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RESEARCH ARTICLE

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Gene transcriptional expression of cortical thinning during childhood and adolescence

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Abstract

The cognitive and behavioral development of children and adolescents is closely related to the maturation of brain morphology. Although the trajectory of brain development has been depicted in detail, the underlying biological mechanism of normal cortical morphological development in childhood and adolescence remains unclear. By combining the Allen Human Brain Atlas dataset with two single-site magnetic resonance imaging data including 427 and 733 subjects from China and the United States, respectively, we performed partial least squares regression and enrichment analysis to explore the relationship between the gene transcriptional expression and the development of cortical thickness in childhood and adolescence. We found that the spatial model of normal cortical thinning during childhood and adolescence is associated with genes expressed predominantly in astrocytes, microglia, excitatory and inhibitory neurons. Top cortical development-related genes are enriched for energy-related and DNA-related terms and are associated with psychological and cognitive disorders. Interestingly, there is a great deal of similarity between the findings derived from the two single-site datasets. This fills the gap between early cortical

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development and transcriptomes, which promotes an integrative understanding of the potential biological neural mechanisms.

KEYWORDS

adolescence, child, cortical thinning, gene expression, MRI

1 | INTRODUCTION

Under the interaction of heredity and environment, physiological and psychological development of human individuals from birth to death has been constantly changing, especially in childhood and adolescence, in which stable self-concept, values, and behavior patterns of the youth are formed and key social cognitive functions are also developed (Gorrese & Ruggieri, 2012; O'Brien & Bierman, 1988; Oldehinkel et al., 2007). The brain, the material basis of cognition and behavior, develops rapidly in a dynamic process with a region-specific pattern. Neuroimaging studies have shown that cortical thinning is the most obvious morphological feature of brain development during childhood and adolescence (Walhovd et al., 2017). A cross-sectional study indicated that the posterior parietal cortex, occipital cortex, and orbitofrontal cortex thin faster and tend to stabilize in childhood and adolescence, while the rate of change in the precentral gyrus, postcentral gyrus, and medial temporal lobes are smaller or even not significant with age (Amlien et al., 2016). Using four separate longitudinal samples including 854 magnetic resonance imaging (MRI) scans from 7 to 29 years, Tamnes et al. (2017) found the parietal lobe shows the largest while the occipital lobe shows the smallest decrease in cortical thickness. These findings indicate that the cortical thickness in different brain regions develops differently with age in the early stage.

The spatial gradient of the cerebral cortex is related to cell structure, tissue morphology, spatial proximity, and functional network structure, which reflects the patterns of cortical expansion during human evolution and development, and emphasizes the early influence of genes on cortical development in different brain regions (Adler-Wagstyl et al., 2015; Collins et al., 2010; Felleman & Van Essen, 1991; Margulies et al., 2016). Based on MRI images of 110 pairs of identical and 92 pairs of fraternal twins, Panizzon et al. (2009) found the genetic explanation for cortical thickness was up to 81%. Genes involved in brain development precisely regulate a large number of biological processes, such as neuronal migration, synaptic development, and so forth, in which a small error can lead to brain abnormalities and then may develop into mental disorders (Ayala et al., 2007; Bagni & Zukin, 2019). Neuroimaging studies have found significant morphological differences in the cortex between patients with psychiatric disorders and healthy people, such as abnormal nonlinear growth of cortical thickness in the prefrontal lobes of patients with schizophrenia and thinner temporal lobes of patients with autism (Alexander-Bloch et al., 2014; van Rooij et al., 2018). On the other hand, these neurodevelopmental disorders are also associated with genetic variation (Sanders et al., 2015). Therefore, there is a strong association between genetic variation, brain morphology, and psychological abnormalities.

Compared with the traditional correlation analysis between genotype and brain, it is a more direct method to explore the relationship between gene transcription expression level and brain morphology. The Allen Human Brain Atlas dataset (AHBA, http://human.brain-map.org), detailing the transcriptional expression of more than 20,000 genes in the brain with high spatial resolution, makes it possible to bridge the gap between the cortical developmental model of young people and transcriptomes (Hawrylycz et al., 2012). Combining the AHBA dataset and neuroimaging, researchers found that abnormal gene transcription may be the basis of cortical morphological variation (Shin et al., 2018; Whitaker et al., 2016). Abnormalities in gene transcription have also been found in common mental disorders, such as major depressive disorder and autism spectrum disorder (Li et al., 2018; Li et al., 2021). In the field of cortical development, based on the data of the Pediatric Imaging, Neurocognition and Genetics Study, Ball et al. (2020) found developing cortical thinning in adolescence is related to spatially varying gradients of gene expression. However, the results derived from participants from several US MRI sites may be affected by site effects, and cross-ethnicity/race generalization of transcriptional expression of brain development remains unclear.

In this work, we combine postmortem gene expression databases with two single-site adolescent MRI samples to advance the understanding of the relationship between molecular mechanisms and structural development of the cerebral cortex. First, we depict typical linear developmental patterns of cortical thickness in childhood and adolescence. Second, we establish the relationship between development-related changes in the cortex and anatomically patterned gene expressions to obtain development-related genes. Third, we conduct enrichment analysis to reveal the ontological pathways of development-related genes and link these genes to common mental disorders and typical cell types. The observations derived from two different samples can help us further understand the underlying mechanism of typical brain development in school age and pay attention to the mental health of children and adolescents from the perspective of genes.

2 | METHODS

2.1 | Participants

In the discovery dataset, 503 Chinese students were voluntarily recruited from the local schools in Chongqing, China. All the participants were examined by a neurologist to exclude a history of

psychological or neurological diseases. After excluding the data with low quality of imaging ($n = 76$), 427 Chinese children and adolescents aged from 6 to 18 years (209 males, 218 females, mean age = 10.28 ± 2.56) were included in the subsequent analysis. This study was approved by the Institutional Human Participants Review Board of the Southwest University Imaging Center for Brain Research. All study participants provided written assent and their legal guardians provided written informed consent.

The validation sample was selected from the Healthy Brain Network (HBN) (Alexander et al., 2017), an ongoing initiative focused on collecting and sharing a biobank of data from up to 10,000 New York children and adolescents (https://healthybrainnetwork.org/). To avoid the impact of different scanning instruments on imaging, this study only included the MRI data acquired from CitiGroup Cornell Brain Imaging Center (CBIC), in which 1079 subjects' MRI data have been shared publicly until April 2022. We selected the "ANAT_T1W-RU" series as the analysis object in this study, including 1013 subjects who have been scanned completely. After excluding the data with bad imaging quality ($n = 263$) and the subject whose age was more than 18 years ($n = 17$), 733 subjects aged from 5 to 18 years (469 males, 264 females, mean age = 10.69 ± 3.32) were included. The approval for analyzing the HBN data had been obtained from the relevant administrator.

2.2 | MRI data acquisition

All the Chinese participants in the discovery sample were scanned on a 3.0 Tesla Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany) at Southwest University in Chongqing, China. High-resolution T1-weighted anatomical images covering the whole brain were acquired with a magnetization prepared rapid gradient echo. The data of 427 Chinese participants were obtained from two collect batches: the first batch is the first-wave measurements of the Chinese Color Nest Project in Southwest University (Liu et al., 2021; Yang et al., 2017; Zuo et al., 2017), including 188 subjects (age: 6–18) were collected from December 2013 to July 2014 (TR = 2600 ms, TE = 3.02 ms, flip angle = 8°, the field of view = 256 × 256 × 176 mm^3, voxel size = 1 × 1 × 1 mm^3), and the second including 239 subjects (age: 6–12) were collected from July 2016 to October 2018 (TR = 2530 ms, TE = 3.45 ms, flip angle = 7°, the field of view = 256 × 256 × 192 mm^3, voxel size = 1 × 1 × 1 mm^3).

All 733 subjects in the validation sample were scanned on a 3.0 Tesla Siemens Prisma MRI scanner (Siemens Medical, Erlangen, Germany) at CBIC in New York, America. High-resolution T1-weighted anatomical images covering the whole brain were acquired (TR = 2500 ms, TE = 3.15 ms, flip angle = 8°, the field of view = 256 × 256 × 179.2 mm^3, voxel size = 0.8 × 0.8 × 0.8 mm^3).

2.3 | MRI data preprocessing

All the T1-weighted structural scans were processed using FreeSurfer (version 5.3.0, http://surfer.nmr.harvard.edu; RRID: SCR_001847). With the command "recon-all," an automated brain segmentation process was executed, including skull stripping, segmentation of brain tissue, separation of hemispheres and subcortical structures, and construction of the gray/white interfaces and the pial surfaces (Fischl & Dale, 2000). The cortical surfaces were divided into 308 contiguous regions derived from the 68 cortical regions in the Desikan–Killiany atlas (Romero-Garcia et al., 2012). Using a backtracking algorithm, this parcellation resulted in approximately equal size (~500 mm^2) for each region, which minimizes the influence from the variability in parcel sizes (Paksarian et al., 2020). Then, the parcellated atlas was transformed to each participant's surface to obtain the cortical thickness for each region of each subject. In addition, no manual corrections were applied. Both original and processed images were visually inspected by two specialists to identify excessive motion artifacts. According to the proposal of Klapwijk et al. (2019), the criteria for visual quality control in this study include: (1) whether the reconstructed image is affected by movement; (2) whether the temporal pole is missing in the reconstruction; (3) whether the non-brain tissue is included in the reconstruction of the pial surface; and (4) whether parts of the cortex are missing in the reconstruction. A 4-point score was used. If either of the two specialists thought the result of any above item was bad (score 1), this participant would be excluded.

2.4 | Estimation of the developmental model of cortical thickness

To examine the linear developmental model of cortical thickness of young people, a linear regression model was conducted with age as the independent variable and regional cortical thickness values as the dependent variable. Sex, intracranial volume, and batch for data collection in the discovery sample were added as covariates. Briefly, the following model was used: regional cortical thickness value ~ intercept + β1 × (age) + β2 × (sex) + β3 × (intracranial volume) + β4 × (batch). Negative β1 means the cortical thickness of the brain region decreases with age and vice versa. The higher the absolute value of β1, the faster the change rate of the thickness in the brain region. Significance was set at $p < .05$ with FDR correction for multiple comparisons across 308 regions to control type I error.

2.5 | Estimation of regional gene expressions

Brain-wide gene expressions produced from the AHBA dataset were measured in six postmortem brains (male/female = 5/1; age = 42.5 ± 13.4 years) with 3702 spatially distinct samples, and the expression levels of more than 20,000 genes could be quantified. The AHBA dataset was processed according to the proposal of the previous study to ensure consistency and reproducibility of the results (Arnatkeviciute et al., 2019). Specifically, there were six processing steps to obtain a region × gene matrix: (1) using the Re-annotator toolkit to verify probe-to-gene annotations (Arloth et al., 2015), remaining 45,821 probes corresponding to 23,232 genes; (2) filtering probes that do not exceed background noise intensity, excluding at

least 50% of samples across participants; (3) selecting the probe with the highest correlation with the RNA-seq data to increase the reliability; (4) assigning samples to the Desikan–Killiany 308 atlas; (5) normalizing expression values for each participant through a scaled robust sigmoid to account for inter-individual variabilities such as ethnicity, sex, and postmortem interval; and (6) filtering genes based on differential stability to reduce donor-specific variance and focus on brain-relevant genes. Because only two right hemisphere data existed in the AHBA dataset, to minimize variability across regions, in this study, only the left hemisphere was considered (Li et al., 2021). Finally, the transcriptional level of each gene at each brain region in the left hemisphere was calculated to obtain the matrix (152 regions × 10,027 gene expression levels). A schematic overview of the study is provided in Figure 1.

2.6 | Regional cortical development and gene expression

Partial least squares (PLS) regression was used to explore the relationship between regional changes of cortical thickness with age (β1 of 152 left cortical regions) and transcriptional activity for all 10,027 genes (Abdi, 2010). To better present the development rate of cortical thickness in different regions, the cortical thickness change rate (β1) was normalized from −1 to 1 and applied in the subsequent analysis. Gene expression data (152 × 10,027 matrix) were used as predictor variables of regional cortical thickness changes in the PLS regression. The first component of the PLS regression result (PLS1) was a linear combination of the gene expression values that were most significantly correlated with regional cortical thickness development. Permutation test based on spherical rotations (Váša et al., 2017), which aimed to account for spatial autocorrelation of the brain map, was used 5000 times to test the hypothesis that the variance of PLS1 explaining cortical thickness development was significantly higher than expected by chance (Romero-García et al., 2019). After obtaining the PLS weights of each gene, bootstrapping was used 5000 times to determine the variability of each gene. The ratio of the weight to the bootstrap standard error of each gene was used to calculate its *Z* score (Morgan et al., 2019). According to the proposal of Bigdeli et al. (2016), FDR inverse quantile transformation correction for the Z scores was used to account for winner's curse bias. Only genes that passed the FDR correction of $p < .05$ ($Z > 1.96$) were included in subsequent analysis. Finally, two gene lists were obtained: the genes whose expression levels were significantly positively associated with cortical thickness developmental change rate (PLS1+), and the genes whose expression levels were significantly negatively associated with cortical thickness developmental change rate (PLS1−).

2.7 | Enrichment analysis

Metascape (https://metascape.org/gp/index.html#/main/step1), an online gene annotation and analysis resource, provides automated meta-analysis to understand either unique or common pathways in 40 independent knowledge databases (Zhou et al., 2019). Using this tool, we can explore whether the genes related to cortical thickness development in young people were enriched in some biological processes and reveal the underlying biological meaning of this gene expression pattern. In this study, two gene lists were input into the Metascape website, respectively, and performed overrepresentation

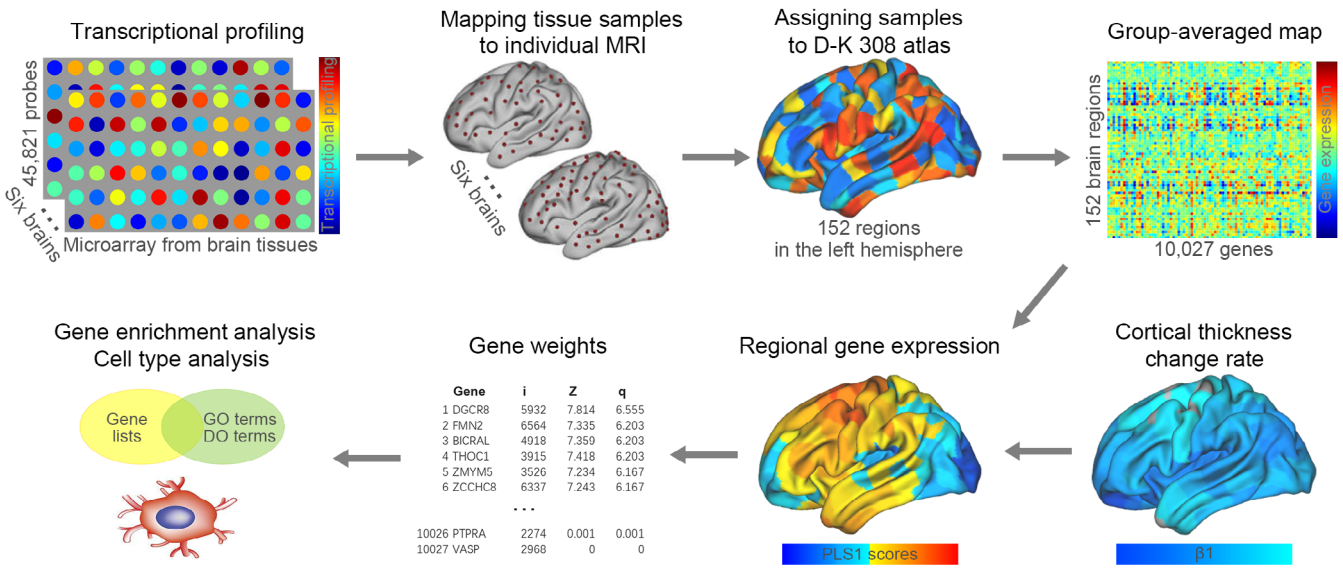

FIGURE 1 Schematic overview of the methodology. Gene expression profiles in the left hemisphere were averaged across six postmortem brains. Partial least squares regression was used to identify the relationship between regional changes in cortical thickness with age and transcriptional activity. Gene enrichment analysis and cell type analysis were performed on the gene list associated with the first component of the partial least squares regression.

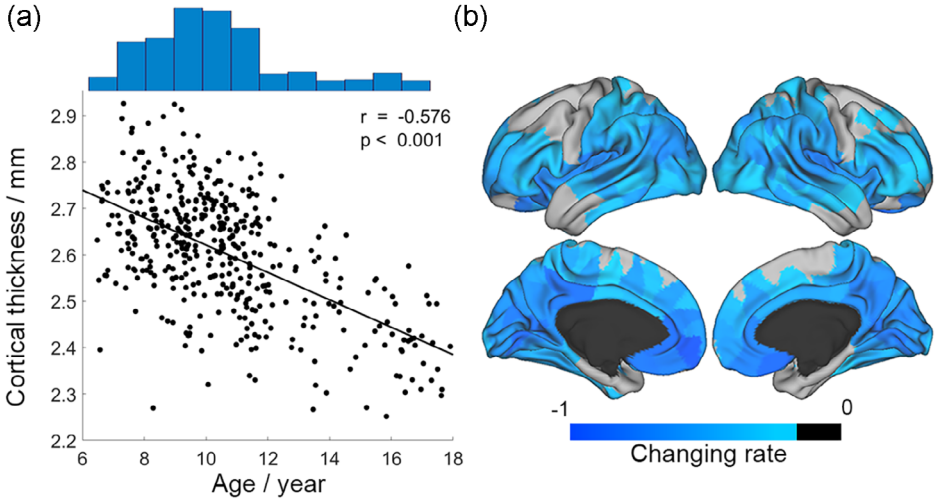

FIGURE 2 The change in cortical thickness with age during childhood and adolescence. (a) The age distribution of subjects and the mean cortical thickness across 308 brain regions in the whole cortex of each subject. (b) The spatial model of normal cortical thinning. Cortical thickness of brain regions with color decreased significantly with age. The changing rate has been normalized; $p_{FDR} < .05$.

analysis for gene ontology (GO) and disease ontology (DO) terms. Additionally, a multigene list meta-analysis was performed to reveal the biological processes that are shared between two samples. All enrichment pathways obtained were corrected by the FDR threshold for significance at 5%.

2.8 | Assigning related genes to cell types

To further understand the relationship between cortical development and cell types, we assigned development-related genes obtained by PLS regression to cell types. To get gene sets from each cell type, five different single-cell studies that used postmortem cortical samples from human participants were compiled (Darmanis et al., 2015; Habib et al., 2017; Lake et al., 2018; Li et al., 2018; Zhang et al., 2016), which avoided bias based on acquisition methodology or analysis, leading to the initial inclusion of 58 cell classes. Many classes were overlapping due to constituent genes or nomenclature. Following the procedure in Seidlitz et al. (2020), cell types were organized into seven canonical classes (astrocytes, microglia, endothelial cells, oligodendrocytes, oligodendrocyte precursors, excitatory and inhibitory neurons). Then, we overlapped the gene set of each cell type with two gene lists. A permutation test was used to obtain the *p*-value of the number of overlapped genes for each cell type, and FDR with $p < .05$ was applied for multiple comparison correction (Romero-García et al., 2019).

3 | RESULTS

3.1 | Developmental model of cortical thickness

In the discovery sample, the mean cortical thickness of the full brain decreased with age in children and adolescents ($r = -.576$, $p < .001$; Figure 2a). Based on the template dividing the cortex into 308 regions, after FDR correction, the cortical thickness of 248 significant brain regions decreased with age, in which the orbitofrontal cortex had the fastest rate of shrinkage (mean β1 [normalized]: −0.73; range: −1 to −0.48; Figure 2b). There was no brain region whose cortical thickness increased significantly with age in childhood and adolescence. The change rate value of each brain region was presented in Supplemental Table 1.

3.2 | Cortical gene expression related to brain development

The distribution of the PLS1 score map reflected an anterior–posterior gradient of cortical gene expression (Figure 3a). After 5000 times permutation tests, PLS1 could explain 30.59% of the variance of cortical thickness change ($p = .009$). PLS1 scores were significantly positively associated with the cortical thickness changing rate with age ($r = .553$, $p < .001$; Figure 3b). Bootstrapping analysis found that 1717 genes were significantly overexpressed (PLS1+, $Z > 1.96$, $p_{FDR} < .05$), and 1887 genes were under-expressed (PLS1−, $Z < -1.96$, $p_{FDR} < .05$) as cortical development in childhood and adolescence.

3.3 | Biological processes and disorders associated with cortical development

The GO biological processes were aligned with PLS1+ and PLS1− gene list using Metascape, respectively. After correcting for enrichment terms with the FDR, the top significant GO biological processes and common DO terms were presented in Figure 4. Genes in PLS1+ were enriched for biological processes such as "generation of precursor metabolites and energy" and "mitochondrion organization." Genes in PLS1− were enriched for biological processes such as "chromatin organization" and "cellular response to DNA damage stimulus." Based on DisGeNET, we found genes related to adolescent brain development are significantly associated with psychiatric disorders (DO terms: Neurodevelopmental Disorders, Autistic behavior,

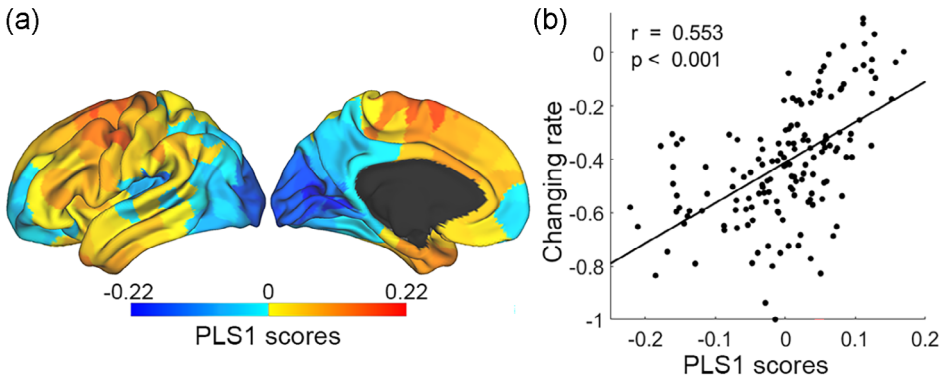

FIGURE 3 Normal cortical thinning during childhood and adolescence is associated with regional gene transcriptional expression. (a) The spatial distribution of the first component score through partial least squares regression (PLS1). (b) The relationship between the PLS1 score and the changing rate of cortical thickness of each brain region.

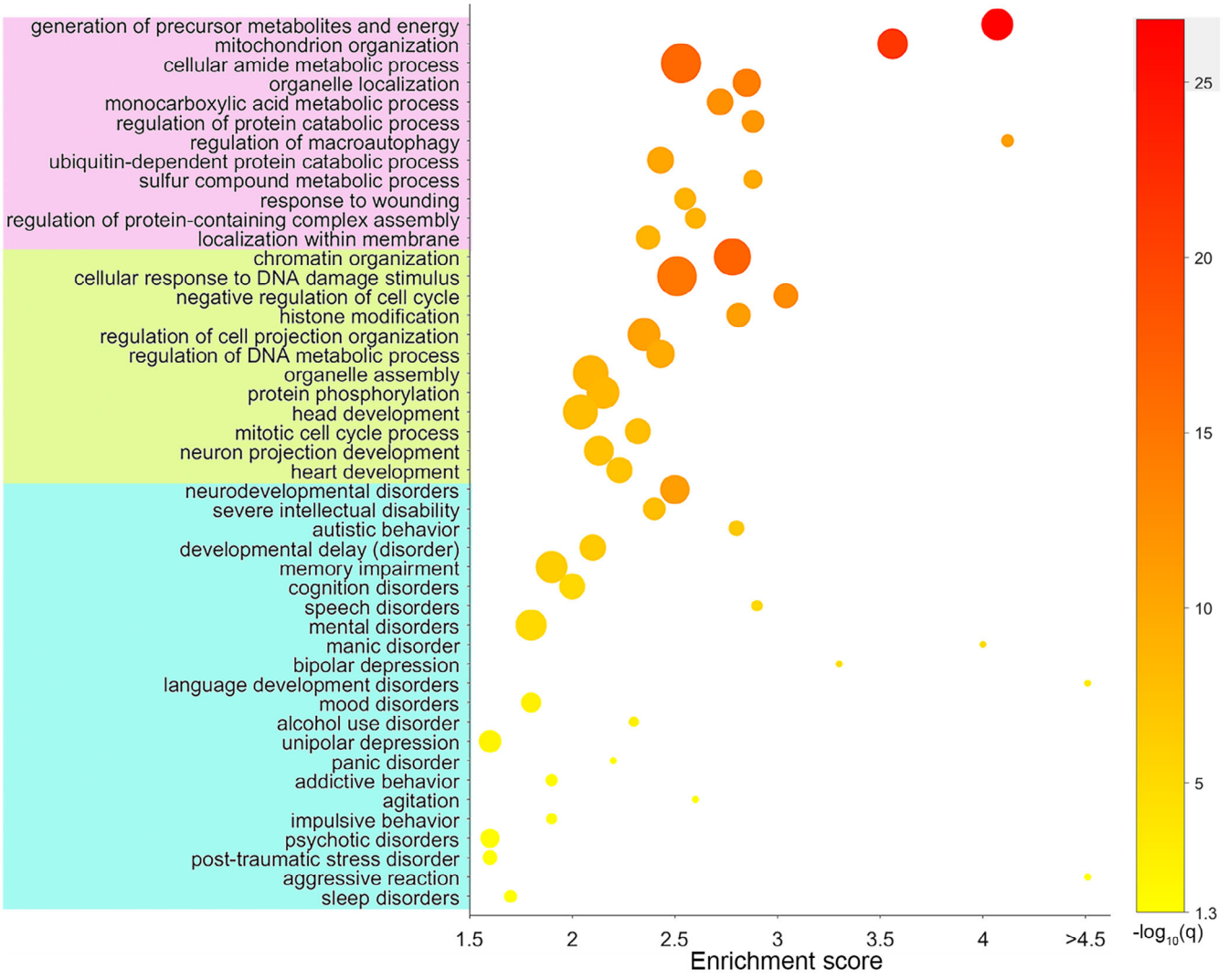

FIGURE 4 Functional enrichment of gene transcripts ($q < 0.05$). Purple: the biological processes terms of gene ontology for PLS1+ genes. Green: the gene ontology terms for PLS1− genes. Azure: the disease ontology terms for genes related to cortical development during childhood and adolescence. The size of the circle means the number of genes involved in both a given term and the significant gene list (PLS1+ or PLS1−). The color of the circle represents the degree of enrichment.

Psychotic Disorders, Post-Traumatic Stress Disorder); affective disorders (Mental disorders, Manic Disorder, Bipolar Depression, Mood Disorders, Unipolar Depression, Panic Disorder, Agitation); cognitive disorders (Developmental delay disorder, Severe intellectual disability, Memory impairment, Cognition Disorders, Speech Disorders, Language Development Disorders); and behavior disorders (Alcohol Use Disorder, Addictive Behavior, Impulsive Behavior, Aggressive reaction, Sleep Disorders).

3.4 | Cell types of development-related genes

The results of the cell type analysis are shown in Figure 5. Permutation test found that genes in the PLS1+ were significantly involved in astrocytes ($n = 117/665$, $p_{FDR} = .011$) and microglia ($n = 142/480$, $p_{FDR} < .001$), and genes in the PLS1− were significantly involved in excitatory neurons ($n = 239/996$, $p_{FDR} < .001$S) and inhibitory neurons ($n = 174/717$, $p_{FDR} < .001$).

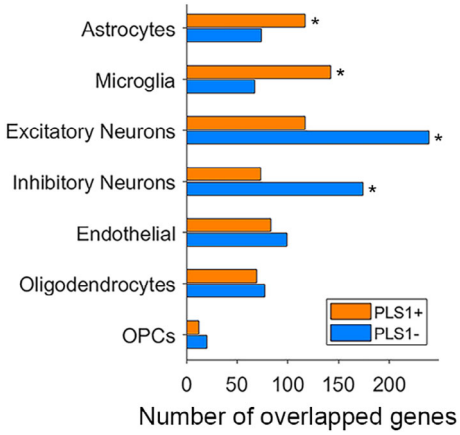

FIGURE 5 Cell type-specific expression to cortical development-related genes. The asterisk indicates that the item is significantly associated with cortical development. $p_{FDR} < .05$.

3.5 | Validation analysis

To validate the findings, a single-site MRI database, including 733 adolescents from the United States, was used as a replication sample to repeat the above analysis. There were similar spatial patterns of cortical thickness change with age in both samples ($r = .786$, $p < .001$; Figure 6a). PLS1 of the replication sample could explain 31.65% of the variance of cortical thickness change ($p = .010$). The PLS1 scores of each brain region acquired from the discovery sample and replication sample were highly consistent ($r = .989$, $p < .001$; Figure 6b). In the replication sample, 1899 PLS1+ ($Z > 1.96$) genes and 1971 PLS1− ($Z < -1.96$) genes were significantly overexpressed, which were highly overlapped with the discovery sample (PLS1+: odds ratio [OR] = 267.5, $p < .001$; PLS1−: OR = 291.6, $p < .001$; Figure 6c). In addition, cell types analysis found that cortical development-related genes were significantly involved in astrocytes (PLS1+, $n = 133$,

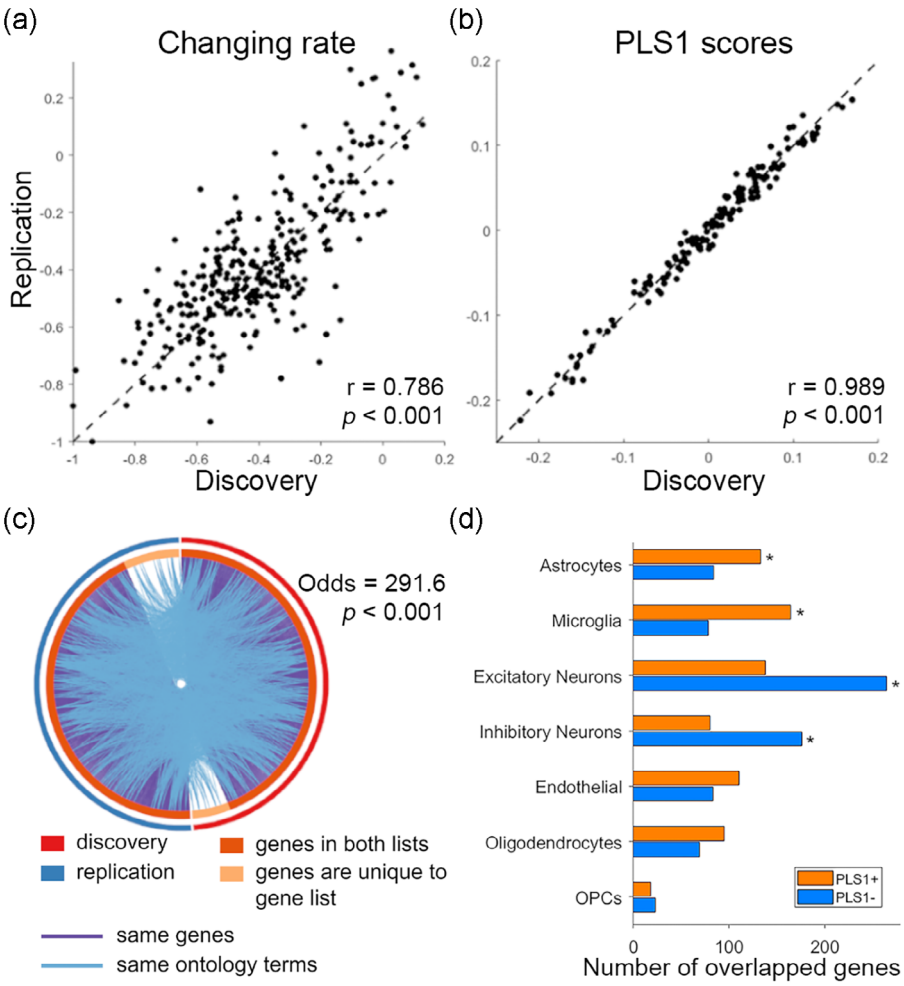

FIGURE 6 Validation of gene transcriptional expression of cortical thinning during childhood and adolescence. (a) Relative cortical thickness change in the discovery sample and replication sample were correlated across regions. (b) PLS1 scores of each brain region derived from the discovery sample and replication sample were highly consistent. (c) Circos plot of genes and ontology terms overlapped between two samples. (d) Cell type-specific expression to cortical development-related genes from replication sample.

$p_{FDR} = .016$; Figure 6d), microglia (PLS1+, $n = 164$, $p_{FDR} < .001$), excitatory neurons (PLS1−, $n = 264$, $p_{FDR} < .001$) and inhibitory neurons (PLS1−, $n = 176$, $p_{FDR} < .001$).

4 | DISCUSSION

This study aims to explore the underlying molecular mechanisms of cortical structural development during childhood and adolescence. Using more than 1000 structural MRI images and postmortem gene expression databases, we find linear development pattern of cerebral cortical thickness in childhood and adolescence is associated with spatially varying gene transcriptional expression. Genes related to cortical thinning are expressed predominantly in astrocytes, microglia, excitatory and inhibitory neurons, and ontologically enriched for energy-related and DNA-related terms. Cortical development-related genes are associated with psychological and cognitive disorders. Additionally, results from two single-site MRI samples suggest a great deal of similarity in cortical development and its gene expression in children and adolescents from different cultures and regions. These findings reveal cortical development-related molecular mechanisms and bridge the gap between early cortical development and transcriptomes, which promote an integrative understanding of the potential biological neural mechanisms of cortical development in children and adolescents.

In this study, we replicate the result that the global mean cortical thickness showed a decreasing trend, and this is a typical hallmark of brain development (Amlien et al., 2016; Bethlehem et al., 2022; Tamnes et al., 2017). The orbitofrontal cortex, associated with decision-making, has the fastest rate of shrinkage, which indicates the rapid development of higher cognitive function during childhood and adolescence (Bechara et al., 2000; Yates & de Oliveira, 2016). Cortical thickness decreases significantly in the majority (80%) of the cortex, and the faster thinning rate is mainly distributed in the default mode and visual networks, which is consistent with previous studies (Ball et al., 2020). In contrast, the brain regions that did not change significantly with age are mainly distributed in the somatomotor network. Coupled with function, the lower-order somatomotor cortex is already developed in early childhood so that thickness does not change significantly (Hill et al., 2010). In addition, we also explored the nonlinear change in cortical thickness with age during adolescence. After FDR correction, only 13/308 (4%) brain regions showed significant nonlinearity distributed primarily in superior temporal gyrus, pericalcarine cortex, and lingual gyrus (Figure S1). Therefore, compared to nonlinear changes, the linear development of cortical thickness in most brain regions during childhood and adolescence provides an opportunity for subsequent analysis.

PLS regression analysis revealed that the normal development of the cortex in childhood and adolescence is associated with the transcriptional expression of a large number of genes. Through GO analysis, the most important functional term in PLS1+ is the generation of precursor metabolites and energy, and mitochondrion organization. Mitochondrion organization results in the assembly, arrangement of constituent parts, or disassembly of a mitochondrion. Mitochondria are multi-functional organelles involved in many metabolic processes including energy production and biomolecule synthesis, accordingly, inseparable from other top functional terms in PLS1+, such as cellular amide metabolic process and organelle localization, and are essential to neuronal and cortical development (Baum & Gama, 2021; Son & Han, 2018). In PLS1−, the most important term is chromatin organization. Chromatin is a highly organized mixture of DNA and proteins that forms chromosomes in the cell nucleus during cell division and is directly related to other top biological processes including cellular response to DNA damage stimulus, regulation of DNA metabolic process, and protein phosphorylation (Felsenfeld, 1978). In addition, downregulated genes are enriched for head, heart, and neuron projection development (Figure 4), which also highlights the vast amount of information contained in the cortex. Thus, overregulated genes in cortical development during childhood and adolescence are highly enriched for energetic processes, and downregulated genes are more associated with processes related to DNA.

Extending the above findings to a comprehensive single-cell transcriptome database covering six canonical cell classes, we found normal cortical thinning in childhood and adolescence is associated with genes expressed in glial cells (astrocytes and microglia, PLS1+) and neurons (excitatory and inhibitory, PLS1−). Astrocytes, the most abundant glial cells in the brain, are closely related to synapses, providing nutrients to neural tissues and maintaining extracellular ion balance, and regulating cerebral blood flow (Freeman & Rowitch, 2013; Suzuki et al., 2014). Microglia, making up 10–15% of all cells in the brain, plays a key role in the normal functioning of the brain, constantly clearing away damaged or unnecessary neurons and synapses, and infectious agents in the central nervous system (Gehrmann et al., 1995; Ginhoux et al., 2013; Lawson et al., 1992). Due to the supporting role of astrocytes and microglia at the synapse, loss of the spines may result in a local reduction in the involvement of these glial cells, and then greater cortical thinning in brain regions with lower expression (Ben Achour & Pascual, 2010; Kettenmann et al., 2013). Excitatory and inhibitory neurons, involved in the dendritic remodeling, synaptic elimination, and transmission processes, are also the basis of early brain development (Elston et al., 2009; Huttenlocher & Dabholkar, 1997; Pereda, 2014). The disruption of these cells plays a critical role in many psychiatric disorders, such as attention-deficit/hyperactivity, autism spectrum disorder, bipolar disorder, major depressive disorder, obsessive–compulsive disorder, and schizophrenia, which highlights underlying shared biological mechanisms across mental disorders and cortical development during adolescence (Nagy et al., 2020; Writing Committee for the Attention-Deficit/Hyperactivity Disorder et al., 2021).

Through DO analysis, we found that cortical development-related genes are associated with a variety of psychological and cognitive disorders. Influenced by the interaction of heredity and environment, the first stage of most psychological disorders occurs during childhood and adolescence, when the prevalence is much higher than in the general population (Bronsard et al., 2016). Cognitive disorders related to memory, language, and intelligence often result from neurodevelopmental

disorders, which are caused by abnormal brain maturation and emerge in childhood (Jeste, 2015). The results are also consistent with the previous findings that some neurodevelopmental disorders are encoded by cortical development-related genes (Ball et al., 2020). Therefore, the occurrence of psychological and cognitive disorders is related to abnormal transcriptional expression of genes and abnormal cortical morphology. Vice versa, the healthy physical and mental development of children and adolescents not only benefits from the normal expression of related genes but also relates to the normal development of the cerebral cortex.

There is a high degree of consistency between the results of two adolescent MRI samples. A sufficient sample size ensures the reliability of the findings, and single-site data can control the systematic deviation of cortical thickness measures collected by different machines. Although researchers have proposed some methods to control the error of the big data merged by multiple sites (Fortin et al., 2018), the most direct and effective method, though the most time-consuming, is to collect it from one site. The six postmortem brains in the AHBA dataset include three Caucasians, two African Americans, and one Hispanic, while the discovery sample is all East Asians. In the process of gene expression estimation, we have made corresponding efforts to reduce the influence of ethnicity (step 5). The high similar explain variances of PLS1 from the discovery sample (30.59%) and the replication sample (31.65%) indicate that although the ethnicity effect exists, these genes are mainly related to cortical development rather than ethnicity. Repeating the analyses based on different thresholds for screening top-ranked genes, there is still a lot of genetic overlap between the two samples (Figure S2), which indicates that normal cortical development and underlying biological mechanisms are almost identical in children and adolescents coming from different countries and ethnicities.

There are some limitations to this study. First, cortical thickness was selected as the analysis index, which cannot completely represent individual brain morphology. We repeated the same analysis based on the cortical surface area, an additional fundamental structural index. However, there is no significant relationship between mean surface area across 308 brain regions and age (discovery: $r = -.054$, $p = .261$, Figure S3a; replication: $r = -.002$, $p = .962$). Compared to the changing rate of cortical thickness, there is higher heterogeneity in surface area development between the two samples (Figure S3b), and the development of the surface area in childhood and adolescence cannot be significantly explained by gene transcription expression (discovery: 11.50%, $p = .440$; replication: 17.61%, $p = .204$). Second, it is preferred to explore the mechanism of brain development using longitudinal data to increase the validity. In addition, the discovery sample contains two collection batches with different scanning parameters. The first batch including 188 subjects with full age coverage was selected for control analysis. Results show that there is a high correlation between the changing rate of cortical thickness obtained from 188 and 433 subjects, respectively (Figure S4), and it can still explain the relationship between cortical development and gene transcription expression (41.31%, $p < .001$). In addition, the gene expression was calculated from six adult postmortem brains, and while normalizing expression values for each participant and filtering genes were used to account for age effects, applying this to studies of children and adolescents was problematic. Future research will focus on finding a more stable and comprehensive index that combines different measures to explore the biological mechanisms of brain development.

5 | CONCLUSIONS

In summary, based on two single-site MRI databases and a human brain transcriptional expression database, we revealed the spatial model of cortical thinning during brain morphological development in childhood and adolescence, which is associated with gene transcription expression. Cortical development-related genes are enriched for energy-related and DNA-related terms and are associated with psychological and cognitive disorders. These findings reveal cortical development-related molecular mechanisms of childhood and adolescence, promoting an integrative understanding of brain development at school age.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Human gene expression data are available in the Allen Brain Atlas ("Complete normalized microarray datasets," https://human.brainmap.org/static/download). The availability of the first batch in the discovery dataset containing 188 subjects requires approval from Xi-Nian Zuo. The availability of the second batch in the discovery dataset containing 239 subjects requires approval from Hong Chen and Shaozheng Qin. The validation dataset is available in the Healthy Brain Network (https://healthybrainnetwork.org/).

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