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Associating Multimodal Neuroimaging Abnormalities With the Transcriptome and Neurotransmitter Signatures in Schizophrenia

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***Background and Hypothesis*: Schizophrenia is a multidimensional disease. This study proposes a new research framework that combines multimodal meta-analysis and genetic/molecular architecture to solve the consistency in neuroimaging biomarkers of schizophrenia and whether these link to molecular genetics. *Study Design*: We systematically searched Web of Science, PubMed, and BrainMap for the amplitude of low-frequency fluctuations (ALFF) or fractional ALFF, regional homogeneity, regional cerebral blood flow, and voxel-based morphometry analysis studies investigating schizophrenia. The pooled-modality, single-modality, and illness duration-dependent meta-analyses were performed using the activation likelihood estimation algorithm. Subsequently, Spearman correlation and partial least squares regression analyses were conducted to assess the relationship between identified reliable convergent patterns of multimodality and neurotransmitter/transcriptome, using prior molecular imaging and brain-wide gene expression. *Study Results*: In total, 203 experiments comprising 10 613 patients and 10 461 healthy controls were included. Multimodal meta-analysis showed that brain regions of significant convergence in schizophrenia were mainly distributed in the frontotemporal cortex, anterior cingulate cortex, insula, thalamus, striatum, and hippocampus. Interestingly, the analyses of illness-duration subgroups identified aberrant functional and structural evolutionary patterns: Lines from the striatum to the cortical core networks to extensive cortical and subcortical regions. Subsequently, we found that these robust multimodal neuroimaging abnormalities were associated with multiple neurobiological abnormalities, such as dopaminergic, glutamatergic, serotonergic, and GABAergic systems. *Conclusions*: This work links transcriptome/neurotransmitters with reliable structural and functional signatures of brain abnormalities underlying disease effects in schizophrenia, which provides novel insight into the understanding of schizophrenia pathophysiology and targeted treatments.**

Key words: Schizophrenia/Disconnected model/Meta-analysis/Allen Human Brain Atlas/Cortical networks/Neurotransmitter

Introduction

Efforts to develop new interventions for schizophrenia have made limited progress, in part because our understanding of the brain changes and biological mechanisms underlying schizophrenia is still in its infancy.[1] However, due to the complexity of schizophrenic symptoms, small sample sizes, and methodological variations in individual studies, our understanding of the pathological mechanisms is further hampered.[2] As such, the identification of consistent and robust neuroimaging biomarkers, and clarification of the neuroimaging-neurotransmitter/genetic relationships are crucial for a better understanding of schizophrenia pathophysiology and targeted treatments.

Meta-analysis is treated as an efficient tool for synthesizing inconsistent results and identifying true-positive findings in the literature.[3–5] Recently, several meta-analyses of neuroimaging studies integrated inconsistent results on the dysfunction of functional activities and alteration of gray matter volume in schizophrenia.[6–11] Although these individual resting-state indicators have greatly clarified the aberrant intrinsic brain functional activities in schizophrenia,

the common pathological mechanism behind these has not yet been established. And how these abnormal functions depend on the synergistic structural changes in the gray matter remains unknown. Thus, the application of the multimodal meta-analytic method is needed to reveal shared pathology in the structure–function of schizophrenia.

The lifetime course of schizophrenia is modeled as both neurodevelopmental and neurodegenerative.[12,13] The neurodevelopmental model attributes schizophrenia to the interaction of multiple genetic/biological and environmental characteristics, which stem from the early development process. However, the neurodegenerative models identify progressive degeneration as its core, which may also be associated with genetic expression. Much of the evidence for both models were derived from a single perspective of neuroimaging studies or measurements of neuronal synaptic activity and neurotransmitters in postmortem samples.[13] Few studies have considered the shared alteration of cerebral structure–function, and the interaction between these alterations and genetic/molecular architecture.[14–21] In parallel, owing to small sample sizes, clinical heterogeneity, and statistical power, no consensus has yet been reached as to how the brain function and structure change dynamically as the disease progresses in patients with schizophrenia using magnetic resonance imaging. Recently, the integration of postmortem gene expression with in vivo neuroimaging data and the coupling of connectivity-neurotransmitter in healthy populations have provided unprecedented opportunities for bridging the gap between neuroimaging features and the transcriptional/neurotransmitter signatures of the brain.[22–25] Therefore, we argue that a combination of cerebral structure–function and neurotransmitter/transcriptomics may provide insight into advancing schizophrenia research.

Here, to identify consistent neuroimaging markers and to determine the molecular genetic underpinnings of these brain changes in schizophrenia, we propose a new framework that combines multimodal meta-analysis and genetic/molecular architecture. First, based on previous resting-state functional and structural magnetic resonance imaging studies,[26–28] we hypothesized multimodal neuroimaging abnormalities in schizophrenia were mainly distributed in frontotemporal, thalamus, insula, and striatum, and these abnormalities would show progressive patterns as the schizophrenic disease evolves. Converging evidence indicates that schizophrenia is a polygenic disease, and most schizophrenia-related genes are involved in synaptic function.[29–31] A growing body of evidence has shown that genetic risk for schizophrenia underlies dysfunction of multiple neurotransmitters,[32,33] such as dopamine. Therefore, we further hypothesized that these identified multimodal neuroimaging convergences of schizophrenia were spatially related to the molecular architecture and gene expression.

To address the above hypothesis, we first used the coordinate-based activation/anatomical likelihood estimation (ALE) meta-analysis approach[34–37] to uncover the robust multimodal neuroimaging abnormalities of schizophrenia at the whole-brain level. A whole-brain approach can effectively avoid artificial biases related to the regions of interest (ROIs).[38] The multimodal neuroimaging publications included voxel-based morphometry (VBM) and voxel-based function (VBF). The VBF studies included amplitude of low-frequency fluctuations (ALFF) or fractional ALFF (fALFF), regional homogeneity (ReHo), and regional cerebral blood flow (rCBF). Second, the stage-specific analysis procedure according to the schizophrenic duration has been used in our previous works and effectively revealed the progression of gray matter abnormalities in schizophrenia.[39] Therefore, we conducted the multimodal subgroup meta-analyses based on the reported mean duration of illness information to reveal the developmental brain changes as the schizophrenia disease progressed. Finally, Spearman correlation analysis was used to test the hypothesis that these identified multimodal convergences of schizophrenia were spatially related to the molecular architecture from the prior in vivo molecular imaging studies.[40] In parallel with this transition, we utilized partial least squares regression (PLSR) analysis, as well as brain-wide gene expression data from the Allen Human Brain Atlas (AHBA),[41] to investigate the genetic underpinnings of aberrant patterns from the functional and structural co-localization in schizophrenia. This combined transcriptome/neurotransmitter and imaging approach has been used in previous studies,[22,42] yet the present study is the first attempt to integrate it with multimodal neuroimaging meta-analysis to explore the pathophysiology of schizophrenia.

Methods

Experimental Design and Quality Assessment

The experimental design of this study is summarized in figure 1. To provide an optimal and comprehensive analysis, we followed the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines[43,44] (figure 1A). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration no. CRD42022362286). To avoid data redundancy and risk of bias, we carefully screened the publications and reached a consensus after screening by 2 authors. As this study was based on published and open data, the requirement for ethical approval was waived.

Literature Search and Study Selection

A literature search of Web of Science, PubMed, and BrainMap was performed to identify functional and structural neuroimaging studies of whole-brain comparisons between schizophrenia patients and healthy controls (HCs) published up to November 1, 2021. We focused on studies that reported ALFF/fALFF, ReHo, rCBF, and

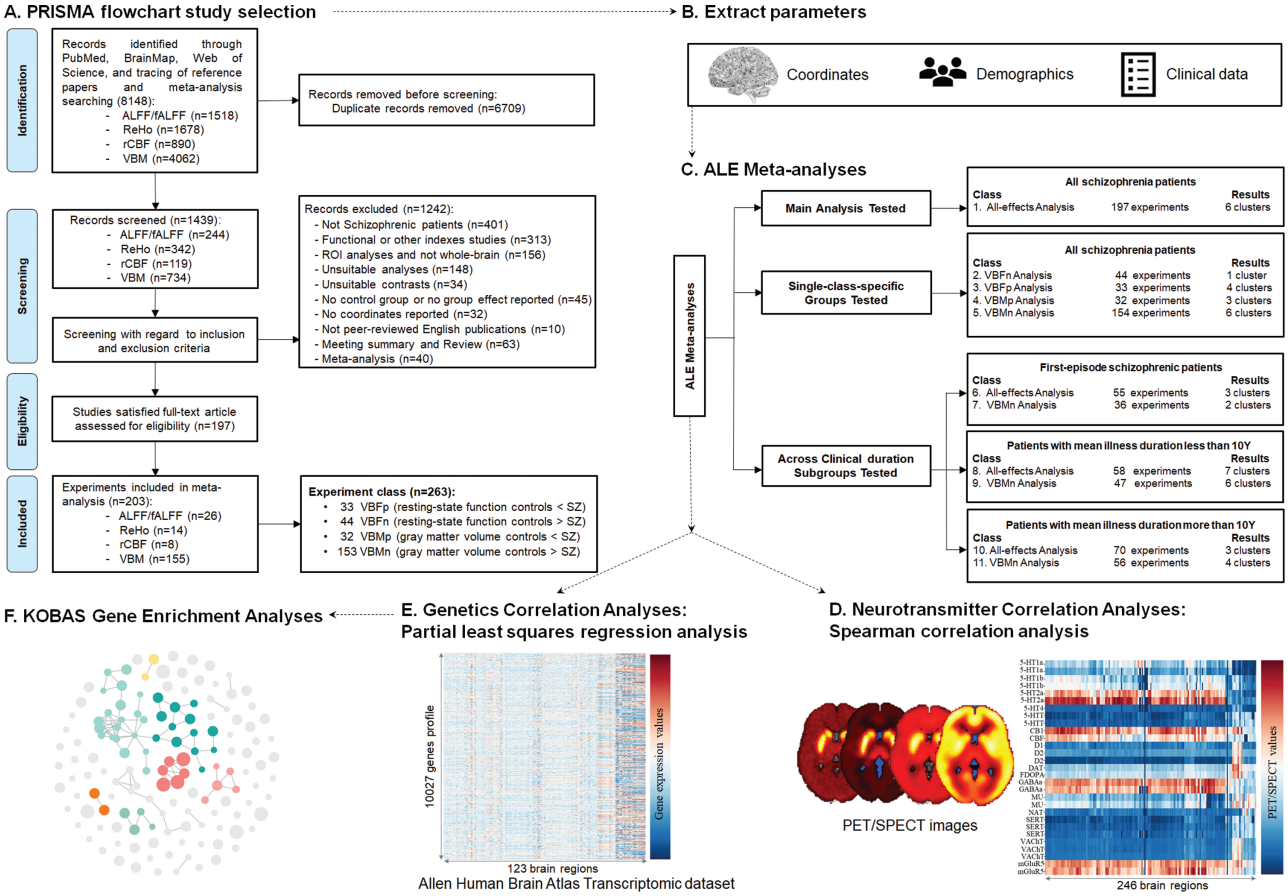

Fig. 1. A schematic of the analysis pipeline for a new research framework that combines multimodal meta-analysis and genetic/molecular architecture in schizophrenia. (A) The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The literature searches yielded a sample of 197 independent studies reporting 203 experiments. (B) Parameters from each article were extracted including coordinates of significant differences in comparison between-group. (C) The groups tested and the results of the activation/anatomical likelihood estimation (ALE) meta-analysis for the neuroimaging studies in schizophrenia. (D) The neurotransmitter data profiles came from the open PET/SPECT database.[40] (E) Transcriptional profiles from the Allen Human Brain Atlas transcriptomics dataset were averaged across 6 postmortem brains (123 regions in the left brain). (F) The KOBAS gene set enrichment analysis was conducted on the gene-list related to the PLSR1.

VBM experiments. After a rigorous qualification review, we obtained the eligible 197 articles. Data from each article were extracted including demographic characteristics (eg, number of participants, age, and gender), clinical data (eg, Positive and Negative Syndrome Scale [PANSS], illness duration, chlorpromazine equivalents [CPZ]), coordinates and space of significant differences in the comparison between groups. Further details of the search items, eligibility criteria for article selection, and extraction of data were provided in supplementary methods.

Different Meta-Analytic Groupings

To comprehensively access multimodal neuroimaging convergent abnormalities in schizophrenia, we conducted 11 different meta-analyses categories as follows:

1. All-effects analysis: To investigate the schizophrenia-related convergent abnormalities in structural and functional co-localization disease effects, we integrated all included experiments (N = 197 studies) to generate a unified all-effects meta-analytic category (the distribution of foci of the major meta-analysis categories is given in supplementary figure S1). This method has proven to be a powerful and efficient tool for integrating findings from structure/function and increase/decrease.[45] In the case of different experimental contrasts on the same subject group (for example, ALFF/fALFF and ReHo and VBM in the same article), to avoid double counting of subjects, all coordinates need to be concatenated and distinguished by adding notes.[46]
2. Single-class-specific group meta-analysis: Since ALE is blind to the sign (+/−) of effects, to assess single-modality-specific effects in schizophrenia, we performed 4 types of single-class-specific meta-analyses. They were designed to detect whether schizophrenic patients showed significantly weaker or stronger properties in function and structure compared with

HCs: Increased function activities (VBFp, schizophrenia patients > HCs); decreased function activities (VBFn, schizophrenia patients < HCs); increased gray matter morphometry (VBMp, schizophrenia patients > HCs); and decreased gray matter morphometry (VBMn, schizophrenia patients < HCs) (figure 1A). Each category satisfied the criterion of minimum number (N > 17) of experiments for robust ALE analysis.[47]

3. Meta-analyses across clinical duration subgroups: To assess the progressive convergent abnormalities of multimodal neuroimaging in schizophrenia, all included studies were categorized into 3 clinical subgroups based on the mean duration of illness reported in each publication State I: First-episode schizophrenia (FES) subgroup (N = 55 studies); State II: Schizophrenia with a mean illness duration less than or equal to 10 years (N = 58 studies); and State III: Schizophrenia with a mean illness duration more than 10 years (N = 70 studies) according to reported mean illness duration in each publication (figure 1C). We conducted 2 meta-analytic classes (all-effects and VBMn analyses) across 3 clinical subgroups, each subgroup followed the minimum number of meta-analyses (N > 17) and almost an equal number of criteria.[47] In addition to the clinical subgroups above, we also considered attempting other subgrouping strategies (eg, symptoms subgroup, treatment-resistant subgroup), however, there were insufficient studies for further analysis.

Activation Likelihood Estimation

The ALE[34,47,48] meta-analyses were conducted using the GingerALE software package (version 3.0.2, *brainmap.org/ale*) (more details are given in supplementary methods). All coordinates were converted to Montreal Neurological Institute (MNI) standard space. All results were set at a cluster-level family-wise error inference threshold of P < .05 and a cluster-forming threshold of P < .001.[47,49–51]

Meta-Regressions

To explore the relationship between clinical symptoms and multimodal neuroimaging features in schizophrenia, we conducted meta-regressions using the Seed-based mapping (SDM) software[52] (sdm_v6.21: https://www.sdmproject.com/software/). Different from the ALE, the SDM recreates the effect sizes (Hedge's d) for each included study based on their respective coordinates, statistical values, and sample sizes.[53] The SDM also combines, compares, and synthesizes findings from multiple studies by using meta-regression analysis while adjusting for the effect of available covariates on the response variable.[54] In the current study, the potential regressors included clinical symptoms (positive, negative, general, and total symptoms in PANSS, mean illness duration, mean CPZ), demographic variables (mean age of patients, the ratio of male to all patients and the proportion of medicated patients in each study) (more details are given in supplementary table S3). For the sake of comparison, we performed a transformation of the scales, converting the scale for assessment of positive symptoms and the scale for the assessment of negative symptoms into PANSS values using the formula of Van Erp et al.[55] To minimize the detection of spurious findings, the threshold for all meta-regression analyses was set at P < .0005.[52]

Spatial Correlation Analysis With Neurotransmitter Data

To assess potential neurotransmitter and genetics drivers of multimodal convergence regions, spatial correlation analyses between molecular/genetic structure and the results of all effects were performed in all patients and the FES subgroup. The subgroup analysis of FES offered us an opportunity to avoid the influence of antipsychotic treatment, which in turn validated whether our findings of molecular architecture and transcriptomics in all patients' all-effects were repeatable.

First, the Spearman correlation analyses were conducted to investigate the relationship between neurotransmitters and these identified reliable convergences (figure 1D). The neurotransmitter data came from the open positron emission tomography (PET) and single-photon emission computed tomography (SPECT) data from the prior in vivo molecular imaging studies (N = 29 maps)[40] (https://github.com/netneurolab/hansen_receptors/tree/main). Detailed methods are shown in supplementary methods. Given the spatial autocorrelation for each calculation, we conducted permutation tests (5000 times)[56] to obtain a null distribution of the correlation coefficients. The P-value was determined by empirically observing the true spatial similarity values compared to the null distribution. The significance level was set at P < .05.

Correlation Analysis With Gene Expression Data

Second, we performed PLSR analyses using the AHBA transcriptomics dataset with gene expression measurements (N = 6 donors, mean age: 42.5 years, range: 24–57 years, 5 male, and 1 female)[41] (http://human.brain-map.org) (figure 1E) to examine the relationship between multimodal convergences and transcriptome signatures. First, the AHBA gene expression microarray data of brain tissue samples were preprocessed according to the default recommended 6-step processing pipeline[23] (https://github.com/BMHLab/AHBAprocessing) (detailed preprocessing methods are provided in supplementary methods). Then, the tissue samples from the AHBA were mapped to the 246 ROIs atlas of Jiang et al.[57] Considering the lack of brain tissue samples in the right hemisphere of 4 donors, only data in the left hemisphere were included. The application of this preprocessing resulted in 123 brain regions × 10027 gene expression matrix that could be used for subsequent analyses.

Next, used the PLSR analyses to examine the relationship between multimodal convergences and transcriptional signatures for all 10 027 genes. First, we assigned the ALE value map (no thresholding) of all-effects analysis to the 246 ROIs atlas of the brain, as in the previous correlation analysis with PET/SPECT data. This processing produced a 123 brain regions × 1 ALE value matrix in the left hemisphere for further analyses. Then, PLSR was used to explore the relationship between gene expression profiles and the ALE value. A growing number of studies have confirmed that gene expression profiles could be used as predictor variables that can explain most of the variance in neuroimaging changes (response variables).[22,58] In our PLSR model, the gene expression matrix (123 × 10027) was entered as predictor variables, and the ALE value matrix of all effects (123 × 1) was entered as response variables. The first component of PLSR (PLSR1) is considered the linear combination of the gene expression values that are most strongly associated with schizophrenia-related multimodal neuroimage abnormalities. Permutation tests (5000 times) were conducted to assess the significance of the PLSR result as a function of the number of components included.[56,59] For PLSR1, the bootstrapping method was used to estimate the error of each gene's weight, and then the weight of each gene was divided by its estimated standard error to obtain the corrected weight as the Z scores.[60] We ranked the genes based on Z scores, which represent their contribution to PLSR1. The top-ranked related genes were extracted for further analysis, including up- and downregulated significance (false discovery rate [FDR], $P < .05$) by the t-test.

Subsequently, we identified 52 schizophrenia-related genes from the in situ hybridization (ISH) gene expression database as the schizophrenia disease-related genes list[61] (see Supplementary table S6). Then, we assessed the contribution of the schizophrenia-related genes using the overlapping genes from the top-ranked related genes (corrected by FDR, $P < .05$) in PLSR1 and 52 schizophrenia-related genes in ISH. Spearman correlation analyses were conducted to estimate the relationship between the overlapped genes and the ALE value of the all-effects meta-analysis in the left hemisphere. Considering spatial autocorrelation, we conducted permutation tests (5000 times)[56] to obtain a null distribution of correlation coefficients for each overlapped gene and ALE-value map. The P-value was determined by empirically observing true spatial similarity values compared to the null distribution. The significance level was set at $P < .05$.

Finally, we introduced a novel gene enrichment analysis method called KEGG Orthology-Based Annotation System (KOBAS) (http://kobas.cbi.pku.edu.cn) to better understand the underlying biological functions of related genes (figure 1F). KOBAS introduced a novel machine learning-based approach named Combined Gene set analysis incorporating Prioritization and Sensitivity. This incorporated 7 functional class scoring tools and 2 pathway topology tools into a single ensemble score and intelligently prioritized the relevant biological pathways.[62] The ordered genes were uploaded to version 3.0 of KOBAS (http://bioinfo.org/kobas) for gene-list enrichment analysis, and the enrichment significance threshold was set at $P < .05$ with FDR correction.

Results

A total of 197 studies with 203 individual experiments, comprising 10613 patients with schizophrenia and 10461 HCs were included through rigorous screening, which incorporated 26 ALFF/fALFF experiments, 14 ReHo experiments, 8 rCBF experiments, and 155 VBM experiments (figure 1A). The list of all studies included in the meta-analysis is shown in Supplementary table S1, S2, and S3.

Convergent Abnormality in Meta-Analysis: All-Effects Analysis

Six regional clusters were identified as demonstrating schizophrenia-related convergent abnormalities in structural and functional disease effects during the all-effects analysis of 2447 foci from 197 publications. The major regions comprising these clusters included the frontal lobe, superior temporal gyrus (STG), insula, anterior cingulum cortex, striatum, thalamus, and hippocampus, as detailed in figure 2A and table 1. According to the independent-modal convergence effect of 4 single-class-specific groups, increased functional and structural features were observed in the striatum, and the reductions in structural features were found in extensive cortical-subcortical gray matter, whereas functional reduction was only found in the orbital frontal cortex (see figure 2B and Supplementary table S4).

Convergent Abnormality in Meta-Analysis: Across the Clinical Duration Subgroup Analysis

We found that the convergence of illness duration-dependent all-effects and VBMn-effects showed highly similar patterns as the disease progressed (figure 3, Supplementary table S5 and figure S2). *First*, consistent abnormal brain regions identified within the FES clinical subgroup mainly included the striatum, thalamus, and STG. *Second*, with the progression of the disease, aberrant areas were found mainly in the anterior insula, STG, orbital frontal lobe, hippocampus, and amygdala in the schizophrenia subgroup with a mean illness duration of fewer than 10 years, in which the cortical core networks such as the salience network and frontoparietal executive network were included. *Finally*, as the disease progressed furthermore, functional and structural alterations were found to extend to the extensive insula, STG, frontal lobe, hippocampus, amygdala, and thalamus region in the schizophrenia subgroup with a mean illness duration of more than 10 years.

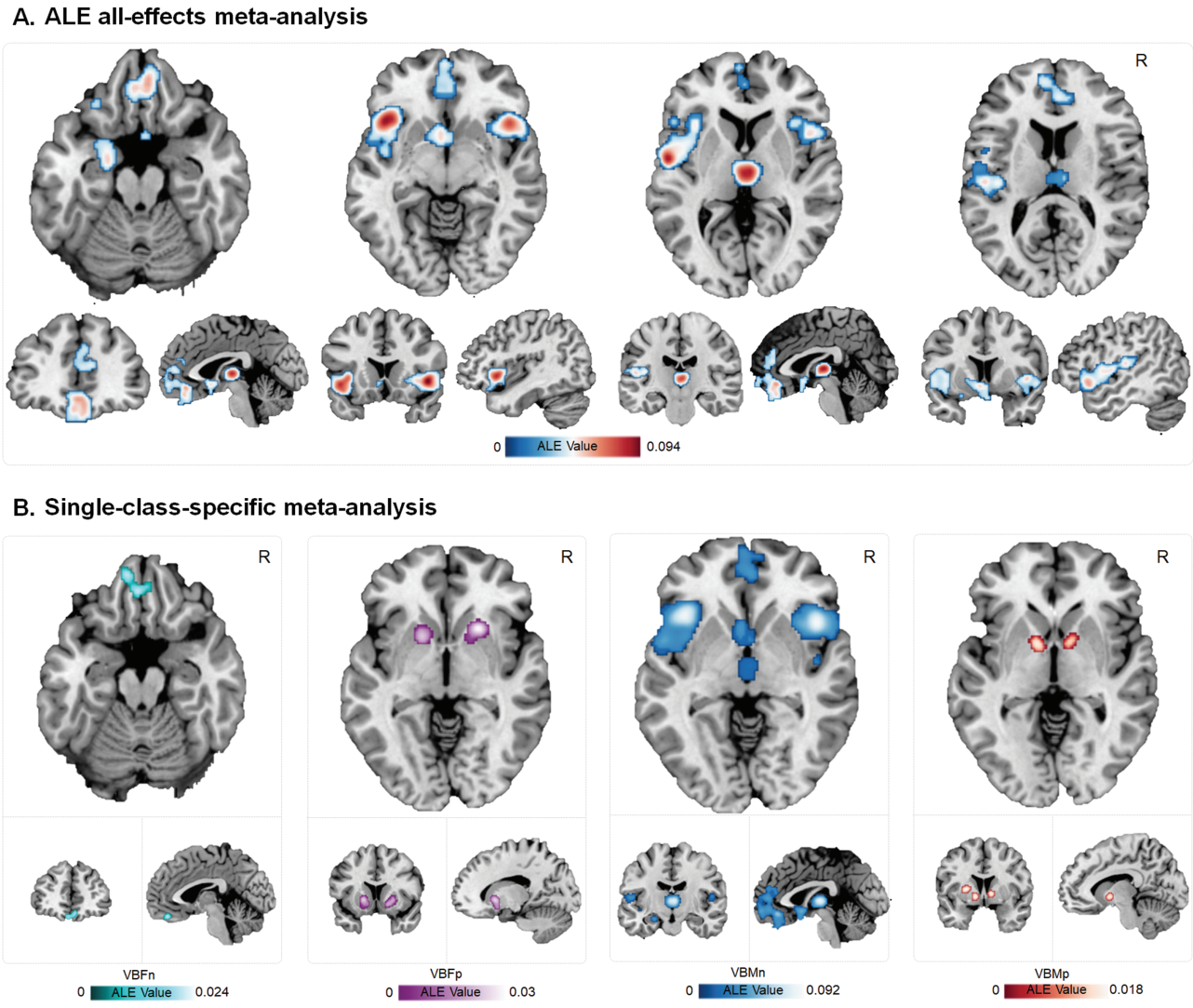

Fig. 2. Abnormal regions identified in an all-effects meta-analysis and 4 types of single-class-specific meta-analyses of neuroimaging studies in schizophrenia. (A) The all-effects meta-analytic results of brain structural and functional abnormalities were identified in schizophrenia by combining all selected studies. (B) The meta-analytic results of altered positive/negative function and structure by 4 single-modality-specific ALE-analysis separately in schizophrenia. Decreased voxel-based function (VBFn) in patients with schizophrenia compared with healthy controls (HCs) is shown in green in the left superior orbital frontal gyrus and rectus. Increased function (VBFp) is shown in purple in the bilateral putamen. Results in blue indicate regions, which included the insula, frontotemporal lobe, ACC and thalamus, hippocampus, and amygdala, showed decreased gray matter (VBMn) from the voxel-based morphometry (VBM) meta-analysis in schizophrenia, while red indicated increased gray matter (VBMp) in pallidum and putamen relative to HCs. The color bar represents the ALE value of any given voxel, that is, its degree of nonrandom convergence in activation between experiments. All clusters are overlaid onto standardized Montreal Neurological Institute (MNI) templates (Colin27_T1_seg_MNI.nii) anatomical brain from GingerALE's website.

Meta-Regressions

The meta-regression analyses revealed that the multimodal abnormality of the right cuneus cortex was positively correlated with the mean negative symptoms of PANSS in schizophrenia (SDM-Z = 3.867, P < .000). The mean total symptoms of PANSS were negatively associated with the convergence of structure–function in right middle frontal gyrus (SDM-Z = −3.463, P = .000). The structural–functional aberrance of the left putamen in schizophrenia was shown to be modulated by age (SDM-Z = −3.353, P = .000) (see supplementary figure S3). No significant linear associations were observed in positive and general symptoms of PANSS, mean illness duration, mean CPZ, the ratio of male to all patients, and the proportion of medicated patients.

Convergent Abnormalities Linked With Molecular Architecture and Transcriptomics: All-Effects Across All Patients

In the correlation analysis between neurotransmitters/genetics and a convergent pattern of functional and structural co-localization across all schizophrenic

Table 1. Regions Demonstrating Abnormality in the All-Effects Meta-Analysis of Neuroimaging Studies in Schizophrenia

Clusters	Cluster Voxels	Side	Brain Regions	Region Voxels	Peak Voxel MNI Coordinates[a]			ALE Value	*Z* Score
					x	y	z		
Cluster 1	2029	L	Insula	571	−42	20	−8	0.093	7.84
		L	Superior temporal gyrus	425					
		L	Orbital inferior frontal gyrus	329					
		L	Rolandic operculum	266					
		L	Superior temporal pole	211					
		L	Triangular inferior frontal gyrus	100					
		L	Heschl	78					
		L	Opercular inferior frontal gyrus	49					
Cluster 2	1263	R	Rectus	237	0	38	−14	0.064	5.84
		L	Orbital medial frontal gyrus	235					
		L	Rectus	201					
		R	Anterior cingulum cortex	169					
		R	Orbital medial frontal gyrus	148					
		L	Medial superior frontal gyrus	129					
		L	Anterior cingulum cortex	111					
		R	Orbital superior frontal gyrus	33					
Cluster 3	764	R	Insula	425	46	14	−4	0.094	7.90
		R	Superior temporal pole	113					
		R	Opercular inferior frontal gyrus	92					
		R	Orbital inferior frontal gyrus	88					
		R	Putamen	46					
Cluster 4	348	R	Thalamus	192	4	−16	4	0.090	7.63
		L	Thalamus	156					
Cluster 5	140	L	Caudate	73	−4	10	−8	0.053	4.99
		L	Olfactory	38					
		L	Putamen	29					
Cluster 6	237	L	Parahippocampal gyrus	78	−20	−6	−22	0.054	5.07
		L	Amygdala	90					
		L	Hippocampus	69					

[a]indicates the Montreal Neurological Institute Coordinate of the voxel with size = 2 × 2 × 2mm^3. All brain regions >23 voxels. ALE, activation likelihood estimation; MNI, Montreal Neurological Institute; L, left hemisphere; R, right hemisphere.

patients, first, we found that the identified disease-related aberrant regions were significantly positively correlated with dopamine receptor D2 (D2, indexed by [^{18}F]FALLYPRIDE PET; $r_{(spear)}$ = 0.30, $P_{(permuted)}$ = −.021) and dopamine transporter (DAT, indexed by [^{123}I] FP-CIT SPECT; $r_{(spear)}$ = 0.25, $P_{(permuted)}$ = .049), noradrenaline transporter (NAT, indexed by [^{11}C]MRB PET; $r_{(spear)}$ = 0.37, $P_{(permuted)}$ = .006), negatively correlated with the 5-hydroxytryptamine receptor 4 (5-HT4, indexed by [^{11}C]SB207145 PET; $r_{(spear)}$ = −0.32, $P_{(permuted)}$ = .018), and cannabinoid receptor type 1 (CB1, indexed by [^{18}F] FMPEP-D2 PET; $r_{(spear)}$ = −0.24, $P_{(permuted)}$ = .049) (see figure 4A). To ensure the stability of the correlations, we also calculated the correlation at the whole-brain level and found similar results (supplementary figure S4).

Second, we found the PLSR1 explained 31.7% of the variance in the spatial convergent abnormalities of multimodal neuroimaging. And we found 25 overlapping genes between our identified schizophrenia-related gene list and 52 schizophrenic disease-related genes from ISH (supplementary table S6), including 3 positive correlations and 22 negative correlations (figure 4B). Among them, the gene with the largest positive correlation was HTR2C ($r_{(spear)}$ = 0.56, $P_{(permuted)}$ < .0001), and the gene with the largest negative correlation was apolipoprotein L2 (APOL2) ($r_{(spear)}$ = −0.60, $P_{(permuted)}$ < .0001) (figure 4B).

Finally, pathway analyses based on KOBAS gene ontology categories (total 3205 genes, FDR, P < .05) revealed that these genes were significantly (FDR-corrected, all P < .05) enriched for "Parkinson's disease et al.," "Insulin signal pathway," "Internal secretion," "Synapse" and "Biosynthesis and metabolism of amino acids" (for details see figure 4C).

In addition, comparing the neurotransmitter/genetic correlation analyses in all patients and FES groups (see supplementary results and figure S5), we found the shared neurotransmitters DAT and 5-HT4, indicating that dopamine and serotonin systems were involved in the whole pathophysiological process of schizophrenia.[32,63] The schizophrenia-related genes were largely overlapped and mostly associated with synaptic function. Further gene enrichment analyses of both groups showed that multiple synaptic pathways, amino acids, and derivatives were involved in

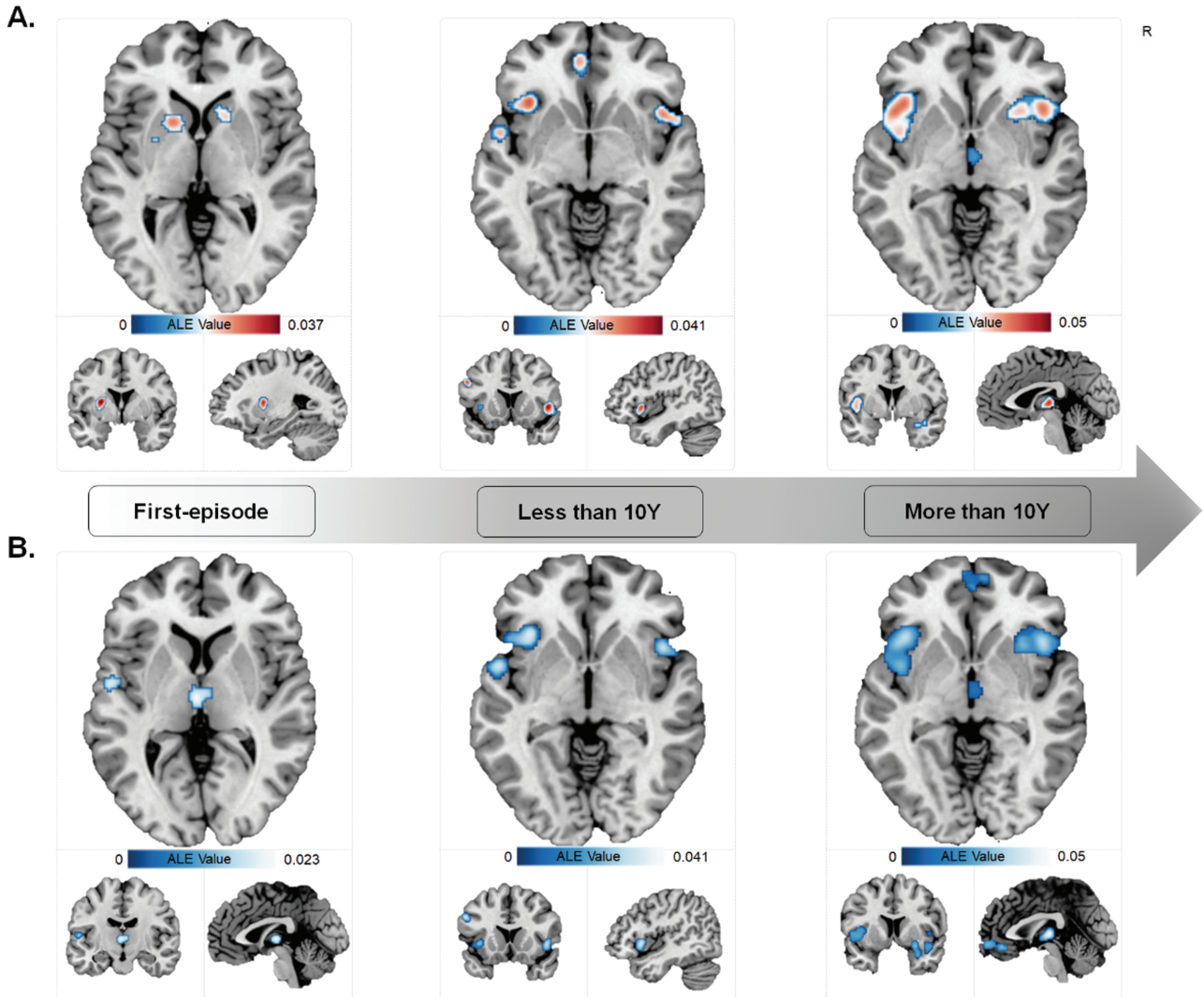

Fig. 3. Abnormal regions were identified in 3 clinical subgroups, based on the first episode and mean duration of illness of patients with schizophrenia reported in each publication. (A) The all-effects meta-analytic results of brain structural-functional abnormalities in clinical subgroups. (B) The mean illness duration-specific gray matter morphometry reductions (VBMn) in patients with schizophrenia relative to healthy controls. Taken together, with the emergence and progression of schizophrenia disease, cerebral abnormalities in the structure–function present a progression pattern: A line from the striatum to cortical core networks to extensive cortical and subcortical regions. The color bar represents the activation likelihood estimation (ALE) value of any given voxel, that is, its degree of nonrandom convergence in activation between experiments. All clusters are overlaid onto standardized Montreal Neurological Institute (MNI) templates (Colin27_T1_seg_MNI.nii) anatomical brain from GingerALE's website.

the neurobiological pathophysiology of schizophrenia, particularly dopaminergic, glutamatergic, GABAergic, and serotonergic pathways.

Discussion

To better understand the psychopathology of schizophrenia, we have developed a new research framework that combines multimodal neuroimaging meta-analysis and genetic/molecular architecture to identify reliable multidimensional biomarkers. First, a multimodal meta-analysis identified that brain regions of significant convergence in schizophrenia were mainly distributed in the insula, frontotemporal, anterior cingulate, striatum, thalamus, and hippocampus. Second, we found an evolutionary pattern of cerebral abnormalities: A line from the striatum to cortical core networks to the extensive cortical and subcortical areas following schizophrenic disease progression. Third, the association analysis of molecular neurotransmitter and brain-wide gene expression recognized that the spatial distribution of multiple neurobiological systems including dopamine and serotonin would recapitulate these consistent patterns of multimodal neuroimaging abnormalities in the schizophrenic brain. Overall, these findings revealed the multidimensional abnormal signatures in schizophrenia and

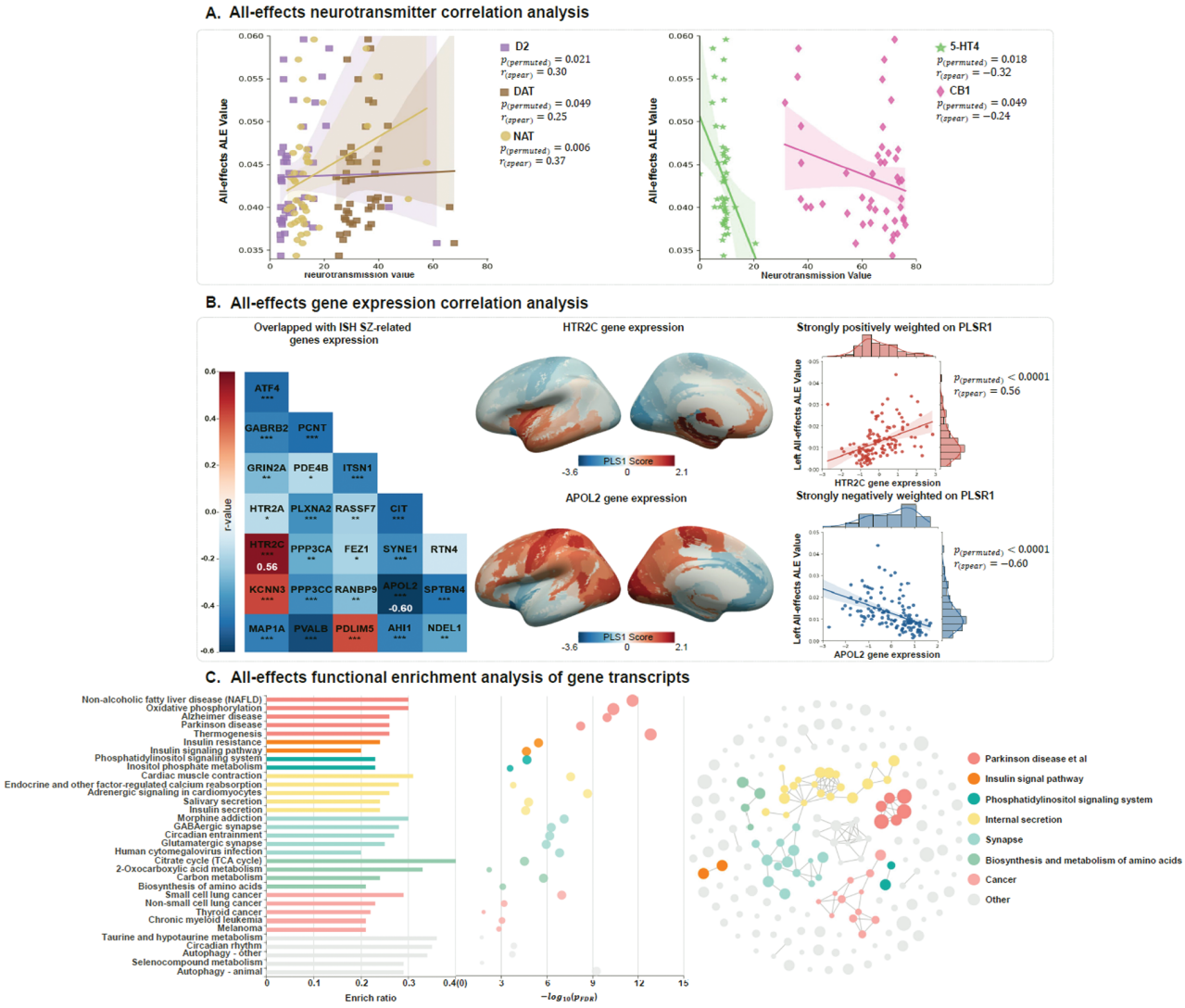

Fig. 4. Molecular architecture and gene transcriptional profiles related to the identified convergent abnormalities of structure-function in schizophrenia. (A) The significant correlations between neurotransmitters and a convergent pattern of functional and structural colocalization in schizophrenia. Identified schizophrenia-related aberrant regions were significantly positively correlated with dopamine receptor D2, dopamine transporter (DAT), and noradrenaline transporter (NAT), negatively correlated with the 5-hydroxytryptamine receptor 4 (5-HT4) and cannabinoid receptor type 1 (CB1). (B) The schizophrenia-related gene expression was correlated with identified aberrant distribution of function–structure in schizophrenia all-effects meta-analysis. The left panel showed the overlapped genes between our identified schizophrenia-related genes and the schizophrenia-related genes from in situ hybridization gene expression database. The blue/red indicated the negative/positive associations with the aberrant convergence of function–structure in schizophrenia, respectively. The right panel showed the gene of strongly positively weighted on PLSR1 (HTR2C) was associated positively with identified left ALE-value of all-effects meta-analysis ($r_{(spear)} = 0.56$, $p_{(permuted)} < .0001$), whereas the gene of strongly negatively weighted on PLSR1 (APOL2) was associated negatively with identified left ALE-value of all-effects meta-analysis. All *P*-values were performed permutation tests 5000 times, $P < .05$. (C) The KOBAS enrichment analysis of schizophrenia-related gene expressions. The left presents different enriched ontology terms for PLSR1 up- and downregulated significant genes (FDR, $P < .05$). The right shows the view of circular function map (enriched *P*-value <.05, FDR, correlation >0.35 and top $N = 7$). The color of the bar and the circle represent different clusters of terms (ie, nodes in the same color belong to the same cluster). The length of the bar represents the enrich ratio, which is calculated as the proportional of the number of input genes and the number of background genes. The node size represents 6 levels of *P*-value, from small to large: [.05,1), [.01,.05), [.001,.01), [.0001,.001), [1e-10, .0001), and [0,1e-10). The edge means correlations larger than the predefined threshold of 0.35.

established a novel link between the robust convergence of cerebral structure–function and neurotransmitters/genetics in schizophrenia, advancing an integrative understanding of psychopathology in schizophrenia.

Identified Convergence of Neuroimaging Abnormalities in Schizophrenia

The conjoint and independent multimodal meta-analyses identified reliable convergence patterns of brain

abnormalities in schizophrenia, which were mainly distributed in the frontotemporal cortex, insula, anterior cingulum cortex, striatum, and thalamus regions. Using a spatially unbiased approach, the pattern integrated previous large-scale abnormal models from various schizophrenia studies, such as circuit abnormalities in the cortico-thalamic-basal ganglia,[64–66] cortico-striatum dysconnectivity,[67,68] and salience-insula dysfunction.[69,70] Additionally, meta-regression analysis revealed that multimodal abnormalities in the right cuneus cortex and the right middle frontal gyrus were associated with the severity of clinical symptoms in schizophrenia. These findings support the hypothesis that schizophrenia is a multifaceted disorder that is associated with functional and structural specific alterations in multiple regions and circuits, thus leading to various clinical presentations.[39,71,72] Notably, the analysis for all-effects produces a statistical summary across all functional and structural studies, rather than that these aberrant brain regions of structure–function were observed in the same patient. Therefore, the convergence of spatial patterns in widespread cortical-subcortical structures implies a characteristic alteration in schizophrenia and reveals disease-specific effects of structural and functional co-localization, providing a basis for understanding the mechanisms and refining the target of intervention therapy in schizophrenia.

Furthermore, we identified the evolutionary pattern of cerebral abnormalities: a line from the striatum to cortical core networks to extensive cortical and subcortical areas as the schizophrenic disease progresses, extending previous single-modal research to multimodality.[14,21,39,73,74] The illness duration-specific convergence in brain regions demonstrated that schizophrenia was associated with progressive abnormalities. Subcortical regions, including the striatum and thalamus, were important during the early course, which could account for the evolution of schizophrenic disease dynamics.[21,74] However, causal relationships between brain alterations and illness duration, especially in chronically schizophrenic patients, should be interpreted with caution given the effects of age and antipsychotics, and treatment-related epiphenomena.[75,76] Our meta-regression analysis also confirmed that the multimodal abnormalities of putamen were indeed modulated by patient age, although it was only an indirect result and should be interpreted with caution. Notwithstanding, our findings still provide preliminary neuroimaging evidence for clarifying neurodegenerative models to advance schizophrenia research, suggesting that it is necessary for further longitudinal exploration.

Molecular Architecture Linked to Convergent Abnormalities in Schizophrenia

The widely accepted and classic dopamine hypothesis suggested that hyperactive dopaminergic function leads to the positive symptoms of schizophrenia.[77] The latest theory further indicates that dopamine hyperactivity in the dopamine pathway is a downstream consequence of hypofunctional N-methyl-d-aspartate glutamate receptors on GABAergic interneurons in the prefrontal cortex and/or serotonin hyperactivity at 5-HT2A receptors on glutamate neurons in the cortex.[63] Our findings were consistent with dopamine theory that the aberrant convergent patterns of cortical-subcortical regions in schizophrenia were related to dopamine receptor/transporter (D2/DAT) and serotonin receptor (5-HT4). We also found similar results in the FES subgroup, which in turn suggested that our findings in all patients were robust and unaffected by the effects of antipsychotic therapies, which also indirectly suggested that the disturbance of dopaminergic and serotonergic functions was maintained since onset and throughout the whole course of schizophrenia.[78,79]

In addition, the noradrenaline transporter (NAT), another major neuromodulator of brain function and neural gain tightly interacting with dopamine,[80] influences psychiatric and cognitive symptoms in schizophrenia through synaptic mechanisms, ie, regulation of Ca^{2+} and Ih channels.[81] Evidence from animal and human studies has demonstrated that the dysregulation of cannabinoid receptor 1 (CB1) in multiple brain regions, is involved in the progression of schizophrenia by compromising complex circuits mediating cognition and memory.[82] Thus, our findings and previous studies converge in suggesting that abnormal brain structure–function synergistic with disorganized neurotransmitters (NAT and CB1, also including dopamine and serotonin) are participating in the pathophysiology of schizophrenia. Concerning this interaction in future studies should be helpful for advancing the clinical development of new drugs and therapies.

Transcriptional Profiling Linked to Convergent Abnormalities in Schizophrenia

Schizophrenia-related gene analysis discovered that HTR2C and APOL2 genes contributed to the greatest correlation of multimodal brain abnormalities in all patients. Enriched functional categories further revealed that multiple neurobiological abnormalities, such as synaptic pathways (ie, dopaminergic, glutamatergic, GABAergic, and serotonergic systems), insulin, amino acids, and internal secretion were involved in the disease-related mechanisms of schizophrenia. Especially, the enrichment of Parkinson-related terms showed high significance supporting the high involvement of dopamine in the pathophysiology of schizophrenia.[77] Parkinson's Disease appears owing to the loss of dopamine-producing neurons in the midbrain,[83] which in turn leads to dopamine deficits and changes of other neurotransmitters (glutamate, GABA, serotonin, etc.).[84] Collectively, these findings support the view that schizophrenia is a polygenic disease,[29,30] and most of the genes associated with

schizophrenia are involved in synaptic function,[79] including GABAergic,[85] glutamatergic, and dopaminergic synapse.[32] Highly similar transcriptome results were found in the FES subgroup, which also in turn strongly confirmed the stability of the all-patient all-effects analysis.

The other nonsynaptic pathways identified (ie, "insulin signaling pathway," "biosynthesis and metabolism of amino acids" and "internal secretion") may provide supplementary evidence for the involvement of other factors in the pathophysiology of schizophrenia.[86–88] The development of central insulin resistance is related to alterations in dopaminergic reward systems and homeostatic signals affecting body weight, glucose metabolism, food intake, and cognitive performance.[87] Amino acids and derivatives are involved in the biosynthesis and downstream effects of abundant neurotransmitters.[86] Thus, this could reflect important implications for future biomarker discovery efforts and contribute to personalized treatment strategies based on subject stratification.

Taken together, the neurotransmitter correlation and gene enrichment analyses revealed that the abnormalities of multiple brain regions were closely related to multiple neurobiological processes, among which dopaminergic, glutamatergic, serotonergic, and GABAergic systems may contribute significantly to the generation of schizophrenia symptoms. These findings converge strongly with previous etiological evidence of schizophrenia from treatment, postmortem, neuroimaging, and animal studies, that suggest at least 3 interacting pathologic mechanisms: dopaminergic dysregulation, disturbed glutamatergic neurotransmission, GABAergic dysfunction, and increased proinflammatory status in the brain.[32,89,90] Our results provide a robust multimodal neuroimaging signature bridging the genetic and neurotransmitter aspects, which collectively contribute to the pathophysiology of schizophrenia.

Limitations

Some limitations of this study should be acknowledged while also suggesting recommendations for future research considerations. First, we were unable to avoid the influence of medication because the dose information was not always available, although most publications in our FES subgroup reported the patients were drug-naïve. Second, the clinical patient subgroups were largely limited to mean illness duration in our definition because the illness duration information of each patient was not available. Other clinical subgroups, including specific symptoms (eg, hallucination/nonhallucination subgroup, negative/positive symptoms subgroup), the severity of disease (treatment-resistant/nonresistant), and comorbid conditions, did not satisfy the criterion of minimum experiments for meta-analysis,[47] which warrants further investigation. Third, the progression line we found should be treated as preliminary results of a cross-sectional study, and more longitudinal follow-up studies are needed in the future. Fourth, our current study only reveals schizophrenia disease-specific effects of structural and functional co-localization and cannot account for structural and functional causality. Future studies with substantial longitudinal data are needed to further elucidate potential causal relationships between structure and function.

Conclusions

Overall, we proposed a new framework that combines multimodal neuroimaging meta-analysis and genetic/molecular architecture to identify reliable biomarkers of schizophrenia. Combining the currently largest number of functional and structural neuroimaging studies on schizophrenia, we identified reliable spatial convergence patterns and found that the frontotemporal, insula, thalamus, and striatum were the core regions affected by schizophrenia. Furthermore, we provide evidence that schizophrenia is associated with progressive structural and functional abnormalities: A line from the striatum to cortical core networks to extensive cortical and subcortical regions. Then, the significant relationships between robust convergences in neuroimaging abnormalities and genetic/molecular profiles highlight a link among neuroimaging-transcriptome-neurotransmitter, suggesting that schizophrenia is a multidimensional serious mental illness, involving multiple abnormalities in genetics, molecular architecture, brain structure and function. None of them alone play a prominent role in the onset and aggravation of schizophrenia, but interact with each other and jointly contribute to the pathophysiology of the disease. This understanding may lead to novel therapeutic targets and approaches.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin.

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Data Availability

Molecular architecture (Density maps of neurotransmitter receptors and transporters) for the integration of positron emission tomography and single-photon emission computed tomography from the prior vivo molecular imaging studies are available at https://github.com/netneurolab/hansen_receptors/tree/main/data and https://github.com/juryxy/JuSpace. Human brain-wide gene expression samples from the Allen Human Brain Atlas are available at https://human.brain-map.org/static/download. Schizophrenia disease-related genes (N = 52) from in situ hybridization are available at https://human.brain-map.org/ish/search. All data generated or analyzed during the current study are included in the published article (and its Supplementary Materials). The additional information of this study is available from the corresponding author on reasonable request.

Code availability

The Activation Likelihood Estimation meta-analysis software package (GingerALE version 3.0.2) was available on the website (https://brainmap.org/ale). The standardized MNI template (Colin27_T1_seg_MNI.nii) anatomical brain from GingerALE's website (https://brainmap.org/ale). The Seed-based mapping (SDM) software (sdm_v6.21) was available on the website (https://www.sdmproject.com/software/). The code for gene expression analysis can be found at https://github.com/BMHLab/AHBAprocessing. The code for PLSR analysis can be found at https://github.com/SarahMorgan/Morphometric_Similarity_SZ. The KOBAS toolbox of gene enrichment analysis (version 3.0) was available at http://bioinfo.org/kobas. The brain maps were presented using the Mango toolbox (http://ric.uthscsa.edu/mango) and FreeSurfer software (https://surfer.nmr.mgh.harvard.edu/fswiki).

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