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Review

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Recent developments in imaging transcriptomics for psychiatric disorders

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Abstract

Mental disorders refer to abnormal states that affect an individual's thinking, emotion, behavior, and perception, and are generally associated with dysregulation of brain function. They exhibit genetic heterogeneity as well as multi-level structural and functional abnormalities of the brain. Magnetic resonance imaging has been widely applied to detect macroscopic neurophenotypic alterations in patients with psychiatric disorders; however, it remains limited in directly revealing the underlying molecular and cellular mechanisms. Imaging transcriptomics, by integrating whole-brain gene expression atlases with neuroimaging features, offers a novel paradigm for exploring the associations between microscopic genetic expression and macroscopic neuroimaging phenotypes. This review systematically summarizes the methodological framework of imaging transcriptomic association studies and highlights recent advances in their application to psychiatric disorders such as depression. A growing body of evidence has revealed spatial coupling between structural and functional abnormalities in disease-related brain regions and gene expression in synaptic transmission, ion channels, neurodevelopment, and immune signaling. Imaging transcriptomics not only facilitates a multiscale understanding of the pathophysiological mechanisms of psychiatric disorders but also provides potential pathways for disease classification, targeted intervention, and precision diagnosis and treatment. Future research should further promote the integration of longitudinal imaging omics and spatial transcriptomic data to construct translatable multimodal models, thereby accelerating the translation of psychiatric neuroimaging from mechanistic research to clinical application.

Keywords imaging-transcriptomics association studies, psychiatric disorders, Allen Human Brain Atlas, magnetic resonance imaging, gene expression

Introduction

Mental disorders refer to abnormal conditions that affect an individual's thinking, emotions, behavior, and perception, and are generally associated with dysregulation of brain function. They encompass not only psychological abnormalities but also the combined effects of physiological, biological, and social factors. A mental disorder is defined as a syndrome characterized by clinically significant disturbances in cognition, emotional regulation, or behavior, reflecting dysfunction in the psychological, biological, or developmental processes underlying mental functioning (Stein *et al.*, 2021). Mental disorders not only lead to reduced quality of life and impaired social functioning but also significantly increase the risk of suicide and substance misuse (Onaemo *et al.*, 2022, 2024). Importantly, mental disorders are not homogeneous conditions attributable to a single etiology; rather, they constitute complex disease spectra with pronounced clinical and biological heterogeneity (Insel *et al.*, 2010), which may complicate precise diagnosis and treatment. Accordingly, interest in neuroimaging biomarker-based subtyping has been steadily increasing (Drysdale *et al.*, 2017). Therefore, elucidating the biological mechanisms underlying mental disorders holds significant public health importance.

Neuroimaging technologies play an irreplaceable role in quantifying brain structure and function. Among them, magnetic resonance imaging (MRI), with its noninvasive nature, has greatly deepened our understanding of the macroscopic neurophenotypes of the human brain. In recent years, continuous advancements in MRI technology have substantially expanded its breadth and depth of application in brain science research. For instance, MRI has been increasingly employed in brain network analysis, mental imagery reconstruction, and visual interpretation of neural language models (Andersson *et al.*, 2019; Koide-Majima *et al.*, 2024). However, the spatial and temporal resolution of MRI remains relatively limited, making it difficult to reveal the underlying molecular and cellular characteristics of brain disorders.

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Transcriptomics, enabled by high-throughput sequencing technologies such as RNA sequencing (RNA-seq), can quantify gene expression levels in cells or tissues and reveal regulatory mechanisms under different conditions (Wang *et al.*, 2009). Nevertheless, overcoming the limitations of single-modality inference requires integrative analyses that bridge neuroimaging and genomic/transcriptomic data. Imaging genetics aims to infer the molecular basis of macroscopic neurophenotypes by examining genome-wide associations between allelic variation at one or multiple loci and neuroimaging phenotypic changes. Its workflow typically involves five key steps: hypothesis formulation, data acquisition, data preprocessing and analysis, statistical testing, and result validation (Mashhour *et al.*, 2025). However, gene activity is jointly influenced by environmental and other factors, and gene expression varies across brain regions; consequently, the mechanisms through which genetic variation shapes neuroimaging phenotypes remain incompletely understood. With the establishment and development of whole-brain gene expression atlases, imaging transcriptomics has emerged as a pioneering paradigm for investigating the associations between microscopic genetic expression in the brain and macroscopic neuroimaging phenotypes. By linking regionally varying gene expression to large-scale neuroimaging features, this framework makes it possible to interrogate the correspondence between transcriptomic patterns and neuroimaging phenotypes. Compared with imaging genetics, imaging transcriptomics enables the direct mapping of neuroimaging features to transcriptional patterns within a shared stereotaxic space, providing spatially specific mechanistic interpretations and offering a novel methodological foundation for elucidating gene-expression mechanisms in neuropsychiatric disorders (Arnatkeviciute *et al.*, 2022; Mandal *et al.*, 2022). However, it should be emphasized that both imaging genetics and imaging transcriptomics are indirect, correlational approaches. They can support inferences about gene–brain–behavior relationships, but they cannot independently establish causal mechanisms. In contrast, approaches based on individual-level genetic data (e.g. genome-wide association studies, GWAS) can directly extract genetic variation from patient genomes and link genetic risk to imaging-derived phenotypes (IDPs), thereby probing more direct genetic mechanisms in psychiatric disorders and potentially providing validation and complementary evidence for associations identified by imaging transcriptomics. Multi-omics and cross-scale approaches can more clearly and intuitively elucidate the neuropathological and genetic mechanisms underlying major mental disorders. They enable the identification of appropriate biomarkers for the etiology of major psychiatric conditions, provide reliable evidence, enhance diagnostic accuracy, facilitate the understanding of disease progression, evaluate the effectiveness of psychopharmacological treatments, and guide the development of personalized clinical interventions.

Imaging transcriptomics research

Overview of imaging transcriptomics

Imaging transcriptomics is a research paradigm that employs spatial correlation analyses to investigate the spatial covariation between gene expression profiles revealed by transcriptomics and the structural and functional characteristics of the brain depicted by neuroimaging. This approach aims to elucidate the potential pathophysiological mechanisms underlying neuroimaging biomarkers. By leveraging whole-brain gene expression atlases as a bridge, imaging transcriptomics closes the scale gap between microscopic molecular biological processes and macroscopic brain imaging phenotypes. It not only reveals the spatial correspondence between gene expression patterns and multilevel brain phenotypes but also provides a rich framework for evaluating pathophysiological hypotheses and potential mechanisms (Wei *et al.*, 2022). The Allen Human Brain Atlas (AHBA) provides high-spatial-resolution coverage of nearly the entire human brain, integrating the expression data of more than 20 000 genes obtained from 3702 spatially localized tissue samples. These samples are precisely mapped to a standardized stereotaxic space, enabling researchers to directly establish quantitative association models between the spatial variation of gene expression and the spatial patterns of IDPs (Fornito *et al.*, 2019). Although several brain atlas resources have been developed to characterize spatiotemporal gene expression patterns across developmental stages, their spatial sampling density is considerably lower than that of the AHBA. For example, the HB Atlas data (https://hbatlas.org) were generated from 1340 tissue samples collected via macrodissection and integrate datasets from earlier studies conducted by the same group (Johnson *et al.*, 2009; Kang *et al.*, 2011). In addition, several human brain atlas resources, such as BrainSpan (http://www.brainspan.org/) (Miller *et al.*, 2014), PsychENCODE (http://resource.psychencode.org/) (Wang *et al.*, 2018), GTEx (https://www.gtexportal.org/) (Anon., 2013, 2015), the Human Protein Atlas (https://www.proteinatlas.org/humanproteome/brain) (Sjöstedt *et al.*, 2020), Brain RNA-Seq (http://www.brainrnaseq.org/) (Zhang *et al.*, 2016), UCSC Cell Browser (https://cells.ucsc.edu/?ds=cortex-dev) (Nowakowski *et al.*, 2017; Speir *et al.*, 2021), and GBMseq (http://gbmseq.org/) (Darmanis *et al.*, 2017) provide rich and high-quality datasets. Compared with these resources, the AHBA, with its near-whole-brain coverage and high-resolution mapping of gene expression, has become the preferred open resource for exploring associations between gene expression and interindividual differences in neuroimaging phenotypes. Its excellent spatial resolution has laid a crucial methodological foundation for the emergence and development of imaging transcriptomics as a research field (Fornito *et al.*, 2019). In view of these advantages, the present review focuses primarily on imaging transcriptomics studies based on the AHBA, while summarizing major findings from other transcriptomic resources (e.g. BrainSpan) as complementary evidence.

General methodology of imaging transcriptomic association studies

The analytical workflow of imaging transcriptomic association studies typically comprises several key steps, including transcriptomic data preprocessing, brain imaging–transcriptomic data association analysis, correction for spatial effects, and evaluation of gene specificity and enrichment analyses (Fig. 1) (Arnatkeviciute *et al.*, 2023).

Preprocessing of transcriptomic data

The complete raw gene expression data from the AHBA can be openly accessed at http://www.brain-map.org. The preprocess-

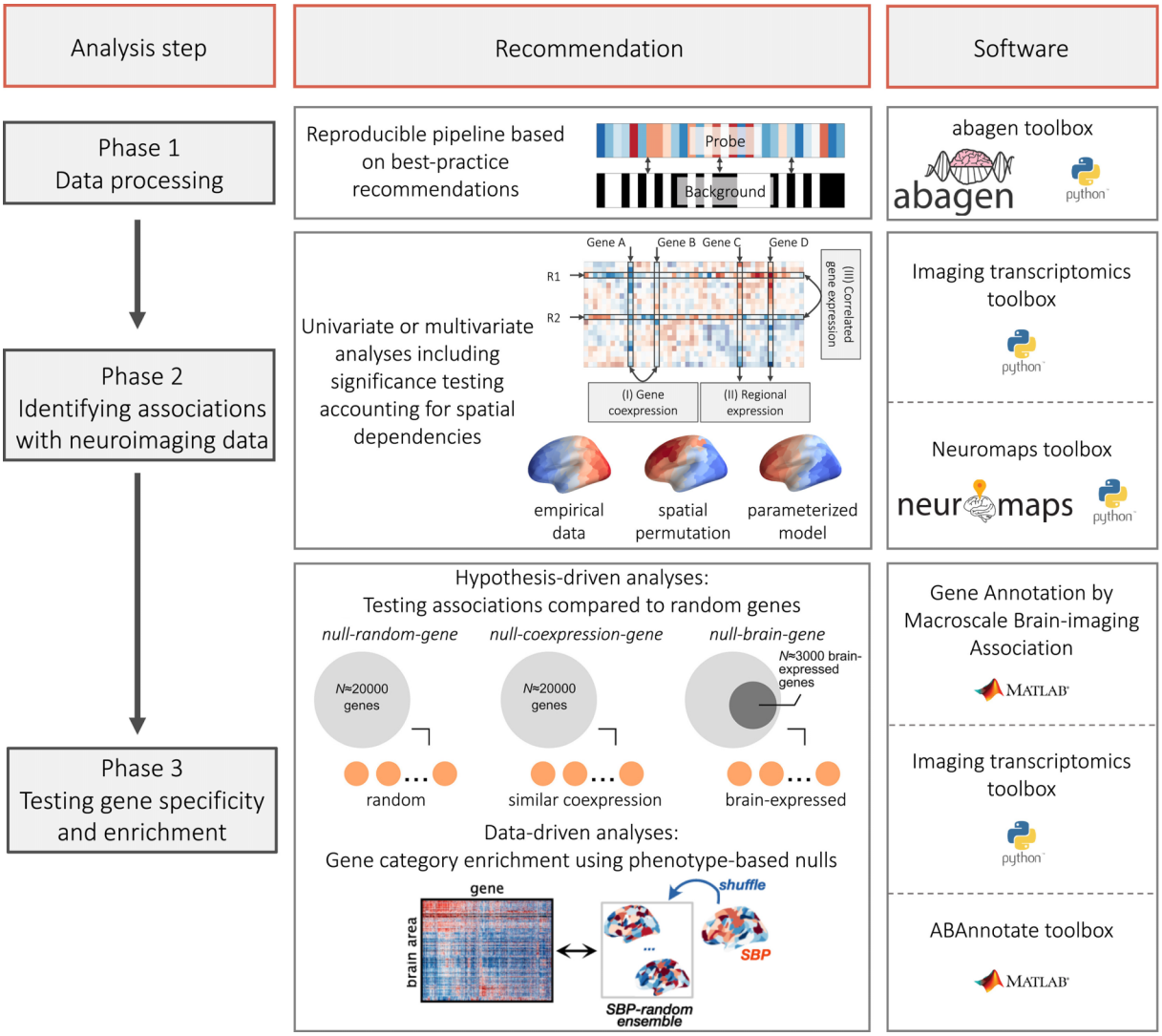

Figure 1 General recommendations for imaging transcriptomic analyses of the human brain using the Allen Human Brain Atlas across three analysis phases. R, region; SBP, spatial brain phenotype (Arnatkeviciute et al., 2023).Reproduced under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0).

ing workflow generally includes the following six steps: (i) Gene re-annotation; (ii) Probe filtering; (iii) Selection of representative probes; (vi) Assignment of tissue samples to macroscopically defined brain regions; (v) Data normalization; and (vi) Selection of genes with consistent expression patterns across donor brains.

Association analysis between neuroimaging and transcriptomic data

After converting the transcriptomic data into a region-wise gene expression matrix, the next step is to associate these measurements with specific neuroimaging phenotypes. Imaging transcriptomic association analyses typically adopt three main strategies, as shown in Fig. 2. The first class of methods focuses on the expression patterns of regional genes (RGEs) and aims to identify correlations between the spatial variation of gene expression and regionally specific differences in anatomically defined brain areas (Patel *et al.*, 2020; Nørgaard *et al.*, 2021). A difference map can be generated by comparing the spatial pattern of a given IDP between patients and controls; this difference map is then spatially correlated with the expression pattern of genes of interest to obtain the transcriptional correlates of that IDP. For example, one study selected inflammation-related genes and genes associated with antipsychotic treatment response—based on two previous reviews and genome-wide association studies—and examined their relationships with changes in cortical thickness (CT) and surface area. The authors found that CT alterations in individuals with schizophrenia (SZ) were associated with the expression of monocyte-related genes (Cui *et al.*, 2023). The second type of analysis considers correlated gene expression (CGE), which primarily quantifies the transcriptional similarity of a set of genes between pairs of brain regions. CGE can then be related to interregional imaging phenotypes, such as structural or functional connectivity (FC) (Richiardi *et al.*, 2015; Fulcher and Fornito, 2016; Arnatkevičiūtė *et al.*, 2018). The third type of analysis measures gene co-expression (GCE). This approach assesses the similarity of spatial expression patterns between pairs of genes to construct a gene–gene matrix, which is then subjected to sta-

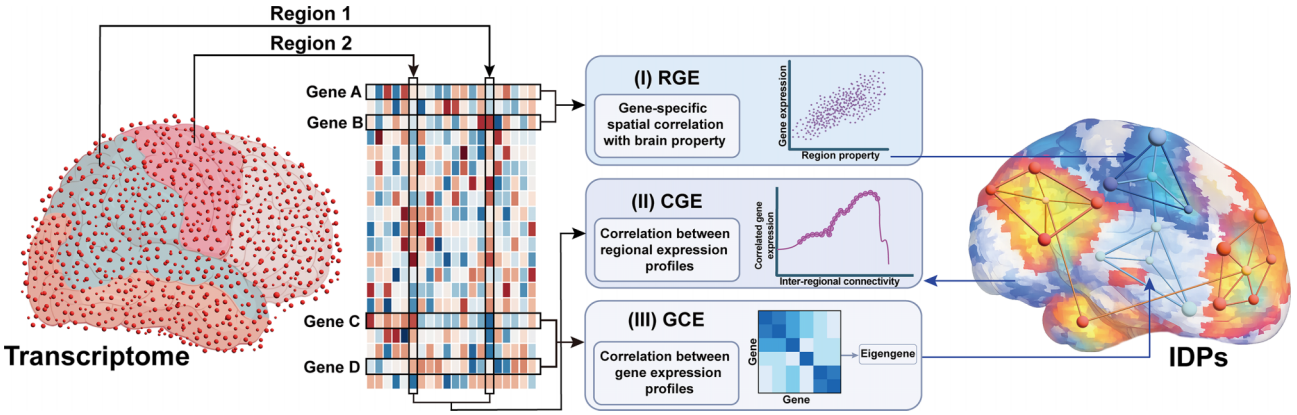

Figure 2 Three approaches for imaging-transcriptomic association analysis. The figure includes a schematic of the gene expression atlas (left) and imaging-derived phenotypes (IDPs) (right). Each sample is characterized by expression measurements for thousands of genes. The data can be aggregated into region-by-gene expression matrices. (I) RGE (regional gene expression): the brain property is spatially correlated with the expression pattern of genes of interest to obtain the transcriptional correlates of that brain property. (II) CGE (correlated gene expression): the gene expression vectors of each region (columns in the expression matrix) are correlated with one another. The resulting CGE values can then be associated with pairwise measures of brain structure or function, such as inter-regional connectivity. (III) GCE (gene co-expression): co-expression can be estimated for each pair of genes to obtain a gene co-expression matrix. Summary measures of expression patterns from this matrix, such as module eigengenes, can subsequently be mapped onto the brain.

tistical analysis. For instance, one can compute module eigengenes for groups of co-expressed genes and correlate them with interregional differences in imaging phenotypes. Because of the multiple-comparison burden, weighted gene co-expression network analysis (WGCNA) is commonly employed for such analyses (Oldham *et al.*, 2008; Forest *et al.*, 2017). The fundamental concept of WGCNA is to perform clustering on the gene–gene matrix for dimensionality reduction, thereby significantly decreasing the number of multiple comparisons. After obtaining the gene–gene matrix, a proximity measure like the Topological Overlap Matrix (TOM) is calculated. Hierarchical clustering is then applied to generate a dendrogram of genes, followed by module identification using the dynamic tree cut method (these clusters are typically referred to as “modules”). Since each module comprises multiple genes, an eigengene is subsequently computed for each module via singular value decomposition, which is then used for further statistical analysis with other sample data. For instance, using this analytical approach, Shen *et al.* (2021) found that the distribution of the zReHo metric across neocortical regions correlates with specific gene expression patterns. The choice among these analytical strategies depends on the specific hypothesis and imaging phenotype under investigation. Most studies rely on RGE- or CGE-based analyses: regional differences in neuroimaging phenotypes can be linked to regional gene-expression patterns using data-driven or hypothesis-driven approaches, whereas CGE is particularly well suited to capturing shared transcriptional patterns between brain regions and is therefore especially appropriate when the imaging phenotype of interest is defined in terms of pairwise measures of structural or FC.

Spatial effects

Neuroimaging and gene transcription measurements typically exhibit a certain degree of spatial autocorrelation—that is, imaging features or gene expression values across different brain regions are inherently correlated, with the strength of correlation decreasing as the spatial distance between regions increases. Therefore, it is essential to account for this spatial dependency to ensure the validity of the results. Several statistical approaches have been developed to correct for spatial autocorrelation and to control its potential bias on analytical outcomes, among which the spatially constrained null model is the most widely applied (Markello and Misic, 2021). The core concept of this strategy is that, when assessing the correlation between neuroimaging features and gene expression data, alternative brain maps are generated that preserve the original spatial autocorrelation structure by means of a parameterized variogram model or spatial permutation algorithm. For cortical surface data, the most commonly used spatial permutation approach is the spin permutation test. In this procedure, cortical vertices or parcels are projected onto a spherical coordinate system and randomly rotated on the sphere; the rotated configuration is then mapped back onto the original surface and values are reassigned accordingly, thereby generating a set of null brain maps with similar spatial autocorrelation properties to the empirical map. Gene-expression matrices are then computed or reassigned based on these permuted maps and correlated with the imaging data to obtain an empirical null distribution. This strategy can effectively reduce false-positive rates and substantially enhance the robustness and reliability of statistical inference (Stam, 2014; Alexander-Bloch *et al.*, 2018). It should be noted, however, that recent work suggests that spin tests may be influenced by factors such as distance distortions introduced by spherical projection and may not perfectly control false-positive rates in all circumstances. In practice, it is therefore recommended to conduct sensitivity analyses tailored to the data type and parcellation scheme and, when necessary, to cross-validate results using alternative spatial null models (Bazinet *et al.*, 2025).

Evaluation of gene specificity and enrichment analysis

After identifying significantly associated gene sets through spatial association models, further multidimensional functional analyses are required. These include performing Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment

analyses to reveal their synergistic roles in biological processes, as well as constructing gene–protein interaction networks to identify hub genes, thereby providing targeted lines of evidence for elucidating the molecular circuit mechanisms underlying diseases.

Progress in imaging transcriptomics research in mental disorders

As summarized in Table 1, several key findings have emerged for major psychiatric disorders.

Depression

Depression is a common mood disorder and mental illness, representing one of the leading public health issues worldwide, with a global prevalence of 4.4% (Marwaha *et al.*, 2023). The World Health Organization ranks it as the leading cause of disability globally, and adolescents with severe depression are 30 times more likely to die by suicide (Liu *et al.*, 2024). The pathogenesis of depression is complex, involving genetic, metabolic, neurobiological, and psychosocial factors (Kim *et al.*, 2023; Menke, 2024; Mo *et al.*, 2024). Therefore, it is essential to delve deeper into the mechanisms underlying depression and discover more effective diagnostic and therapeutic strategies. Imaging transcriptomics offers a novel approach to uncovering the molecular basis of brain imaging abnormalities in depression.

Imaging transcriptomics has advanced our understanding of the potential mechanisms behind the brain structure and function changes in depression. Different genetic mechanisms underlie the structural and functional abnormalities in the brains of patients with depression, with cortical gene expression playing a key role in cortical developmental abnormalities (Liu *et al.*, 2023). Depression patients show significant reductions in gray matter volume (GMV) in critical regions such as the left prefrontal cortex and visual cortex, with genes associated with these gray matter reductions mainly enriched in neural development and synaptic transmission processes (Zheng *et al.*, 2024). Moreover, a large-scale study involving 1660 patients and 1341 controls found decreased GMV in the left medial prefrontal cortex, bilateral insula, and operculum (Zhu *et al.*, 2024). However, this study did not report significant spatial correlations between GMV changes in depression and GO categories. In addition, complex interactions between brain function changes and genetic factors are observed in depression. At the local neural activity level, an increase in amplitude of low-frequency fluctuations (ALFF) is observed in the frontal and temporal lobes, whereas a decrease in ALFF is seen in the parietal and occipital lobes, with genes related to cell differentiation, development, ion transport, and synaptic signaling being primarily involved (Zhu *et al.*, 2023). Regarding FC, the anterior cingulate cortex (ACC) shows weaker connections with the sensory-motor cortex, parieto-occipital region, and posterior cingulate cortex. The connection strength is negatively correlated with genes related to ion channels and positively correlated with genes related to cellular structures (Lou *et al.*, 2023). Brain states can be conceptualized as dynamically evolving configurations of large-scale networks. Identifying such states from functional neuroimaging data, with an emphasis on capturing whole-brain dynamics across time and space, facilitates a more comprehensive understanding of brain function (Kringelbach and Deco, 2020). Recent studies have provided insights into the genetic basis of these dynamic changes in depression. The genetic architecture underlying dynamic reconfiguration observed in depression is associated with metabolism, biosynthetic pathways, and programmed cell death, underscoring the importance of dynamic brain reorganization in understanding the neural mechanisms of the disorder (Xiao *et al.*, 2024). Dynamic functional features further reveal abnormal neural time scales in the ventromedial prefrontal cortex (vmPFC), ACC, and insula—particularly in patients with a shorter illness duration—and these alterations are linked to genes involved in synaptic development (Han *et al.*, 2022b). Using resting-state functional MRI (rs-fMRI) within a gradient-decomposition framework, researchers can decompose functional brain networks into multiple gradient components that capture the topological organization of the connectome (Biswal *et al.*, 1995; Margulies *et al.*, 2016). Functional-connectome gradients provide a sensitive intermediate phenotype for mapping the hierarchical organization of the brain from sensory processing to higher-order cognition (Huntenburg *et al.*, 2018). Studies have shown that connectome-gradient dysfunction in depression is associated with genes related to synaptic development and calcium signaling (Xia *et al.*, 2022). These findings indicate that FC disturbances in depression reflect dysregulation of synaptic communication and neurotransmitter systems at the molecular level. Concurrently, cerebral blood flow (CBF) studies report increased blood flow in the reward circuit and default mode network (DMN) in depression patients, while blood flow in the visual system is decreased. The related genes are involved in ion channels, synaptic function, and neurotransmitter systems, including key hub genes (GNG2, GNB4, and GNG4) (Sun *et al.*, 2023). Significant changes in white matter voxel-wise functional connectivity (WM-IVFC) have been observed in depression patients, which are associated with various behavioral factors. Genes related to these WM-IVFC changes are enriched in pathways associated with synaptic function, neuronal systems, and ion channels, with predominant expression in both excitatory and inhibitory neurons (Gai *et al.*, 2024).

Imaging transcriptomics has also revealed genetic basis differences in the subtypes of depression. Hippocampal GMV changes in first-episode and recurrent depression are closely related to genes involved in synaptic and axonal functions (e.g. SYTL2, SORCS3, SLIT2, SCG2) (Sun *et al.*, 2025). Furthermore, depressed patients with anxiety traits show gene expression enrichment in ATP generation and synaptic translation pathways in regions with FC abnormalities (Chen *et al.*, 2025a). Large-scale epidemiological studies have shown that the lifetime prevalence of depression is higher in women than in men, and that sex differences in human brain development may be related to the gender disparity in the incidence of adolescent depression. Research has demonstrated that the sexually differentiated development of FC occurs in the DMN, ventral attention and limbic networks, and subcortical nuclei (Dorfschmidt *et al.*, 2022). Sex-stratified analyses reveal significant differences in FC patterns within the DMN and emotion-processing brain regions between male and female patients, with related genes involved in immune signaling, synapse formation, and neurodevelopment, highlighting the importance of sex-specific mechanisms in understanding depression (Talishinsky *et al.*, 2022). These subtypes exhibit distinct patterns of gene enrichment across brain regions with imaging

Table 1 Key findings from recent imaging-transcriptomic studies of psychiatric disorders.

Disease	Study	IDP	Imaging-transcriptome association approach	Key findings
Depression	Zheng *et al.* (2024)	GMV	RGE	In patients, reduced GMV in left prefrontal/visual cortices; associated genes enriched in neural development and synaptic transmission (Zheng *et al.*, 2024).
	Liu *et al.* (2025), Sun *et al.* (2024)	GMV	RGE	ECT induces GMV increases in frontal lobe, insula & hippocampus; spatial patterns align with synaptic signaling & calcium pathway gene expression (Liu *et al.*, 2025; Sun *et al.*, 2024).
	Sun *et al.* (2025)	GMV	RGE	Hippocampal GMV alterations in first-episode and recurrent MDD are linked to genes implicated in synaptic and axonal function (Sun *et al.*, 2025).
	Fang *et al.* (2025)	GMV	CGE	Two structural subtypes were identified based on individualized GMV deviations: Subtype 1 (cerebral increase/cerebellar decrease) linked to excitatory receptor abnormalities; Subtype 2 (opposite pattern) linked to inhibitory receptor dysfunction, indicating distinct molecular mechanisms (Fang *et al.*, 2025).
	Zhu *et al.* (2023)	ALFF	RGE	ALFF increased in frontal/temporal lobes but decreased in parietal/occipital lobes; linked genes involved in neuronal development and signaling (Zhu *et al.*, 2023).
	Lou *et al.* (2023)	FC	RGE	ACC shows reduced FC with key sensory and default mode regions; strength negatively correlates with ion channel genes, positively with structural genes (Lou *et al.*, 2023)
	Chen *et al.* (2025a)	FC	RGE	In MDD patients with anxious traits, FC abnormalities are associated with regional gene expression enriched in pathways of ATP generation and synaptic translation (Chen *et al.*, 2025a).
	Talishinsky *et al.*, 2022	FC	RGE	Sex differences in FC within DMN and emotion-processing regions; associated genes involved in immune signaling, synapse formation, and neurodevelopment, highlighting sex-specific mechanisms in MDD (Talishinsky *et al.*, 2022).
	Li *et al.* (2025)	FC	RGE	Two FC-based subtypes identified; share axonal/synaptic development genes; hypoconnectivity links to glial/GABA/cholinergic genes, hyperconnectivity to neuronal/glutamatergic/cognitive genes (Li *et al.*, 2025).
	Gai *et al.* (2024)	WM-IVFC	RGE	WM-IVFC alterations correlate with behavioral factors; associated genes enriched in synaptic, neuronal, and ion channel pathways, expressed in excitatory/inhibitory neurons (Gai *et al.*, 2024).
	Sun *et al.* (2023)	CBF	RGE	CBF increases in reward/DMN circuits but decreases in visual system; associated genes involve ion channels, synapse, and neurotransmission (Sun *et al.*, 2023)
SZ	Di Biase *et al.* (2022)	CT	RGE	CT heterogeneity in SZ is linked to interindividual differences in the functional properties of specific cell types, revealed through multiscale integration of gene, expression, and morphology data (Di Biase *et al.*, 2022).
	Chen et al. (2025)	ReHo	RGE	Oculomotor and ReHo differences in SZ/CHR cohorts show potential as early markers; spatial correlation of ReHo changes with gene expression profiles reveals genetic basis of functional abnormalities (Chen *et al.*, 2025b)

Table 1 Continued

Disease	Study	IDP	Imaging-transcriptome association approach	Key findings
ASD	Leyhausen *et al.* (2025)	CT	RGE	Integration of imaging and transcriptomic data reveals distinct imaging subtypes linked to differing molecular pathways, including synaptic transmission. (Leyhausen *et al.*, 2025).
	Li *et al*. (2023)	ALFF, ReHo, DC	RGE	Sex-stratified analyses reveal abnormal DMN activity in autism; heterogeneous brain regions correlate with genes involved in neuronal membrane signal transduction (Li *et al*., 2023).
	Buch *et al.* (2023)	FC	RGE	Within subgroups, autism-related FC variations are explained by region-specific expression of distinct gene set (Buch *et al.*, 2023).
	Xiao *et al.*, 2025	GM-IVFC, WM-IVFC	RGE	GM-IVFC and WM-IVFC show regionally heterogeneous distributions. Increased GM-IVFC within DMN/attention networks correlates with genes for sensory organ morphogenesis. Altered WM-IVFC in corpus callosum/SFOF links to astrocyte pathways, both correlating with symptom severity, highlighting complementary roles and biomarker potential (Xiao *et al.*, 2025).
OCD	Zhang *et al.* (2024)	CT	RGE	Comprehensive analysis linked CT changes in OCD to over 600 genes; these genes implicate specific biological processes, cell types, and pathways in cortical pathology (Zhang *et al.*, 2024).
	Yan *et al.*, 2024	CC-FC	RGE	Longitudinal study links altered CC-FC in OCD to specific genetic profiles; these genes represent potential drug targets and biomarkers for diagnosis/progression tracking (Yan *et al.*, 2024).
BD	Zhang *et al.* (2023)	CT	RGE	In structural imaging studies, genes with spatial expression patterns corresponding to CT alterations in pediatric BD were enriched for synaptic signaling gene sets and markers of astrocytes and excitatory neurons (Zhang *et al.*, 2023).
	Lv *et al.* (2025)	ReHo	RGE	Significant ReHo abnormalities were observed in the prefrontal cortex, cingulate gyrus, and parietal regions, in which genes associated with synaptic plasticity, calcium signaling, and energy metabolism were enriched (Lv *et al.*, 2025).
	Zhang *et al.* (2025)	FC	RGE	A pharmacotherapy study linked the recovery of frontoparietal and language network connectivity to transcriptomic profiles enriched in immune and oxidoreductase pathways (Zhang *et al.*, 2025).

SZ, schizophrenia; ASD, autism spectrum disorder; OCD, obsessive–compulsive disorder; BD, bipolar disorder; CHR, clinical high risk; IDP, imaging-derived phenotype; GMV, gray matter volume; CT, cortical thickness; ALFF, amplitude of low-frequency fluctuations; fALFF, fractional ALFF; ReHo, regional homogeneity; DC, degree centrality; FC, functional connectivity; WM-IVFC, white matter voxel-wise functional connectivity; GM-IVFC, gray matter intrinsic voxel-wise functional connectivity; CC-FC, cerebellar–cerebral functional connectivity; CBF, cerebral blood flow; RGE, regional gene expression; DMN, default mode network; ACC, anterior cingulate cortex; ECT, electroconvulsive therapy.

abnormalities, suggesting differences in synaptic mechanisms and energy metabolism. Such findings provide valuable insight into the neural and genetic mechanisms underlying different subtypes of depression and may help inform the development of more targeted and effective treatment strategies. Depression is characterized by abnormal FC within large-scale brain networks. Mapping macroscopic functional changes in major depressive disorder (MDD) onto specific molecular pathways provides a link between altered brain networks and potential targets for antidepressant treatment (Zhu *et al.*, 2025). Moreover, neurobiological sub-

types of depression identified from neuroimaging also appear to have distinct transcriptomic signatures. A study that characterized the heterogeneity of FC in depression identified two distinguishable FC-based subtypes. In both subtypes, FC alterations were associated with a set of commonly enriched genes related to axonal and brain development, as well as synaptic transmission and organization. Hypoconnectivity-related FC alterations were spatially associated with genes involved in glial differentiation and GABAergic and cholinergic receptors, whereas hyperconnectivity-related FC alterations were associated with genes implicated in neuronal differentiation, norepinephrine transporters, glutamate receptors, and cognitive processes such as learning, memory, and attention (Li *et al.*, 2025). Structural subtyping based on individualized gray-matter morphometric abnormalities similarly identified two distinct subtypes. In subtype 1, GMV was increased in many cerebral regions but decreased in the cerebellum, whereas subtype 2 showed the opposite pattern. Subtype 1 was primarily linked to abnormalities in excitatory receptors, whereas subtype 2 was associated with dysfunction of inhibitory receptors, suggesting that different molecular mechanisms underlie the observed brain differences between these structural subtypes (Fang *et al.*, 2025).

Imaging transcriptomics association studies have also advanced our understanding of the genetic mechanisms behind different treatment approaches for depression, highlighting potential genetic targets for understanding and treating depression. Electroconvulsive therapy (ECT) induces increased GMVs in the frontal lobe, insula, and hippocampus, with spatial patterns consistent with synaptic signaling and calcium ion pathway gene expression (Sun *et al.*, 2024; Liu *et al.*, 2025). After repetitive transcranial magnetic stimulation (rTMS) treatment, genes related to synaptic communication and neurotransmission are significantly upregulated, highly aligning with network reconfiguration observed in neuroimaging (Guan *et al.*, 2025). These findings suggest that neuro-regulatory therapies achieve therapeutic effects by influencing synaptic and ion signaling gene pathways, providing a reference for molecular targets in antidepressant treatment.

In line with the AHBA-based findings described above, a meta-analysis of the three largest GWAS of depression identified 102 independent variants, 269 genes, and 15 gene sets associated with the disorder, including genes and pathways related to synaptic structure and neurotransmission, with enrichment analyses further highlighting the importance of prefrontal brain regions (Howard *et al.*, 2019). Variants in the NETRIN1 signaling pathway have been proposed to increase depression risk by affecting multiple white-matter tracts; NETRIN1 is involved in thalamic axon growth (Barbu *et al.*, 2019). As noted earlier, imaging transcriptomic studies have reported that genes associated with abnormalities in white-matter–functional connectivity are enriched in synaptic-function pathways. Studies based on polygenic risk scores (PRS) have found that MDD-PRS is robustly associated with differences in white-matter microstructure, suggesting that microstructural white-matter alterations may serve as causal risk factors for depression (Shen *et al.*, 2020). In addition, higher MDD-PRS is associated with reduced intracranial volume and total cortical surface area, including smaller frontal surface area, as well as reduced thalamic, hippocampal, and pallidal volumes (Fu *et al.*, 2024; Shen *et al.*, 2025). At the functional level, MDD-PRS has been linked to altered resting-state FC (rsFC) patterns between the subgenual ACC (sgACC) and the DMN and frontal regions. Interindividual variability in FC among patients with depression differs significantly from that of healthy controls, suggesting that genetic risk may influence clinical manifestations by modulating the heterogeneity of brain function (Hou *et al.*, 2023; Chen *et al.*, 2025b). Integrating individual-level genetic data with brain-wide transcriptomic atlases thus helps to construct a coherent, multiscale explanatory framework that links disease-associated genetic variation, its potential region-specific effects on gene expression and the resultant macroscopic neuroimaging phenotypes.

Identifying reliable biomarkers is crucial for the early diagnosis and prevention of depression. Imaging transcriptomic studies have shown that structural and functional brain changes in depression are related to multiple biological pathways; at the same time, patterns of abnormalities in structure, ALFF, and other imaging measures repeatedly point, at the molecular level, to pathways involved in synaptic information transfer, suggesting that synaptic dysfunction may represent a common molecular basis for multimodal abnormalities in depression. At the cell-type level, convergent processes are primarily related to neuronal synaptic communication and astrocyte-mediated support, and macroscopic connectivity abnormalities may, to some extent, be anchored to differences in cell lineages and neurotransmitter systems. Hu *et al.* (2024) revealed the structural basis of depression, which may help differentiate depression at an early stage. However, most studies are based on cross-sectional data, making it difficult to clarify causal relationships. Future efforts should integrate high-precision spatial transcriptomics with longitudinal neuroimaging data to comprehensively reveal the dynamic transcriptional mechanisms underlying the progression of depression.

Schizophrenia

SZ is a severe neurodevelopmental psychiatric disorder characterized by substantial clinical and biological heterogeneity, as well as complex genetic and pathophysiological mechanisms. It involves disturbances in multiple domains, including thought, perception, emotion, and behavior, and represents a major public health challenge requiring urgent attention (He *et al.*, 2020). However, the biological mechanisms underlying SZ remain unclear. Currently, SZ diagnosis depends primarily on the assessment of patient symptoms, disease course, functional impairment, and exclusion of other conditions. Many researchers now focus on the relationships between neural connectivity and function, as well as polygenic models in genetic studies. Imaging transcriptomic association research has provided meaningful biological insights into the pathogenesis of schizophrenia at the molecular level.

The brains of SZ patients exhibit significant morphological and functional alterations, yet the cellular and genetic bases of this heterogeneity remain poorly understood. Di Biase *et al.* (2022). measured the standard deviation range of 34 cortical regions in SZ patients and utilized gene set data from the Allen Institute for Brain Science to map cell-type-specific gene expression patterns in the human brain. By systematically integrating information across three biological scales—genes, gene expression, and brain morphology—they demonstrated that CT heterogeneity in SZ is related to interindividual differences in cell-type-specific functional properties. Different subtypes of patients show distinguishable

symptom severity—i.e. distinct brain structural patterns exert separable effects on SZ symptoms. A multiscale analysis integrating genomics, transcriptomics, neuroimaging, and clinical measurements identified 19 distinct genes associated with 16 brain regions, predominantly distributed in the frontal cortex, sensorimotor areas, and temporal and parietal regions. Patients can be further stratified into subtypes according to gray-matter changes in target regions, with additional characterization of symptom profiles (Ma *et al.*, 2019). These findings deepen our understanding of disease heterogeneity and pave the way for psychiatric investigation and intervention. A recent study identified distinct oculomotor patterns and associated changes in regional homogeneity (ReHo) in SZ and in individuals at clinical high risk (CHR) for psychosis, indicating that these differences may serve as early biomarkers. The authors further established spatial correlations between ReHo alterations and gene expression profiles, elucidating genetic mechanisms underlying brain functional abnormalities in SZ and CHR populations (Chen *et al.*, 2025c). Task-based fMRI combined with transcriptomics has also been used to examine the relationship between stress-related brain activity and gene expression. Researchers investigated neural and genetic mechanisms underlying individual differences in cognitive–behavioral responses to stress under competitive contexts. Using bilateral-hemisphere data from two donors in the AHBA for gene-expression analyses, they found that genes transcriptionally associated with stress-induced activation were related to SZ genetic risk. Their results suggest that variation in striatal activity and genetic risk for SZ may contribute to individual differences in working-memory performance under stress-inducing conditions. Poor adaptation to social stress is considered to be associated with increased risk for psychiatric disorders such as SZ (Zhang *et al.*, 2022).

Genetically determined IL-6 is associated with brain structure and may influence regions implicated in developmental neuropsychiatric disorders, including SZ and autism spectrum disorder (ASD) suggesting a genetically mediated, tissue-specific neuroinflammatory cascade that plays a key role in brain structural remodeling in neuropsychiatric disease. These findings can be computationally modeled and should be further tested in preclinical models to obtain mechanistic insights (Williams *et al.*, 2022). In addition to the inflammatory cytokine IL-6, Pan *et al.* (2022) investigated transforming growth factor $\beta 1$ (TGF-$\beta 1$) and found that TGF-$\beta 1$ levels were higher than controls at both the mRNA and protein levels. Compared with controls, SZ patients showed significantly reduced CT in the lateral occipital cortex, which was negatively correlated with TGF-$\beta 1$ protein levels. Correlation analyses between plasma TGF-$\beta 1$ levels and MATRICS Consensus Cognitive Battery (MCCB) total and subscale scores indicated that TGF-$\beta 1$ levels were negatively associated with visual cognition in SZ patients, and the lateral occipital cortex mediated the effect of TGF-$\beta 1$ on visual cognition. Peripheral plasma TGF-$\beta 1$ may therefore serve as an effective biomarker for detecting early cortical or cognitive impairment in SZ (Pan *et al.*, 2022). Given that immune dysregulation may be involved in the pathogenesis of SZ, obtaining a definitive understanding requires transcending the limitations of single-modality inference. Therefore, it is imperative to conduct multimodal analyses that integrate neuroimaging with transcriptomic data.

Studies based on PRS have shown that higher SZ-PRS is associated with structural alterations such as cortical thinning in frontotemporal regions, reduced hippocampal volume, and changes in the gyrification index of the inferior parietal lobule (Liu *et al.*, 2017; Alnæs *et al.*, 2019). At the functional level, PRS is significantly associated with features including altered activity signals in the striatum and reward-related networks and the hippocampus, prefrontal neural inefficiency, and FC changes in networks such as the visual network and the DMN (Walton *et al.*, 2014; Chen *et al.*, 2018; Lancaster *et al.*, 2019; Cao *et al.*, 2021). Abnormal striatal FC patterns can serve as a novel biological marker for screening SZ patients and predicting treatment response (Li *et al.*, 2020). Imaging transcriptomics anchors group-level imaging abnormality patterns to specific cell types and molecular pathways, whereas individual-level genetic approaches link cumulative genetic risk to macroscopic brain phenotypes, thereby providing more direct evidence.

In summary, integrative results across multiscale data (i.e. genetics, neuroimaging, and behavior) are expected to provide a more complete understanding of SZ genetic and biological mechanisms. The studies reviewed above, combining transcriptomics and MRI, suggest that macroscopic abnormalities in SZ can manifest at multiple levels—including cortical morphological heterogeneity, prefrontal functional efficiency, and hippocampal activity—and that these phenotypes correspond to polygenic risk and widespread connectome-level alterations. Imaging transcriptomic studies indicate that implicated molecular pathways commonly converge on synaptic/neurotransmitter-related processes and immune–inflammatory processes. At the cell-type level, CT heterogeneity in SZ is explained by interregional gene-expression levels in five of seven neural cell types: astrocytes, endothelial cells, oligodendrocyte precursor cells (OPCs), excitatory neurons, and inhibitory neurons. However, most studies rely on mining existing databases, and combining large-scale molecular data with neuroimaging results is highly complex; thus, rigorous standardization and appropriate preprocessing are essential. Moreover, MRI-based studies have identified neurobiological subtypes of SZ (Honnorat *et al.*, 2019; Jiang *et al.*, 2023c). As objective biological markers, neuroimaging features show high correspondence with SZ clinical phenotypes and can provide biological interpretations of pathological changes, offering strong potential for subtype stratification. Nonetheless, direct evidence remains limited as to whether these imaging subtypes correspond to distinct molecular pathways, cell types, or gene-regulatory networks. Future work should investigate the molecular mechanisms underlying different imaging subtypes to provide a theoretical basis for precision medicine.

Autism spectrum disorder

ASD is a neurodevelopmental condition characterized by pronounced clinical and genetic heterogeneity (Li *et al.*, 2019). Its core features include deficits in social communication and restricted or repetitive behaviors or interests (Matta *et al.*, 2019), while its etiology remains elusive. Imaging transcriptomics has facilitated a deeper understanding of the molecular mechanisms underlying sex differences in autism.

Sex differences have long been a prominent feature of ASD (Rossignol and Frye, 2012), and imaging transcriptomic analyses have advanced our understanding of the genetic basis underlying these differences. Sex-stratified imaging transcriptomic analyses have revealed abnormal brain functional activity in autism patients of different sexes, primarily located within the DMN. Cor-

relation analyses between neuroimaging and gene transcription further showed that heterogeneous brain regions are highly correlated with genes involved in signal transduction between neuronal plasma membranes (Li *et al.*, 2023a). Moreover, gene expression in the striatum, thalamus, and cortical cells is associated with sex-related differences in FC in autism, deepening our understanding of sex-related heterogeneity within large-scale brain networks in ASD (Namgung *et al.*, 2024).

Imaging transcriptomic association analyses have enhanced our understanding of how genetic factors contribute to alterations in brain structure and function in autism. Cortical complexity changes associated with ASD are closely linked to specific genetic pathways. Significant alterations were observed in the left temporoparietal junction, left peripheral visual areas, right central visual cortex, left somatomotor regions (including the insula), and the left ventral attention network. Partial least squares regression identified gene sets associated with these cortical complexity changes, enriched in biological processes related to synaptic transmission, synaptic plasticity, mitochondrial dysfunction, and chromatin organization (Mamat *et al.*, 2025). Other studies have shown that deviations in CT are related to different sensory subgroups, particularly in brain regions enriched with genes involved in excitatory rather than inhibitory neurotransmission (Ecker *et al.*, 2022). Imaging transcriptomic analyses exploring abnormal cortical functional alterations and potential gene transcriptional mechanisms in autism may further advance our understanding of its underlying pathophysiology (Li *et al.*, 2023b).

Both gray matter intrinsic voxel-wise functional connectivity (GM-IVFC) and WM-IVFC exhibit regionally heterogeneous distributions across the whole brain in ASD patients. Studies have shown that individuals with ASD display increased GM-IVFC primarily within the default mode and attention networks, while WM-IVFC alterations are mainly observed in the corpus callosum and superior fronto-occipital fasciculus. These changes are significantly correlated with symptom severity. GM-IVFC alterations are enriched for genes involved in sensory organ morphogenesis, whereas WM-IVFC alterations are associated with astrocyte-related pathways, emphasizing their complementary roles and supporting their potential as biomarkers (Xiao *et al.*, 2025). ASD is also associated with atypical patterns of dynamic FC, with genes enriched in neurodevelopmental pathways showing significant correlations with atypical dynamic brain states, providing new insights into the characterization of dynamic neural activity (Shan *et al.*, 2025). Functional activity analyses have shown unique alterations in the prefrontal cortex, temporal lobe, and cingulate cortex across the lifespan of individuals with autism, which are also associated with genes primarily expressed in synaptic structures. These findings offer new perspectives on the potential biological abnormalities in ASD (Li *et al.*, 2023b). Within each subgroup, autism-related FC variations are explained by region-specific expression of distinct autism-associated gene sets. These gene sets display differential correlations with molecular signaling pathways involved in immune and synaptic functions, G-protein-coupled receptor signaling, protein synthesis, and other biological processes (Buch *et al.*, 2023). Neuroimaging-based subtypes have potential clinical utility, and imaging transcriptomics provides mechanistic interpretations of this heterogeneity. By integrating imaging phenotypes with transcriptomic data, Leyhausen *et al.* (2025). showed that distinct imaging subtypes correspond to different molecular pathways, with some subtypes being closely related to biological processes such as synaptic transmission. Together, these studies provide novel insights into the genetic and neurobiological foundations of ASD.

Higher ASD-PRS are associated with multiscale structural abnormalities, including atypical developmental changes in CT within sensorimotor cortices (e.g. the precentral and postcentral gyri and the precuneus), altered structural connectivity in hub regions such as the DMN and frontoparietal control network, reduced cerebellar and brainstem volumes, and decreased whole-brain neurite density (Khundrakpam *et al.*, 2020; Alemany *et al.*, 2021; Sha *et al.*, 2021; Khundrakpam *et al.*, 2023; Mohammad *et al.*, 2024; Gu *et al.*, 2025). ASD-PRS is also significantly associated with altered patterns of brain asymmetry in regions supporting language and executive function (e.g. the superior temporal gyrus, inferior frontal gyrus, and inferior parietal lobule), as well as topological reorganization of sensorimotor and cerebellar–brainstem circuits (Alemany *et al.*, 2021; Sha *et al.*, 2021; Khundrakpam *et al.*, 2023). Consistent with the AHBA-based imaging transcriptomics findings summarized above, these results converge at two levels to implicate similar vulnerability networks, jointly supporting the view that ASD is a polygenic brain network disorder.

Imaging transcriptomic association studies have provided new insights into the pathophysiology of ASD. The molecular pathways linked to ASD-related structural and functional abnormalities include neurodevelopmental programs, synapse-related pathways, and mitochondrial energy metabolism. At the cell-type level, ASD imaging abnormalities are associated with gene-expression profiles of excitatory neurons, particularly in sensorimotor and higher-order association cortices. In addition, astrocyte-related genes are enriched in WM-IVFC alterations. As we strive for a deeper understanding of ASD pathophysiology, future research should integrate multiple biological data sources and employ more specific approaches to determine how autism risk genes influence brain structure and function.

Obsessive–compulsive disorder

Obsessive–compulsive disorder (OCD) is a chronic neurodevelopmental disorder characterized by intrusive, repetitive thoughts and compulsive behaviors (Pauls *et al.*, 2014). Significant structural and functional abnormalities have been observed in the brains of OCD patients, yet the underlying genetic mechanisms remain to be fully elucidated.

Imaging transcriptomic association studies have clarified the molecular and transcriptional bases of brain structural alterations in OCD and established links among molecular, transcriptional, and neuroimaging information, thereby promoting a more integrated understanding of the disorder. Studies have shown that patients with OCD exhibit marked gray matter morphological abnormalities across widespread brain regions, including the ACC, thalamus, caudate nucleus, precentral gyrus, and postcentral gyrus. Further analyses revealed that these gray matter morphological abnormalities were significantly associated with dopamine synthesis capacity and were enriched for genes involved in synaptic and neurotransmitter functional pathways, providing molecular evidence for structural abnormalities in OCD (Li *et al.*, 2024). A comprehensive analysis linking CT alterations with transcriptomic data identified over 600 genes associated with CT changes in OCD. Subsequent analyses provided insights into the biological processes, cell types, and pathways implicated in OCD cortical

pathology, offering new perspectives on the genetic and molecular underpinnings of brain abnormalities in OCD (Zhang *et al.*, 2024).

In terms of brain functional studies, a longitudinal investigation explored the genetic basis of altered cerebellar–cerebral functional connectivity (CC–FC) in OCD, examining the complex relationships between CC–FC changes and clinical symptom variations following pharmacological treatment. The study found that CC–FC alterations were linked to specific genetic profiles, with these genes potentially serving as targets for the development of new drugs aimed at modulating their expression or function, as well as biomarkers for diagnosing OCD or tracking its progression, enabling more precise disease monitoring (Yan *et al.*, 2024). The role of the striatum in OCD pathophysiology has been well established, particularly within the cortico-striato-thalamo-cortical (CSTC) circuit, which functions as a recurrent loop where information flows from the cortex to the striatum, integrates in the thalamus, and returns to the cortex (Alexander *et al.*, 1986). Recent studies have investigated the neural circuitry within the striatum in OCD, as well as the relationship between gene expression profiles and alterations in information flow. By performing a detailed parcellation of the striatum, significant changes in degree centrality (DC), FC, and effective connectivity (EC) were observed in striatal subregions of OCD patients before and after treatment. Abnormalities in information flow within the CSTC and cortico-striato-cerebellar circuits indicated excessive top-down control and diminished bottom-up regulation in drug-naïve OCD patients. After treatment, bottom-up information flow improved, accompanied by alleviation of clinical symptoms. This suggests that treatment-induced enhancement of bottom-up regulation influences higher-order brain regions, thereby mitigating OCD symptoms. Moreover, the genes associated with altered information flow between striatal subregions and the rest of the brain, as well as within homologous striatal subregions, showed substantial overlap, providing new insights into the biological substrates underlying striatal EC alterations in OCD patients (Han *et al.*, 2025). Imaging transcriptomic studies of OCD have expanded our understanding of its neural circuitry and genetic mechanisms, offering new directions for precision diagnosis and personalized therapeutic strategies.

Individual-level PRS studies have found that subclinical OCD symptoms in children are associated with percentage asymmetry changes in thalamic volume, suggesting that 3-year changes in right thalamic volume may be related to OCD-PRS (Ravagnani Salto *et al.*, 2021). OCD-PRS is associated with abnormal neural activity in regions such as the dorsolateral prefrontal cortex and inferior parietal lobule during a digit n-back working-memory task and also predicts neural activity in the orbitofrontal cortex; OCD-PRS partly explains variations in brain responses during working-memory performance (Heinzel *et al.*, 2021). Imaging transcriptomic studies, in contrast, indicate that structural abnormalities in regions such as the thalamus are related to genes enriched for synapse-related and neurotransmitter-function pathways. Together, these findings provide complementary evidence for elucidating OCD neural mechanisms.

OCD exhibits abnormalities in both brain structure and function, and these abnormalities are associated with synapse- and neurotransmitter-related processes. In addition, a study using multimodal neuroimaging and semi-supervised learning identified two reproducible OCD subtypes that show marked differences in structural and functional brain patterns, suggesting their potential utility for characterizing OCD heterogeneity (Ding *et al.*, 2024). Han *et al.* (2022a, 2023). applied individualized differential structural covariance network (IDSCN) analysis and GMV-based stratification to divide OCD into two subtypes. Future studies could use imaging transcriptomics to investigate the potential molecular mechanisms underlying distinct OCD imaging subtypes.

Bipolar disorder

Bipolar disorder (BD) is considered one of the most debilitating psychiatric illnesses, characterized by alternating episodes of mania (or hypomania) and depression. These mood fluctuations severely impair patients' daily functioning and social relationships, while also increasing the risk of suicide and violent behaviors (Gergel *et al.*, 2024). The onset of BD is closely associated with various biological and environmental factors, including genetic susceptibility, neurochemical imbalance, and psychosocial stress (Gordovez and McMahon, 2020). Due to the symptomatic overlap between BD and other psychiatric disorders, misdiagnosis is common, often resulting in missed opportunities for early intervention. Although the genetic basis of BD has been shown to alter brain function and morphology, it remains unclear how BD-related genes influence brain structure and function. Therefore, identifying reliable biomarkers for BD diagnosis and elucidating the genetic mechanisms underlying its neurostructural and functional alterations are of great importance. In recent years, neuroimaging–transcriptomic research has provided new perspectives for uncovering the neurobiological mechanisms of BD.

Neural and structural abnormalities in BD are not limited to specific regions or networks but are tightly coupled with gene expression patterns related to energy metabolism, synaptic signaling, glial function, and inflammatory regulation—offering critical evidence for the molecular–neural circuitry basis of BD. In terms of local functional consistency, studies using Kendall's coefficient of concordance ReHo (Kcc-ReHo) and Coherence ReHo (Cohe-ReHo) models revealed altered local synchronization activity and its potential genetic basis in BD patients. Significant ReHo abnormalities were observed in the prefrontal cortex, cingulate gyrus, and parietal regions, where genes associated with synaptic plasticity, calcium signaling, and energy metabolism—such as CACNA1C, BDNF, and ATP2B2—were highly enriched. Furthermore, the integration of imaging and genetic features using machine learning models achieved high accuracy in BD diagnosis and treatment–response prediction, suggesting that local function–gene coupling indices hold promise as potential biomarkers for individualized diagnosis and therapeutic outcome prediction (Lv *et al.*, 2025). Longitudinal studies of FC have further revealed dynamic brain network changes and their molecular correlates in BD. Within the DMN, patients exhibited significant remodeling of connectivity patterns during disease progression—particularly in the medial prefrontal–posterior cingulate coupling—closely linked to emotion regulation impairments. Genes involved in ribosomal function, membrane transport, and enzymatic activity were implicated, suggesting that ribosome-related genes may play key roles in the pathogenesis of BD and associated FC alterations (Cui *et al.*, 2025). Studies on brain network topology have provided new evidence for the systemic functional disruption in BD. Both

depressive and manic phases were characterized by increased local efficiency but decreased global efficiency across the brain network. Node-level analyses revealed disorganization within the frontoparietal, default mode, and somatomotor networks, indicating disrupted balance between integration and segregation. When integrated with transcriptomic data, processes such as "regulation of chemical synaptic transmission," "cell adhesion molecule binding," and "actin binding" were found to be associated with BD risk. These findings highlight the value of combining neuroimaging and transcriptomic approaches to uncover the genetic pathways influencing functional brain network topology and their contributions to BD susceptibility (Ding *et al.*, 2025).

In structural imaging studies, genes with spatial expression patterns corresponding to CT alterations in pediatric BD were enriched for synaptic signaling gene sets and markers of astrocytes and excitatory neurons (Zhang *et al.*, 2023). Expression patterns of BD-associated genes have also been linked to BD-related structural abnormalities in the parahippocampal gyrus, cerebellar vermis, and superior/inferior temporal gyri (McCarthy *et al.*, 2014). The ENIGMA consortium recently reported region-specific case–control differences in CT and surface area across multiple psychiatric diagnoses, including BD, and associated these with cell type-specific gene expression patterns in microglia, astrocytes, and inhibitory neurons using neuroimaging transcriptomics (Patel *et al.*, 2020, 2022). Moreover, large-sample CT analyses further confirmed significant covariance between BD, schizophrenia, and MDD, establishing transcriptomic associations within the cortico-cerebello-thalamic circuit. These results suggest that shared disease effects occur synchronously across hierarchical cortical levels (Hettwer *et al.*, 2022).

Wang *et al.* (2025) further elucidated the neuroanatomical characteristics of suicide risk in BD from a genetic perspective. The study decoded reproducible anatomical deficits associated with suicide effects by quantifying morphometric similarity organization (MSN) across multiple biological features in BD patients. Regional MSN in the entorhinal cortex and left occipital cortex significantly increased with higher suicide risk. Gene expression decoding of the altered MSN revealed enrichment for genes related to morphine addiction and demonstrated their spatial correspondence with excitatory neuron populations, highlighting the genetic substrates underpinning suicide vulnerability in BD (Wang *et al.*, 2025).

In terms of treatment response, a study investigating the effects of pharmacotherapy on brain network and transcriptomic patterns found that FC within the frontoparietal and language networks significantly recovered following treatment. The associated gene profiles were enriched for pathways involving "immune receptor activity" and "oxidoreductase activity," suggesting that transcriptional alterations could explain a substantial portion of the abnormal FC observed in the frontoparietal network in BD, thereby offering a novel perspective on the disorder's genetic mechanisms (Zhang *et al.*, 2025).

BD-PRS is significantly associated with prefrontal cortical structural alterations, as well as atypical development of limbic systems and white-matter fiber tracts in youth at high risk (Takeuchi *et al.*, 2021; Jiang *et al.*, 2023a; Hafeman *et al.*, 2024). Functionally, BD-PRS is associated with inefficiency in the visual association cortex and ventromedial prefrontal regions of the DMN during tasks involving facial emotion and working-memory processing, altered activation in limbic regions, and abnormal rsFC patterns in adolescents (Whalley *et al.*, 2012; Dima *et al.*, 2016; Jiang *et al.*, 2023b). BD-PRS plays an important role in genetic studies of BD, whereas imaging transcriptomics provides spatially specific gene-expression context and emphasizes mechanistic annotation and biological interpretation; at present, the two approaches remain difficult to integrate directly at the data level and are more often linked as complementary evidence within a broader evidence chain.

Spatial patterns of abnormalities in local functional indices and CT in BD often correspond to molecular processes such as synaptic transmission and energy metabolism; at the cell-type level, transcriptomic signatures associated with cortical-thickness alterations are enriched for astrocytic expression profiles. BD exhibits pronounced biological and clinical heterogeneity, and the traditional clinical classification into BD I/II does not fully capture its neurobiological basis. Future work should integrate imaging-defined subtypes with transcriptomic information to deepen mechanistic understanding of BD. Cross-scale integrative paradigms now enable the delineation of BD's neurobiological architecture across molecular, cellular, and systems levels, offering new opportunities for precision diagnosis, treatment–response prediction, and targeted therapy. Future research should combine multi-omics data with longitudinal multimodal imaging to uncover the key molecular pathways driving disease progression and relapse, ultimately achieving truly individualized, mechanism-based interventions for BD.

Findings from other transcriptomic resources in imaging transcriptomics studies of psychiatric disorders

Several studies have also utilized BrainSpan data. In adolescent major depressive disorder (AMDD), alterations in structural–functional brain coupling are related to neurotransmitter systems and cell type-specific gene expression; by integrating human data from BrainSpan, researchers characterized the temporal and spatial expression patterns of depression-related genes during neurodevelopment, highlighting how AMDD may evolve from disrupted development of molecular pathways involved in network integration and neurochemical signaling that align with the adolescent neurodevelopmental milieu (Wu *et al.*, 2025). An integrative omics study combined results from gene co-expression network analyses of the Allen human brain transcriptome with mediation analyses of the BrainSpan proteomic atlas, showing that convergent GMV changes in depression are associated with transcriptomic enrichment in synaptic transmission, metabolism, immune processes, and transmembrane transport; proteins, as products of gene expression, mediate the association between transcriptomic features and volumetric changes in the visual and dorsolateral prefrontal cortices (Sha and Banihashemi, 2022). Developmental and transdiagnostic changes in cortical GMV are widely observed, yet their neurobiological bases remain unclear; using regional expression from the AHBA and validating cross-regional stability with BrainSpan developmental maps, Shin *et al.* (2018) demonstrated that interregional cortical-thickness features are associated with expression of genes marking CA1 pyramidal cells, astrocytes, and microglia. Using hippocampal volume as an auxiliary imaging phenotype, Du *et al.* (2025) identified shared loci across sSZ, BD, and left/right hippocampal volume GWAS and mapped

an overlapping gene set between SZ and BD; co-expression networks of these overlapping genes constructed using BrainSpan showed more prominent prenatal co-expression across multiple cortical regions, suggesting that cross-diagnostic shared genetic mechanisms may influence dimensional clinical phenotypes via developmental cortical networks (Du *et al.*, 2025). By intersecting the SZGene and BrainSpan databases and relating them to GMV, 108 genes significantly associated with GMV were selected as candidate genes, and brain regions associated with these candidate genes were defined as hot clusters (HCs). Among the 108 candidate genes, 19 distinct genes were associated with 16 brain regions, mainly distributed in the frontal cortex, sensorimotor areas, and temporal and parietal regions (Ma *et al.*, 2019).

An increasing number of studies have incorporated BrainSpan and related datasets (Patel *et al.*, 2021; Dear *et al.*, 2024). Future work, together with increasingly comprehensive and precise transcriptomic atlases, is expected to enable measurements across the entire lifespan and in larger cohorts. Efforts are also needed to expand existing transcriptomic resources by increasing the number of donors, generating whole-brain single-cell data, and developing disease-specific brain transcriptomic datasets. These advances will create new opportunities to deepen our understanding of brain tissue, provide a robust framework for studying molecular correlates of brain changes, and link macroscopic phenotypes to physiological and pathophysiological models of disease.

Conclusion and perspectives

Mental disorders are multifactorial and pervasive diseases characterized by genetic heterogeneity and alterations in brain structure and function. However, the correlation and cross-validation between brain structural changes and gene expression remain unclear. Due to the specific nature of psychiatric disorders, it is difficult to obtain large quantities of human brain tissue samples for direct scientific investigation. Quantitative analyses of brain morphology and functional activity using structural and functional MRI, combined with transcriptomics-based cross-scale and multi-omics approaches, have provided new insights. Across different psychiatric disorders and imaging modalities, genes spatially correlated with disease-related structural or functional brain changes often overlap with transcriptionally dysregulated genes identified in postmortem samples from clinical populations. Imaging transcriptomics association studies offer novel perspectives on the mechanisms, diagnosis, and treatment of mental disorders.

Genes related to synaptic transmission and neuroplasticity are broadly enriched in imaging abnormalities across multiple disorders, including pathways involved in synaptic communication, neurotransmitter release, and receptor function, suggesting that dysregulated synaptic signaling may represent a shared molecular mechanism across psychiatric conditions. Neuroimmune imbalance also plays an important role in disease pathology; in SZ, depression, and ASD, disease-related imaging abnormalities are strongly associated with microglia- and astrocyte-specific gene expression. Spatially, imaging alterations in ASD, depression, BD, and SZ are all linked to astrocyte-related expression patterns. Despite these shared features, disorders also show distinct emphases. For example, CT heterogeneity in SZ has been associated with cell type-specific gene expression across multiple neural cell classes—including excitatory and inhibitory neurons, astrocytes, and oligodendrocyte precursor cells—highlighting its neurodevelopmental origins and cellular complexity. Imaging abnormalities in ASD have been linked to pathways related to mitochondrial function and chromatin regulation. BD research emphasizes coupling with genes involved in energy metabolism, ribosomal function, and calcium signaling pathways. In line with these findings, GWAS and PRS further underscore the polygenic architecture and partial genetic comorbidity of these major psychiatric disorders. Prior work indicates that neurobiological subtypes of disorders such as depression, identified from neuroimaging, have distinct genetic architectures; averaged imaging–transcriptomic associations derived from traditional case-control frameworks may obscure within-disorder biological subtypes driven by different molecular pathologies, suggesting that some of the heterogeneity observed at the population level may reflect intrinsic subtypes with distinct molecular bases. Systematic efforts to integrate subtype stratification with transcriptomic analyses remain limited in disorders such as OCD, representing an important gap that warrants focused investigation.

Although imaging transcriptomics effectively bridges the gap between clinical imaging phenotypes and microscopic gene expression, current methodologies face several challenges. For instance, AHBA data typically require extensive preprocessing, and certain procedural choices can alter the generated spatial expression maps and affect final results. The AHBA provides a limited number of donor brain samples, with hemispheric asymmetry and inherent biological differences between postmortem and *in vivo* data. Although analyses have shown that inter-regional gene expression variability exceeds inter-individual variability, the limited number of samples restricts the ability to thoroughly investigate individual-level gene expression differences. Additionally, both gene expression and neuroimaging data exhibit intrinsic spatial autocorrelation. Studies employing parametric or randomization-based statistical methods without preserving this spatial structure may yield overly permissive estimates of statistical significance, inflating false-positive rates. Researchers are therefore striving to advance the field through multiple strategies—such as improving AHBA atlas standardization workflows and conducting systematic clinical and experimental validation for potentially key genes identified in imaging transcriptomics association studies.

Overall, imaging transcriptomic association studies link microscopic pathophysiological models to macroscopic measurements of brain dysfunction, yielding progress in uncovering mechanisms of psychiatric disorders, advancing targeted treatment development, and enabling disease prediction and diagnosis. Further research is needed to strengthen these advances, integrate increasingly comprehensive and precise transcriptomic atlases, place greater emphasis on cross-diagnostic features of major psychiatric disorders, and develop quantifiable objective biomarkers to provide precise targets for diagnosis and treatment.

Author contributions

Juan Liu (Conceptualization, Writing—original draft), Xian Ma (Conceptualization, Writing – original draft), Wanze Xu (Writing—original draft), Xiaoyi Zhang (Writing—original draft), Feifei Liang (Writing—original draft), Jing Li (Writing—original draft), and Yu Dou (Conceptualization, Supervision, Writing—original draft, Writing—review & editing)

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