulates the hypothalamic–pituitary–adrenal (HPA) axis, moderates the association between antenatal maternal depressive symptoms and neonatal right hippocampal volume(50) . For oxytocin receptor (*OTR*) gene variant rs53576, a sex-specific main effect was seen for neonatal hippocampal volume. Left hippocampal volumes were larger in GG-homozygotes compared to A-allele carriers in boys only. Prenatal maternal anxiety interacted with genotype in both sexes: higher maternal anxiety was associated with larger hippocampal volumes in A-allele carriers(51).

Additional details on these studies are found in Table 1. A graphical representation (PhenoGram)(52) of genes and associated phenotypes are given in Figure 2.

Insert Table 1 around Here

Interestingly, imaging genetics studies of infants and young children began at a time when microarray genotyping began making large-scale genotyping practical. The GWAS era quickly highlighted weaknesses in the traditional candidate gene approach. Well-powered GWAS failed to support involvement of many traditional candidate genes for psychiatric disorders. This may partly reflect addressable methodological weaknesses including failure to control for population stratification thereby increasing the risk of false positive associations due to differences in ancestry. However, the key disadvantage of candidate gene approach is likely poor candidate selection, given inadequate knowledge about underlying biological processes. Subsequent meta-analyses of candidate gene studies relevant to psychiatry, including imaging genetics studies in older populations, revealed poor replicability, false positive associations, overestimation of effect sizes, and publication bias(53). While imaging genetics literature for infants and young children is not extensive enough to allow meta-analyses, existing studies likely have similar weaknesses.

One promising approach to addressing these problems is to focus future studies on variants robustly associated with mental and neurological disorders or adult brain imaging phenotypes in large-scale GWAS. The ε4 allele of apolipoprotein E (*APOE*) gene meets this criterion. Not only is ε4 the strongest known risk variant for Alzheimer's, it also has well documented effects on brain structure and cognition in healthy individuals(54,55). In neonates, *APOE* ε3ε4 heterozygotes have significantly lower volumes in temporal regions, compared with ε3 homozygotes, and lower volume in frontal and parietal lobes. ε3ε4 heterozygotes have significantly greater volumes in specific parietal, frontal, and occipital areas(41). Infant ε4 carriers have lower white matter myelin

water fraction (MWF) and GMV measurements in precuneus, posterior/middle cingulate, lateral temporal, and medial occipitotemporal regions, areas preferentially affected by Alzheimer disease, and greater MWF and GMV measurements in frontal regions(56). Decreased myelin in ε4 carriers in the corticospinal tract, splenium of corpus callosum, and frontal white matter, observed in the previous study, was also reported in a longitudinal analysis from the same group following children from birth to 5.5 years(57). Regions in which ε4 carriers had greater MWF early on had decreased rate of MWF development until 5.5 years allowing non-carriers to catch-up and surpass ε4 carriers around 3 years of age. In another study, age-related changes in brain structures and cognition were observed to vary depending on genotype, with smallest hippocampi in ε2ε4 children, lowest hippocampal FA in younger ε4ε4 children, largest medial orbitofrontal cortical areas in ε3ε4 children, and age-dependent thinning of entorhinal cortex in ε4ε4 children(58). All these studies suggest Alzheimer's disease is a neurodevelopmental disorder as well as a neurodegenerative one.

Six SNPs robustly associated with subcortical volumes in adult GWAS have recently been tested for effects in neonates. An association between rs945270 (an intergenic locus downstream of Kinectin 1 (*KTN1*) gene) and putamen volume was reported suggesting that at least some variants have detectable effects across the lifespan(59).

A significant challenge when performing a candidate gene study informed by existing GWAS is how to prioritize genes for follow-up. Fortunately, an increasing array of in silico tools for searching GWAS literature and performing functional characterization of variants can assist with this task(60–62). Another challenge is that candidate gene studies informed by GWAS still focus on only a few selected genes/polymorphisms which account for only a fraction of variants involved in psychiatric risk. One approach to overcome this challenge is to use polygenic risk scores.

Polygenic Risk Score Approaches

Polygenic risk scores (PRS) estimate an individual's susceptibility to a complex trait based on prior GWAS summary statistics(63). Efforts such as the Psychiatric GWAS consortium have produced many well-powered GWAS of psychiatric and neurodevelopmental conditions including schizophrenia, major depressive disorder (MDD), bipolar disorder (BIP), attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASD)(64). Summary statistics are often freely available, and researchers can obtain individual data from controlled-access repositories. By examining associations between PRS and neuroimaging phenotypes measured in infancy and early childhood, researchers are clarifying how genetic risk for these conditions manifests in early life thereby providing new insights into the etiology of psychiatric and neurodevelopmental disorders. This is a key step in identifying individuals who may benefit from early intervention.

One of the first studies to use this approach in early life was Xia et al. (2017) who found that PRS for schizophrenia and ASD were not associated with neonatal TBV(65). Like the above study, Cullen et al. (2022) did not observe associations between neonatal volumes and PRS for schizophrenia. However, PRS for schizophrenia was negatively associated with regional GMV and WMV and total WMV in neonates in a different study(66). PRS for ASD was associated with greater CT and reduced white matter connectivity in children (3 to ~14 years)(67). In preterm infants, a PRS for five conditions (ASD, ADHD, BIP, MDD, and schizophrenia) predicted reduced volume of the lentiform nucleus, which plays a key role in motor control, cognition, and emotion(68). The authors hypothesized that genetic risk for psychiatric disorders increased vulnerability to abnormal lentiform development in the context of perinatal stress associated with preterm birth but did not include term infants for comparison. Other studies have used PRS to

probe relationships between early-life adversity, genetic risk, and neurodevelopment. Ursini et al. (2021) used transcriptomic data to create placental genomic risk scores (PlacGRS) for schizophrenia. PlacGRS were calculated like traditional PRS, but only used markers in genes highly expressed in placenta and differentially expressed in placentae from complicated, compared with normal, pregnancies. PlacGRS negatively associated with neonatal brain volume in children with perinatal complications, especially in males(69). No significant associations were observed for PlacGRSs and non-placental GRSs for other disorders and traits associated with early life complications, suggesting the link between placental biology, genetic risk, perinatal environmental risk, and early brain development outcomes is relatively unique to schizophrenia.

Another important perinatal stressor is maternal depression. Many studies report associations of maternal depressive symptoms with neuroimaging outcomes in early life, but it is unclear whether associations represent causal effects or arise from genetic confounding. PRS can be used to test independent effects of maternal depressive symptoms and genetic risk for MDD as well as their interaction. Qiu et al. (2017), the first to apply this approach, reported significant interactions between PRS for MDD and antenatal maternal depressive symptoms for right amygdala volume in Asian (GUSTO) and US neonates(70). However, direction of effect differed across cohorts. In Finland, Acosta et al. (2020) found similar patterns to the US cohort(71). However, the interaction became nonsignificant after multiple comparisons correction. The Finnish team also investigated associations of MDD PRS with infant striatal volumes and found sex-specific effects: MDD PRS was positively associated with caudate volumes in boys but negatively associated with caudate volumes in girls(72). They did not observe significant interaction effects of PRS with prenatal maternal depressive symptoms for any dorsal striatal volumes.

PRS can also be used to understand how molecular pathways shape individual differences in neurodevelopment. For example, PRS for serum testosterone was recently found to positively associate with total SA development in female infants(73). Researchers interested in this application of PRS may implement expression based PRS (ePRS) rather than traditional PRS. ePRS integrate genotype data with transcriptomic data to predict expression levels of a particular gene or gene network. Morgunova et al. (2021) used this approach to investigate relationships between a coexpression network of the *DCC* gene, which is robustly associated with multiple psychiatric conditions, and TBV in both neonates and older children(74). Higher ePRS for the *DCC* coexpression network were associated with larger brain volumes. A study from GUSTO investigated how genes involved in inflammation interact with maternal depression to shape neonatal brain morphology. They created separate ePRS for 22 cytokine and chemokine genes expressed in fetal brain and found ePRS for *TNFRSF19, IL17RB, BMPR1B, IL1RAP*, and *CXCR4* moderated impact of maternal depression on specific subcortical volumes and regional CT(75). Using longitudinal data from the same cohort, investigators revealed an age dependent involvement for transmembrane receptor (*TGF-β*) variants in moderating effects of prenatal maternal depressive symptoms on amygdala volume(76).

Finally, PRS have been used to investigate how genetic variants linked to adult and adolescent brain morphology influence early brain development. Xia et al. (2017) found PRS for WMV and GMV in adolescence showed positive associations with neonatal WMV and GMV respectively, though the overall proportion of variation explained was low (65). Morgunova et al. (2021) calculated PRS for brain volume using data from UK Biobank, ENIGMA, Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), and the Early Growth Genetics consortia(74). These PRS did not predict brain volume in their neonate and school age community

cohorts. The first large-scale GWAS of adult ICV tested whether a polygenic score generated from 7 genome-wide significant loci predicted head growth in children of European ancestry followed prenatally until 6 years of age(77). They found an age-dependent effect in which the PRS became more predictive in older children, suggesting adult brain volume is strongly shaped by genetic influences operating in early childhood. Cullen et al. (2022) found robust associations between PRS for adult brainstem, hippocampus, putamen, and thalamus volumes and neonatal volumes, suggesting some stability across the life course(59).

Reviewed studies highlight the potential of PRS-based investigations of neuroimaging phenotypes in infancy and early childhood (See Table 2). They also reveal the importance of considering effects of sex and ancestry. A major limitation with this approach is the lack of sufficiently powered GWAS in non-European populations. European-ancestry GWAS do not transfer well to other ancestries and can lead to unpredictable biases(78). Another limitation of PRS studies is that they are based on existing GWAS and hence limited by the power of current datasets. In other words, PRS-based studies, like candidate gene studies, are constrained by current biological knowledge. To fully understand how DNA variants influence brain development, well-powered GWAS of infants and young children encompassing multiple ancestries are needed.

Insert Table 2 around Here

Genome-wide association studies (GWAS)

GWAS being hypothesis free, can identify new associations and overturn prior assumptions. However, GWAS of neuroimaging outcomes in infants and young children are very limited. The first GWAS of healthy infants identified several common variants associated with neonatal brain structure(65). An intronic SNP in *IGFBP7* was significantly associated with GMV. An intronic SNP in *WWOX* fell just short of genome-wide significance for WMV. Many top associations

tagged transcriptional regulators expressed during brain development (*KLF13*, *LMCD1*, *TOX3* and *TBX4*). This study also compared their results to large-scale neuroimaging GWAS in adolescents and adults and concluded that genetic determinants of global brain volumes are highly distinct at different ages. In a subsequent GWAS of white matter microstructure in neonates, an intronic SNP in *PSMF1* was significantly associated with a tractography-based factor capturing shared variation in FA across 44 white matter bundles(26). Additional loci nearing genome-wide significance were in or near genes with roles in axon growth and guidance, fasciculation, and myelination including *B3GAT1*, *TENM2*, *NFATC1*, and *MAP3K13*. The above studies are first of their kind and replication is crucial. Furthermore, these studies were not large enough to generate stable SNP-wise heritability estimates or evaluate genomic correlations between infant neuroimaging phenotypes and psychiatric disorders.

A smaller study in preterm individuals used genome-wide data and pathway-based and network-based approaches(79). The PPAR (peroxisome proliferator-activated receptor) signaling pathway was found to have a role in white matter development with five genes implicated (*AQP7, ME1*, *PLIN1*, *SLC27A1*, *ACAA1*). This inspired the team to examine the PPAR pathway in a larger cohort of preterm children. Using machine-learning analysis they uncovered 3 genes associated with cerebral connectivity (*PPARG*, *ITGA6*, and *FXR1*)(80). GWAS studies are summarized in Table 3 and included in the Figure 2 PhenoGram(52). Gene functions and associated neurological phenotypes/conditions for candidate genes and genes identified via GWAS are provided in Table 4.

Insert Table 3 & 4 around Here

Insert Figure 2 around Here

General strengths and limitations of GWAS studies are reviewed in detail elsewhere(81). In terms of GWAS in infants and young children, the primary limitations of existing studies include 1) under-powered due to small samples, 2) mostly cross-sectional rather than longitudinal, 3) only focused on neonates and preterm infants, and 4) while not specifically excluding individuals of non-European ancestry, these individuals constitute a small proportion of the total samples.

Rigor and reproducibility

When we consider the rigor and reproducibility of published imaging genetics studies in infants and young children, insufficient power and sample size are significant concerns. Sample sizes for early childhood imaging genetic studies are low with a mean of 365 for candidate gene studies (median – 216), 225 for PRS based studies (median – 168), and 344 for GWAS (median – 371.5). Consequently, existing studies are powered to detect variants with large effect sizes. It is likely that most variants impacting infant brain imaging phenotypes will explain between 0.1%-1% of variance, like other complex traits(82). Furthermore, small samples can produce unstable results and homogenous sampling can generate statistical inferences that do not represent the overall population. Independent replication is essential to validate results and improve estimation of effects but is currently rare due to difficulties recruiting and scanning large groups of infants.

To improve rigor and reproducibility and fully understand how DNA variants influence brain development in infancy and early childhood across diverse populations, and implications for future research and clinical care, large, longitudinal studies are needed. The Organization for Imaging Genomics of Infancy (ORIGINs) was founded to facilitate such work.

Organization for Imaging Genomics of Infancy (ORIGINs)

ORIGINs include investigators from different centers around the world (16 sites, 19 cohorts, 5 countries) who are engaged in neuroimaging research in infancy and early childhood. Our goal is to determine how genetic and environmental factors influence development of brain morphometry, anatomical and functional connectivity, and cognitive and emotional function from birth to age 6. In 2020, we received NIH funding to create the largest-ever imaging-genomics dataset focused on infancy and early childhood. In subsequent sections we briefly describe who will be included in this dataset, what is being measured, and our data analysis plans.

Participants:

Subjects will include approximately 6809 children (birth to 6 years of age) participating in neuroimaging studies of early brain development at the University of North Carolina Chapel Hill (UNC), University of California Irvine (UCI), Max Planck Institute for Human Cognitive and Brain Sciences, Rhode Island Hospital, Northwestern University, University of Denver, University of Rochester, Magee-Women's Hospital of the University of Pittsburgh Medical Center, University of Cape Town, Boston's Children Hospital/Harvard University, University of Minnesota, University of Washington, Washington University in St. Louis (WUSTL), Kings College London, and National University of Singapore. 8 cohorts have completed initial data collection and 11 are actively scanning. We estimate that 49% of the sample will be male, 51% will be female, 62% will be White, 20% will be Black, 11% will be Asian, 6% will be more than one ancestry, and 0.05% will be American Indian, Alaska Natives, Native Hawaiians, or Pacific Islanders. Individuals identifying as Hispanic/Latinx are expected to make up 15% of the cohort.

Data Measurements

Demographic and medical history: Health history and demographic information of participants were provided by parents or guardians and/or extracted from medical records. The information includes birth outcomes (gestational age, birthweight), sex, socioeconomic factors (maternal education, total family income), and family history of medical and neuropsychiatric disorders.

Genomic data: Most participating sites have used/are using saliva samples for DNA extraction. Two cohorts (DCHS and GUSTO) used umbilical cord and venous blood specimens. To harmonize data across genotyping platforms, we will impute genomes to a common set of SNPs using the Michigan Imputation Server(113). See supplementary materials for details on harmonization and genotyping platforms used by each cohort.

Behavioral assessments: In a subset of participants (~3800), we will examine 3 behavioral traits – impulsivity/distractibility, anxiety, and aggressive behavior – that can be reliably measured in very young children and are relevant to multiple psychiatric disorders. Behavioral traits will be measured using age-appropriate versions of the Child Behavior Checklist (CBCL)(114) and Behavior Assessment System for Children, Second Edition (BASC-2)(115,116).

Image acquisition and quality control: All cohorts, except for the developing Human Connectome Project (dHCP) and GUSTO, use 3T Siemens scanners (Allegra, Tim Trio, Verio, Skyra and Prisma) and comparable sequences (Supplementary Table 3-6). dHCP data was acquired on a Philips Achieva and newborn T2 structural MRI acquisition for GUSTO was on a 1.5T GE. To ensure consistent processing across datasets with the same tools and appropriately standardized parameter settings, all structural, diffusion, and functional connectivity data will be processed at a central site. T1 and T2 structural MRI, DTI and rsfMRI acquisition parameters, platform, and harmonization pipeline for each site are detailed in supplementary material.

Data analysis plan: Extracted neuroimaging measures will be analyzed using non-linear growth models. Growth model parameters, which we refer to as "developmental imaging phenotypes" (DIPs) will be used to test effects of genetic variants on structural brain development and connectivity using a multi-variate GWAS approach. Canonical correlation analysis will be used to identify association patterns between genetically influenced neurodevelopmental traits and clinically salient behaviors. The data analysis and data sharing plan is detailed in the supplementary material. A schematic for data analysis is provided as Figure 3.

Insert Figure 3 around Here

Conclusions

Imaging genetic studies of infants and young children provide evidence that variants associated with psychiatric disorders influence early neurodevelopment both independently and through interactions with environmental factors. In addition, GWAS studies of neonates and preterm infants have revealed new genes, variants, and molecular pathways implicated in brain development. However, most findings have not been independently replicated. Existing studies, regardless of design, are relatively small and do not encompass diverse ancestries. The ORIGINs initiative is addressing these limitations by creating and harmonizing the largest and most diverse imaging genomics dataset focused on infancy and early childhood to date. This dataset will help reveal how genetic risk for psychiatric disease manifests across infancy and early childhood, in terms of brain structure and function, and assist in early identification of at-risk individuals. Ultimately, identifying genes and molecular pathways associated with early neuroimaging phenotypes could lead to the development of novel prophylactics against complex psychiatric illness.

Acknowledgements

ORIGINs is supported by the NIMH (R01MH123716 to RK). Cohort 1- EBDS study is supported by MH064065, MH070890, HD053000, (PI - JHG) with genotyping funded by MH092335 (PI – RK). Cohort 2 - GUSTO study was supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Programme and administered by the Singapore Ministry of Health's National Medical Research Council (NMRC, NMRC/TCR/004-NUS/2008; NMRC/TCR/012-NUHS/2014) (PI - AQ). Cohort 3- IBIS study was supported by grants from the National Institutes of Health R01-HD055741, P30-HD003110, T32-HD040127, and the Simons Foundation (#140209) (PI - JP). Cohort 4- UNC study was supported through DA022446 (PI - KG). Cohort 5- University of California Irvine (UCI) study was supported by US PHS (NIH) grants R01 HD-060628, R01 MH-105538, UH3 OD-023349 and ERC grant ERC-Stg 639766 (PI - CB). Cohort 6 - The Max Planck Institute for Human Cognitive and Brain Sciences was supported by the German Research Foundation (Heisenberg Grant #433758790) and the Jacobs Foundation (PI- MAS). Cohort 7 – UNC study was supported by NS055754 (PI - WL). Cohort 8 - UNC study was supported by NS055754. Cohort 8 – UNC study was supported by MH104330 (PI – RK and MS). Cohort 9 - Developing Human Connectome Project was funded through a Synergy Grant by the European Research Council (ERC) under the European Union's Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreement n. 319456 (PIs – A. David Edwards, Jo Hajnal, Daniel Rueckert, Stephen Smith). Cohort 10 – Baby Connectome Project was supported by U01MH110274 (PI - WL). Cohort 11- DCHS study was funded by the Bill & Melinda Gates Foundation [OPP 1017641]. Additional support was provided by the Medical Research Council of South Africa. Imaging aspects of the cohort are additionally supported by the National Research Foundation, by NIAAA via (R21AA023887 and

R01AA026834-01), by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) developmental grant (U24 AA014811), and by the US Brain and Behavior Foundation Independent Investigator grant (24467) and the Wellcome Trust through a Research Training Fellowship [203525/Z/16/Z] (PI – DJS and KAD). Cohort 12 – UNC was supported by DA379395 (PI - KG). Cohort 13 (PHBP) and Cohort 15 (W2W) – funded by R01MH121877, R01MH107652, and Ann & Robert H. Lurie Children's Hospital of Chicago/Stanley Manne Children's Research Institute (PI - LSW). Cohort 14 - Boston study was funded by NIH–NICHDR01 HD065762-10, the William Hearst Fund (Harvard University), and the Harvard Catalyst/NIH (5UL1RR025758) (PI – NG). Cohort 16 – University of Denver study was supported by MH109662 and HL155744 (PI – EPD and BLH). Cohort 17 - University of Denver study was supported by HD090068 (PI - PK). Cohort 18 - Rhode Island Hospital study was supported by UG3OD023313 (PI – Sean C L Deoni). Cohort 19 – Rochester-Magee study was supported by 5UG3OD023349 (PI – TGO'C).

Financial Disclosures/Conflicts

DS has received research grants and/or consultancy honoraria from Discovery Vitality, Johnson & Johnson, Kanna, L'Oreal, Lundbeck, Orion, Sanofi, Servier, Takeda and Vistagen, PMT received a research grant from Biogen, Inc., and WL is a consultant of and received travel support from Nestlé SA, Switzerland. The authors report no biomedical financial interests or potential conflicts of interest.

References

1. Strike LT, Couvy-Duchesne B, Hansell NK, Cuellar-Partida G, Medland SE, Wright MJ (2015): Genetics and Brain Morphology. *Neuropsychol Rev* 25: 63–96.

2. Gao W, Grewen K, Knickmeyer RC, Qiu A, Salzwedel A, Lin W, Gilmore JH (2019, January 15): A review on neuroimaging studies of genetic and environmental influences on early brain development. *NeuroImage*, vol. 185. Academic Press Inc., pp 802–812.

3. Thompson PM, Jahanshad N, Ching CRK, Salminen LE, Thomopoulos SI, Bright J, *et al.* (2020): ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. *Transl Psychiatry* 10. https://doi.org/10.1038/S41398-020-0705-1

4. Fatemi SH, Folsom TD (2009): The Neurodevelopmental Hypothesis of Schizophrenia, Revisited. *Schizophr Bull* 35: 528–548.

5. Chen JA, Peñagarikano O, Belgard TG, Swarup V, Geschwind DH (2015): The emerging picture of autism spectrum disorder: genetics and pathology. *Annu Rev Pathol* 10: 111–144.

6. Douet V, Chang L, Cloak C, Ernst T (2014): Genetic influences on brain developmental trajectories on neuroimaging studies: From infancy to young adulthood. *Brain Imaging Behav* 8: 234–250.

7. Patel Y, Shin J, Abé C, Agartz I, Alloza C, Alnæs D, *et al.* (2022): Virtual Ontogeny of Cortical Growth Preceding Mental Illness. *Biol Psychiatry* 0. https://doi.org/10.1016/J.BIOPSYCH.2022.02.959

8. Papageorghiou AT, Sarris I, Ioannou C, Todros T, Carvalho M, Pilu G, Salomon LJ (2013): Ultrasound methodology used to construct the fetal growth standards in the INTERGROWTH-21st Project. *BJOG* 120: 27–32.

9. Lamballais S, Jansen PR, Labrecque JA, Ikram MA, White T (2021): Genetic scores for adult subcortical volumes associate with subcortical volumes during infancy and childhood. *Hum Brain Mapp* 42: 1583–1593.

10. Sparrow S, Manning JR, Cartier J, Anblagan D, Bastin ME, Piyasena C, *et al.* (2016): Epigenomic profiling of preterm infants reveals DNA methylation differences at sites associated with neural function. *Transl Psychiatry* 6. https://doi.org/10.1038/TP.2015.210

11. Fumagalli M, Provenzi L, de Carli P, Dessimone F, Sirgiovanni I, Giorda R, *et al.* (2018): From early stress to 12-month development in very preterm infants: Preliminary findings on epigenetic mechanisms and brain growth. *PLoS One* 13. https://doi.org/10.1371/JOURNAL.PONE.0190602

12. Wheater ENW, Galdi P, McCartney DL, Blesa M, Sullivan G, Stoye DQ, *et al.* (2022): DNA methylation in relation to gestational age and brain dysmaturation in preterm infants. *Brain Commun* 4. https://doi.org/10.1093/BRAINCOMMS/FCAC056

13. Hüls A, Wedderburn CJ, Groenewold NA, Gladish N, Jones MJ, Koen N, *et al.* (2022): Newborn differential DNA methylation and subcortical brain volumes as early signs of severe neurodevelopmental delay in a South African Birth Cohort Study. *World J Biol Psychiatry*. https://doi.org/10.1080/15622975.2021.2016955

14. Gilmore JH, Schmitt JE, Knickmeyer RC, Smith JK, Lin W, Styner M, *et al.* (2010): Genetic and environmental contributions to neonatal brain structure: A twin study. *Hum Brain Mapp* 31: 1174–1182.

15. Smit DJA, Luciano M, Bartels M, van Beijsterveldt CEM, Wright MJ, Hansell NK, *et al.* (2010): Heritability of Head Size in Dutch and Australian Twin Families at Ages 0–50 Years. *Twin Research and Human Genetics* 13: 370–380.

16. Gilmore JH, Knickmeyer RC, Gao W (2018): Imaging structural and functional brain development in early childhood. *Nat Rev Neurosci* 19: 123–137.

17. Jansen AG, Mous SE, White T, Posthuma D, Polderman TJC (2015): What Twin Studies Tell Us About the Heritability of Brain Development, Morphology, and Function: A Review. *Neuropsychol Rev* 25: 27–46.

18. Brouwer RM, Mandl RCW, Schnack HG, Soelen ILC van, Baal GC van, Peper JS, *et al.* (2012): White matter development in early puberty: A longitudinal volumetric and diffusion tensor imaging twin study. *PLoS One* 7. https://doi.org/10.1371/JOURNAL.PONE.0032316

19. Jha SC, Xia K, Schmitt JE, Ahn M, Girault JB, Murphy VA, *et al.* (2018): Genetic influences on neonatal cortical thickness and surface area. *Hum Brain Mapp* 39: 4998–5013.

20. Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, *et al.* (2009): Distinct Genetic Influences on Cortical Surface Area and Cortical Thickness. *Cerebral Cortex* 19: 2728–2735.

21. Chen CH, Fiecas M, Gutiérrez ED, Panizzon MS, Eyler LT, Vuoksimaa E, *et al.* (2013): Genetic topography of brain morphology. *Proc Natl Acad Sci U S A* 110: 17089–17094.

22. Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, *et al.* (2010): Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage* 53: 1135–1146.

23. Geng X, Prom-Wormley EC, Perez J, Kubarych T, Styner M, Lin W, *et al.* (2012): White Matter Heritability Using Diffusion Tensor Imaging in Neonatal Brains. *Twin Res Hum Genet* 15: 336.

24. Lee SJ, Steiner RJ, Luo S, Neale MC, Styner M, Zhu H, Gilmore JH (2015): Quantitative tract-based white matter heritability in twin neonates. *Neuroimage* 111: 123.

25. Vuoksimaa E, Panizzon MS, Hagler DJ, Hatton SN, Fennema-Notestine C, Rinker D, *et al.* (2017): Heritability of white matter microstructure in late middle age: A twin study of tract-based fractional anisotropy and absolute diffusivity indices. *Hum Brain Mapp* 38: 2026.

26. Zhang J, Xia K, Ahn M, Jha SC, Blanchett R, Crowley JJ, *et al.* (2021): Genome-Wide Association Analysis of Neonatal White Matter Microstructure. *Cerebral Cortex* 31: 933–948.

27. Pletikos M, Sousa AMM, Sedmak G, Meyer KA, Zhu Y, Cheng F, *et al.* (2014): Temporal specification and bilaterality of human neocortical topographic gene expression. *Neuron* 81: 321–332.

28. Kang HJ, Imamura Kawasawa Y, Cheng F, Zhu Y, Xu X, Li M, *et al.* (2011): Spatio-temporal transcriptome of the human brain. *Nature* 478. https://doi.org/10.1038/nature10523

29. Gao W, Elton A, Zhu H, Alcauter S, Smith JK, Gilmore JH, Lin W (2014): Intersubject variability of and genetic effects on the Brain's functional connectivity during infancy. *Journal of Neuroscience* 34: 11288–11296.

30. Xu J, Yin X, Ge H, Han Y, Pang Z, Liu B, *et al.* (2017): Heritability of the Effective Connectivity in the Resting-State Default Mode Network. *Cereb Cortex* 27: 5626–5634.

31. Glahn DC, Winkler AM, Kochunov P, Almasy L, Duggirala R, Carless MA, *et al.* (2010): Genetic control over the resting brain. *Proc Natl Acad Sci U S A* 107: 1223–1228.

32. Fu Y, Ma Z, Hamilton C, Liang Z, Hou X, Ma X, *et al.* (2015): Genetic influences on resting-state functional networks: A twin study. *Hum Brain Mapp* 36: 3959–3972.

33. Blanchett R, Chen Y, Aguate F, Xia K, Cornea E, Burt SA, *et al.* (2022): Genetic and environmental factors influencing neonatal resting-state functional connectivity. *Cereb Cortex*. https://doi.org/10.1093/CERCOR/BHAC383

34. Takagi Y, Okada N, Ando S, Yahata N, Morita K, Koshiyama D, *et al.* (2021): Intergenerational transmission of the patterns of functional and structural brain networks. *iScience* 24. https://doi.org/10.1016/J.ISCI.2021.102708

35. Ahtam B, Turesky TK, Zollei L, Standish J, Grant PE, Gaab N, Im K (2021): Intergenerational Transmission of Cortical Sulcal Patterns from Mothers to their Children. *Cerebral Cortex (New York, NY)* 31: 1888.

36. Fehlbaum L v., Peters L, Dimanova P, Roell M, Borbás R, Ansari D, Raschle NM (2022): Mother-child similarity in brain morphology: A comparison of structural characteristics of the brain's reading network. *Dev Cogn Neurosci* 53: 101058.

37. Bouchard TJ (2013): The Wilson Effect: The Increase in Heritability of IQ With Age. *Twin Research and Human Genetics* 16: 923–930.

38. Martin NG, Eaves LJ, Heath AC, Jardine R, Feingold LM, Eysenck HJ (1986): Transmission of social attitudes. *Proc Natl Acad Sci U S A* 83: 4364–4368.

39. Brouwer RM, Panizzon MS, Glahn DC, Hibar DP, Hua X, Jahanshad N, *et al.* (2017): Genetic influences on individual differences in longitudinal changes in global and subcortical brain volumes: Results of the ENIGMA plasticity working group. *Hum Brain Mapp* 38: 4444.

40. Brouwer RM, Klein M, Grasby KL, Schnack HG, Jahanshad N, Teeuw J, *et al.* (2022): Genetic variants associated with longitudinal changes in brain structure across the lifespan. *Nat Neurosci* 25: 421–432.

41. Knickmeyer RC, Wang J, Zhu H, Geng X, Woolson S, Hamer RM, *et al.* (2014): Common variants in psychiatric risk genes predict brain structure at birth. *Cerebral Cortex* 24: 1230–1246.

42. Kawasaki Y, Oishi K, Hernandez A, Ernst T, Wu D, Otsuka Y, *et al.* (2021): Brain-derived neurotrophic factor Val66Met variant on brain volumes in infants. *Brain Struct Funct* 226: 919–925.

43. de Vries CF, Staff RT, Noble KG, Muetzel RL, Vernooij MW, White T, *et al.* (2020): Klotho gene polymorphism, brain structure and cognition in early-life development. *Brain Imaging Behav* 14: 213–225.

44. Krishnan ML, van Steenwinckel J, Schang AL, Yan J, Arnadottir J, le Charpentier T, *et al.* (2017): Integrative genomics of microglia implicates DLG4 (PSD95) in the white matter development of preterm infant. *Nat Commun* 8: 1–11.

45. van Steenwinckel J, Schang AL, Krishnan ML, Degos V, Delahaye-Duriez A, Bokobza C, *et al.* (2019): Decreased microglial Wnt/β-catenin signalling drives microglial pro-inflammatory activation in the developing brain. *Brain* 142: 3806–3833.

46. Boardman JP, Walley A, Ball G, Takousis P, Krishnan ML, Hughes-Carre L, *et al.* (2014): Common genetic variants and risk of brain injury after preterm birth. *Pediatrics* 133. https://doi.org/10.1542/PEDS.2013-3011

47. Douet V, Chang L, Lee K, Ernst T (2015): ERBB4 polymorphism and family history of psychiatric disorders on age-related cortical changes in healthy children. *Brain Imaging Behav* 9: 128–140.

48. Qiu A, Tuan TA, Ong ML, Li Y, Chen H, Rifkin-Graboi A, *et al.* (2015): COMT haplotypes modulate associations of antenatal maternal anxiety and neonatal cortical morphology. *American Journal of Psychiatry* 172: 163–172.

49. Chen L, Pan H, Tuan TA, Teh AL, Macisaac JL, Mah SM, *et al.* (2015): Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism influences the association of the methylome with maternal anxiety and neonatal brain volumes. *Dev Psychopathol* 27: 137–150.

50. Wang C, Shen M, Guillaume B, Chong YS, Chen H, Fortier M v., *et al.* (2017): FKBP5 Moderates the Association between Antenatal Maternal Depressive Symptoms and Neonatal Brain Morphology. *Neuropsychopharmacology 2018 43:3* 43: 564–570.

51. Acosta H, Tuulari JJ, Kantojärvi K, Lewis JD, Hashempour N, Scheinin NM, *et al.* (2021): A variation in the infant oxytocin receptor gene modulates infant hippocampal volumes in association with sex and prenatal maternal anxiety. *Psychiatry Res Neuroimaging* 307: 111207.

52. Wolfe D, Dudek S, Ritchie MD, Pendergrass SA (2013): Visualizing genomic information across chromosomes with PhenoGram. *BioData Min* 6: 1–12.

53. Bogdan R, Salmeron BJ, Carey CE, Agrawal A, Calhoun VD, Garavan H, *et al.* (2017): Imaging Genetics and Genomics in Psychiatry: A Critical Review of Progress and Potential. *Biol Psychiatry* 82: 165.

54. Shaw P, Lerch JP, Pruessner JC, Taylor KN, Rose AB, Greenstein D, *et al.* (2007): Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: an observational study. *Lancet Neurology* 6: 494–500.

55. Burggren AC, Zeineh MM, Ekstrom AD, Braskie MN, Thompson PM, Small GW, Bookheimer SY (2008): Reduced cortical thickness in hippocampal sub-regions among cognitively normal apolipoprotein E e4 carriers. *Neuroimage* 41: 1177.

56. Dean DC, Jerskey BA, Chen K, Protas H, Thiyyagura P, Roontiva A, *et al.* (2014): Brain differences in infants at differential genetic risk for late-onset alzheimer disease: A cross-sectional imaging study. *JAMA Neurol* 71: 11–22.

57. Remer J, Dean DC, Chen K, Reiman RA, Huentelman MJ, Reiman EM, Deoni SCL (2020): Longitudinal white matter and cognitive development in pediatric carriers of the apolipoprotein ε4 allele. *Neuroimage* 222: 117243.

58. Chang L, Douet V, Bloss C, Lee K, Pritchett A, Jernigan TL, *et al.* (2016): Gray matter maturation and cognition in children with different different APOE ε genotypes. *Neurology* 87: 585.

59. Cullen H, Dimitrakopoulou K, Patel H, Curtis C, Batalle D, Gale-Grant O, *et al.* (2022): Common Genetic Variation Important in Early Subcortical Brain Development. *medRxiv* 2022.08.11.22278677.

60. Patnala R, Clements J, Batra J (2013): Candidate gene association studies: a comprehensive guide to useful in silico tools. *BMC Genet* 14. https://doi.org/10.1186/1471-2156-14-39

61. David S (2021): A current guide to candidate gene association studies. *Trends in Genetics* 37: 1056–1059.

62. MacArthur DG, Manolio TA, Dimmock DP, Rehm HL, Shendure J, Abecasis GR, *et al.* (2014): Guidelines for investigating causality of sequence variants in human disease. *Nature* 508: 469–476.

63. Plomin R, Haworth CMA, Davis OSP (2009): Common disorders are quantitative traits. *Nat Rev Genet* 10: 872–878.

64. Sullivan PF, Geschwind DH (2019): Defining the Genetic, Genomic, Cellular, and Diagnostic Architectures of Psychiatric Disorders. *Cell* 177: 162–183.

65. Xia K, Zhang J, Ahn M, Jha S, Crowley JJ, Szatkiewicz J, *et al.* (2017): Genome-wide association analysis identifies common variants influencing infant brain volumes. *Transl Psychiatry* 7: e1188–e1188.

66. Le H, Dimitrakopoulou K, Patel H, Curtis C, Cordero-Grande L, Hajnal J, *et al.* (2022): Effect of schizophrenia common variants on infant brain volumes: cross-sectional study in 207 term neonates in developing Human Connectome Project. https://doi.org/10.21203/RS.3.RS-1950696/V1

67. Khundrakpam B, Vainik U, Gong J, Al-Sharif N, Bhutani N, Kiar G, *et al.* (2020): Neural correlates of polygenic risk score for autism spectrum disorders in general population. *Brain Commun* 2. https://doi.org/10.1093/BRAINCOMMS/FCAA092

68. Cullen H, Krishnan ML, Selzam S, Ball G, Visconti A, Saxena A, *et al.* (2019): Polygenic risk for neuropsychiatric disease and vulnerability to abnormal deep grey matter development. *Scientific Reports 2019 9:1* 9: 1–8.

69. Ursini G, Punzi G, Langworthy BW, Chen Q, Xia K, Cornea EA, *et al.* (2021): Placental genomic risk scores and early neurodevelopmental outcomes. *Proc Natl Acad Sci U S A* 118. https://doi.org/10.1073/PNAS.2019789118/SUPPL_FILE/PNAS.2019789118.SD04.XLSX

70. Qiu A, Shen M, Buss C, Chong YS, Kwek K, Saw SM, *et al.* (2017): Effects of Antenatal Maternal Depressive Symptoms and Socio-Economic Status on Neonatal Brain Development are Modulated by Genetic Risk. *Cerebral Cortex* 27: 3080–3092.

71. Acosta H, Kantojärvi K, Hashempour N, Pelto J, Scheinin NM, Lehtola SJ, *et al.* (2020): Partial Support for an Interaction Between a Polygenic Risk Score for Major Depressive Disorder and Prenatal Maternal Depressive Symptoms on Infant Right Amygdalar Volumes. *Cerebral Cortex* 30: 6121–6134.

72. Acosta H, Kantojärvi K, Tuulari JJ, Lewis JD, Hashempour N, Scheinin NM, *et al.* (2020): Sex-specific association between infant caudate volumes and a polygenic risk score for major depressive disorder. *J Neurosci Res* 98: 2529–2540.

73. Alex AM, Ruvio T, Xia K, Jha SC, Girault JB, Wang L, *et al.* (2021): Influence of Gonadal Steroids on Cortical Surface Area in Infancy. *Cereb Cortex*. https://doi.org/10.1093/CERCOR/BHAB410

74. Morgunova A, Pokhvisneva I, Nolvi S, Entringer S, Wadhwa P, Gilmore J, *et al.* (2021): CCNP innovations in neuropsychopharmacology award: DCC gene network in the prefrontal cortex is associated with total brain volume in childhood. *Journal of Psychiatry and Neuroscience* 46: E154–E163.

75. Wu Y, Zhang H, Wang C, Broekman BFP, Chong YS, Shek LP, *et al.* (2020): Inflammatory modulation of the associations between prenatal maternal depression and neonatal brain. *Neuropsychopharmacology 2020 46:2* 46: 470–477.

76. Qiu A, Zhang H, Wang C, Chong YS, Shek LP, Gluckman PD, *et al.* (2021): Canonical TGF-β signaling regulates the relationship between prenatal maternal depression and amygdala development in early life. *Translational Psychiatry 2021 11:1* 11: 1–10.

77. Adams HHH, Hibar DP, Chouraki V, Stein JL, Nyquist PA, Rentería ME, *et al.* (2016): Novel genetic loci underlying human intracranial volume identified through genome-wide association. *Nat Neurosci* 19: 1569–1582.

78. Martin AR, Gignoux CR, Walters RK, Wojcik GL, Neale BM, Gravel S, *et al.* (2017): Human Demographic History Impacts Genetic Risk Prediction across Diverse Populations. *The American Journal of Human Genetics* 100: 635–649.

79. Krishnan ML, Wang Z, Silver M, Boardman JP, Ball G, Counsell SJ, *et al.* (2016): Possible relationship between common genetic variation and white matter development in a pilot study of preterm infants. *Brain Behav* 6: 434.

80. Krishnan ML, Wang Z, Aljabar P, Ball G, Mirza G, Saxena A, *et al.* (2017): Machine learning shows association between genetic variability in PPARG and cerebral connectivity in preterm infants. *Proc Natl Acad Sci U S A* 114: 13744–13749.

81. Tam V, Patel N, Turcotte M, Bossé Y, Paré G, Meyre D (2019): Benefits and limitations of genome-wide association studies. *Nature Reviews Genetics 2019 20:8* 20: 467–484.

82. Park JH, Gail MH, Weinberg CR, Carroll RJ, Chung CC, Wang Z, *et al.* (2011): Distribution of allele frequencies and effect sizes and their interrelationships for common genetic susceptibility variants. *Proc Natl Acad Sci U S A* 108: 18026–18031.

83. Houdou S, Takashima S, Suzuki Y (1993): Immunohistochemical expression of peroxisomal enzymes in developing human brain. *Mol Chem Neuropathol* 19: 235–248.

84. Luo R, Fan Y, Yang J, Ye M, Zhang DF, Guo K, *et al.* (2021): A novel missense variant in ACAA1 contributes to early-onset Alzheimer's disease, impairs lysosomal function, and facilitates amyloid-β pathology and cognitive decline. *Signal Transduction and Targeted Therapy 2021 6:1* 6: 1–16.

85. Vance JE, Hayashi H (2010): Formation and function of apolipoprotein E-containing lipoproteins in the nervous system. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1801: 806–818.

86. Reichardt LF (2006): Neurotrophin-regulated signalling pathways. *Philos Trans R Soc Lond B Biol Sci* 361: 1545–1564.

87. Uellendahl-Werth F, Maj C, Borisov O, Juzenas S, Wacker EM, Jørgensen IF, *et al.* (2022): Cross-tissue transcriptome-wide association studies identify susceptibility genes shared between schizophrenia and inflammatory bowel disease. *Communications Biology 2022 5:1* 5: 1–15.

88. Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Männistö PT (2007): Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *J Neurosci* 27: 10196–10202.

89. Hormozdiari F, Penn O, Borenstein E, Eichler EE (2015): The discovery of integrated gene networks for autism and related disorders. *Genome Res* 25: 142–154.

90. Porteous DJ, Millar JK, Brandon NJ, Sawa A (2011): DISC1 at 10: connecting psychiatric genetics and neuroscience. *Trends Mol Med* 17: 699–706.

91. Sundermann EE, Maki PM, Bishop JR (2010): A Review of Estrogen Receptor α Gene (ESR1) Polymorphisms, Mood, and Cognition. *Menopause* 17: 874.

92. Holt RJ, Young RM, Crespo B, Ceroni F, Curry CJ, Bellacchio E, *et al.* (2019): De Novo Missense Variants in FBXW11 Cause Diverse Developmental Phenotypes Including Brain, Eye, and Digit Anomalies. *The American Journal of Human Genetics* 105: 640–657.

93. Shen M, Guo Y, Dong Q, Gao Y, Stockton ME, Li M, *et al.* (2021): FXR1 regulation of parvalbumin interneurons in the prefrontal cortex is critical for schizophrenia-like behaviors. *Molecular Psychiatry 2021 26:11* 26: 6845–6867.

94. Khlghatyan J, Evstratova A, Chamberland S, Marakhovskaia A, Bahremand A, Toth K, Beaulieu JM (2018): Mental illnesses-associated Fxr1 and its negative regulator Gsk3b are modulators of anxiety and glutamatergic neurotransmission. *Front Mol Neurosci* 11: 119.

95. Agis-Balboa RC, Arcos-Diaz D, Wittnam J, Govindarajan N, Blom K, Burkhardt S, *et al.* (2011): A hippocampal insulin-growth factor 2 pathway regulates the extinction of fear memories. *EMBO J* 30: 4071–4083.

96. Ambalavanan A, Girard SL, Ahn K, Zhou S, Dionne-Laporte A, Spiegelman D, *et al.* (2016): De novo variants in sporadic cases of childhood onset schizophrenia. *Eur J Hum Genet* 24: 944–948.

97. Dahlhoff M, Pfister S, Blutke A, Rozman J, Klingenspor M, Deutsch MJ, *et al.* (2014): Peri-conceptional obesogenic exposure induces sex-specific programming of disease susceptibilities in adult mouse offspring. *Biochim Biophys Acta* 1842: 304–317.

98. Zhong H, Beaulaurier J, Lum PY, Molony C, Yang X, MacNeil DJ, *et al.* (2010): Liver and adipose expression associated SNPs are enriched for association to type 2 diabetes. *PLoS Genet* 6: 32.

99. Kunde SA, Rademacher N, Tzschach A, Wiedersberg E, Ullmann R, Kalscheuer VM, Shoichet SA (2013): Characterisation of de novo MAPK10/JNK3 truncation mutations associated with cognitive disorders in two unrelated patients. *Hum Genet* 132: 461–471.

100. Mei L, Xiong WC (2008): Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nat Rev Neurosci* 9: 437–452.

101. Bradley KC, Groth RD, Mermelstein PG (2005): Immunolocalization of NFATc4 in the adult mouse brain. *J Neurosci Res* 82: 762–770.

102. Khatchadourian A, Bourque SD, Richard VR, Titorenko VI, Maysinger D (2012): Dynamics and regulation of lipid droplet formation in lipopolysaccharide (LPS)-stimulated microglia. *Biochim Biophys Acta* 1821: 607–617.

103. Sargazi S, Sargazi FM, Moudi M, Nia MH, Saravani R, Mirinejad S, *et al.* (2020): Impact of Proliferator-Activated Receptor γ Gene Polymorphisms on Risk of Schizophrenia: A Case-Control Study and Computational Analyses. *Iran J Psychiatry* 15: 286.

104. Liu Y, Qu HQ, Chang X, Tian L, Glessner J, Sleiman PAM, Hakonarson H (2022): Expansion of Schizophrenia Gene Network Knowledge Using Machine Learning Selected Signals From Dorsolateral Prefrontal Cortex and Amygdala RNA-seq Data. *Front Psychiatry* 13: 285.

105. Hegde AN, Upadhya SC (2011): Role of ubiquitin-proteasome-mediated proteolysis in nervous system disease. *Biochim Biophys Acta* 1809: 128–140.

106. Xu L, Pan CL, Wu XH, Song JJ, Meng P, Li L, *et al.* (2021): Inhibition of Smad3 in macrophages promotes Aβ efflux from the brain and thereby ameliorates Alzheimer's pathology. *Brain Behav Immun* 95: 154–167.

107. Muñoz MD, de la Fuente N, Sánchez-capelo A (2020): TGF-β/Smad3 Signalling Modulates GABA Neurotransmission: Implications in Parkinson's Disease. *International Journal of Molecular Sciences 2020, Vol 21, Page 590* 21: 590.

108. Mitchell RW, On NH, del Bigio MR, Miller DW, Hatch GM (2011): Fatty acid transport protein expression in human brain and potential role in fatty acid transport across human brain microvessel endothelial cells. *J Neurochem* 117: 735–746.

109. Zandi PP, Belmonte PL, Willour VL, Goes FS, Badner JA, Simpson SG, *et al.* (2008): Association Study of Wnt Signaling Pathway Genes in Bipolar Disorder. *Arch Gen Psychiatry* 65: 785.

110. Evgrafov O v., Armoskus C, Wrobel BB, Spitsyna VN, Souaiaia T, Herstein JS, *et al.* (2020): Gene Expression in Patient-Derived Neural Progenitors Implicates WNT5A Signaling in the Etiology of Schizophrenia. *Biol Psychiatry* 88: 236–247.

111. Chen CM, Orefice LL, Chiu SL, LeGates TA, Hattar S, Huganir RL, *et al.* (2017): Wnt5a is essential for hippocampal dendritic maintenance and spatial learning and memory in adult mice. *Proc Natl Acad Sci U S A* 114: E619–E628.

112. Safran M, Rosen N, Twik M, BarShir R, Stein TI, Dahary D, *et al.* (2021): The GeneCards Suite. *Practical Guide to Life Science Databases* 27–56.

113. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, *et al.* (2016): Next-generation genotype imputation service and methods. *Nat Genet* 48: 1284–1287.

114. Achenbach T, Rescorla L (2000): Manual for the ASEBA preschool forms and profiles. *Article in Journal of Child and Family Studies*. https://doi.org/10.1007/s10826-014-9968-6

115. Reynolds CR, Kamphaus RW (2004): *Behavior Assessment System for Children, Second Edition*. Pearson Assessments.

116. Reynolds CR, Kamphaus RW (2005): BASC-2 Behavior Assessment System for Children. *Manual Supplement for the Self-Report of Personality--Interview.*, 2nd ed. AGS Publishing.

Figure Legends

Figure 1: Early neurodevelopment is a sensitive period for accumulating transdiagnostic risk for psychiatric disorders. Neurodevelopment in human brain begins from approximately two weeks after conception. Neurogenesis and neural migration are primarily prenatal processes, and neurite outgrowth is minimal after 4 years of age. Myelination and synaptic pruning continue beyond 6 years of age (indicated by the small arrows). Genetic influences on these various processes contribute to psychiatric risk which accumulates across development and may not manifest until later in life (large orange arrow).

Figure 2: Phenogram of genes associated with brain imaging phenotypes in infants and young children from candidate gene studies site and GWAS. ICV – Intracranial volume; WM FA – White matter fractional anisotropy; TBV – Total brain volume; GMV- Gray matter volume; WMV – White matter volume; CT- Cortical thickness; WM MWF – White matter myelin water fraction; SA –Surface Area.

Figure 3: Data analysis plan for the ORIGINs

Table 1: Candidate gene studies of imaging phenotypes in infancy and childhood

Article	Participants (N)	Age group	Ancestry	Gene/SNP - Brain Phenotype association	Findings
Studies on Genetic Effects					
Knickmeyer et al.,2014 (41)	272	Neonates (gestational age at MRI: 261-433 days)	Maternal ethnicity - white	*ESR1* (rs9340799) - ICV; *DISC1* (rs821616), *COMT*, *NRG1*, *APOE*, *ESR1* (rs9340799), and *BDNF* - GMV	Associations in *DISC1* and *COMT* mirrored findings in adults.
Dean et al., 2014 (56)	162	2- to 25-month-old infants	Not reported	*APOE* ε4 allele - ↓ MWF and GMV in precuneus, posterior/middle cingulate, lateral temporal, and medial occipitotemporal regions. *APOE* ε4 allele - ↑ MWF and GMV in extensive frontal regions	Infant apolipoprotein E (*APOE*) ε4 allele carriers had lower white matter myelin water fraction (MWF) and gray matter volume (GMV) measurements than noncarriers in areas preferentially affected by Alzheimer disease
Boardman et al., 2014 (46)	83 preterm infants	Neonates (post menstrual age 23+2 to 32+6 weeks)	Multi ancestry	*ARVCF* (rs2518824) and FADS2 (rs174576) - White matter FA	
Douet et al., 2015 (47)	971 (PING study)	3-20 years	Multi ancestry	*ERBB4 (*rs7598440) – Cortical structures	In the full sample children with the TT- genotype had smaller SA in the occipital and temporal lobes at ages less than 5 years. When stratifying by family history of schizophrenia and/or bipolar TT children show steeper increases in frontal SA in early childhood.

Chang et al., 2016 (58)	1187 (PING study)	3 to 20 years	Multi ancestry	*APOE (*ε2ε4 - ↓ Hippocampus; ε4ε4 - ↓ hippocampal FA; ε3ε4 - ↑ medial orbitofrontal cortical areas)	The ε4ε4 and ε2ε4 genotypes may negatively influence brain development and brain aging at the extremes of age
Krishnan et al., 2017 (44)	preterm infants (cohort 1: n = 70; cohort 2 (EPRIME study): n = 271)	cohort 1 - mean postmenstrual age at scan 40+3 weeks; cohort 2 - mean postmenstrual age at scan 42+4 weeks	Multi ancestry	*DLG4* (rs17203281) - FA	*DLG4* (rs17203281) was associated with structural white matter changes
Steenwinckel et al., 2019 (45)	290 preterm infants (EPRIME study)	gestational age of 38.29 to 58.28 weeks	Multi ancestry	*NFATC4*, *CSNK1A1*, *MAPK10*, *WNT2B*, *SMAD3*, *FBXW11*, *NLK*, *CSNK1A1L*, *PLCB2* and *WNT5A* - White matter structural connectivity	Genomic variation in the Wnt pathway is associated with the levels of connectivity found in their brains.
De Vries et al., 2020 (43)	1387 (PING study)	3–21 years	Multi ancestry	Klotho allele KL-VS; KL -CS X age interaction - TBV, TGMV; Kl-VS X Sex - TWMV	A replication in a cohort of 2306 children aged 6–12 years (Generation R sample) showed no significant associations. KL-VS's influence may depend on age and sex.

Remer et al., 2020 (57)	223	2–68 months	Multi ancestry	*APOE* ε4 carriers - MWF	ε4 carriers - significant MWF trajectory differences in multiple neuroanatomical locations
Kawasaki et al., 2021 (42)	66	Newborn infants (37.9–47.6 postmenstrual weeks)	Multi ancestry	*BDNF*-Val66Met variant – hippocampi, amygdalae, TWMV	Met + group - ↓hippocampi, amygdalae, age-dependent declines in % total white matter volumes, slower age-dependent declines in total brain volumes
Cullen et al., 2022 (59)	208(dHCP study)	0- 6 weeks	European	rs945270 (intergenic locus downstream of the Kinectin 1 (*KTN1*) gene) - Putamen volume	greater number of C alleles associated with larger volume
Studies on interaction between genetic and environmental effect					
Qiu et al., 2015 (48)	146 (GUSTO cohort)	Neonates (5 to 17 days)	Asian	*COMT* - cortical thickness	*COMT* SNPs (val158met, rs737865 and rs165599) - role in moderating the relationship of antenatal maternal anxiety with dorsolateral prefrontal and parietal cortical thickness in neonates.
Chen et al., 2015 (49)	237 (GUSTO)	Neonates (4–17 days)	Asian	*BDNF* (Val66Met) - hippocampus, amygdala	*BDNF* (Val66Met) - regulate the sensitivity of the methylome with differential effects on amygdala and hippocampal volume
Wang et al., 2017 (50)	164 Mother-offspring dyads (GUSTO)	Neonates (5 to 14 days)	Asian	*FKBP5* - Hippocampus	17 SNPs in the *FKBP5* gene showed significant interaction effects with antenatal maternal depressive symptoms on right hippocampal volume

Acosta et al., 2021 (51)	105	11–54 days old	European	*OTR* rs53576 X Sex - Hippocampus	For oxytocin receptor (*OTR*) SNP rs53576, in boys compared to girls, left hippocampal volumes were significantly larger in GG-homozygotes compared to A-allele carriers. Higher maternal anxiety was associated both with larger hippocampal volumes in A-allele carriers than GG-homozygotes.

Table 2: Polygenic risk score (PRS) studies of imaging phenotypes in infancy and childhood

Article	Participants (N)	Age group	Ancestry	PRS	Findings
Studies on main genetic effects					
Xia et al., 2017 (65)	561	6-161 days	Multi ancestry	a) polygenic scores for GM and WM from adolescent cohort; polygenic scores for ICV from adolescent and adult cohort b) PRS for schizophrenia and ASD	a) Adolescent WM and GM scores showed positive associations with neonatal WM and GM; Adult polygenic scores for ICV did not predict neonatal ICV b) PRS did not predict global brain volumes.
Cullen et al.,2019 (68)	194 preterm infants	mean postmenstrual age at scan 42.6 weeks	Multi ancestry	(68)PRS from meta-analysis of genome-wide SNP data for five psychiatric disorders (autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia)	↑PRS - ↓ lentiform volume in the mixed ancestral cohort and a European subsample.
Khundrakpam et al., 2020 (67)	391 (PING study)	3-21 years	Multi ancestry	PRS for ASD	↑ PRS for autism spectrum disorder - ↑ cortical thickness for a large age span starting from 3 years up to ∼14 years in several cortical regions localized in bilateral precentral gyri and the left hemispheric postcentral gyrus and precuneus, ↓white matter connectivity between the frontal and parietal regions
Morgunova et al.,2021 (74)	142	Neonates (27 ± 13 days)	Multi ancestry	Expression-based polygenic risk score (ePRS) was created based on the DCC coexpression gene	↑ ePRS - ↑ total brain volume (grey and white matter, adjusted by intracranial volume).

				network in the prefrontal cortex (PFC)	
Alex et al., 2021 (73)	430	Birth – 2 years	European	PRS for serum testosterone	↑ PRS- ↑ SA development over time in female infants.
Cullen et al., 2022 (59)	208	0- 6 weeks	European	a) Genome-wide polygenic scores (GPSs) for adult subcortical brain volumes b) GPSs for psychiatric disorders autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, major depressive disorder, and cross-disorder (including eight psychiatric disorders: anorexia nervosa, ADHD, ASD, bipolar disorder, major depression, obsessive-compulsive disorder, schizophrenia, and Tourette syndrome)	a) neonatal volumes of hippocampus, brainstem, putamen, and thalamus associated with adult GPS b) None of the neonatal brain volumes showed an association with psychiatric GPS
Le et al., 2022 (66)	257	postmenstrual age at scan 38 - 45 weeks	prelim analysis: European; secondary; European and Asian	PRS for Schizophrenia	↑PRS - ↓ right frontal lobe white matter, ↓grey and white matter superior temporal gyrus volumes and ↓total white matter volume
Studies on interaction between genetic and environmental risk					

Qiu et al., 2017 (70)	168 (GUSTO) and 85 (US) mother–infant dyads	Neonates: GUSTO (5–14 days), US (Post-Conceptual Age at the MRI visit 43.02 ± 2.1 weeks)	GUSTO - Asian; US - mixed ancestry	Genomic profile risk score for major depressive disorder (GPRSMDD)	Significant interaction was observed between antenatal maternal depressive symptoms and infant GPRSMDD on right hippocampal volume in Asian cohort and right amygdala volume in both cohorts. Significant interaction between SES and infant GPRSMDD on the right amygdala and hippocampal volumes and shapes in the Asian cohort.
Wang et al., 2017 (50)	164 Mother-offspring dyads (GUSTO)	Neonates (5 to 14 days)	Asian	A genetic risk score was calculated for individual neonates by summing the number of minor alleles of 19 FKBP5 SNPs	Neonates with the genetic risk score lower than or equal to its median showed a positive association between antenatal maternal depressive symptoms and the right hippocampal volume. Neonates with the genetic risk score greater than its median showed a negative association between antenatal maternal depressive symptoms and the right hippocampal volume.
Acosta et al., 2020 (71)	105	11–54 days old	European	PRS MDD	A nonsignificant interaction effect between polygenic risk scores for major depressive disorder (PRS-MDD) and prenatal maternal depressive symptoms on right amygdala volume was observed.
Acosta et al.,2020 (72)	105	11–54 days old	European	PRS MDD	No significant interaction effects of PRS-MDD with prenatal maternal depressive symptoms were found for infant dorsal striatal volumes. PRS-MDD was more positively associated with caudate volumes in boys compared to girls.

Wu et al., 2020 (75)	161 mother–child dyads (GUSTO)	Neonates (5–14 days)	Asian	A genetic expression score (GES) was calculated for individuals by summing the number of minor alleles across the SNPs of the gene that were highly correlated with its expression level according to the existing expression quantitative trait loci (eQTL) database.	Positive associations of prenatal maternal depressive symptoms with the hippocampal volume, auditory and prefrontal cortical thickness in neonates high in GESs of the TNF, IL-1, IL17, chemokine, and TGF family and receptors.
Ursini et al., 2021 (69)	242	10-60 days	European	Fractionated genomic risk scores for schizophrenia based on placental gene-expression loci (PlacGRSs)	↑PlacGRSs -↓ neonatal brain volume in singletons and offspring of multiple pregnancies with a history of early-life complications.
Qiu et al., 2021 (76)	162 (GUSTO)	Birth – 6 years	Asian	genetic expression score (GES) was calculated for individuals by summing the number of alleles across the SNPs of the gene that was correlated with TGF-βRI expression level according to the existing expression quantitative trait loci (eQTL) database	In neonates with a high GES of *TGF-βRI*, higher levels of prenatal maternal depressive symptoms were associated with a smaller right amygdala volume. In children with a low GES of *TGF-βRI*, greater prenatal maternal depressive symptoms predicted greater left and right amygdala volumes at 6 years of age.

Table 3: Genome wide association studies of imaging phenotypes in infancy and childhood

Article	Participants (N)	Age group	Ancestry	Findings
Krishnan et al., 2016 (79)	72 preterm infants	Gestational age 23 + 2 to 32 + 6 weeks	Multi ancestry	Identified significant role for lipid pathways, and PPAR (peroxisome proliferator-activated receptor) signaling in influencing development of white matter in preterm infants. Five genes were found to be highly associated with the phenotype: *AQP7*, *ME1*, *PLIN1*, *SLC27A1*, and *ACAA1*.
Krishnan et al., 2017 (80)	272 preterm infants	gestational age 42 wk+4d	Multi ancestry	*PPARG* (six SNPs), *ITGA6* (four SNPs), *FXR1* (two SNPs) are associated with preterm cerebral endophenotype, particularly insular cortex
Xia et al., 2017 (65)	561	6-161 days	Multi ancestry	An intronic* single-nucleotide polymorphism (SNP) in *IGFBP7* (rs114518130) achieved genome-wide significance for gray matter volume. An intronic SNP in *WWOX* (rs10514437) neared genome-wide significance for white matter volume.
Zhang et al., 2021 (26)	471	Neonates (days post conception 293.4 ± 16.6)	Multi ancestry	An intronic SNP in the gene *PSMF1* was significant for a tractography-based factor that captured shared variation in fractional anisotropy across 44 white matter bundles.

*Intronic SNPs are located in a segment of a DNA or RNA molecule which does not code for proteins and interrupts the sequence of genes.

Table 4: Brain imaging phenotype associated gene, their function, and associated neurologic phenotype/disorder

Gene	Abbreviation	Function	Associated neurologic phenotype/disorder
Acetyl-CoA acyltransferase 1	*ACAA1*	Involved in neuronal growth and myelinogenesis (83)	Alzheimer's (84)
Apolipoprotein E	*APOE*	Facilitates the transfer of cholesterol and phospholipid between cells, key role in neuronal development, brain plasticity, and repair (85)	Alzheimer's, Schizophrenia (41)
Aquaporin 7	*AQP7*	Allows movement of water, glycerol, and urea across cell membranes*	
Armadillo repeat gene deleted in velocardiofacial syndrome	*ARVCF*	Modulates neural cell-cell adhesion and migration (46)	Schizophrenia (46)
Brain-derived neurotrophic factor	*BDNF*	Regulates cell survival, axonal outgrowth, dendritic growth, and synaptic plasticity (86)	Depression, Bipolar, Schizophrenia, Anxiety, Autism, Attention deficit hyperactivity disorder (ADHD),

			Substance abuse, Eating disorders, Alzheimer's (41)
Casein kinase 1, alpha 1	*CSNK1A1*	Suppressor of Wnt/β-catenin signaling*	Schizophrenia (87)
Casein kinase 1, alpha 1-like	*CSNK1A1L*	Involved in negative regulation of canonical Wnt signaling pathway and peptidyl-serine phosphorylation*	
Catechol-O-methyltransferase	*COMT*	Degrades dopamine and other catecholamines (88)	Schizophrenia (41)
Discs large MAGUK scaffold protein 4	*DLG4*	Synapse structure and development (44)	Intellectual disability, Epilepsy, Autism spectrum disorder, Schizophrenia (44,89)
Disrupted in schizophrenia 1	*DISC1*	neural migration, neurite outgrowth, and dendritic arborization (90)	Schizophrenia, Bipolar, Autism, Depression (41)
Erb-B2 Receptor Tyrosine Kinase 4	*ERBB4*	Role in neurodevelopment such as glial and neuronal migration, myelination, excitatory neuronal	Schizophrenia, Bipolar Disorder (47)

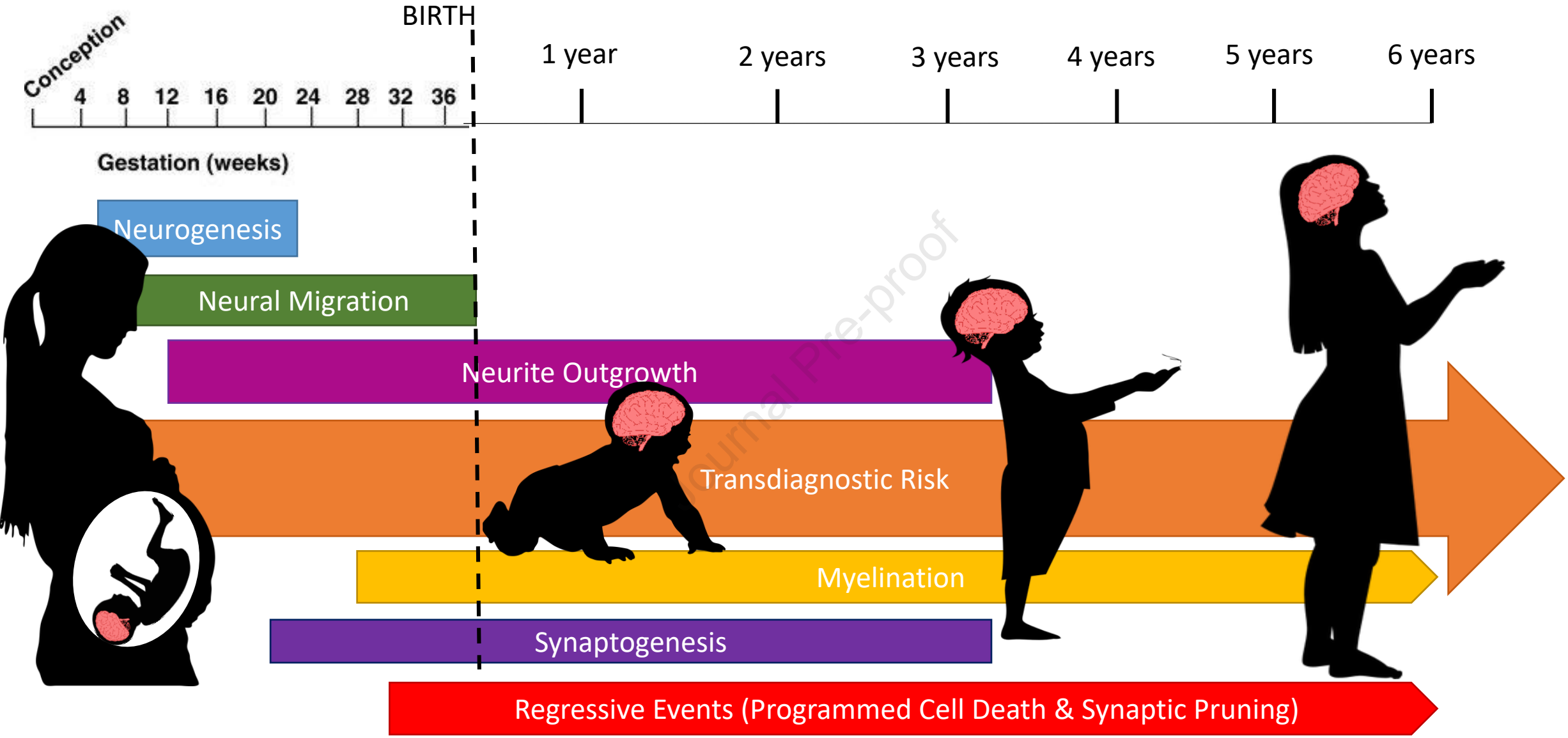
		receptor expression and the onset of puberty (47)	
Estrogen Receptor 1	*ESR1*	Mediates estrogen effects on synaptogenesis, growth factor production, and responses to oxidative stress (91)	Anxiety, Depression, Schizophrenia, Alzheimer's (41)
Fatty acid desaturase 2	*FADS2*	Essential for neurogenesis, neurotransmission, and protection from oxidative stress (46)	interact with early dietary exposures to influence childhood IQ (46)
F-box and WD repeat domain containing 11	*FBXW11*	Involved in ubiquitination and proteasomal degradation (92)	Autism spectrum disorder (92)
FK506-binding protein 5	*FKBP5*	Transcriptional regulation of the HPA axis (50)	Depression, PTSD (50)
Fragile X Mental Retardation, Autosomal Homolog 1	*FXR1*	levels of FXR1 are important for Parvalbumin interneurons (99)	Schizophrenia, Bipolar disorder (94)
Insulin-like growth factor-binding protein 7	*IGFBP7*	Regulation of availability of insulin-like growth factors (IGFs)*	Learning and memory (95)
Integrin Subunit Alpha 6	*ITGA6*	Involved in insulin-like growth factor 1 signaling (80)	Schizophrenia (96)

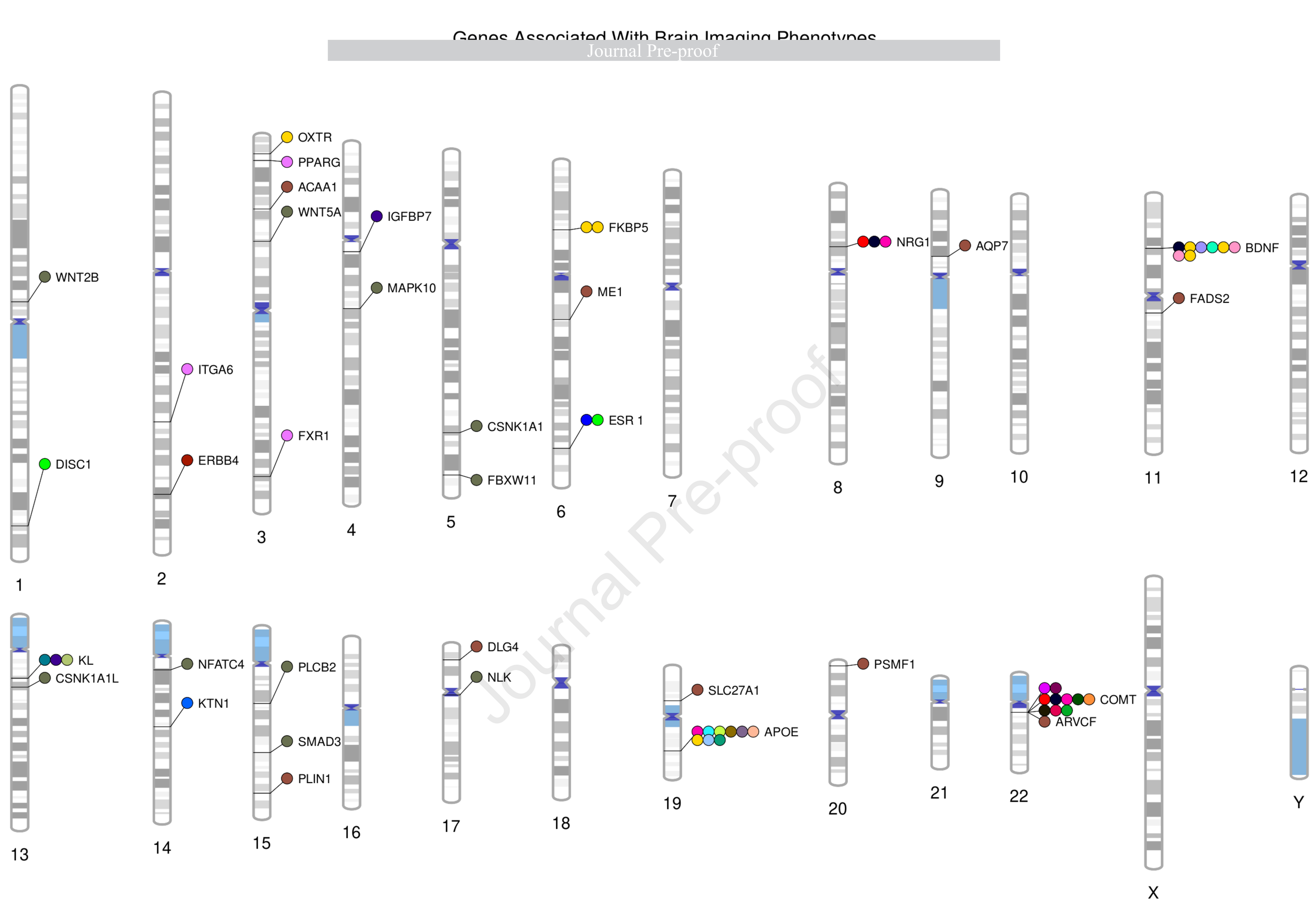
Kinectin 1	*KTN1*	Encodes the protein kinectin, a receptor that allows vesicle binding to kinesin and is involved in organelle transport (59)	ADHD (59)
Klotho	*KL*	Health and survival(43)	Cognition (43)
Malic enzyme 1	*ME1*	Sex-specific gene regulation in the offspring, key regulator of a T2DM-specific gene expression network (97,98)	
Mitogen-activated protein kinase 10	*MAPK10*	Neuronal proliferation, differentiation, migration, and programmed cell death*	Cognition(99)
Nemo-like kinase	*NLK*	Positive effector of the non-canonical Wnt signaling pathway and Negative regulator of the canonical Wnt/beta-catenin signaling pathway*	
Neuregulin 1	*NRG1*	Mediate cell-cell interactions in the brain and other organs, neuronal migration and specification, oligodendrocyte differentiation and myelination, regulation of acetylcholine, and expression of	Schizophrenia, Bipolar (41)

		glutamate and γ-aminobutyric acid (GABA) receptors (100)	
Nuclear factor of activated T-cells, cytoplasmic 4	*NFATC4*	Hippocampal plasticity, axonal growth, neuronal survival, and apoptosis (101)	Cognition
Oxytocin receptor	*OTR*	Receptor for oxytocin (51)	Depression, Autism, Eating disorder (51)
Perilipin 1	*PLIN1*	Regulates droplet formation in lipopolysaccharide-stimulated microglia (102)	
Peroxisome Proliferator Activated Receptor Gamma	*PPARG*	Regulator of adipocyte differentiation*	Schizophrenia (103)
Phospholipase C, beta 2	*PLCB2*	Catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate*	Schizophrenia (104)
Proteasome Inhibitor Subunit 1	*PSMF1*	Inhibits activation of the 26S proteasome, a multicatalytic proteinase complex that may play a role in developmental axonal pruning and synaptic plasticity (105)	
SMAD family member 3	*SMAD3*	Involved in regulating inflammatory responses(106)	Alzheimer's(106), Cognition(107)

Solute carrier family 27 (fatty acid transporter), member 1	*SLC27A1*	Involved in fatty acid transport across the blood–brain barrier (108)	
Wingless-type MMTV integration site family, member 2B	*WNT2B*	Regulation of cell growth and differentiation*	Bipolar disorder(109)
Wingless-type MMTV integration site family, member 5A	*WNT5A*	Essential role in regulating developmental pathways during embryogenesis*	Schizophrenia(110), Memory(111)

*GeneCards(112)





- ICV
- Frontal Lobe
- Temporal Lobe
- Occipital Lobe
- Parietal Lobe
- Supplementary Motor Area
- Hippocampus
- Primary Motor Area
- Somatosensory Cortex
- WM FA
- TBV
- Total GMV
- Total WMV
- Amygdala
- CT in Ventrolateral PFC
- CT in Precentral Gyrus
- CT in Dorsolateral PFC
- CT in Superior Parietal Cortex
- CT in Precuneus
- CT in Posterior Cingulate
- WM MWF
- Precuneus
- Cingulate Region
- Occipitotemporal Region
- Lateral Temporal Region
- Superior Parietal Gyrus
- CT in Entorhinal Cortex
- WM Structutal Connectivity
- Putamen
- WM Tracts
- Cortical SA

6809

Aim 1a: Harmonized Genomes
6400

Aim 1b: Harmonized Imaging Data
Structural MRI: 5700
DTI: 5500
fMRI: 5100

Aim 1c: Harmonized Behavior Data
3800

Aim 2a: Genomic Heritabilities & Correlations
Structural MRI: 5400
DTI: 5200
fMRI: 4800

Aim 2b: Association Analysis

Modality	Discovery	Validation
Structural	4100	1300
DTI	4000	1200
fMRI	3700	1100

Aim 2c: Integration with PGC data
MRI: 4100
DTI: 4000
fMRI: 3700

Aim 3: Identify correlations between genetically influenced DIPs and clinically salient behavior
2900