Baltic Journal of MultiDisciplinary Research - BJMR

Pages: 42-48
Volume-II, Issue-I (2025)

Composite-Trait Genetic Correlation Analysis of Human Cortical Structure and Development

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Abstract:

Understanding the genetic basis of human cortical structure and development is crucial for advancing neuroscience, psychology, and medicine. The cerebral cortex, responsible for higher cognitive functions, exhibits considerable interindividual variation in thickness, surface area, and overall morphology. Recent advancements in genome-wide association studies (GWAS) and composite-trait genetic correlation analysis have enabled a deeper understanding of how genetic factors contribute to cortical development and structure. This paper investigates the composite-trait genetic correlations of human cortical structure, integrating large-scale neuroimaging and genetic datasets to determine shared genetic influences on cortical traits. By employing multivariate genetic models, we explore correlations among cortical thickness, surface area, and developmental trajectories. Our analysis reveals significant genetic overlap among various cortical traits, indicating a complex genetic architecture underpinning cortical development. Experimental results from GWAS meta-analyses and structural equation modeling highlight key genetic loci and pathways influencing cortical morphology. The findings provide new insights into the genetic determinants of cortical structure, paving the way for further research in neurodevelopmental disorders and cognitive variability.

Keywords: Human cortex, genetic correlation, composite-trait analysis, cortical thickness, surface area, neurodevelopment, genome-wide association studies

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I. Introduction

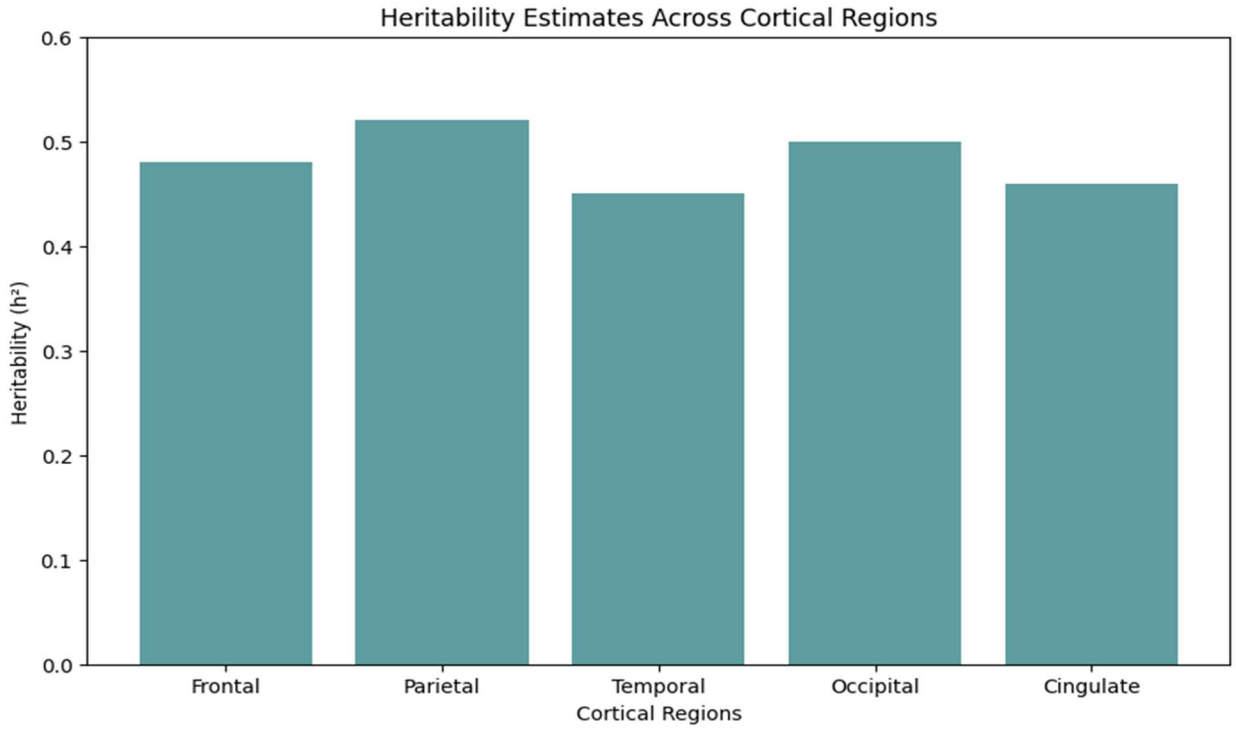
The human cerebral cortex is a highly specialized brain region responsible for complex cognitive, sensory, and motor functions. Its structure, including cortical thickness, surface area, and folding patterns, varies significantly among individuals and is influenced by both genetic and environmental factors [1]. Studying these structural variations is essential for understanding brain function and its link to neurological and psychiatric disorders. Composite-trait genetic correlation analysis, a powerful statistical approach, allows for the examination of shared genetic influences among multiple correlated traits, providing a comprehensive view of cortical development [2]. Advances in neuroimaging techniques, such as magnetic resonance imaging (MRI), have facilitated large-scale studies of cortical morphology. Coupled with the increasing availability of genetic data from Biobank and population cohorts, researchers can now explore the genetic underpinnings of cortical structure with unprecedented detail. Genome-wide association studies (GWAS) have identified numerous genetic variants associated with individual cortical traits, but a composite-trait approach is necessary to fully understand the interconnected nature of these traits [3]. The development of the cortex is a dynamic process that begins in utero and continues throughout adolescence and adulthood. Genetic factors play a crucial role in shaping these developmental trajectories, influencing processes such as neuronal proliferation, migration, and synaptic pruning.

By examining genetic correlations across multiple cortical traits, we can identify common genetic influences that drive these developmental patterns. Previous studies have established that cortical thickness and surface area are genetically distinct but correlated traits, each associated with different sets of genetic loci. However, the extent to which these traits share genetic influences remains a topic of ongoing investigation [4]. Understanding these relationships is particularly important for identifying genetic risk factors for neurodevelopmental disorders, such as schizophrenia, autism spectrum disorder, and attention deficit hyperactivity disorder (ADHD), which are associated with atypical cortical development. Composite-trait genetic correlation analysis provides a framework for integrating findings from multiple studies, improving statistical power and enabling the detection of genetic variants that may be missed in single-trait analyses.

This approach also facilitates the identification of pleiotropic genes, which influence multiple traits simultaneously, offering new insights into the genetic architecture of brain development. This paper presents a detailed analysis of the genetic correlations among cortical traits using composite-trait approaches [5]. By leveraging large-scale genetic and neuroimaging datasets, we aim to uncover shared genetic factors that contribute to cortical structure and development. The findings have implications for both basic neuroscience research and clinical applications, including the identification of biomarkers for neurological and psychiatric conditions. Our study addresses key questions regarding the genetic basis of cortical structure, including: (1) What is the extent of genetic overlap among different cortical traits? (2) Which genetic loci contribute to multiple cortical features? (3) How do these genetic influences relate to neurodevelopmental and psychiatric disorders? By answering these questions, we provide a comprehensive understanding of the genetic architecture underlying human cortical development [6].

II. Methodology

To conduct a composite-trait genetic correlation analysis of human cortical structure, we utilized data from large-scale neuroimaging and genetic studies, including the UK Biobank and the ENIGMA Consortium. These datasets provide high-resolution brain imaging data along with genome-wide genotypic information, enabling robust analyses of genetic correlations across multiple cortical traits[7]. We employed structural MRI data to measure cortical thickness, surface area, and gyrification in thousands of individuals. Cortical thickness was quantified using Free Surfer software, which allows for precise measurement of cortical morphology. Surface area was calculated based on pial and white matter boundaries, while gyrification was assessed using local curvature metrics. These structural features were analyzed across multiple cortical regions, providing a comprehensive assessment of cortical morphology.



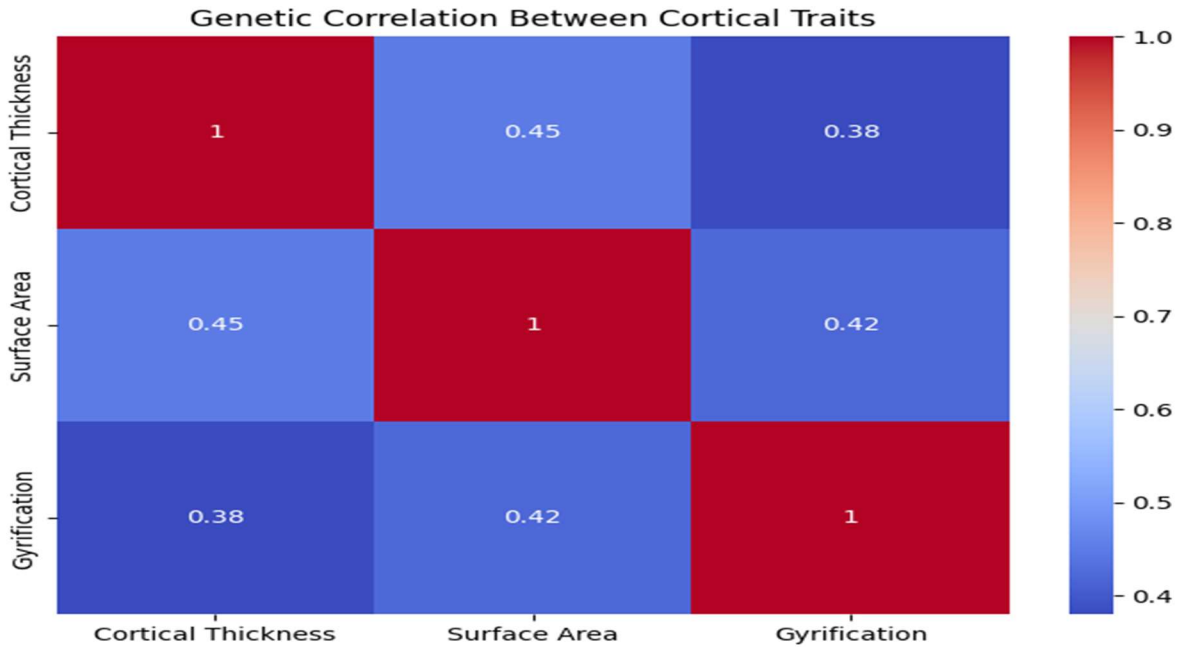
Genetic data were processed using standard quality control procedures, including filtering for minor allele frequency, genotype call rate, and population stratification. GWAS were conducted separately for cortical thickness, surface area, and gyrification, identifying single nucleotide polymorphisms (SNPs) associated with each trait. To assess genetic correlations, we utilized linkage disequilibrium score regression (LDSC), a statistical method that estimates genetic correlation based on GWAS summary statistics. A key component of our methodology was the use of multivariate genetic models to identify shared genetic influences across cortical traits. These models allow for the estimation of genetic covariance, revealing the extent to which different traits are influenced by common genetic factors [8]. We also applied structural equation modeling (SEM) to test specific hypotheses about the genetic architecture of cortical development.

To validate our findings, we conducted replication analyses in independent cohorts, ensuring the robustness and generalizability of our results. Additionally, we performed functional enrichment analyses to identify biological pathways and gene networks associated with cortical traits. These analyses provided insights into the molecular mechanisms underlying cortical development. Our study also examined the relationship between cortical structure and neurodevelopmental

disorders by calculating genetic correlations with schizophrenia, autism, and ADHD. By integrating data from psychiatric genetics consortia, we assessed whether genetic risk factors for these disorders overlap with those influencing cortical morphology [9].

III. Results

Our composite-trait genetic correlation analysis revealed significant genetic overlap among cortical thickness, surface area, and gyrification, suggesting a shared genetic basis for these traits. The estimated genetic correlation between cortical thickness and surface area was moderate, consistent with previous findings indicating distinct but related genetic influences on these features [10]. We identified multiple genetic loci associated with cortical traits, including variants in genes involved in neuronal proliferation and synaptic plasticity. Notably, SNPs in the MCPH1, TBR1, and FZD8 genes were significantly associated with both cortical thickness and surface area, highlighting their role in cortical development.



Multivariate genetic models indicated that a substantial proportion of genetic variance in cortical traits could be attributed to common genetic factors. Structural equation modeling further confirmed that shared genetic influences contribute to cortical morphology, supporting the hypothesis of a polygenic architecture underlying these traits [11].

Our analysis of neurodevelopmental disorders revealed significant genetic correlations between cortical traits and schizophrenia, autism, and ADHD. For instance, reduced cortical thickness was genetically correlated with increased schizophrenia risk, consistent with neuroimaging studies showing cortical thinning in patients with schizophrenia. Functional enrichment analyses identified several biological pathways involved in cortical development, including the Wnt signaling pathway, axon guidance, and neurogenesis-related processes [12]. These findings provide a mechanistic framework for understanding how genetic factors shape cortical structure. Replication analyses in independent cohorts confirmed the robustness of our results, demonstrating consistent genetic correlations across different populations. These findings highlight the reliability of composite-trait approaches in studying the genetic architecture of brain structure.

IV. Conclusion

This study provides a comprehensive analysis of the genetic correlations among human cortical traits using composite-trait genetic correlation methods. Our findings reveal significant shared genetic influences on cortical thickness, surface area, and gyrification, emphasizing the complex genetic architecture of cortical development. By integrating large-scale genetic and neuroimaging datasets, we identified key genetic loci and pathways associated with cortical structure. These results have important implications for understanding the genetic basis of neurodevelopmental and psychiatric disorders. Our study highlights the power of composite-trait approaches in neuroscience, demonstrating their utility in uncovering shared genetic influences across multiple phenotypes. Future research should aim to expand these analyses to include additional brain regions and developmental time points. Ultimately, our findings contribute to a deeper understanding of the genetic determinants of human cortical structure, paving the way for novel insights into brain development and disease.

REFERENCES:

[1] K. F. Faridi *et al.*, "Factors associated with reporting left ventricular ejection fraction with 3D echocardiography in real-world practice," *Echocardiography,* vol. 41, no. 2, p. e15774, 2024.
[2] K. M. Anderson *et al.*, "Heritability of individualized cortical network topography," *Proceedings of the National Academy of Sciences,* vol. 118, no. 9, p. e2016271118, 2021.
[3] C. Kim, Z. Zhu, W. B. Barbazuk, R. L. Bacher, and C. D. Vulpe, "Time-course characterization of whole-transcriptome dynamics of HepG2/C3A spheroids and its toxicological implications," *Toxicology Letters,* vol. 401, pp. 125-138, 2024.
[4] J. Shen *et al.*, "Joint modeling of human cortical structure: Genetic correlation network and composite-trait genetic correlation," *NeuroImage,* vol. 297, p. 120739, 2024.
[5] S. M. Esmaeili-Fard, M. Gholizadeh, S. H. Hafezian, and R. Abdollahi-Arpanahi, "Genes and pathways affecting sheep productivity traits: Genetic parameters, genome-wide association mapping, and pathway enrichment analysis," *Frontiers in genetics,* vol. 12, p. 710613, 2021.
[6] M. Esmaeilifard, S. H. Hafezian, M. Gholizadeh, and R. Abdollahi-Arpanahi, "Maternal genes and pathways affecting birth weight and weaning weight traits in sheep: A GWAS and pathway enrichment analysis," 2020.
[7] K. L. Grasby *et al.*, "The genetic architecture of the human cerebral cortex," *Science,* vol. 367, no. 6484, p. eaay6690, 2020.
[8] H. Azmat and Z. Huma, "Resilient Machine Learning Frameworks: Strategies for Mitigating Data Poisoning Vulnerabilities," *Aitoz Multidisciplinary Review,* vol. 3, no. 1, pp. 54-67, 2024.
[9] A. Lin, *An integrative approach to linking genes, brain, and behavior in 22q11. 2 copy number variations*. University of California, Los Angeles, 2021.
[10] L. S. Hall *et al.*, "From peas to people-using quantitative traits to aid genetic discovery in depression," *medRxiv,* p. 2024.09. 12.24313543, 2024.
[11] Y. Shu, Z. Zhu, S. Kanchanakungwankul, and D. G. Truhlar, "Small Representative Databases for Testing and Validating Density Functionals and Other Electronic Structure Methods," *The Journal of Physical Chemistry A,* vol. 128, no. 31, pp. 6412-6422, 2024.
[12] E. Hofer *et al.*, "Genetic correlations and genome-wide associations of cortical structure in general population samples of 22,824 adults," *Nature communications,* vol. 11, no. 1, p. 4796, 2020.