Imaging Transcriptomics of the Brain for Schizophrenia

ABSTRACT

Schizophrenia is a severe mental disorder with a neurodevelopmental origin. Although schizophrenia results from changes in the brain, the underlying biological mechanisms are unknown. Transcriptomics studies quantitative expression changes or qualitative changes of all genes and isoforms, providing a more meaningful biological insight. Magnetic resonance imaging (MRI) techniques play roles in revealing brain structure and function. We give a narrative focused review on the current transcriptome combined with MRI studies related to schizophrenia and summarize the research methodology and content of these studies to identify the research commonalities as well as the implications for future research, in an attempt to provide new insights into the mechanism, clinical diagnosis, and treatments of schizophrenia.

Keywords: Schizophrenia, transcriptomics, magnetic resonance imaging

Introduction

Schizophrenia is a severe mental disorder that affects about 1% of the population worldwide.[1] The disease is considered a neurodevelopmental disorder. Genetic and environmental factors can lead to early damage that accompanies the entire period of neurodevelopment.[2] Patients with schizophrenia often experience severe mental and emotional disorders, which manifest as avoidance of reality, hallucinations, disconnection from emotional cues, and degenerative behaviors. Such symptoms were thought to be caused by complex interactions between multiple genetic and environmental factors.[3] However, the underlying biological mechanism of schizophrenia is still unclear. Whether microscopic molecular changes could affect the macroscopic characteristics of the brain is a question that further needs to be explored.

As a result of the research difficulties and clinical dilemmas, recent years have seen the emergence of approaches combining multi-omics. Transcriptomics was designed to explore the quantitative expression changes or qualitative changes of all genes and their subtypes. Research on transcriptomics can provide more meaningful biological insights into the pathogenesis of schizophrenia at the molecular level.[1] The development of non-invasive neuroimaging has revolutionized the study of human brain tissue. Magnetic resonance imaging (MRI) allowed for an exploration of how brain structure and function[4-8] change in psychiatric disorders,[9] which plays an essential role in the clinical evaluation and prognosis prediction in schizophrenia patients. Besides, the latest research progress on joint transcription and neuroimaging allows us to achieve the opportunity to connect microscopic and macroscopic data by using the transcription dataset analysis of the Allen Human Brain Atlas (AHBA).[10] The gene expression microarray data of the brain tissue samples can be preprocessed by using the AHBA processing pipeline (https://github.com/BMHLab/AHBAprocessing) with the recommended default setting.[11] This procedure is a systematic assessment of the workflow combining AHBA and neuroimaging data.[11] This mini-review focuses on the current schizophrenia-related transcriptome combined MRI studies and tries to explore new directions in the 2 research areas, thus providing insights for the future mechanism analysis, clinical diagnosis, and drug therapy of schizophrenia. An initial comprehensive search was performed in

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Alpha Psychiatry 2024;25(1):9-14

Gu et al. Trans-Scale Neuroscience of Schizophrenia

PubMed with the keywords: (Schizophrenia AND transcriptome AND magnetic resonance imaging). There was no restriction on the publication's date. By searching, 14 studies were found. We would like to highlight the trans-scale neuroscience of this disorder,[12] integrating findings at different scales (imaging and transcriptome) for a more comprehensive and in-depth understanding of brain function and behavior. Therefore, 8 studies combining both MRI and transcriptomic approaches in these articles have been retained in the present review (Figure 1).

Transcriptomics and Structural Magnetic Resonance Imaging in Schizophrenia

Schizophrenia is a disease associated with the evolution of the human brain.[13] An increased risk of brain dysfunction may present along with the development of cognitive brain networks, which is related to the promotion of higher-order cognitive areas. Through comparative transcriptomic analysis, Wei et al[14] found that compared with chimpanzees and macaques, human acceleration region (HAR) genes were more differentially expressed in human higher-order cognitive networks. Using Genome-Wide Association Study statistics provided by the Psychiatric Genomics Consortium, significant HAR/HAR-BRAIN gene associations with genetic variation in schizophrenia were observed. Using voxel-based morphometry, they found that spatial patterns of cerebral cortex significantly correlated with gene expression patterns of the HAR-BRAIN gene. This suggests that genes playing an important role in the evolution of the human brain also influence the development of psychiatric disorders. This finding has important implications for further exploration of the etiology of schizophrenia.

Another study also emphasized the exploration of the pathologic process of schizophrenia. According to the potential causal relationship between inflammatory cytokines and schizophrenia,[15] Williams attempted to reveal the relationship between inflammation and brain structure in order to further explore the transcriptome-driven functional basis relevant to mental illness.[16] The clinical, genome, and neuroimaging data of 20 688 participants were collected from the UK Biobank, and RNA microarray data from AHBA were also collected. Differential gene expression in the AHBA data was mapped to brain regions that were significant in the MRI analysis. Analysis of the whole brain revealed that the genes highly expressed in the middle temporal gyrus (MTG) further formed a highly connected protein–protein interaction network with interleukin-6 (IL-6). The different genes expressed in the MTG were rich in the biological processes of schizophrenia, autism spectrum disorder, and epilepsy.

MAIN POINTS

- This review integrates transcriptomics and magnetic resonance imaging to offer new insights into schizophrenia, highlighting a unique method that combines molecular and neuroimaging data.
- It explores the association between genetic expressions and brain changes in schizophrenia, emphasizing the importance of merging vast molecular data with neuroimaging findings.
- The article suggests further research into individual-level trans criptomics–neuroimaging correlations and recommends advanced methods to enhance understanding and treatment of schizophrenia.

In addition to the inflammatory cytokine IL-6, Pan[17] studied another cytokinetransforming growth factor β1 (TGF-β1).[17] It is worth noting that gene transcription data were obtained from AHBA in the 2 studies mentioned above. But in Pan's[17] study, the whole blood RNA sequencing was conducted on 75 drug-naive schizophrenia patients and 44 healthy controls, detecting the gene expression and plasma TGF-β1 level. Compared with the control group, the TGF-β1 of patients with schizophrenia increased both at the mRNA and plasma protein levels. Combined with MRI T1-weighted imaging, it was found that the thickness of multiple cortical areas in schizophrenia patients was reduced, especially the lateral occipital cortex (LOC). The level of plasma TGF-β1 protein was negatively related to the thickness of the LOC. The transcriptional data of the dorsolateral prefrontal cortex retrieved by the CommonMind Consortium for gene function clusters was also used. They found that there was no difference in the mRNA level of TGF-β1 between the schizophrenia group and the control group. However, patients with schizophrenia had a smaller number of genes co-expressed with TGF-β1. By combining transcriptomics with structural MRI, the above 2 studies suggested that dysregulation of the immune system may be related to the pathogenesis of schizophrenia.[18,19]

Ma et al[20] explored the relationship between genetic variation and changes in brain structure and clinical scores in patients with schizophrenia. Using the intersection of the SZGene database and the BrainSpan database, they correlated it with the volume of gray matter. One hundred and eight genes that significantly related to the volume of gray matter were selected as candidate genes. Brain regions associated with candidate genes were defined as hot clusters (HCs). Among these 108 candidates, 19 different genes were associated with 16 HC regions, mainly in the frontal cortex, sensorimotor regions, and temporal and parietal regions (Table 1). Patients were further subtyped by the average gray matter volume of HCs. It was found that patients with different subtypes had distinguishable Positive and Negative Syndrome Scale (PANSS) scores. In summary, by combining transcriptomic data and brain structural phenotypes, the above studies have identified the genetic basis of development for schizophrenia, as well as the dysregulation of the immune system, providing ideas for cross-scale studies of schizophrenia.[20]

Transcriptomics and Functional Magnetic Resonance Imaging in Schizophrenia

Neuroimaging research has shown that patients with schizophrenia present brain structural and functional alterations.[21] Functional connectivity was associated with both psychopathological and cognitive manifestations in drug-naïve first-episode schizophrenia.[22] Functional MRI can provide information about the activity of the cerebral cortex. Zhang[23] explored the relationship between stress-related brain activity and gene expression combined with task-based functional MRI and transcriptome. Social competition influences human behavior by inducing psychosocial stress. The researchers investigated the neural and genetic mechanisms underlying individual differences of cognitive-behavioral response to stressful situations in the context of competition. Gene expression analysis was performed using data of bilateral hemispheres from 2 donors in the AHBA dataset. Genes transcriptionally associated with stress-induced activation were found to be related to the genetic risk of schizophrenia. Their study suggests that changes in striatal activity and genetic risk in schizophrenia may play a role
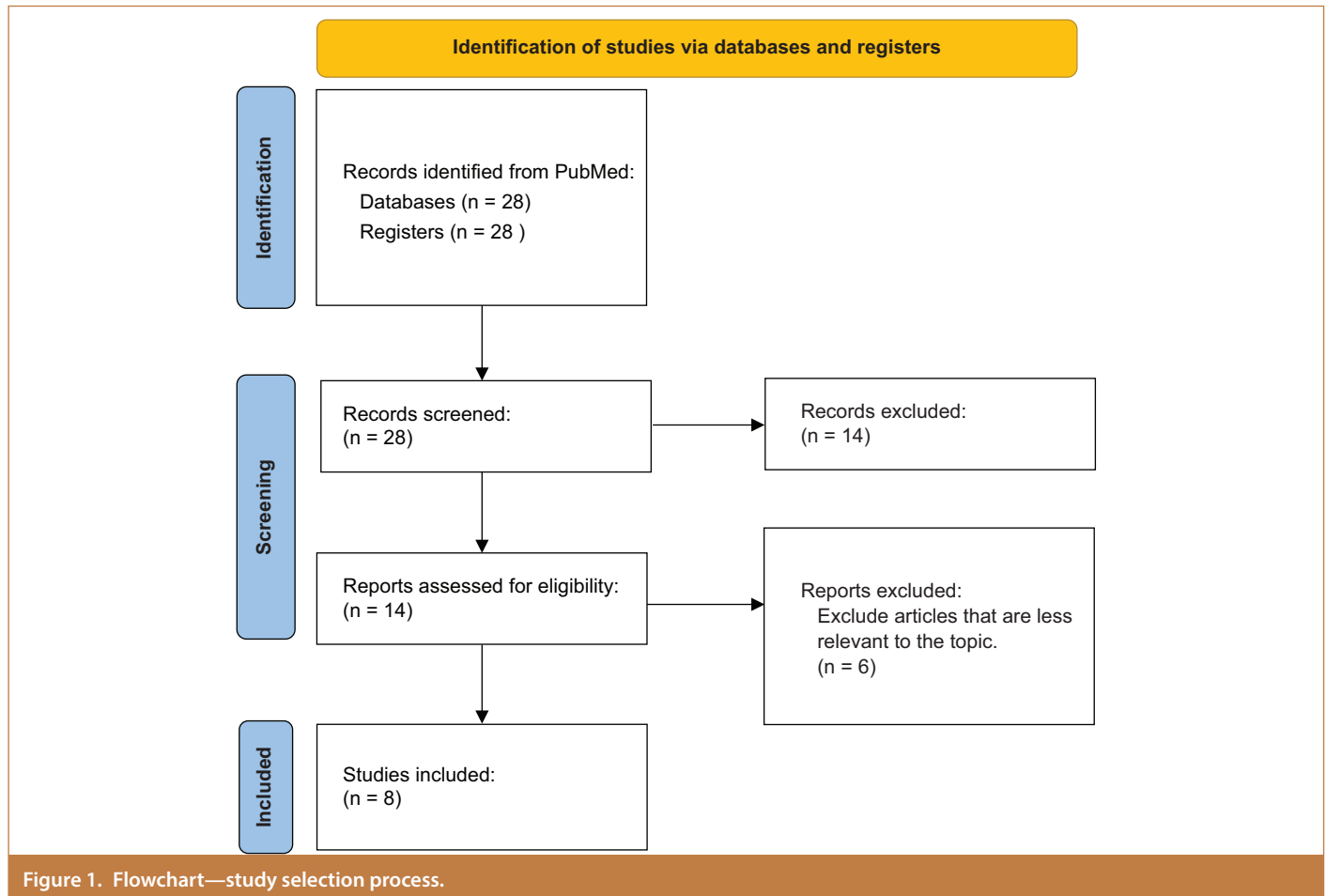
Gu et al. Trans-Scale Neuroscience of Schizophrenia

Alpha Psychiatry 2024;25(1):9-14

Identification of studies via databases and registers

Figure 1. Flowchart—study selection process.

in differences in individual behavior regarding working memory under stress-induced conditions. Poor adaptation to social pressure was considered to be related to the risk of mental illness, such as schizophrenia.[24]

In addition to mission-state functional MRI, resting-state MRI data combined with transcriptome analysis was used to explore the auditory verbal hallucinations (AVHs) in schizophrenia patients. Auditory verbal hallucinations, one of the main symptoms of schizophrenia and an essential part of the schizophrenia diagnostic criteria, have been found to be associated with hyperconnectivity and abnormal network function between the putamen and prefrontal cortex.[25,26] Zhu et al[27] studied auditory hallucination symptoms of schizophrenia by combining high-throughput RNA sequencing from AHBA and resting-state fMRI data. It was found that the expression of the long noncoding RNA (lncRNA)–mRNAinteraction network centered on lncRNA MSTRG.96171.1 was upregulated in patients with AVHs. Functional connectivity in the default mode network (DMN) was positively correlated with the severity of AVHs and the expression of MSTRG.96171.1. Additionally, Yu et al[28] found the upregulated expression of this interactive network and the positive correlation between functional connections in the DMN region and lncRNA expression. These 2 studies initially provide clues to transcriptional and neuroimaging changes associated with AVHs in patients with schizophrenia, which may elucidate its neural mechanism and have important clinical significance for the treatment of this severe mental disease.

Table 1. Hot Clusters (HCs) and Associated Genes

	Associated Genes	AAL Region	Brain Region*	Cluster Size
HC1	CACNA1A ERBB4	Insula_R	SM	945
HC2	PPP1R1B	Precuneus_L	TP	438
HC3	ATP2B2	Temporal_Pole_Sup_L	TP	118
HC4	PPP3CA NRG3	Temporal_Pole_Mid_R	TP	134
HC5	ZBTB20 RELN	Precentral_R	SM	157
HC6	OPCML	SupraMarginal_R	TP	74
HC7	INPP4B	Frontal_Mid_L	FC	63
HC8	ZNF365	Temporal_Mid_R	TP	44
HC9	ANK3	Precuneus_L	TP	47
HC10	ZBTB20	Parietal_Inf_L	TP	31
HC11	PSAP	Lingual_L	OC	33
HC12	BMP6 EIF2B5	Supp_Motor_Area_R	SM	20
HC13	NRG3 PRKCA	Precuneus_R	TP	16
HC14	FGF1	Angular_L	TP	11
HC15	SLIT3	Cingulate_Mid_R	FC	8
HC16	GFRA2	Hippocampus_R	SC	11

The number of voxels contained in the hot clusters is listed in the last column. Table adapted from Ma et al (2019[20]).
FC, frontal cortex; OC, occipital regions; SC, subcortical regions; SM, sensory–motor regions; TP, temporal and parietal regions.

Alpha Psychiatry 2024;25(1):9-14

Gu et al. Trans-Scale Neuroscience of Schizophrenia

Pergola et al[29] explored the relationship between the schizophrenia gene risk and working memory behavior and brain activity by starting from the dopamine D2 receptor gene DRD2 co-expression pathway rich in schizophrenia risk genes. The degree of DRD2 pathway co-expression was predicted by the Polygenic Co-expression Index (PCI). Brain activity in both the patient and control groups was obtained using task-based BOLD-fMRI. They found that the higher the PCI, the more the DRD2 pathway was co-expressed in the prefrontal lobe. Furthermore, the fMRI suggested that the prefrontal activity was more active. At the same time, the working memory response time was longer, which means that the working memory was inefficient. They also conducted a pharmacogenetic study of treatment responses, and they found that in 2 separate samples of schizophrenia patients, patients with a larger PCI responded better to antipsychotic treatment. Through this multiscale analysis, the dopamine D2 receptor gene DRD2 co-expression pathway was associated with working memory behavior, brain activity, and treatment response in schizophrenia. In other words, genetic variation modulating molecular pathways of schizophrenia risk genes may recapitulate part of the variance of schizophrenia-related phenotypes in healthy and clinical populations.[29]

Conclusions

In conclusion, the combined results of cross-multiscale data (i.e., genetics, neuroimaging, and behavior) are expected to provide a complete understanding of schizophrenia's genetic and biological mechanisms. The results are expected to elucidate how genetic variation and changes in brain structure and activities are associated with different symptoms. Although the above studies explored the biological mechanisms of schizophrenia through the combination of transcriptomics and MRI, we can find that most of the studies were based on mining existing databases (Figure 2). Integrating a massive amount of molecular data with neuroimaging findings is of great complexity. It is important to ensure standardization of the data as well as proper preprocessing. Further analyses are performed by selecting features that correlate with specific biological processes or disease states, as well as data dimension reduction. Finally, molecular transcription data and neuroimaging findings are integrated and correlated. It is due to the difficulty of integrating the database that we wish to directly characterize the genetics and imaging of the disease at the individual level. There is a lack of research directly linking transcriptome data from patients with schizophrenia to brain function and structural changes detected by MRI because it is quite difficult to obtain gene expression data from the patient's brain tissue. However, examining gene expressions from blood samples provides a feasible way to investigate participant-level transcriptomics–neuroimaging associations in vivo considering the correspondence of gene expressions between blood and brain.[30] Recently, it is noted that the schizophrenia imaging laboratory data (n = 665; 319 patients, 48 first-degree relatives, and 298
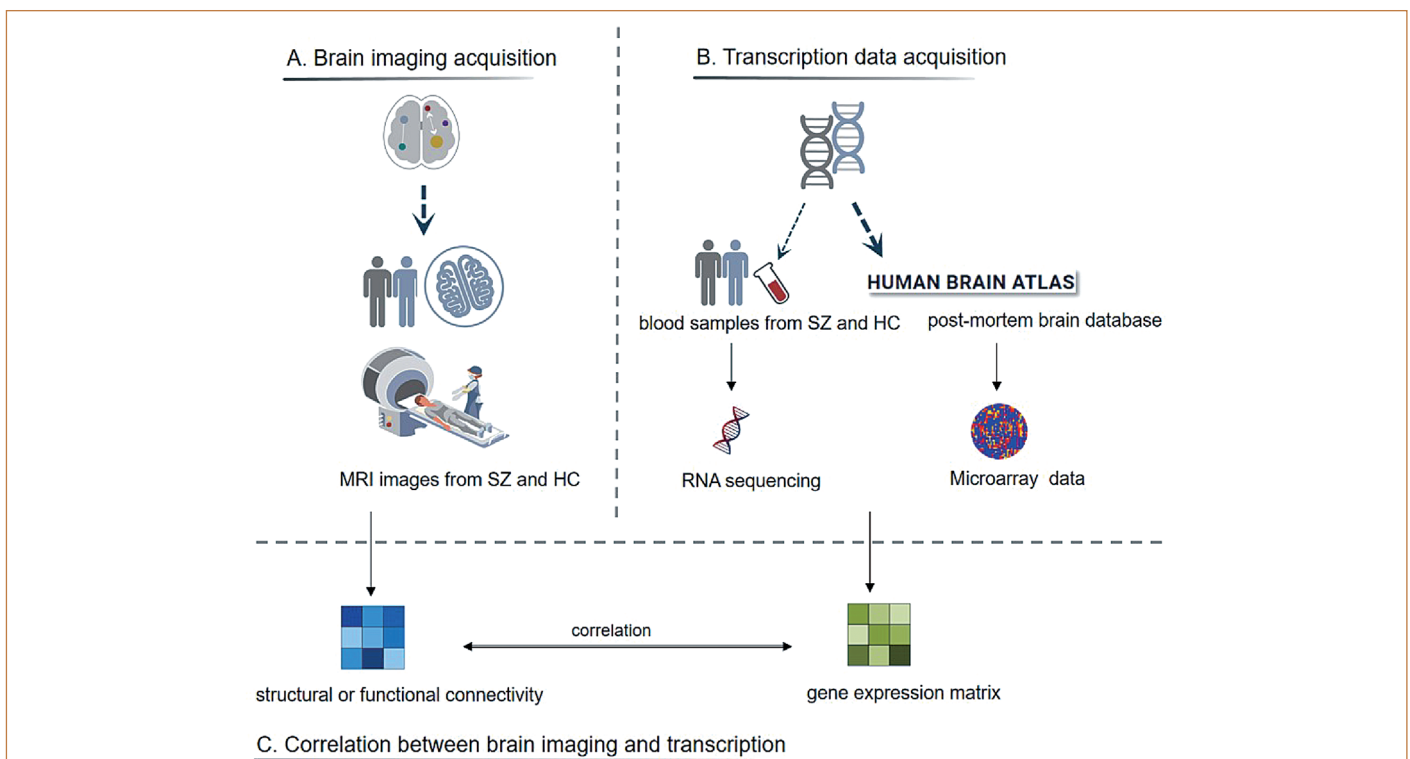

Figure 2. Pipeline of data processing. A. Brain imaging acquisition. Brain imaging data of schizophrenia patients (SZ) and healthy controls (HC) are acquired by magnetic resonance imaging scanning. B. Transcription data acquisition. Most gene expression values were obtained in databases such as the Allen Human Brain Atlas, while another approach was to perform transcriptome sequencing of peripheral blood leukocytes from schizophrenia and HC, thereby obtaining gene expression data. C. Correlation between brain imaging and transcription: brain structural and functional connectivity or other brain imaging metrics are generated from step A, and a gene expression matrix is generated in step B, leading to further calculation of correlations between the 2.

Gu et al. Trans-Scale Neuroscience of Schizophrenia

Alpha Psychiatry 2024;25(1):9-14

control participants) contains MRI scans, including T2-weighted imaging, high-resolution T1-weighted imaging, functional imaging, diffusion-weighted imaging, and arterial spin labeling, and 103 participants had transcriptome-wide data of whole blood.[31] Imaging data, whole transcriptome data, and clinical data from the same subjects can help us explore cross-scale relationships between genes, brain, and clinical indicators at the individual level (Figure 2). Besides, researchers have adopted a novel approach called the nomothetic network psychiatry (NNP), which uses machine learning methods to construct neuroscience-informed classifications using all features of the disorder, including multi-dimensional data.[32] Future studies could use these new methods like NNP and the multimodal data of brain imaging–gene transcription–efficacy assessment to explain the potential molecular biological mechanism,[33] thereby further providing new insights for the clinical diagnosis and treatment of schizophrenia.

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