

Genetic and neuroanatomical correlates of bipolar disorder in high-risk youth

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ABSTRACT

Objectives Bipolar disorder (BD) often begins in adolescence, a period marked by dynamic neurodevelopment. However, the neurobiological basis from genetic risk and subthreshold symptoms to diagnosed BD remains unclear.

Methods We conducted a cross-sectional analysis using data from the Recognition and Early Intervention of Prodromal Bipolar Disorders cohort (NCT01863628), including 392 participants aged 12–25 years with a balanced sexual distribution, stratified into five groups: offspring of patients with BD with (OBDs, n=48) or without (OBDns, n=62) subthreshold symptoms, individuals without BD family history but with subthreshold symptoms (nOBDs, n=63), patients diagnosed with BD (n=133) and healthy controls (HCs, n=86). Cortical thickness relative to HC was assessed using high-resolution T1-weighted images and FreeSurfer V.7.3.2. Gene expression patterns were derived from the Allen Human Brain Atlas, and partial least squares regression, along with gene enrichment analyses, were applied to link cortical alterations with underlying transcriptomic profiles.

Findings Cross-sectional analyses revealed graded cortical thickness differences across the BD risk spectrum, with patients with BD showing the most pronounced deviations and high-risk individuals with subthreshold symptoms displaying intermediate features relative to HCs. Cortical changes were significantly associated with spatial gene expression patterns, particularly in genes involved in mitochondrial ATP production, oxidative phosphorylation and synaptic signalling. Gene set enrichment revealed that BD-specific cortical thinning correlated with downregulation of excitatory synaptic pathways and excitatory neuron-related gene expression. Conversely, high-risk individuals exhibited upregulation of both excitatory and inhibitory neuronal markers. Developmental transcriptomic enrichment further linked significant genes to mid-childhood and adolescence.

Discussion By identifying distinct transcriptomic signatures associated with cortical thinning at different stages, our findings underscore the potential of transcriptomic markers for early detection and intervention in BD.

Clinical implications The findings highlight the potential for using transcriptomic markers for early detection and intervention, suggesting that identifying these markers could lead to improved outcomes for at-

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Before this study, it was known that bipolar disorder (BD) often begins in adolescence, a time of significant neurodevelopment, but the trend from genetic risk and subthreshold symptoms to a formal diagnosis was poorly understood.

WHAT THIS STUDY ADDS

⇒ This study adds new insights by demonstrating a continuum of cortical thinning that correlates with different risk stages, revealing that high-risk individuals with subthreshold symptoms show intermediate neurobiological changes.
⇒ Importantly, it links these cortical alterations with specific gene expression patterns related to mitochondrial function and synaptic signalling.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings highlight the potential for using transcriptomic markers for early detection and intervention, suggesting that identifying these markers could lead to improved outcomes for at-risk adolescents.
⇒ This research has the potential to inform clinical practices and policies aimed at early screening and preventive strategies for BD.

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INTRODUCTION

Bipolar disorder (BD) is a severe psychiatric condition characterised by extreme mood fluctuations, with a global prevalence of approximately 1%–2%.¹ Adolescence and early adulthood represent key windows for BD onset, coinciding with dynamic changes in brain structure, function and genetic expression.² During this critical developmental period, individuals with genetic risk for BD or early signs of mood instability may exhibit subtle changes that precede the onset of the full disorder.³



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This developmental intersection highlights a vital opportunity to investigate early markers of BD pathogenesis.

Genome-wide association studies and molecular research have robustly implicated pathways related to neurodevelopment, synaptic activity and mitochondrial function in the pathophysiology of BD,^{4–6} while structural neuroimaging has consistently identified cortical abnormalities, particularly in the prefrontal and temporal lobes.⁷ However, these lines of inquiry have largely remained separate. Consequently, the neurobiological basis linking genetic risk and subthreshold symptoms to diagnosed BD remains unclear. Specifically, there is a paucity of research integrating these modalities to understand how molecular and neuroanatomical changes converge in high-risk adolescents.

To address this gap, we hypothesised that adolescents at high genetic risk exhibit intermediate patterns of cortical aberrance and gene expression compared with individuals with formal BD diagnoses. In this study, we used data from the Recognition and Early Intervention of Prodromal Bipolar Disorders (REI-PBD) initiative to analyse a cohort spanning the risk continuum. By applying partial least squares (PLS) regression, we linked macroscopic cortical variation with microscopic gene expression profiles derived from the Allen Human Brain Atlas.⁸ This integrative approach offers a novel framework for dissecting the genetic and neurobiological factors underlying BD risk, with the aim of identifying robust transcriptomic markers for early detection and targeted intervention.

MATERIALS AND METHODS

Study design and participants

We analysed cross-sectional data from the REI-PBD initiative (NCT01863628).^{3,9} The cohort included 392 participants stratified into five groups: offspring of parents with BD exhibiting subthreshold mood symptoms (OBDs, n=48); offspring of parents with BD without symptoms (OBDNs, n=62); individuals without a family history of BD but exhibiting subthreshold symptoms (nOBDs, n=63); clinically stable patients with diagnosed BD (n=133) and healthy controls (HCs, n=86).

Symptom severity and global functionality were assessed using standard clinical scales (eg, Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HAM-D), Young Mania Rating Scale (YMRS), Global Assessment Scale (GAS)). Psychiatric diagnoses were validated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (for participants <18 years) or

Structured Clinical Interview for DSM Disorders – Patient Edition (for ≥18 years), while familial history was confirmed via the Family Interview for Genetic Studies. Detailed methodologies can be found in online supplemental material.

Inclusion and exclusion criteria

General exclusion criteria for all participants included a history of neurocognitive disorders (eg, traumatic brain injury), serious medical illnesses, intellectual disabilities and substance use. The bipolar offspring and control groups were excluded if they had any current or past Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-defined disorders or use of psychotropic medications. Subthreshold symptoms were defined as major depression or hypomania not meeting full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria due to insufficient symptom count or duration. Detailed inclusion and exclusion criteria, including specific definitions for subthreshold syndromes, are provided in online supplemental methods.

MRI acquisition and processing

T1-weighted images acquired on a 3.0 T Philips scanner were processed using Freesurfer 7.3.2 to derive vertex-wise cortical thickness. Data were parcellated into 400 regions using the Schaefer atlas. Detailed acquisition parameters and quality control procedures are outlined in online supplemental methods. The analytic workflow is displayed in figure 1.

Cortical thickness analysis

We applied a linear mixed-effects (LME) model to test for group differences in cortical thickness, controlling for age, gender and their interactions with group. The age×group interaction was included to capture deviations from typical adolescent cortical thinning trajectories. Significance was assessed using two-sided t-tests compared with HCs. We applied a spatially informed null model (1000 permutations) to account for spatial autocorrelation, with false discovery rate (FDR) correction at $q<0.05$.¹⁰

Transcriptomic and enrichment analyses

Regional gene expression data were derived from the Allen Human Brain Atlas.⁸ A standard processing pipeline was used to generate a region-by-gene expression matrix (400 regions×15 633 genes) spatially matched to the neuroimaging parcellation (details in online supplemental methods).

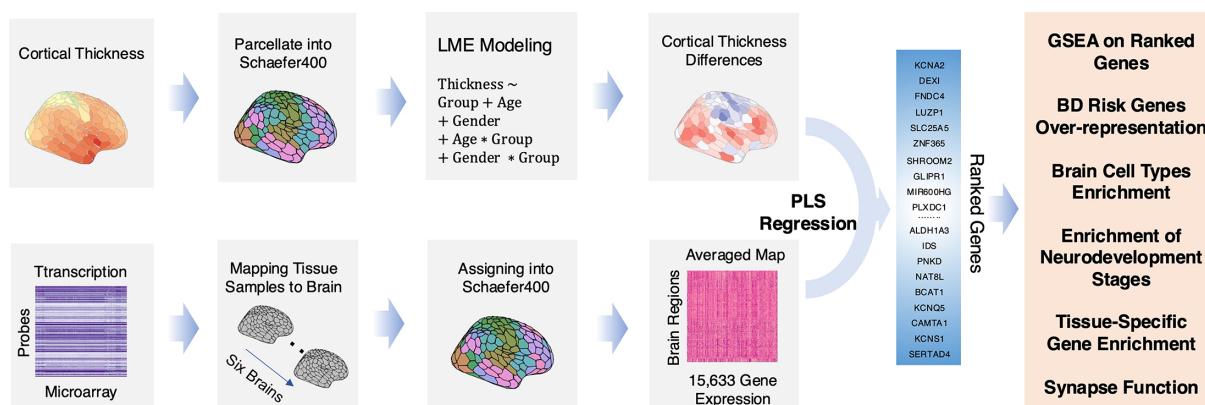


Figure 1 Study workflow. This diagram illustrates the integration of MRI-derived cortical thickness with microarray gene expression data. Key analytical steps include brain parcellation, statistical modelling of cortical thickness using linear mixed-effects (LME) models and linking brain structure to genetics via partial least squares (PLS) regression and gene set enrichment analysis (GSEA). BD, bipolar disorder.

PLS regression was employed to identify gene expression patterns spatially correlated with group-specific cortical thickness variations (t-values). The first latent component (PLS1), explaining maximal covariance, was assessed for significance via permutation testing (10 000 iterations), and gene stability was determined using bootstrapping.¹¹

Genes significantly contributing to the PLS model ($p<0.05$, permutation test) underwent functional enrichment analysis. We used gene set enrichment analysis (GSEA) to identify associated biological processes and cellular components.¹² To further contextualise findings, we analysed enrichment for specific brain cell types using single-nucleus RNA sequencing data,¹³ neurodevelopmental stages using BrainSpan data¹⁴ and synaptic functions using the SynGO database.¹⁵

RESULTS

Demographics

A comparative analysis of demographic and clinical variables across five distinct groups is provided in online supplemental table 1. The analysis indicated that there are significant differences in age ($F(5, 387)=40.98$, $p<0.001$). Differences in age, particularly between the BD group and others, prompted us to add an interaction term in the LME model to control the rate of cortical thickness decline, as prior research found no major differences in cortical thickness or its decline rate from adolescence to adulthood.¹⁶ Furthermore, notable differences were observed in clinical measures. HAM-D scores differed significantly among the groups, as did HAM-A, YMRS, BPRS and GAS scores ($p<0.001$).

Trend of cortical thinning from at-risk adolescence to BD

In the LME model used to analyse cortical thickness changes, which considers varying rates of cortical thinning across groups, significant group differences were identified in three comparisons: OBDs versus HC, OBDns versus HC and BD versus HC. No significant differences were found ($p\text{-FDR}<0.05$, 1000 spin permutation).

While HC shows symmetrical cortical thickness between the left and right hemispheres (online supplemental figures 1 and 2), the other four groups exhibit varying degrees of hemispherical asymmetry, with significantly greater cortical thickness in the left hemisphere than in the right (figure 2A). This asymmetry follows a trend, with cortical thinning intensifying from non-BD individuals with genetic predisposition (OBDs) to those diagnosed with BD. Notably, the left hemisphere demonstrates a steeper rate of cortical thinning compared with the right, with this asymmetry accelerating in groups with genetic risk and subthreshold symptoms, reaching its peak in the BD group. The mean cortical thickness across the five groups demonstrates the trend: OBDs>OBDns>nOBDs>HC>BD (online supplemental figure 3). The declining trend of parcels in parietal cortex and lateral prefrontal cortex in five groups can be found in online supplemental figure 4.

The brain regions showing significant changes ($p\text{-FDR}<0.05$, spin permutation) also reflect this trend (figure 2B). In the OBDs and OBDns groups, large areas of the left hemisphere, particularly the lateral prefrontal cortex, temporoparietal junction and extensive temporal regions are significantly thicker compared with HC. The nOBDs group appears at an intermediate stage: while cortical thickness is greater in the left hemisphere and reduced in the right, these differences do not reach statistical significance. On transitioning to BD, however, cortical thinning accelerates in the right hemisphere, notably within the lateral and

medial prefrontal cortices, temporal cortex and parietal cortex, while the left insula also shows thinning relative to controls.

PLS component scores and gene weights

The PLS regression analysis generated 10 components for each group, with component 1 (PLS1) consistently explaining a substantial portion of the variance. PLS1 scores reflect the projection of gene expression pattern in each brain region onto PLS1, indirectly reflecting the relationship between cortical variation and gene expression. The variance explained by PLS1 was 20.4% (BD), 20.6% (nOBDs), 24.2% (OBDns) and 21.9% (OBDs). Notably, PLS1 in all four groups was significant based on permutation testing ($p<0.05$). The variance plots for all the components can be found in online supplemental figure 5.

In the BD group (figure 2C), PLS1 scores correlated strongly positively with the left somatomotor, parietal and posterior cingulate cortices, and strongly negatively with the medial prefrontal and insula cortices. For nOBDs, high positive correlations were seen in the left prefrontal and somatomotor cortices, with high negative ones in the occipital cortex. OBDns showed strong positive correlation in the left prefrontal cortex and strong negative correlations in the insula and medial prefrontal cortices. Similarly, OBDs exhibited high positive correlations in the left prefrontal, somatomotor and occipital cortices, alongside high negative correlations in the insula and medial prefrontal cortices.

Crucially, Pearson's correlation analysis revealed robust, statistically significant positive associations between PLS1 scores and cortical thickness t-values across all cohorts (figure 2D). The strength of these associations was consistent across the risk continuum: patients with obsessive-compulsive disorder (OBD) ($r=0.47$, $p=1.62\times 10^{-20}$), non-symptomatic OBD carriers (OBDns) ($r=0.49$, $p=9.15\times 10^{-23}$), non-OBD individuals (nOBDs) ($r=0.47$, $p=1.62\times 10^{-20}$) and patients with BD ($r=0.45$, $p=4.29\times 10^{-19}$). These results indicate that the gene expression patterns captured by PLS1 are strongly predictive of the cortical thickness alterations observed in each group. To identify the specific molecular drivers, we extracted PLS1 gene weights using a bootstrapping procedure (10 000 iterations). These weights were highly stable, with intercorrelations of gene weights among the four cohorts ranging from 0.634 to 0.936 (online supplemental figure 6), suggesting a shared genetic foundation underlying these cortical changes.

Cellular component, biological process and molecular function across four groups

GSEA of Gene Ontology (GO) terms revealed distinct biological patterns driven by the weighted gene ranks (figure 3A–D). First, a shared metabolic signature emerged across all four groups: terms related to mitochondrial ATP synthesis, oxidative phosphorylation and the electron transport chain were significantly positively enriched. This consistency suggests that mitochondrial dysfunction and compromised energy metabolism are core neurobiological features underlying cortical thinning, regardless of the individual's risk stage or aetiology.

Second, we observed a clear divergence based on genetic liability. The high-risk offspring groups (OBDs and OBDns) exhibited specific enrichment for potassium channel-related terms. In contrast, these terms were not significant in the groups without familial history (nOBDs and BD). This dissociation implies that dysregulated potassium channel activity may be a heritable trait linked to cortical alterations in genetically predisposed youth, even in the absence of current subthreshold symptoms.

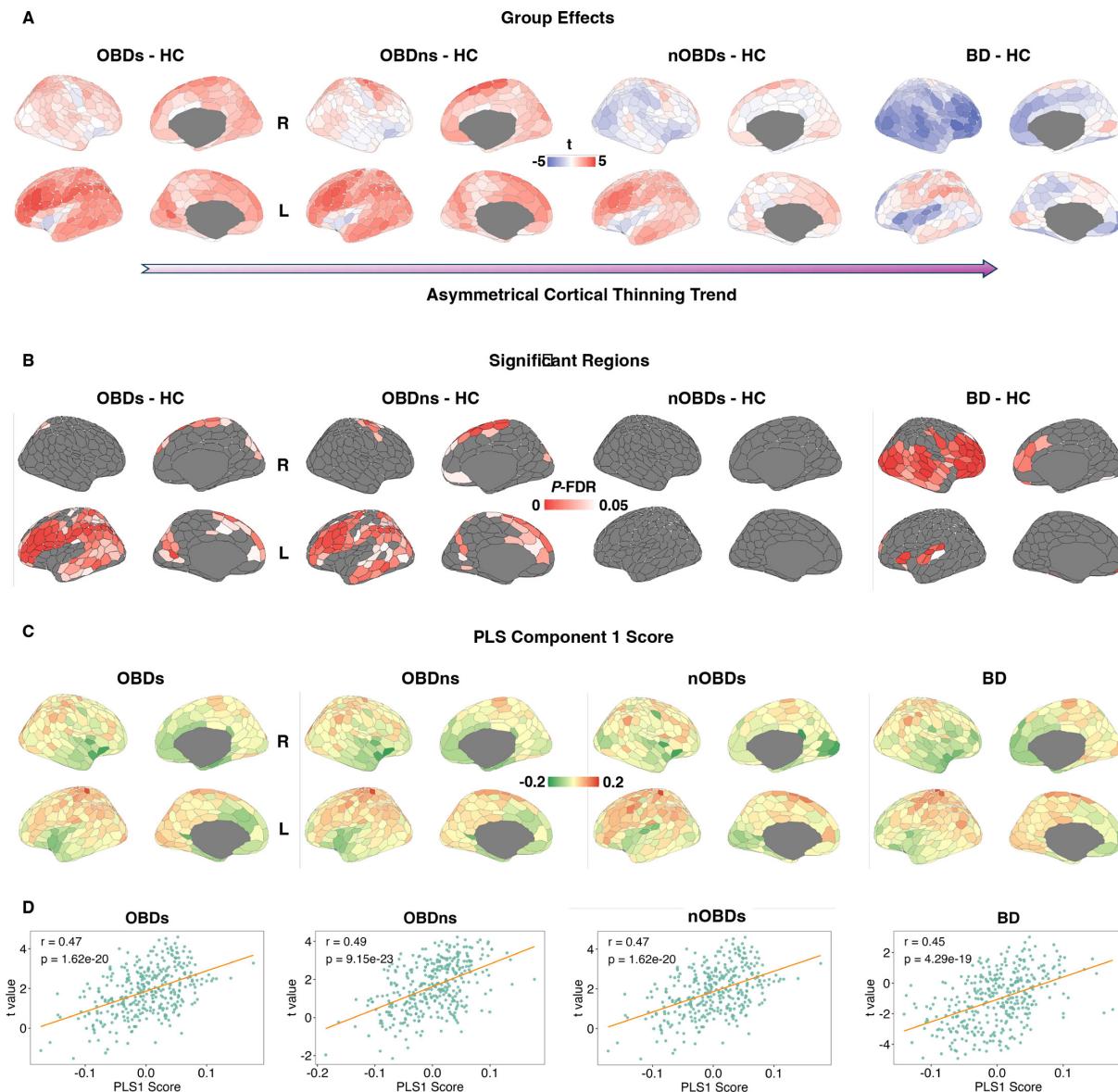


Figure 2 Cortical thickness differences and PLS regression analysis. (A) T-maps showing cortical thickness differences between each at-risk group and HCs. Red indicates greater thickness and blue indicates reduced thickness. (B) Brain regions showing statistically significant group differences (FDR-corrected $p < 0.05$). (C) Spatial map of scores for the first partial least squares (PLS) component (PLS1), linking gene expression to cortical variation. (D) Scatter plots correlating cortical thickness t-values with PLS1 scores. BD, bipolar disorder; HC, healthy controls; nOBDs, non-BD offspring with subthreshold symptoms; OBDns, BD offspring without subthreshold symptoms; OBDs, BD offspring with subthreshold symptoms.

Finally, the BD group displayed a unique neuroplasticity profile characterised by the significant negative enrichment (downregulation) of neurotransmission-related terms, including synapse organisation, glutamatergic synapse and excitatory postsynaptic potential (online supplemental table 2). This downregulation contrasts with the patterns observed in the at-risk adolescents, pointing to a potential loss of synaptic integrity specific to the established disease state. The gene interaction networks and enrichment maps detailing these biological processes can be found in online supplemental figures 7 and 8.

Brain cell types, synaptic function and neurodevelopmental stages enrichment

To explore the cellular and functional basis of these cortical alterations, we integrated cell type-specific expression and SynGO database analyses (figure 4A). Cell type enrichment

revealed a striking divergence in excitatory signalling. The BD group exhibited significant negative enrichment for excitatory neuron markers, contrasting sharply with the positive enrichment observed in the high-risk groups (OBDs and OBDns). This suggests that while established BD is characterised by a downregulation of excitatory phenotypes, genetic risk may manifest initially as compensatory hyperactivity. Inhibitory neuron markers showed a more complex pattern, with significant positive enrichment in the OBDs group but negative trends in the BD and nOBD groups.

In all groups, PLS1 gene ranks showed significant associations with cortical signatures during mid-late childhood, adolescence and young adulthood, suggesting that dysregulated development during these stages may contribute to cortical thickness changes compared with healthy subjects (figure 4B–E). Notably, the gene ranks were also enriched for early fetal-stage cortical signatures,

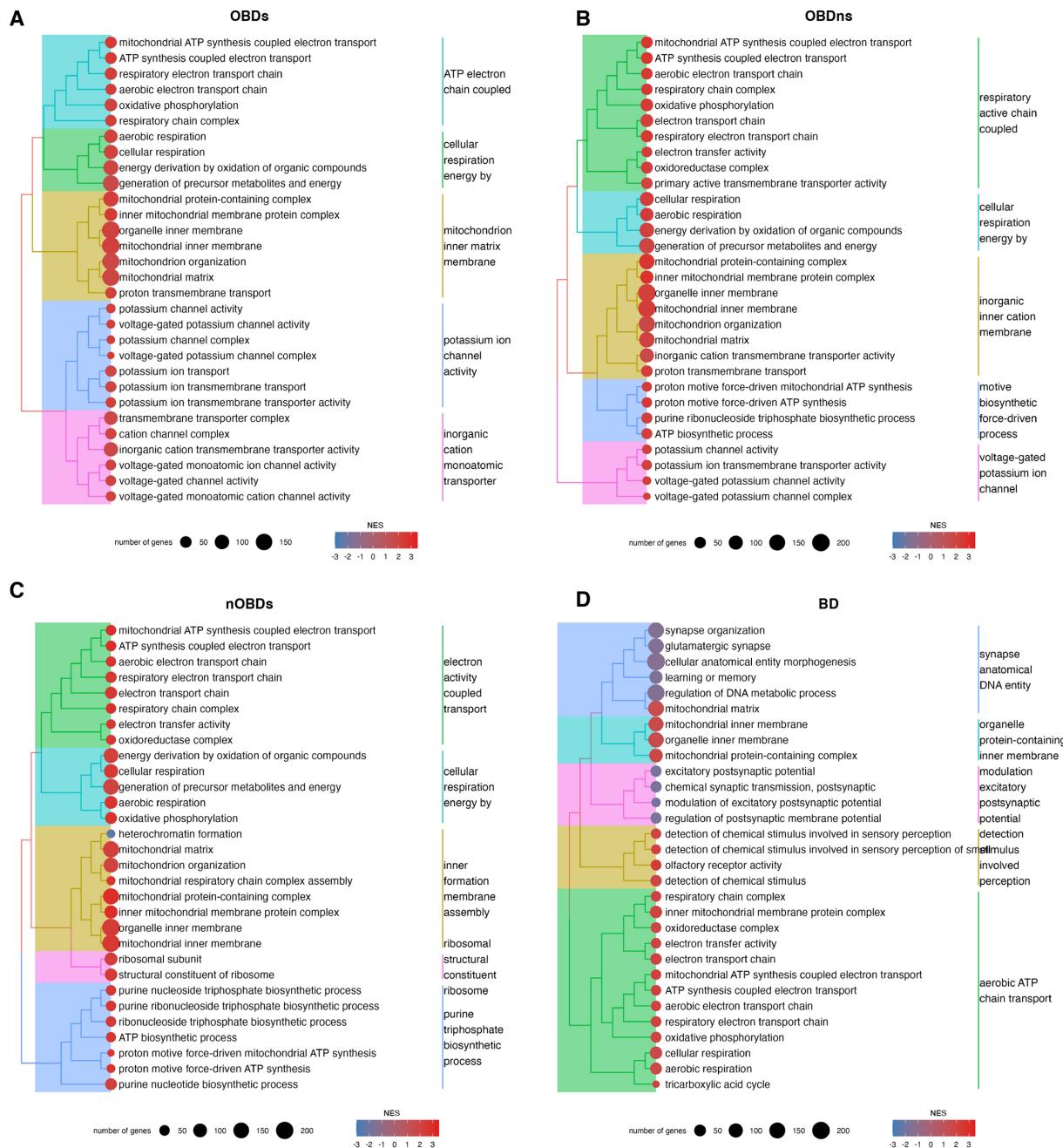


Figure 3 Gene Ontology (GO) enrichment analysis. These panels show enriched biological processes, molecular functions and cellular components for the (A) OBDs, (B) OBDns, (C) nOBDs and (D) BD groups. Circle size corresponds to the number of genes in a given term, and the colour indicates the normalised enrichment score. BD, bipolar disorder; OBDs, BD offspring with subthreshold symptoms; OBDns, BD offspring without subthreshold symptoms; nOBDs, non-BD offspring with subthreshold symptoms.

with the BD group showing a higher FDR p value compared with the OBDs and OBDns groups, and no significant correlation observed in the nOBDs group.

Synapse-centric enrichment (figure 4F–M) provided granular insight into these cellular shifts. In the genetic risk groups (OBDs and OBDns), significant enrichment was clustered around presynaptic and postsynaptic membranes and processes regulating membrane potentials and ion channel activity (eg, regulation of presynaptic membrane potential, $q=1.87\times10^{-7}$ in OBDs). While the nOBDs group showed similar but less robust associations, the BD group displayed strong enrichment for genes involved in synaptic signalling ($q=1.04\times10^{-4}$) and trans-synaptic communication, reinforcing that the observed cortical

thinning is underpinned by a progressive disruption of synaptic architecture—transitioning from dysregulated potential maintenance in at-risk youth to broad signalling deficits in diagnosed patients.

DISCUSSION

This study provides valuable insights into the neurodevelopmental trajectory of BD, examining cortical variation and gene expression across four cohorts: adolescents at varying genetic risks and patients with BD. Our findings reveal a gradient of neurobiological alterations from high-risk adolescents to patients diagnosed with BD, highlighting a progressive pattern of cortical



Figure 4 Enrichment analyses for cell types, neurodevelopmental stages and synaptic function. (A) Brain cell type enrichment analysis. (B–E) Enrichment across brain regions and developmental stages for each study group. Hexagon size indicates specificity and colour indicates significance. (F–M) Synapse function enrichment for cellular component (CC) and biological process (BP) ontologies for each group. Ast, astrocytes; BD, bipolar disorder; Ex(x), excitatory neurons; In(x), inhibitory neurons; Mic, microglia; nOBDs, non-BD offspring with subthreshold symptoms; OBDns, BD offspring without subthreshold symptoms; OBDs, BD offspring with subthreshold symptoms; Oli, oligodendrocytes; OPC, oligodendrocyte precursor cells; Per, pericytes.

asymmetry and thinning that corresponds with symptom emergence and severity. The gene expressions in various regions were significantly correlated with cortical thinning across different groups, and the enrichment analysis highlighted biological processes related to metabolic and respiratory functions mediated by mitochondria. GSEA showed significant enrichment of BD risk genes in the OBDs, nOBDs and BD groups, indicating a strong genetic predisposition in these groups. Analysis of cell types revealed significant enrichment of pathways related to synaptic structures and processes, particularly in presynaptic and postsynaptic membrane components and the regulation of membrane potentials. This trend underscores the critical role of neurodevelopmental alterations in BD and emphasises the need for early identification and intervention in genetically predisposed youth.

However, it is crucial to emphasise that this neurodevelopmental trajectory is an inference based on our cross-sectional design. Our findings represent a 'snapshot' in time, comparing different individuals across the risk spectrum rather than tracking changes within the same individuals over time. Therefore, future longitudinal studies are essential. By following the same high-risk youth as they develop, such studies can definitively confirm whether the cortical and transcriptomic signatures identified here can predict the eventual onset of BD and truly map the individual pathways of illness pattern.

The translational implications of these findings align with the emerging framework of nomothetic networks psychiatry, which advocates for integrating multilevel data to construct generalisable, causal models of mental illness.¹⁷ Our use of PLS regression to model the relationship between cortical structure and gene expression across a continuum of BD risk is a direct application of this approach. The resulting discovery of a progressive gradient of neurobiological alterations, linked to specific molecular pathways like mitochondrial function and synaptic signalling, provides foundational elements for a nomothetic network of BD. This integrative model supports a shift from symptom-based classification towards a biologically grounded framework, which promises to identify robust biosignatures for risk stratification and the development of targeted, early interventions.

Translating these findings into clinical practice requires moving beyond descriptive associations towards predictive utility. The identification of a neurobiological gradient—from genetic risk to subthreshold symptoms to overt disease—supports the development of multimodal predictive models that integrate cortical morphometry with transcriptomic risk scores. Such tools could refine early screening protocols by stratifying adolescents based on their biological proximity to the disease state rather than subjective symptom reporting alone. Furthermore, the specific molecular pathways identified here, particularly mitochondrial modulators and synaptic regulators, represent viable targets for preventive interventions. By validating these biomarkers in longitudinal settings, future clinical frameworks could use them to monitor disease progression or treatment response, facilitating a precision psychiatry approach that intervenes before the onset of irreversible neurodevelopmental trajectories.

Cortical asymmetrical trend

The observed asymmetrical cortical thickness thinning, particularly within the prefrontal cortex, temporal cortex and parietal cortex in both hemispheres, aligns with a large multisite study of BD.⁷ There are few established studies using a comprehensive cohort, encompassing individuals with genetic risk, those with and without subthreshold symptoms and individuals with a

diagnosed condition. Our results show that the left hemisphere exhibits steeper cortical thinning rates in cohorts with high genetic risk, with this asymmetry most pronounced in patients with BD. This pattern of cortical change may indicate an underlying neurodevelopmental vulnerability that accelerates with age and symptom severity. The trend of cortical asymmetry could serve as a potential biomarker for identifying individuals at different stages of risk and for tracking the development of BD.

Mitochondrial functions and energy metabolism

Our results consistently highlight mitochondrial function and energy metabolism as central biological features across the entire BD risk continuum. The robust enrichment of pathways such as ATP synthesis, oxidative phosphorylation and the electron transport chain suggests that mitochondrial dysfunction is not merely a consequence of the disorder but a core pathophysiological component present even in at-risk adolescents. This aligns with the hypothesis that compromised cellular energetics undermines neuronal stability, making neural networks more vulnerable to the physiological demands of mood regulation.¹⁸ Crucially, the persistence of these metabolic signatures from the high-risk stage to confirmed diagnosis supports the view of metabolic dysregulation as a stable trait marker rather than a transient state. These findings resonate with prior research indicating that mitochondrial modulation may underlie the efficacy of certain existing treatments; for instance, symptom remission following antidepressant therapy has been linked to the normalisation of mitochondrial activity.¹⁹ Consequently, targeting bioenergetic pathways represents a promising avenue for novel therapeutic interventions aimed at bolstering cellular resilience early in the disease course.

Cell type-specific pathways in BD and related cohorts

Our cell type-specific analysis offers critical insights into the cellular mechanisms driving the transition from risk to disease. We observed a striking divergence in pathway regulation: while patients diagnosed with BD exhibited a broad downregulation of excitatory and inhibitory signatures, the high-risk cohorts (OBDs and OBDns) displayed a marked upregulation of excitatory pathways. This contrast suggests that the early stages of genetic risk may be characterised by compensatory neuronal hyperactivity or heightened synaptic engagement, whereas the onset of overt illness involves a collapse of this homeostatic regulation.²⁰ The nOBDs group presented a complex intermediate profile, featuring excitatory upregulation alongside inhibitory and oligodendrocyte downregulation, pointing to a distinct interplay of cellular dysfunction in those without genetic risk. Collectively, these findings imply that dynamic shifts in excitatory-inhibitory (E/I) balance and glial function are pivotal in the neurodevelopmental trajectory of BD. These results align with prior magnetic resonance spectroscopy evidence of glutamatergic and astrocytic abnormalities in BD, reinforcing the potential of targeting synaptic stability and E/I restoration as precise therapeutic strategies.²¹

Spatiotemporal patterns of significant gene expression across different groups

Significant gene expression in the BD group shows a notable developmental trend, beginning with the thalamus during the early fetal stage and later extending to the amygdala in the late middle fetal period before encompassing the cerebral cortex. This pattern suggests a developmentally dynamic shift in gene expression that aligns with crucial periods of brain



development.²² For the OBDs and OBDns groups, the significant gene expression begins in the thalamus and cerebellum during the early fetal period, but the different gene expression in the OBDs group shows sustained expression in these regions and the cortex throughout development. This pattern indicates that BD with family history may have a genetic and developmental profile involving early and consistent expression in brain regions critical for sensory integration, motor function and higher-order cognition.²³ The sustained cortical expression suggests potential impacts on cognitive processing and behavioural regulation from an early stage, which may contribute to the manifestation of symptoms in individuals predisposed to BD.

Limitations

Despite its strengths, this study has several limitations. First, the cross-sectional design precludes the establishment of causal relationships, an issue that longitudinal studies could address. Second, potential confounding biases arise from our sample characteristics; these include the significant age differences between groups, the confounding effects of psychotropic medication in the BD cohort and a sample size that may not capture the full heterogeneity of the disorder. Finally, our transcriptomic analysis relied on the Allen Human Brain Atlas, which is based on adult postmortem samples and may not fully capture the dynamic gene expression changes of adolescence. Future studies should integrate adolescent-specific transcriptomic datasets, such as BrainSpan or single-cell RNA sequencing from younger cohorts.

CONCLUSIONS

In conclusion, this study supports a model of BD as a disorder with a distinct neurodevelopmental trajectory, marked by progressive cortical thinning and molecular alterations in gene expression from at-risk adolescents to patients with BD. Our findings emphasise the potential for genetic and neuroanatomical markers to identify high-risk individuals before the onset of full BD, advocating for early intervention strategies aimed at mitigating the trajectory of neurodevelopmental alterations associated with BD.

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Contributors KL conceptualised and overviewed the design of this study and is the guarantor. JWang and XLiu collected the data, performed the data analyses

and wrote the first draft. JWang, KL and BY-HL revised the manuscript based on reviewers' comments. JWang, XLiu, BY-HL, WL, JC, AC, RS, XLi, RW, FX, BG, FD, RSM, JWu and KL reviewed and finalised the writing of this manuscript.

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Patient consent for publication Not applicable.

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