Int J Clin Exp Med 2017;10(2):1866-1878
www.ijcem.com /ISSN:1940-5901/IJCEM0042057

Review Article

Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: a multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies

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Received August 30, 2016; Accepted December 14, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: *Objective:* The alteration of neuroimaging endophenotypes in schizophrenic patients and their unaffected relatives might be excellent clinical features for examining the association between neurodevelopmental abnormalities and genetic and environmental risk factors. However, the evidence is inconsistent. We aimed to identify abnormalities in the brain structure and activity of both schizophrenic patients and their unaffected relatives by performing a multimodal meta-analysis. *Methods:* Twelve studies of brain structural magnetic resonance imaging and four of resting-state functional magnetic resonance imaging containing total 432 schizophrenic patients, 744 unaffected relatives, and 548 healthy controls were included in the meta-analyses, which were performed using the AES-SDM software. *Results:* Compared to relatives, patients had decreased gray matter (GM) in left insula (z=-4.544, P=0.00005) and right inferior frontal gyrus (z=-4.354, P=0.00009) but increased in left putamen (z=1.068, P=0.00001). Compared to controls, patients had decreased GM in left insula (z=-5.344, P=0.00002) and right insula (z=-4.258, P=0.00017) but increased in right cerebellum (z=2.459, P=0.00010) and right inferior temporal gyrus (z=2.462, P=0.00006), while relatives had decreased GM in left insula (z=-2.849, P=0.00011), left inferior temporal gyrus (z=-2.480, P=0.00072), and right inferior network (z=-2.404, P=0.00099) and decreased brain activity in left precuneus (z=-1.884, P=0.00019) and right inferior frontal gyrus (z=-1.804, P=0.00023) but increased in left optic radiations (z=1.215, P=0.00003) and left fusiform gyrus (z=1.217, P=0.00002). None of the brain regions contained abnormalities in both structure and activity. The results of the structural magnetic resonance imaging meta-analysis remained widely unchanged in sensitivity and subgroup analyses. *Conclusions:* Patients with schizophrenia and their unaffected relatives share decreased GM in the left insula, which may be crucial for both the development of schizophrenia and the genetic and environmental susceptibility to the disease.

Keywords: Schizophrenia, voxel-based morphometry (VBM), magnetic resonance imaging (MRI), resting-state, meta-analysis

Introduction

Schizophrenia is a severe and highly heritable brain disorder with a prevalence of approximately 1% worldwide [1]. The pathogenic mechanism of schizophrenia is not yet understood, although various studies have been carried out to examine the heritability of schizophrenia. Several studies have revealed that the interaction between genetic and environmental factors plays a key role in the susceptibility to schizophrenia [2]. The heritability of this disorder has been estimated to be approximately 80% [3]; therefore, first-degree relatives of a person with schizophrenia would have a 10-fold higher risk of developing schizophrenia than non-relatives [4]. Twin studies have suggested that the concordance rate of schizophrenia in monozygotic twins (MZ) is more than 50% [5]. Moreover, the unaffected relatives of schizophrenic persons tend to have a number of schizophrenic subclinical symptoms, such as withdrawal, irritability, and oversensitivity [6]. One possible explanation for this finding is that patients with schizophrenia and their unaffected relatives may share common inherited

genetic variants as well as a common environment [7].

Studies of autopsy and magnetic resonance imaging (MRI) in patients with schizophrenia have found abnormalities in brain structure, function, and activity [8-10]. Several recent MRI studies have identified that patients with schizophrenia have brain structural abnormalities in the superior parietal cortices, the gray matter (GM) of temporal and parietal lobes and the white matter of the cingulate/parietal cortex [11-13]. Through functional MRI (fMRI) analyses, several brain regions have been suggested to be associated with specific dysfunctions in patients with schizophrenia, including the anterior cingulate cortex and prefrontal cortex [14, 15]. In addition, resting-state fMRI (rs-fMRI) studies have found changes in the activity of the lingual gyrus, precuneus, and the left parahippocampal gyrus in patients with schizophrenia [16].

The unaffected relatives of schizophrenic patients tend to also have brain abnormalities, likely due to shared genetic risk factors associated with schizophrenia. Previous MRI studies in unaffected relatives have revealed that there may be changes to the GM in the cerebellum [17], insula [18], and the frontotemporal brain regions [19], as well as altered brain activity in the right-side frontal, parietal and temporal regions, compared to healthy controls [20]. A meta-analysis using effect-size signed differential mapping (ES-SDM) showed that the unaffected relatives of schizophrenic patients tend to have abnormalities in a variety of brain regions, decreased GM and hypo-activation of the thalamus, and hyper-activation of the left inferior frontal gyrus/amygdala [21]. However, the association between altered brain structures and changes in brain activity in the context of schizophrenia have not been well clarified.

Early studies using a manually derived region of interest (ROI) method revealed abnormal changes in the brains of both patients with schizophrenia and their unaffected relatives using MRI scans [22, 23]. However, manual ROI, which is a regional analysis and therefore easily affected by the subjectivity of the operator and clinician, may make it difficult to investigate the complex structural and functional changes in neuropsychosis [18]. Voxel-based morphometry (VBM), another method used to analyze brain structure, can be used to assess anatomical abnormalities in the whole brain, thus avoiding the biases that can occur with the ROI method [19, 24]. To examine brain function and activity, task-fMRI and rs-fMRI can be used to identify abnormal brain regions. However, the latter has more advantages, including increased effectiveness, simplicity, and non-invasiveness [25]. VBM structural MRI (s-MRI) and rs-fMRI have been widely used to identify abnormalities of both brain structure and activity in patients with schizophrenia and their unaffected relatives [18, 19, 26, 27].

The neuroimaging endophenotypes of patients with schizophrenia and their unaffected relatives may be useful to examine the association between neurodevelopmental abnormalities and genetic and environmental risk factors of schizophrenia [28]. Any shared neuropathological characteristics between patients with schizophrenia and their unaffected relatives may represent intermediate phenotypes that could be used to further investigate the genetic susceptibility to schizophrenia. In the future, these characteristics may even be used as biomarkers for detecting relatives of schizophrenic patients who may be at high risk of developing schizophrenia. However, current studies using VBM s-MRI or rs-fMRI to examine altered brain structure and activity in schizophrenic patients and their unaffected relatives are inconsistent. Furthermore, few studies have examined both brain anatomical and activity abnormalities together in a same meta-analytic map [19]. Meanwhile, overlapped regions of abnormal structure and activity in patients with schizophrenia and their unaffected relatives have not yet been identified. The present study aimed to conduct a multimodal meta-analysis to identify regions with abnormalities or alterations in the brain structure or activity of patients with schizophrenia and their unaffected relatives. These findings may contribute to the understanding of the association between brain abnormalities and the pathogenesis of schizophrenia.

Materials and methods

Study design

The study was designed using a multimodal meta-analysis based on clinical data collected

from previous case-control trials of s-MRI or rs-fMRI with regard to changes in the GM and brain activity of patients with schizophrenia, as well as their unaffected relatives. Two researchers independently reviewed the literature and selected studies to use in the meta-analysis. Any disagreements were resolved through a group discussion.

Searching strategies

The literature searches were performed in related databases including PubMed, Medline, Web of Knowledge, Science Direct, and Scopus before August 2015. The following search terms were used: "schizophrenia", "voxel", "MRI/fMRI", "resting-state", "regional homogeneity/ReHo", "amplitude of low frequency fluctuation/ALFF", and "relative/sibling/twin". Publications from conferences, monographs, or reference lists in identified studies were also regarded as potential sources to be included in the meta-analysis.

Inclusion and exclusion criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29], the following criteria were used for inclusion in the meta-analysis: 1) original publications in a peer-reviewed journal, conference or monograph; 2) whole-brain analyses was used in s-MRI or rs-fMRI studies; 3) studies included a comparison of GM or brain activity between patients with schizophrenia and their unaffected relatives or between relatives and healthy controls; 4) the coordinates (either Talairach or Montreal Neurologic Institute) of altered brain regions were detailed; and 5) the publication was in English. In addition, the following studies were excluded: 1) ROI or small volume correction (SVC) approaches; 2) studies not performed using s-MRI or rs-fMRI (eg. PET, DTI, and EEG); and 3) studies in which the comparisons were only between patients with schizophrenia and healthy controls. Two researchers examined the abstract or full text of all searched articles to find studies that fit the above criteria. When multiple studies used the same patient cohort, the one with the largest sample size was selected.

Data extraction

Two researchers independently exacted the data from the included studies. The general characteristics of each study, including the first author, year of publication, study population, sample size, medication use, tesla of MRI, image package, full width half maximum (FWHM), stereotactic space of the coordinates, and the threshold, were extracted as the basic data. Furthermore, the voxel-based data were also obtained. This included the *t/z* values of statistically significant differences in GM or brain activity between patients with schizophrenia and their unaffected relatives or between relatives of schizophrenic patients and healthy controls, as well as between patients with schizophrenia and healthy controls. Any missing data were acquired from the corresponding authors of the study by e-mail. If the missing data could not be acquired, the papers should be excluded. Any disagreements about the data were resolved through group discussions with consensus. All of the data were checked for internal consistency.

Multimodal meta-analysis

The meta-analyses of both the s-MRI and rs-fMRI studies were performed using AES-SDM, which has been used previously in meta-analyses in several neuropsychiatric disorders including depression [30], obsessive-compulsive disorder [31], and schizophrenia [21]. AES-SDM software is a voxel-based meta-analytic approach that allows for the use of reported peak coordinates of structure or activity difference in whole brain studies [32]. The SDM method has been described previously [33].

In total, six analyses were performed: 1) GM morphometric differences between patients with schizophrenia and their unaffected relatives in whole brain s-MRI studies; 2) morphometric differences in GM between relatives of schizophrenic patients and healthy controls in whole-brain s-MRI studies; 3) morphometric differences in GM between patients with schizophrenia and healthy controls in whole-brain s-MRI studies; 4) brain activity differences between relatives of patients and healthy controls in whole-brain rs-fMRI studies; 5) multimodal meta-analysis methods using AES-SDM were performed to examine the consistent or overlapping regions with both structural and activity abnormalities from the results of both 2 and 4; and 6) sensitivity and subgroup analyses were performed in the s-MRI meta-

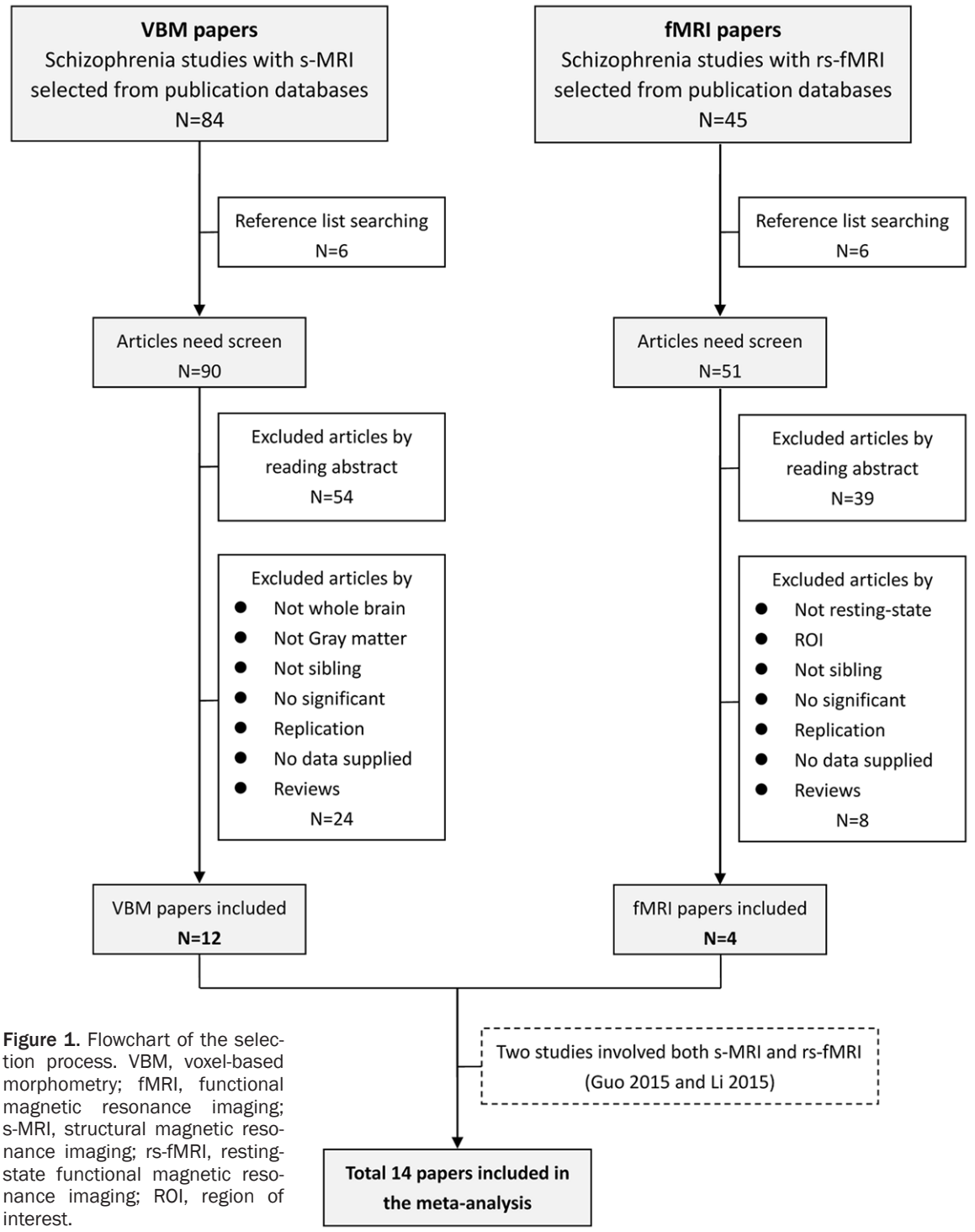

Figure 1. Flowchart of the selection process. VBM, voxel-based morphometry; fMRI, functional magnetic resonance imaging; s-MRI, structural magnetic resonance imaging; rs-fMRI, resting-state functional magnetic resonance imaging; ROI, region of interest.

analysis to control for possible methodological differences and heterogeneity (eg. population, relative degrees, medication usage, and threshold setting) of the included studies.

Researchers YN performed the meta-analyses. The main threshold was set at uncorrected P=0.005 (voxel level) with a z score > 1 (peak height) and cluster extent ≥10 voxels based on a study by Radua et al. [33], which found that 0.005 was the appropriate threshold for balancing sensitivity and specificity. The default settings in the AES-SDM software were used for other parameters.

Table 1. General characteristic of the included studies for meta-analysis of structural MRI

Author	Year	Population	No. of Patients	No. of Relatives	No. of Controls	First-episode	Medicine	Tesla	Imaging package	FWHM (mm)	Referential	Threshold
Marcelis [17]	2003	Netherland	31	32 (first-degree)	27	No	Yes	1.5	BAMM	4.2	Tal	Uncorrected
Hulshoff Pol [34]	2006	Netherland	11	11 (monozygotic twin) 11 (dizygotic twin)	-	No	Yes	1.5	Not Stated	4	Tal	Corrected
Honea [35]	2008	American	169	213 (Sibling)	212	No	Yes	1.5	SPM 2	6	Mni	Uncorrected
Lui [18]	2009	China	-	10 (first-degree)	10	-	-	3	SPM 2	8	Mni2tal	Corrected
Borgwardt [36]	2010	Switzerland	9	9 (monozygotic twin)	-	No	Yes	1.5	SPM 2	8	Mni	Corrected
Tian [39]	2011	China	-	55 (first-degree)	29	-	-	3	SPM 5	6	Mni	Corrected
Boos [37]	2012	Netherland	155	186 (first-degree)	-	Not Stated	Not Stated	1.5	Not Stated	4	Tal	Corrected
Hu [38]	2013	China	51	45 (Sibling)	59	Yes	No	3	SMP 8	8	Mni	Uncorrected
Guo [40]	2014a	China	-	45 (first-degree)	43	-	-	3	SMP 8	8	Mni	Uncorrected
Guo [19]	2015	China	-	46 (sibling)	46	Not Stated	Not Stated	3	SMP 8	8	Mni	Corrected
Wagshal [26]	2015	American	-	16 (Sibling)	45	Not Stated	Not Stated	3	FSL-VBM 5	Not Stated	Mni	Corrected
Li [28]	2015	China	6	6 (monozygotic twin)	14	No	Yes	3	SMP 8	8	Mni	Corrected

Table 2. General characteristics of the included studies for meta-analysis of resting-state fMRI

Author	Year	Population	No. of Patients	No. of Relatives	No. of Controls	First-episode	Medicine	Tesla	Imaging package	FWHM (mm)	Referential	Threshold
Liao [27]	2012	China	-	13 (first-degree)	13	-	-	1.5	SPM 2	Not Stated	Mni	Uncorrected
Guo [41]	2014b	China	-	46 (sibling)	50	-	-	3	SPM 8	8	Mni	Corrected
Guo [19]	2015	China	-	46 (first-degree)	46	-	-	3	SPM 8	8	Mni	Corrected
Li [28]	2015	China	6	6 (monozygotic twin)	-	No	Yes	3	SMP 8	8	Mni	Corrected

Table 3. Meta-analysis of structural MRI showed gray matter differences in brain regions

Brain region	Peak					Cluster	
	MNI coordinate (X, Y, Z)			SDM-Z	*P*	Voxels	Breakdown (Voxels)
Decreased (Patients < Relatives)							
Left insula	-40	12	-8	-4.544	0.00005	700	L BA48 (285) L BA38 (221) L BA47 (60)
Right inferior frontal gyrus	60	10	14	-4.354	0.00009	621	R BA48 (160) R BA6 (122) R BA45 (112) R BA44 (92) R frontal aslant tract (43)
Increased (Patients > Relatives)							
Left putamen	-26	-2	8	1.068	0.00001	358	L BA48 (223) L striatum (108)
Decreased (Relatives < Controls)							
Left insula	-38	-4	-14	-2.849	0.00011	1089	L BA21 (273) L BA48 (227) L inferior network (114) L BA38 (109) L BA34 (76) L BA20 (18)
Left inferior temporal gyrus	-58	-46	-22	-2.480	0.00072	53	L BA20 (45)
Right inferior network	30	-52	-8	-2.404	0.00099	51	L inferior network (31) R BA37 (14)
Decreased (Patients < Controls)							
Left insula	-46	6	-6	-5.344	0.00002	518	L BA48 (282) L BA38 (149) L temporal pole (58)
Right insula	50	8	-4	-4.258	0.00017	337	R BA48 (208) R BA38 (46) Right insula (25) R temporal pole (14)
Increased (Patients > Controls)							
Right cerebellum	12	-72	-18	2.459	0.00010	197	R BA37 (39) R BA19 (34) R hemispheric lobule VI (33) R BA18 (32)
Right inferior temporal gyrus	46	-26	-22	2.462	0.00006	131	R BA20 (74) R inferior network (17)

Results

Selection of studies

The process of study selection is shown in the flowchart (**Figure 1**). Twelve VBM s-MRI studies and four rs-fMRI studies yielded a sample size of 432 patients with schizophrenia, 744 relatives, and 548 healthy controls. Seven VBM papers [17, 28, 34-38] found significant differences between the GM of patients with schizophrenia and their unaffected relatives, nine papers reported differences between relatives and controls [17-19, 26, 28, 35, 38-40], and four papers reported a difference between patients and controls [17, 28, 35, 38]. In addition, three rs-fMRI papers [19, 27, 41] reported significant differences in brain activity between unaffected relatives and controls, and one paper [28] found differences between patients with schizophrenia and their relatives. Notably, two studies [19, 28] were included in

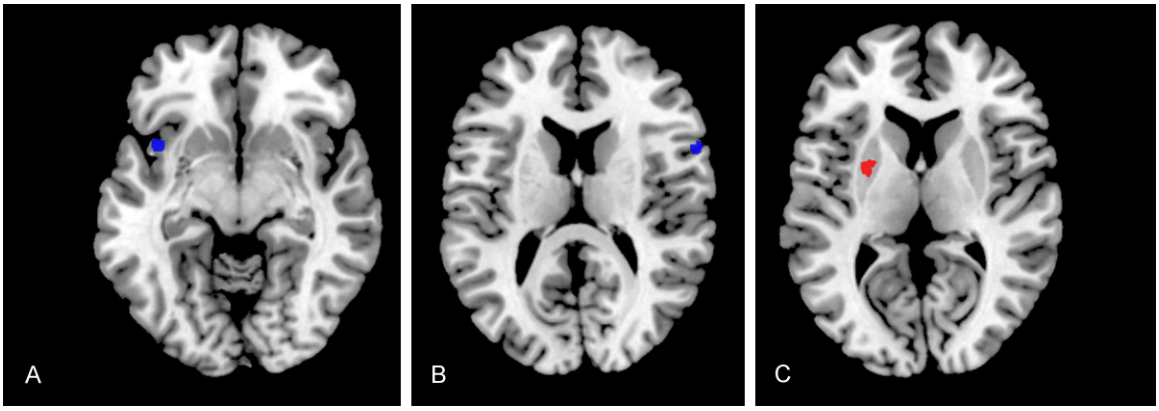

Figure 2. Meta-analysis results of VBM structural MRI studies (patients vs. relatives). A. Left insula; B. Right inferior frontal gyrus; C. Left putamen. Regions highlighted in blue signify decreases in gray matter and red signifies increases in gray matter in patients with schizophrenia compared with their unaffected relatives.

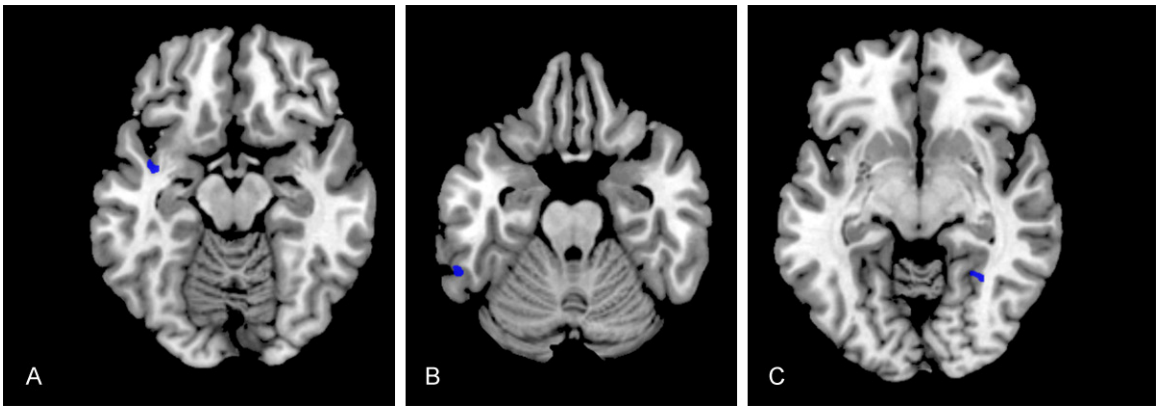

Figure 3. Meta-analysis results of VBM structural MRI studies (relatives vs. controls). A. Left insula; B. Left inferior temporal gyrus; C. Right inferior network. Regions highlighted in blue signify decreases in gray matter in the unaffected relatives of schizophrenic patients compared with healthy controls.

both the VBM and fMRI meta-analyses. The demographic and methodological details of the included studies are described in **Tables 1** and **2**.

Differences in gray matter

First, differences in GM between patients with schizophrenia and their unaffected relatives were examined using a meta-analysis of seven VBM studies. Compared with their relatives, schizophrenic patients had decreased GM in the left insula (z=-4.544, P=0.00005) and right inferior frontal gyrus (z=-4.354, P=0.00009), and increased GM in the left putamen (z=1.068, P=0.00001). **Table 3** and **Figure 2** show the altered GM patterns in the patients.

Next, we examined GM differences between unaffected relatives of schizophrenic patients and healthy controls. We observed that the relatives had decreased GM in the left insula (z=-2.849, P=0.00011), left inferior temporal gyrus (z=-2.480, P=0.00072), and right inferior network (z=-2.404, P=0.00099) compared to healthy controls (**Table 3** and **Figure 3**). The relatives of schizophrenic patients did not have any areas with increased GM compared with the controls.

The third analysis examined GM differences between patients with schizophrenia and healthy controls using a meta-analysis of four VBM studies. Compared with healthy controls, patients with schizophrenia had decreased GM in the left insula (z=-5.344, P=0.00002) and right insula (z=-4.258, P=0.00017) and increased GM in the right cerebellum (z=2.459, P=0.00010) and right inferior temporal gyrus

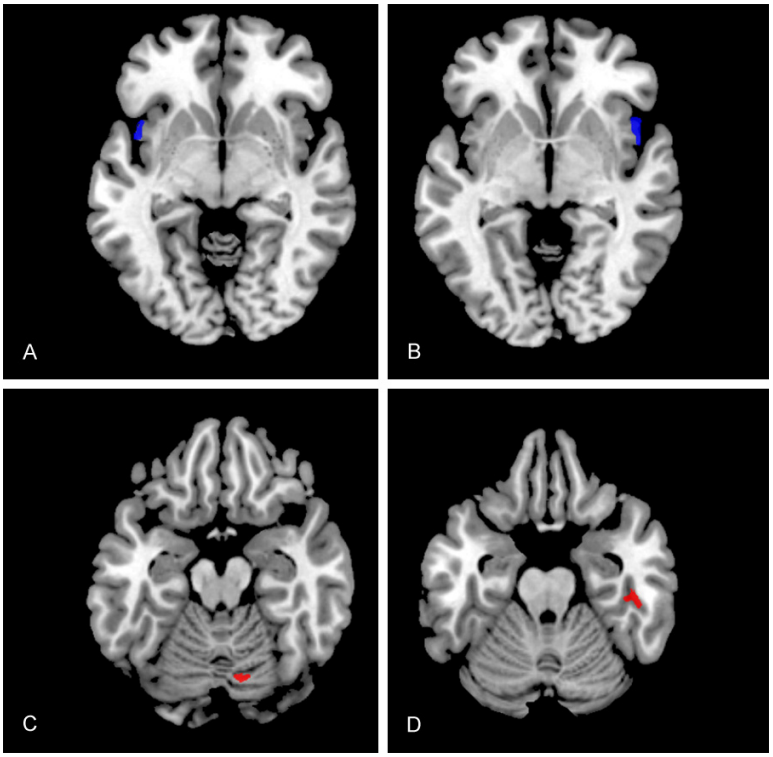

Figure 4. Meta-analysis results of VBM structural MRI studies (patients vs. controls). A. Left insula; B. Right insula; C. Right cerebellum; D. Right inferior temporal gyrus. Regions highlighted in blue signify decreases in gray matter and red signifies increases in gray matter in patients with schizophrenia compared with healthy controls.

(*z*=2.462, *P*=0.00006). **Table 3** and **Figure 4** show the altered GM patterns.

Brain activity differences

In the included studies, brain activity changes were denoted by the differences of regional homogeneity (ReHo) or the amplitude of low frequency fluctuation (ALFF) values between "case and control". The meta-analysis of the resting-state fMRI studies revealed that the brain activity of relatives of schizophrenic patients is decreased in the left precuneus (*z*=-1.884, *P*=0.00019) and right inferior frontal gyrus (*z*=-1.804, *P*=0.00023) but increased in the left optic radiations (*z*=1.215, *P*=0.00003) and left fusiform gyrus (*z*=1.217, *P*=0.00002) compared with healthy controls (**Table 4** and **Figure 5**). Only one study [28] found significant differences between the brain activity of patients with schizophrenia and their relatives, and a meta-analysis of that comparison could not be conducted using the AES-SDM software.

The structural MRI and resting-state fMRI results were then analyzed in a single meta-analytic map using multimodal meta-analysis methods. However, no region was observed that contained both altered GM and brain activity.

Sensitivity and subgroup analyses of structural MRI

For voxel-based s-MRI, sensitivity and subgroup analyses were performed to control for possible methodological differences. An analysis using the jackknife method showed that the significant results were highly reproducible. Furthermore, these results remained widely unchanged even when subgroup analyses were conducted and limited to homogenously methodological groups, such as studies with only twins or only Chinese subjects, or when using a corrected statistical threshold (**Table 5**).

Discussion

In this study, we focused on VBM s-MRI and rs-fMRI studies that examined abnormal levels of GM and brain activity in patients with schizophrenia and their unaffected relatives. While many of these studies contained inconsistent results, we conducted multimodal meta-analyses to reveal overall trends and determine abnormal brain regions in schizophrenic patients and their relatives. These results may contribute to the understanding of the association between brain abnormalities and the pathogenesis of schizophrenia. Furthermore, alterations of the shared neuroimaging endophenotypes in patients with schizophrenia and their unaffected relatives may point to clinical features that would be useful for examining the association between neurodevelopmental abnormalities and the genetic and environmental factors leading to schizophrenia.

We found that patients with schizophrenia had decreased GM in several regions, including the

Table 4. Meta-analysis of resting-state fMRI showed altered activity in brain regions

Brain region	Peak					Cluster	
	MNI coordinate (X, Y, Z)			SDM-Z	*P*	Voxels	Breakdown (Voxels)
Decreased (Relatives < Control)							
Left precuneus	-4	-54	42	-1.884	0.00019	2176	R BA23 (685) L BA23 (611) R cingulum (172) L precuneus (171) L cingulum (148) Corpus callosum (123) R precuneus (67) R BA24 (17) L BA24 (16)
Right inferior frontal gyrus	42	34	26	-1.804	0.00023	947	R BA45 (453) R BA46 (217) Corpus callosum (99) R BA48 (82) R BA44 (41)
Increased (Relatives > Control)							
Left optic radiations	-18	-96	0	1.215	0.00003	513	L BA18 (251) L BA17 (161) L inferior network (57)
Left fusiform gyrus	-24	-38	-16	1.217	0.00002	274	L inferior network (124) L BA37 (75) L BA30 (33) L BA19 (32)

left insula, right inferior frontal gyrus, and right insula, but increased GM in the left putamen and right inferior temporal gyrus compared with their relatives or control subjects. Meanwhile, the relatives of schizophrenic patients had decreased GM in the left insula, left inferior temporal gyrus, and the right inferior network compared with control subjects. These results were widely reproduced in the sensitivity and subgroup analyses, particularly the abnormalities in the left insula. A previous meta-analysis conducted by Glahn et al. showed that patients with schizophrenia had decreased GM in brain regions such as the bilateral insular cortex and anterior cingulate compared with control subjects [42]. Moreover, a recent multimodal meta-analysis found both increases and decreases in the GM density of relatives of schizophrenic patients in a variety of brain regions using VBM [21]. Our results were partially replicated in the above-mentioned meta-analyses; the differences may result from our inclusion of more recent studies, the software that performed the analysis, and the particular settings of the parameters. Notably, the advantage of our meta-analysis was the systematic and comprehensive comparison of three populations: the schizophrenic patients, their relatives, and control subjects. These results may help to identify the role of genetic and environmental factors in the abnormal neurodevelopment that occurs in schizophrenia.

Several studies have demonstrated that the brain structural alterations in schizophrenia are associated with pathological processes occurring during neurodevelopment [43-45]. However, the genotypes and environment of individuals may also affect brain structure during neurodevelopment [46]. Brain structural changes in brain regions, such as the left insula and right inferior frontal gyrus in schizophrenic patients and the left insula and right inferior network in their unaffected relatives, may be important areas to examine for pathophysiologic mechanisms. The present study revealed that patients with schizophrenia and their unaffected relatives share decreased GM in the left insula, although this decrease was more notable in schizophrenic patients compared to their relatives. The insula is involved in many biological behavioral functions that can be impaired in

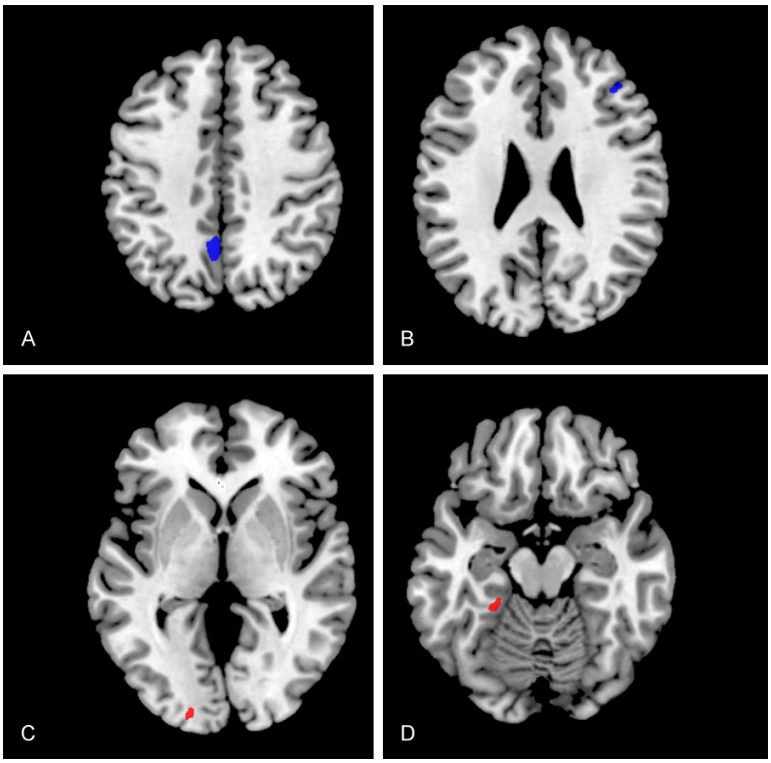

Figure 5. Meta-analysis results of resting-state fMRI studies. A. Left precuneus; B. Right inferior frontal gyrus; C. Left optic radiations; D. Left fusiform gyrus. Regions highlighted in blue signify decreased brain activity and red signifies increased brain activity in the relatives of patients with schizophrenia compared with healthy controls.

schizophrenia, including delusions and hallucinations, and ROI-based MRI and VBM analyses revealed that these abnormalities are more prominent on the left side of the insula [47-49]. Importantly, the abnormalities in this region have been shown to be related to the severity of psychotic symptoms [48]. Taken together, our data suggest that the left insula may be crucial for the development of schizophrenia and a person's susceptibility to genetic and environmental factors. This region may even be considered as a potential biomarker for detecting relatives of schizophrenics who might be at high risk of developing schizophrenia.

In our meta-analysis of rs-fMRI studies, we found that brain activity was decreased in the left precuneus and the right inferior frontal gyrus/triangular part but increased in the left optic radiations and left fusiform gyrus of unaffected relatives of schizophrenics. These findings are consistent with a previous study of the Chinese population [19, 41]. Recently, a meta-analysis of task-based fMRI studies in relatives of schizophrenic patients demonstrated that the right inferior frontal gyrus was hyperactive during cognitive tasks but hypoactive during emotional tasks [20]. The above-mentioned findings suggest that the right inferior frontal gyrus, which functions to modulate attention and cognitive speed, may be an important region in the pathogenesis of schizophrenia [50]. Patients with an established diagnosis of schizophrenia have cognitive impairments that may be associated with this brain region [51]. However, in our multimodal meta-analysis of both s-MRI and rs-fMRI studies, we did not find a brain region that contained both structural and activity changes in the unaffected relatives of schizophrenic patients. Although the GM of the right inferior frontal gyrus was decreased in patients with schizophrenia, its activity was decreased compared to their unaffected relatives. In fact, changes in the activity of certain brain regions have been demonstrated to reflect physiological abnormalities associated with the early stages of schizophrenia, while structural changes may represent long-term and stable abnormalities in schizophrenic patients [19, 52].

In summary, our multimodal meta-analyses identified several abnormal brain regions in schizophrenic patients and their relatives. These abnormalities may reflect the progression of the disease (right inferior frontal gyrus) or the susceptibility to genetics/environmental factors and may predict whether a given individual is at high risk to develop schizophrenia (left insula). There were, however, a few limitations to this study. First, the study did not include research without coordinates or with negative results. Second, the publications containing rs-fMRI data or comparisons between patients and relatives were limited, and this limitation may cause an inadequate sample

Table 5. Subgroup analysis of structural MRI

Studies	No. of Papers	Patients < Relatives		Patients > Relatives	Relatives < Controls			Patients < Controls		Patients > Controls	
		LI	RIFG	LIN	LI	LITG	RIN	LI	RI	RC	RITG
Included twins	3	No	No	No	-	-	-	-	-	-	-
Included siblings	7	Yes	No	Yes	Yes	No	No	Yes	No	No	Yes
Included Chinese	6	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Included Netherlander	3	Yes	Yes	No	-	-	-	-	-	-	-
Included medicine received patients	5	Yes	Yes	No	-	-	-	Yes	No	No	Yes
With correction	8	Yes	No	No	Yes	Yes	Yes	-	-	-	-

LI, left insula; RIFG, Right inferior frontal gyrus; LIN, Left lenticular nucleus; LITG, Left inferior temporal gyrus; RIN, Right inferior network; RC, Right cerebellum; RITG, Right inferior temporal gyrus.

size. Third, the AES-SDM software only allows peak coordinates or statistical maps to be entered as original data. Thus, the meta-analyses only included the rs-fMRI studies that used ALFF or ReHo as a physiologically meaningful indicator of regional neural activity. In addition, no brain region with both structural and activity abnormalities was found in the same individual. This finding may partly impede a complete understanding of the association between brain abnormalities and the pathogenesis of schizophrenia. Therefore, that fact encourages us to next focus on the studies of brain abnormalities of morphological structure, activity, as well as function, in patients with schizophrenia and their unaffected relatives.

Disclosure of conflict of interest

None.

Authors' contribution

Author YN and LZ designed the study. Author YN and RC wrote the protocol and the first draft of the manuscript. Author BP and BL managed the literature searches. Author YN and YM finished the data extraction. Author YN and ZL undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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