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ORIGINAL RESEARCH

Association Between ZNF804A Gene rs1344706 Polymorphism and Brain Functions in Healthy Individuals: A Systematic Review and Voxel-Based Meta-Analysis

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Objective: Zinc finger protein 804A (ZNF804A) protein participates in embryonic neural repair and development. The single nucleotide polymorphism rs1344706 in ZNF804A gene is closely related to functional abnormalities of the human brain. However, these results are inconsistent. This association was verified by meta-analysis in this study.

Methods: Fifteen studies on functional magnetic resonance imaging involving 1710 healthy individuals were included in the systematic review and meta-analysis used by Anisotropic Effect-Size Signed Differential Mapping software.

Results: Functional connectivity of the right dorsolateral prefrontal cortex (rDLPFC)–left hippocampus in the rs1344706 risk allele carrier was significantly increased ($z = 2.066$, $p < 0.001$), while those in the rDLPFC–left middle frontal gyrus ($z = -1.420$, $p < 0.001$) and rDLPFC–right middle frontal gyrus ($z = -1.298$, $p < 0.001$) were significantly decreased. Neural activity of the left anterior cingulate gyrus in the rs1344706 risk allele carrier was significantly decreased ($z = -2.525$, $p < 0.001$). Sensitivity analysis was almost stable, and no publication bias was found.

Conclusion: The changes in brain function have a clear correlation with ZNF804A gene in healthy individuals, which indicate the contribution of genetic variants on brain dysfunction.

Registration Number: This meta-analysis is registered in PROSPERO (No. CRD42016051331).

Keywords: functional magnetic resonance imaging, zinc finger protein 804A, meta-analysis

Introduction

Genome-wide association (GWA) studies have revealed that zinc finger protein 804 (ZNF804A) gene is associated with the susceptibility of mental disorders, such as schizophrenia, bipolar disorder, and depression.[1–3] ZNF804A encodes a transcription factor; it is highly expressed in the brain and involved in the development and functionality of the human brain.[4] Carriers with risk allele in ZNF804A have higher risk for developing mental illnesses than non-carriers.[3] A single-nucleotide polymorphism (SNP) named rs1344706 in ZNF804A was first identified by a previous GWA study in worldwide population.[5] From the studies that detected the functional effect of ZNF804A gene polymorphisms, the most reproducible result is that the risk allele A in rs1344706 is associated with the neurophenotype of mental disorders, patients' performance, and their treatment prognosis.[6,7] Our previous meta-analysis in

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Chinese population detected the relationship between rs1344706 genotype distribution and susceptibility and drug efficacy for schizophrenia and concluded that risk allele A carriers in this SNP had higher risk for schizophrenia but not for treatment efficacy.[8] Furthermore, another meta-analysis that included studies in worldwide population demonstrated a very strong association between the risk allele A in rs1344706 and risk for schizophrenia.[9]

The human brain is the foundation of mental activity. Brain injury and developmental abnormalities can directly lead to the occurrence of mental disorders.[10] Neuroimaging studies suggest that patients with mental disorders, such as schizophrenia, have certain abnormalities on brain function.[11,12] "Imaging genetics" aims to detect the associations between risk genes and the changes in brain function and/or structure of individuals with mental disorders, and to clarify the contributions of these risk genes to abnormalities in the development of the human brain. Numerous studies showed that the ZNF804A gene might be associated with brain function and structure in healthy individuals and patients with mental disorders.[13,14] Lencz et al verified the effects of rs1344706 in schizophrenia risk allele gene ZNF804A on neuroanatomy and neurocognitive phenotype.[15] Research on functional connectivity by Esslinger et al found that the risk allele in rs1344706 carrier had a significantly increased functional coupling in the right amygdala.[16] However, another study revealed that risk allele in rs1344706 had a negative effect on functional connectivity between the right dorsolateral prefrontal cortex (rDLPFC) and the left hippocampus.[17] For neural activity studies in healthy individuals, risk allele carriers exhibited a significant risk allele dose effect on neural activity in the medial prefrontal cortex and left temporoparietal cortex under a theory-of-mind task.[18] In a neural activity research based on the amplitude of low-frequency fluctuation, the risk allele A exhibited a negative effect on the left calcarine gyrus.[19]

Several studies have explored the effects of risk allele in rs1344706 of ZNF804A gene on human brain functional connectivity and neural activity in healthy individuals. However, the affected brain regions and effect sizes are inconsistent due to the differences in clinical baselines and research methods. Previous brain imaging studies also have a relatively small sample size and low statistical test power. In addition, systematic conclusions to comprehensively determine the effects of risk allele A on brain function are lacking. Therefore, this study aimed to explore these effects by signed differential mapping meta-analysis and systematic review in healthy individuals, which could further determine the important role of the SNP rs1344706 in ZNF804A gene in the development of schizophrenia.

Materials and Methods

Registration

This systematic review and meta-analysis was registered in PROSPERO (CRD42016051331).

Study Design

Voxel-based and general meta-analysis methods based on clinical data of statistical maps, peak coordinates, and statistical effect size, which were collected from previous association studies of brain function changes and ZNF804A gene rs1344706 polymorphism, were used to design the study.

Search Strategy

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement.[20] PubMed, Medline, ScienceDirect, and Scopus were used to search for literature from January 2006 until April 2021. The following search terms were combined and used: "functional MRI/fMRI/functional magnetic resonance imaging/brain function" and "ZNF804A/rs1344706." Publications from conferences, monographs, theses, or reference lists in identified studies were also regarded as potential sources to be included in the systematic review.

Selection Criteria

The studies that met the following criteria were included in the meta-analysis: 1) original cross-sectional research that detected the association between ZNF804A gene and brain function; 2) individuals scanned by functional magnetic resonance imaging (fMRI) in the whole brain; 3) comparison of brain function among different genotypes in rs1344706 polymorphism; 4) English publication in peer-reviewed journals and monographs. Studies were excluded if they met the following criteria: 1) data were unavailable or generated from region of interest approaches; 2) repetitive publications; 3) conference papers; 4) fMRI method was not used for detection. Two researchers (LY and FX) independently performed the study search and selection. Furthermore, the citations in

the included studies were searched to identify potential eligible studies.

Data Extraction and Literature Quality Assessment

Two independent reviewers (LY and SW) extracted the data. In the first screening, all eligible titles and abstracts of studies were carefully reviewed using Endnote software (EndNote X8, Thomson Corporation). The full texts of the remaining papers were evaluated for inclusion in the meta-analysis. Disagreements were resolved through discussion. The two reviewers independently extracted the specific information in the included articles and recorded these in detail in pre-set standard electronic form. The extracted contents were not limited to the following: 1) general information of the studies (publication year and last name of the first author); 2) characteristics of the investigated sample (sample cohort, gender, mean age, size); 3) scanning parameter, including but not limited to the full width at half maximum; 4) distribution of genotypes and alleles of rs1344706; 5) effect size and its peak coordinates of voxel-based data in brain function of statistically significant differences. If the incomplete data could not be addressed by obtaining the rest of the data from the original authors, then the study was excluded. All data were checked for internal consistency. The quality of the included studies was assessed following the checklist that focused on the clinical and demographic aspects of individual study samples and imaging-specific methodology.[21]

AES-SDM Analysis

Anisotropic effect-size version of seed-based *d* mapping (AES-SDM) is a meta-analytic method for voxel-based imaging studies. It reports the peak coordinates of gray and/or white matter differences in the whole brain. The user instructions have been described in a previous study.[22] Several meta-analyses on neuropsychiatric disorders were conducted by AES-SDM, including our two previous works.[21,23] Four researchers (FX, YH, YL, and ZC) performed the meta-analysis. The main threshold was set at uncorrected $p<0.001$ (empirically equivalent to corrected $p<0.05$) with cluster extent≥20 voxels and z score>1.[21] Q statistic value with a threshold of $p<0.05$ was considered to be significantly heterogeneous.[24] A leave-one-out jackknife method was used in the sensitivity analysis. Funnel plots were then obtained through Egger's test to evaluate the possibility of publication bias.[25]

Results

General Characteristics of the Included Studies

A flowchart of the search process is presented in Figure 1. PRISMA checklist of this meta-analysis is presented in the supplement material. Fifteen studies[16–19,26–36] on brain functional connectivity and activity involving 1710 healthy individuals were included in the systematic review and meta-analysis. The general characteristics and research quality assessment of the included studies are shown in Table 1. The main results of risk allele affected regions in healthy individuals in each study are summarized in Table 2. The different brain regions and different effects of rs1344706 risk allele A on functional connectivity and neural activity were exhibited.

Effect of ZNF804A Gene rs1344706 Risk Allele on Brain Functional Connectivity

The seed regions reported in 12 studies[16–18,26,27,30–36] regarding functional connectivity are summarized in Figure 2. Due to the high frequencies of rDLPFC-based seed (reported by eight studies[16–18,26,27,30,32,36]), the subsequent AES-SDM analysis of brain functional connectivity mainly focused on the rDLPFC seed. In the healthy population, the functional connectivity of the rDLPFC–left hippocampus in the rs1344706 risk allele carrier was significantly increased ($z=2.066$, $p<0.001$), while those in the rDLPFC–left middle frontal gyrus ($z=-1.420$, $p<0.001$) and rDLPFC–right middle frontal gyrus ($z=-1.298$, $p<0.001$) were significantly reduced (Table 3 and Figure 3). Result of connectivity coupling between rDLPFC and left middle frontal gyrus had a significant heterogeneity ($p<0.05$). The area of interest with peak coordinate only reported in one study was not included in AES-SDM meta-analysis. Generally, the risk allele of rs1344706 showed mainly negative effects on functional connectivity (Table 4).

Effect of ZNF804A Gene rs1344706 Risk Allele on Neural Activity

Seven studies[18,19,27–30,34] reported significant results in neural activity. However, only five studies[18,19,27–29] had peak coordinates. AES-SDM analyzed the effect of ZNF804A gene rs1344706 risk allele on neural activity. After data integration and image reconstruction, the neural activity of the left anterior cingulate gyrus was significantly decreased in the rs1344706 risk allele carrier of

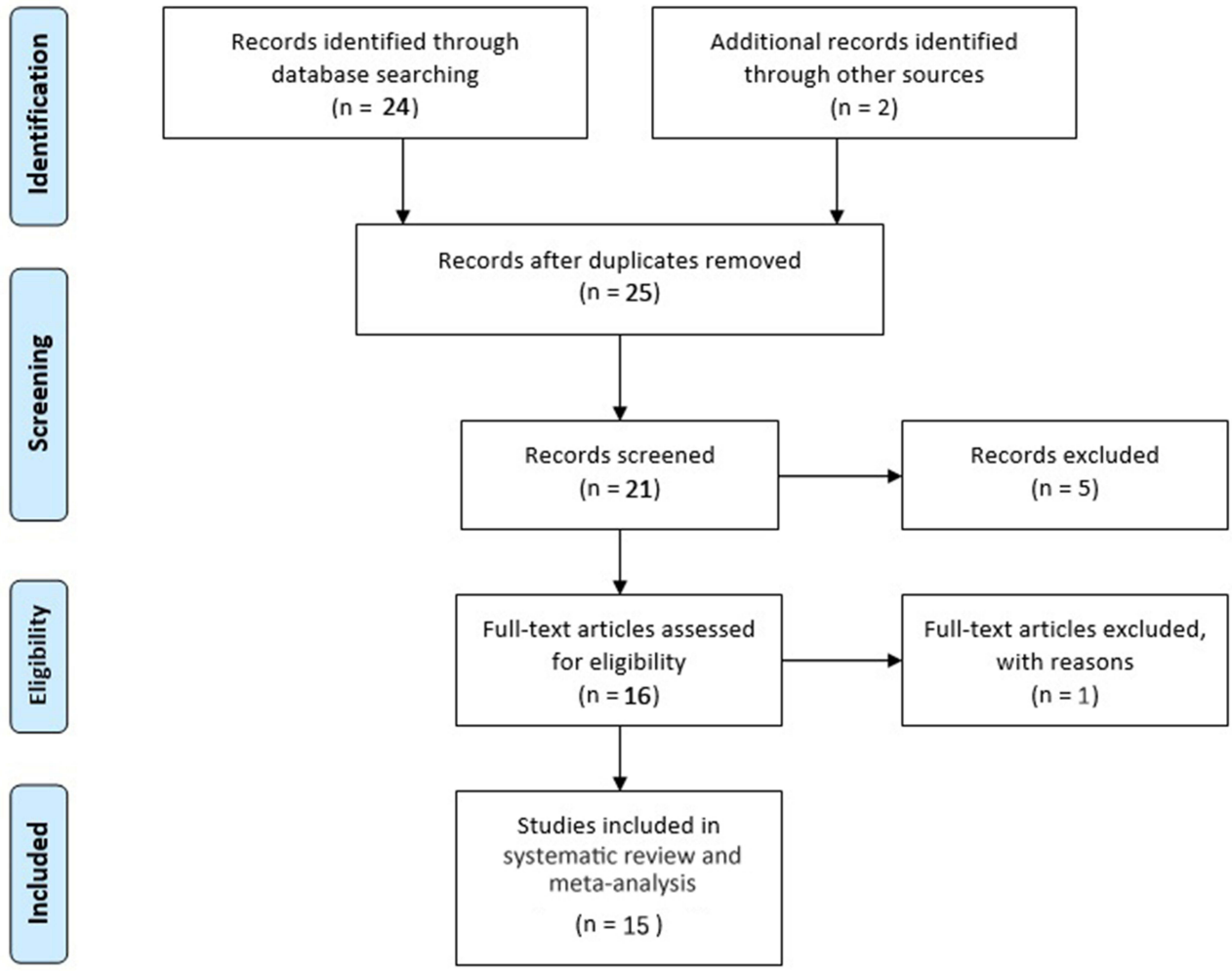

Figure 1 Flowchart of the selection process.

the healthy population (MNI: x=0, y=34, z=22; z=−2.525, p<0.001; voxels=2463), and no other brain area showed significantly increased neural activity (Figure 4). Result of this brain region had no heterogeneity (p>0.05). The remaining two studies[30,34] had a negative result of neural activity or did not report the peak coordinates in healthy individuals (Table 4).

Sensitivity Analysis and Publication Bias

Leave-one-out jackknife analyses showed that most functional connectivity and neural activity results were not significantly changed. When removed the study of Esslinger,[16] Rasetti,[17] or Thurin,[27] respectively, the results were slightly changed (Table 5). Further sensitivity analysis excluded the studies of Esslinger[26] and Zhao[36] due to the potential partially duplicated sample. However, the results were not significantly changed (Table 6).

In addition, according to Egger's test, no publication bias was found in functional connectivity and neural activity analyses (t=1.410, p=0.208; t=0.05, p=0.963; Figure 5).

Discussion

In this study, AES-SDM was used in the meta-analysis of studies regarding the effects of risk allele in rs1344706 polymorphisms of ZNF804A gene on brain function. The AES-SDM analysis found that in healthy populations, the functional connectivity of the rDLPFC–left hippocampus in the rs1344706 risk allele carrier was significantly increased, but those of the rDLPFC–right middle frontal gyrus and rDLPFC–left middle frontal gyrus were significantly decreased. Analysis of local activity revealed that the neural activity in this risk allele carrier was significantly decreased in the left anterior cingulate gyrus.

Table 1 General Characteristics, Imaging Scan Features and Quality Assessment Results Included in the Study

Author	Year of Publication	Sample Size(n)	Age (Years)	Sex (Male, n)	Ancestry	Genotype Distribution				fMRI Information			Indicators	Quality
						AA	AC	CC	HWE	Tesla	FWHM (mm)	Task		
Esslinger[16]	2009	115	33.8	49	Caucasian	43	51	21	Yes	3.0	9	N-back	FC	High
Esslinger[26]	2011	111	33.8	49	Caucasian	40	50	21	Yes	3.0	9	N-back, Face match	FC	High
Rasetti[17]	2011	96	35	44	NS	37	45	14	NS	3.0	8	2-back	FC	High
Walter[18]	2011	109	32.3	47	Caucasian	42	49	18	Yes	3.0	9	Theory of mind	FC, Activity	High
Linden[28]	2013	43	32.3	24	Caucasian	11	21	11	NS	1.5	NS	Face paradigm	Activity	Medium
Paulus[30]	2013	94	23.1	66	Caucasian	27	46	21	NS	3.0	NS	N-back	FC, Activity	Medium
Thurin[27]	2013	208	31.4	103	Caucasian	89	93	26	Yes	3.0	8	Eriksen Flanker	FC, Activity	High
Mohnke[29]	2014	188	34.1	94	Caucasian	63	87	38	Yes	3.0	9	Theory of mind	Activity	High
Cousijn[31]	2015	50	24	23	Caucasian	25	0	25	Yes	3.0	6	Resting state	FC	High
Zhang[32]	2016	87	27.6	68	Chinese	23	43	21	Yes	3.0	8	N-back, Resting state	FC	High
Chen[33]	2018	128	27	99	Chinese	32	62	34	Yes	3.0	4	Resting state	FC	High
Tecelão[34]	2018	80	39.1	34	Caucasian	NS	NS	NS	Yes	1.5	5	Verbal Fluency	FC, Activity	High
Zhang[35]	2018	99	25.8	49	Chinese	25	45	24	Yes	3.0	NS	Resting state	FC	High
Cui[19]	2019	218	29.0	85	Chinese	49	120	49	Yes	3.0	6	Resting state	Activity	High
Zhao[36]	2020	84	21.2	19	Chinese	23	40	21	Yes	3.0	8	Resting state	FC	High

Abbreviations: HWE, Hardy-Weinberg' equilibrium; HC, healthy control; NS, not reported; FWHM, full width half height; FC, functional connectivity.

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Table 2 The Main Results of Risk Allele Effected Regions in Healthy Individuals in the Included Studies

Study	Significant Region in Functional Connectivity	Significant Region in Neural Activity
Esslinger 2009[16]	Right amygdala, rDLPFC-HF	-
Esslinger 2011[26]	rDLPFC-left middle frontal gyrus, rDLPFC-right middle frontal gyrus, rDLPFC-right superior frontal gyrus, et al.	-
Rasetti 2011[17]	rDLPFC-HF, rDLPFC-inferior parietal lobule	-
Walter 2011[18]	lTPJ-inferior frontal gyrus, lTPJ-cuneus, rDLPFC-middle frontal gyrus, rDLPFC-precentral gyrus, et al.	DLPFC, DMPFC, VLPFC, TPJ, IPL, PCC
Linden 2013[28]	-	Right inferior frontal gyrus
Paulus 2013[30]	rDLPFC-left HF, rDLPFC-right HF	No significant region was found
Thurin 2013[27]	rDLPFC-anterior cingulate cortex	rDLPFC, anterior cingulate cortex
Mohnke 2014[29]	lTPJ-inferior frontal gyrus	TPJ, DMPFC, PCC
Cousijn 2015[31]	Hippocampal-prefrontal cortex	-
Zhang 2016[32]	rDLPFC-left HF	-
Chen 2018[33]	No significant region was found	-
Tecelão 2018[34]	-	Left inferior frontal gyrus
Zhang 2018[35]	Left HF-rDLPFC	-
Cui 2019[19]	-	Left calcarine gyrus
Zhao 2020[36]	rDLPFC-left HF	-

Abbreviations: DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; IPL, inferior parietal lobe; PCC, posterior cingulate cortex; TPJ, temporo-parietal junction; HF, hippocampus formation.

The outcomes of the present meta-analysis are generally consistent with previous observational studies, although some differences were observed. The

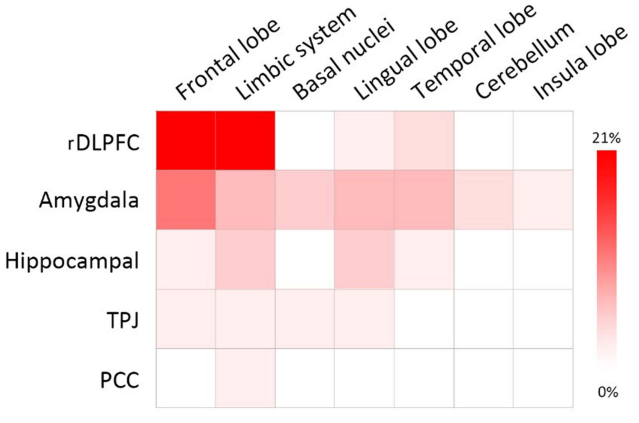

Figure 2 Frequency distribution of brain regions involved in brain functional connectivity.
Abbreviations: rDLPFC, right dorsolateral prefrontal cortex; TPJ, temporoparietal junction; PCC, posterior cingulate cortex.

Table 3 Effect of Rs1344706 Risk Allele on Brain Functional Connectivity Based on rDLPFC Seed Region

Connected Region	Peak Coordinate					Cluster Size in Voxels
	MNI (x, y, z)			SDM-z	*p*	
Positive effects of rs1344706 risk alleles						
Left hippocampus	−32	−24	−12	2.066	<0.001	888
Negative effects of rs1344706 risk alleles						
Left middle frontal gyrus	−46	32	34	−1.420	<0.001	226
Right middle frontal gyrus	30	50	32	−1.298	<0.001	150

Abbreviation: rDLPFC, right dorsolateral prefrontal cortex.

connectivity couplings such as rDLPFC–inferior parietal lobule, rDLPFC–anterior cingulate cortex, and rDLPFC–precentral gyrus was reported by other studies.[18,26,27] However, they were not significant in our meta-analysis. Furthermore, we found that risk allele A was associated

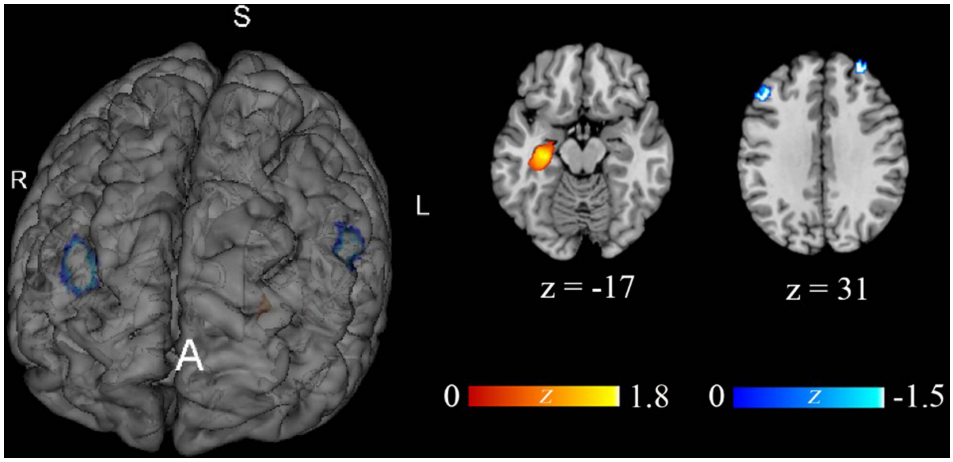

Figure 3 Effect of rs1344706 risk allele on brain functional connectivity on the basis of rDLPFC seed region.

with neural activity only in the left anterior cingulate gyrus but not in rDLPFC, dorsomedial prefrontal cortex, left calcarine gyrus, and posterior cingulate cortex, which were reported in other studies.[18,19,29] These differences may be due to a higher statistical powerful in our meta-analysis. Thus, relatively less regions were found to be associated with risk allele A. However, the total effect of this risk allele on brain function was never changed in our meta-analysis in healthy individuals.

The functional connectivity of the rDLPFC–left hippocampus in the rs1344706 risk allele carrier was significantly increased, which showed the positive and obviously strong effect of this gene in our meta-analysis. However, in patients with chronic schizophrenia, the hippocampal–prefrontal functional connectivity seemed to be reduced in the resting state, suggesting the negative effect of rs1344706 risk allele.[37] On the one hand, it may be due to differences in the observation indicators and clinical baselines of the included samples. On the other hand, it may be due to the difference in the races of subjects because the frequency of rs1344706 allele distribution varies widely among different populations, and this difference may directly affect the results of association studies.

Imaging genetic studies generally evaluate the risks of specific genes on functional development of the cerebrum. However, how the protein or nucleic acid produced by gene coding affects the execution of brain function is not clear. ZN804A is a schizophrenia susceptibility gene that is strongly supported by GWA analysis. In our meta-analysis and previous studies, rs1344706 risk allele influenced the different

Table 4 Summary of Functional Connectivity and Neural Activity Studies Not Included in AES-SDM Analysis

Study	Indicator Characteristic	A>C	C>A	C=A	Reasons of No Including
Functional connectivity					
Cousijn 2015[31]	Hippocampal theta seed	√			No rDLPFC seed
Tecelão 2018[34]	Left inferior frontal gyrus		√		No rDLPFC seed
Zhang 2018[35]	Left hippocampal seed		√		No rDLPFC seed
Chen 2018[33]	Degree centrality method		√		No rDLPFC seed
Neural activity					
Paulus 2013[30]	Working memory related			√	No significant result
Tecelão 2018[34]	Verbal fluency related		√		No peak coordinate in healthy individuals

Notes: A>C means risk allele had positive effect on functional connectivity or neural activity; C>A means risk allele had negative effect on functional connectivity or neural activity; C=A means risk allele had no significant effect on functional connectivity or neural activity.
Abbreviation: rDLPFC, right dorsolateral prefrontal cortex.

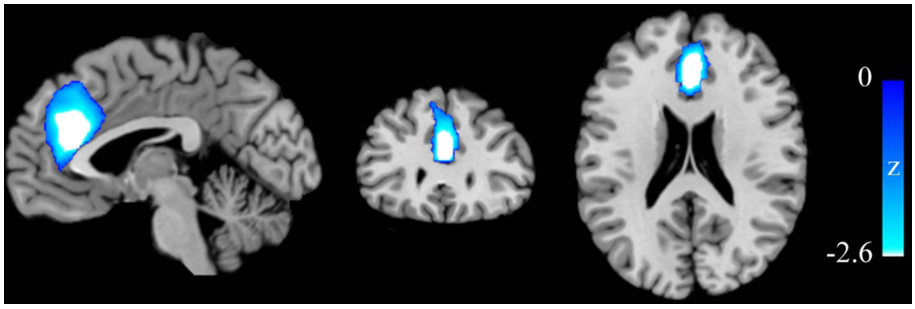

Figure 4 Effect of rs1344706 risk allele on neural activity.

regions of the brain. In complementary gene expression analyses, the rs1344706 risk allele was found to be associated with increased ZNF804A exonic transcription levels in the hippocampus, medulla oblongata, occipital cortex, and other regions.[34,38] Hence, the effects of the risk allele on brain function may result from the different expression of ZNF804A gene in different brain regions. The dosage of ZNF804A may determine some functions of the human brain. Animal experiments, biological information analysis, and functional MRI scanning suggested that the polymorphic site of rs1344706 affects human brain functional connectivity and is related to the development of white matter circuits.[39]

For the ZNF804A gene, studies have shown that the gene only affects the early development of the brain, but has no effect on the mature adult brain.[40] However, from the perspective of autopsy, the ZNF804A gene showed differential expression between healthy individuals and patients with schizophrenia.[41–43] These pieces of evidence indirectly or directly reveal that ZNF804A expression is associated with brain development and different phenotypes. Nevertheless, direct experimental data on the ZNF804A gene rs1344706 risk allele are still lacking to determine how brain development affects different individuals to exhibit different brain function characteristics.

Table 5 Leave One Out Jackknife Sensitivity Analysis Results

Study of Leave Out	Functional Connectivity			Neural Activity
	rDLPFC-Left Hippocampus	rDLPFC-Left Middle Frontal Gyrus	rDLPFC- Right Middle Frontal Gyrus	Left Anterior Cingulate Gyrus
Functional connectivity				
Esslinger 2009[16]	No significant changed	Peak coordinate changed	No significant changed	-
Esslinger 2011[26]	No significant changed	No significant changed	No significant changed	-
Rasetti 2011[17]	No significant changed	Reported no region	Reported no region	-
Walter 2011[18]	No significant changed	No significant changed	No significant changed	-
Paulus 2013[30]	No significant changed	No significant changed	No significant changed	-
Thurin 2013[27]	No significant changed	No significant changed	No significant changed	-
Zhang 2016[32]	No significant changed	No significant changed	No significant changed	-
Zhao 2020[36]	No significant changed	No significant changed	No significant changed	-
Neural activity				
Walter 2011[18]	-	-	-	No significant changed
Linden 2013[28]	-	-	-	No significant changed
Thurin 2013[27]	-	-	-	Peak coordinate changed
Mohnke 2014[29]	-	-	-	No significant changed
Cui 2019[19]	-	-	-	No significant changed

Abbreviation: rDLPFC, right dorsolateral prefrontal cortex.

Table 6 Sensitivity Analysis of Function Connections Based on rDLPFC Seed Region When Removed Two Studies

Connected Region	Peak Coordinate					Cluster Size in Voxels
	MNI (x, y, z)			SDM-z	*p*	
Positive effects of rs1344706 risk alleles						
Left hippocampus	−28	−20	−14	1.763	<0.001	578
Negative effects of rs1344706 risk alleles						
Left middle frontal gyrus	−46	32	36	−1.494	<0.001	210
Right middle frontal gyrus	28	50	30	−1.342	<0.001	167

Abbreviation: rDLPFC, right dorsolateral prefrontal cortex.

ZNF804A is closely related to the cognitive function of the brain.[44] An investigation in healthy subjects showed that cortical connectivity and activation were related to rs1344706 during performance on a theory of mind task (which measures the participant's ability to infer mental state).[16] The regional activation of the temporoparietal cortex and rDLPFC, which are implicated in the function in theory of mind, was found to be affected by the dosage of risk allele.[18] Our meta-analysis conducted in healthy individuals revealed the association between ZNF804A rs1344706 allele gene expression and rDLPFC seeded functional connectivity, highlighting the key role of

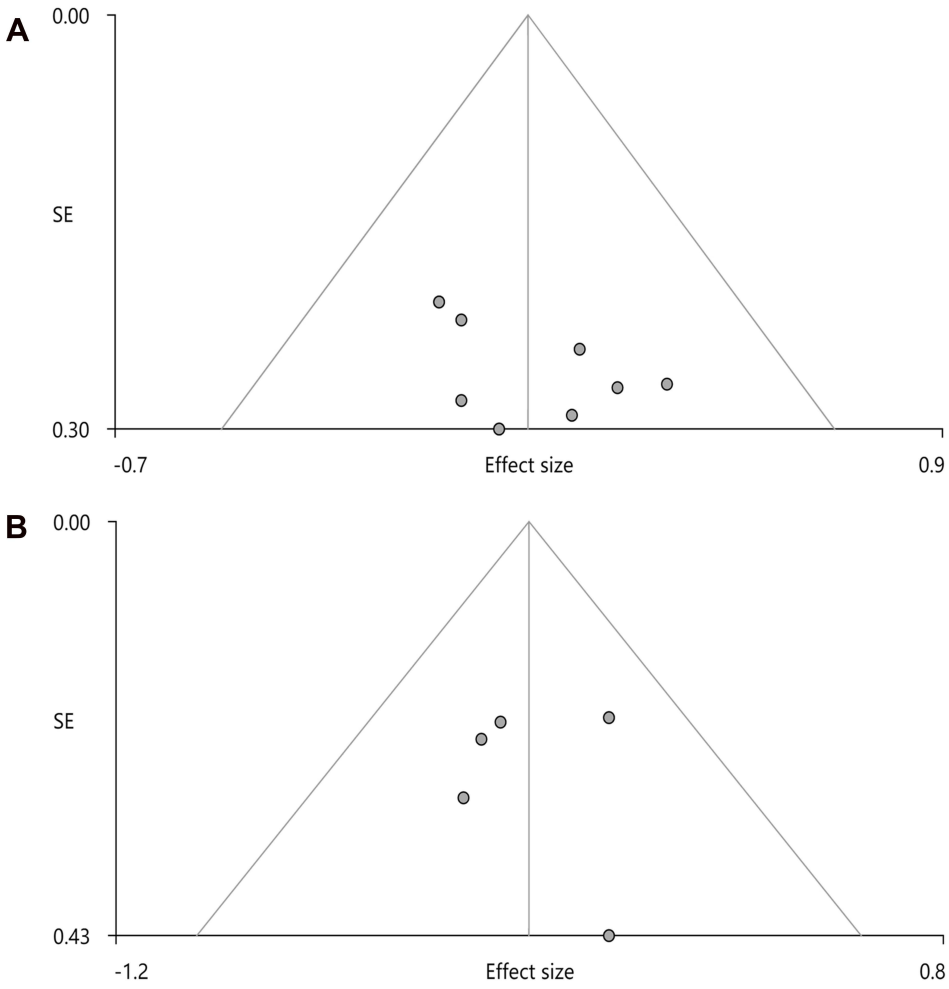

Figure 5 Publication bias of funnel plots.
Note: (**A**) Functional connectivity; (**B**) Neural activity.

ZNF804A in cognitive function. One important characteristic of patients with schizophrenia is impaired cognitive function. Thus, the function of this risk gene in healthy individuals could also reflect the potential effect of rs1344706 on the abnormal cognitive function of patients with schizophrenia.

No publication bias was found in this meta-analysis, but a significant heterogeneity existed when synthesizing functional connectivity indicators. The heterogeneity most likely come from the different analytical indicators and scanning models among the including studies. In general, this study clarified the effect of ZNF804A gene rs1344706 risk allele on function through meta-analysis and provided a more in-depth reference for the study of genetic related pathogenesis of mental disorders such as schizophrenia.

Conclusion

The ZNF804A gene rs1344706 polymorphism has a strong correlation with brain functional connectivity and neural activity in healthy individuals. The risk allele A may be associated with abnormal or changed brain function in individuals and play a key role in the execution of brain function. This meta-analysis provides important information for the further study of genetic related mechanisms of schizophrenia and other mental disorders. The relationship between the rs1344706 risk allele of ZNF804A and brain dysfunction also provides an important reference for the prevention and treatment of mental disorders.

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Author Contributions

All authors contributed to data analysis, drafting, and revision of the article. All authors have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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