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REVIEW ARTICLE

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Neuroimaging genomic studies in major depressive disorder: A systematic review

Hui-Feng Zhang[1] | David Mellor[2] | Dai-Hui Peng[1]

[1]Division of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

[2]School of Psychology, Deakin University, Melbourne, Australia

Correspondence
Dai-Hui Peng, Division of Mood Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
Email: pdhsh@126.com

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Summary

Genetic-neuroimaging studies could identify new potential endophenotypes of major depressive disorder (MDD). Morphological and functional alterations may be attributable to genetic factors that regulate neurogenesis and neurodegeneration. Given that the association between gene polymorphisms and brain morphology or function has varied across studies, this systematic review aims at evaluating and summarizing all available genetic-neuroimaging studies. Twenty-eight gene variants were evaluated in 64 studies by structural or functional magnetic resonance imaging. Significant genetic-neuroimaging associations were found in monoaminergic genes, BDNF genes, glutamatergic genes, HPA axis genes, and the other common genes, which were consistent with common hypotheses of the pathogenesis of MDD.

KEYWORDS
genomics, major depressive disorder, neuroimaging, pathophysiology

1 | INTRODUCTION

Major depressive disorder (MDD) is one of the leading contributors to the global burden of disease.[1] It has a 1-month prevalence of 2.1%,[2] annual prevalence of 6.6%, and lifetime prevalence of 16.2%.[3] Although an increasing number of studies have implicated pathophysiological mechanisms in the etiology of MDD,[4] the causes of MDD are yet to be fully elucidated. Recently, genetic-neuroimaging studies have provided new insights into the neurobiological basis of MDD.

A meta-analysis of studies of the genetic epidemiology of MDD suggested that both genes and environment contribute to MDD susceptibility.[5] However, while the heritability of MDD is up to 37%,[6] candidate gene studies have failed to yield robust evidence related to any particular gene.[5,7] This outcome is consistent with the suggestion that candidate genes alone exert minor biological effects on the susceptibility to MDD; rather, the joint effects of numerous genes may generate relatively large effects.[8] A genome-wide association revealed that MDD patients carrying HOMER1 homozygous allele had significantly decreased prefrontal activity during executive cognition and an anticipation of monetary reward task.[7] Another study suggested that MDD patients with a brain-derived neurotrophic factor (BDNF) Met-allele had significantly reduced caudal middle frontal thickness that contributed to MDD susceptibility.[9] These findings indicate that risk genotypes of MDD do not directly modulate phenotype at behavioral levels, but affect brain morphology or function via molecular and cellular mechanisms.[10] Considerable genetic-neuroimaging literature indicates that there are significant associations between genetic variants and structural and/or functional neuroimaging alterations in MDD, implying new neuroimaging phenotypes to MDD.[11-15]

Although no specific pathophysiological mechanism of MDD had been reliably identified, genetic-neuroimaging studies reveal that genetic variants are implicated in some common hypotheses of the pathogenesis of MDD,[4] such as monoamine-deficiency hypothesis, hypothalamic-pituitary-cortisol hypothesis, and altered

glutamatergic neurotransmission. Monoaminergic genes and BDNF genes have repeatedly been studied, which were associated with morphological and functional alterations of emotion-related brain areas and made it susceptible to MDD.[11,13] Hence, numerous genetic-neuroimaging studies have attempted to explore the pathophysiological mechanisms of MDD via analyzing the associations between genetic variants and structural and/or functional neuroimaging abnormalities. However, previous review only focused on the role of 5-HT and BDNF genes in structural and functional alterations in emotion- and memory-related brain areas and failed to provide a comprehensive overview of all available genetic variants expected to play a pathophysiological role in MDD.[13] In addition, different neuroimaging techniques or genetic variants may be potential confounding factors that would result in heterogeneity of genetics-neuroimaging studies. Therefore, our systematic review aims at summarizing all available genetic-neuroimaging studies of MDD and investigating the association between all available genetic variants and neuroimaging changes. Then, we might evaluate some new endophenotypes of MDD to provide a comprehensive overview for MDD pathology.

2 | METHODS

2.1 | Inclusion criteria

We included original genetic-neuroimaging studies evaluating the association between genetic polymorphisms and neuroimaging in patients with MDD. MDD patients were diagnosed based on the standard diagnostic criteria (such as DSM-IV and ICD-10). The studies included in this review were case-control studies that compared MDD patients carrying high-risk alleles to other MDD patients and/or healthy controls (HC) who were noncarriers of the investigated risk genotype. Only articles written in English were included.

2.2 | Exclusion criteria

(i) Health studies and animal studies, case reports, reviews, meeting abstracts, and editorials were excluded; (ii) studies that adopted positron emission tomography or electroencephalogram or computed tomography other than structural and/or functional magnetic resonance imaging (MRI) were excluded; (iii) patients with mixed diagnoses were also excluded.

2.3 | Search strategy

The search was conducted on the PubMed database from inception up to August 1, 2017, using the search terms (major depression OR unipolar depression) AND (MRI OR magnetic resonance imaging) AND (gene OR genetic*). In addition, the reference lists of each eligible article were then manually searched to identify additional studies.

2.4 | Study selection

The title and abstract of each retrieved study were screened to identify whether the study met the inclusion or exclusion criteria. Next, the full texts of eligible studies were reviewed and assessed for eligibility.

2.5 | Data extraction

For each eligible study, the following data were extracted and recorded: author(s) and year of publication; name of genes and genetic polymorphisms; sample size and sex distribution; age of participants; imaging methods and imaging field strengths; regions of interest (ROI); and the main results of the association between genetic variants and brain structure and/or activity.

2.6 | Data synthesis

Quantitative analysis, such as meta-analysis, was not conducted due to the high level of heterogeneity in the genetic variants included in the genetic-neuroimaging studies. Instead, we adopted a qualitative systematic review approach to investigate the relationship between genetic variants and structural and/or functional neuroimaging in MDD patients.

3 | RESULTS

3.1 | Characteristics of included studies

Our search initially retrieved 464 studies, and 11 additional references were found by checking the reference lists of these studies. Of these 475 studies screened for eligibility, 411 were excluded based on title/abstract screening. After reviewing the full texts of the retained studies, only 64 met the full inclusion criteria. The characteristics of these 64 studies are listed in Tables 1 and 2.

Forty-one studies reported the association between genetic variants and brain structure using voxel-based morphometry (VBM) and/or diffusion tensor imaging (DTI), and 22 studies used blood-oxygen-level-dependent (BOLD) fMRI methods to assess the association between genetic variants and functional brain imaging. In addition, one study investigated the association between genetic variants and both structural and functional neuroimaging. These studies investigated 28 independent candidate genes, and 4 of them investigated the synergistic effect of several candidate genes (5-HTTLPR, BDNF and COMT, COMT and MTHFR, 5-HTR2A and MAOA, 5-HTTLPR and 5-HTR1A).

3.2 | Association of genetic polymorphisms with structural MRI

Thirty-six genetic-neuroimaging studies were focused on 18 risk candidate genes. Two of those studies investigated the synergistic effect of COMT and MTHFR, and 5-HTTLPR, BDNF, and COMT. Six of the 18 candidate genes were investigated in replication studies

TABLE 1 Studies investigating the association between genetic polymorphisms and brain structure in MDD patients using structural MRI or DTI

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Ahdidan et al (2013)[33]	5-HTTLPR	MDD 23 HC 33	LL/LS/SS (L = La, S = Lg + S)	19/4 24/9	39.4 ± 12.3 36.6 ± 11.1	sMRI, 1.5T	Previous findings of association between 5-HTTLPR and hippocampal size in patients with major depressive disorder (MDD) could not be replicated
Frodl et al (2008)[11]	5-HTTLPR	MDD 60 HC 60	LL/LS/SS (L = La, S = Lg + S)	29/31 29/31	44.2 ± 11.8 41.6 ± 12.3	sMRI, 3.0T	Patients with the LaLa genotype had significantly smaller hippocampal gray matter and white matter than La/La controls; within the patient group, the La/La homozygous genotype had significantly smaller hippocampal white matter volumes than the La/(Lg + S) or (Lg + S)/(Lg + S) genotype
Frodl et al (2008)[30]	5-HTTLPR	MDD 77 HC 77	LL/LS/SS (L = La, S = Lg + S)	35/42 35/42	42.6 ± 12.4 40.5 ± 11.6	sMRI, 1.5T	Patients with depression show reduced GM volumes, particularly when they are homozygous for the LA-allele
Hickie et al (2007)[31]	5-HTTLPR	MDD 45 HC 16	LL/LS/SS	30/15 9/7	52.0 ± 12.8 55.8 ± 10.3	sMRI, 1.5T	In those with depression, the short allele of 5-HTT was associated with smaller caudate nucleus volumes
Frodl et al (2004)[119]	5-HTTLPR	MDD 40 HC 40	LL/LS/SS	19/21 19/21	44.4 ± 11.7 41.7 ± 12.1	sMRI, 1.5T	Patients with the L/L homozygous genotype had significantly smaller hippocampal gray matter and white matter volumes than controls with this genotype; patients with the L/L genotype had significantly smaller hippocampal white matter volumes than those with the L/S or S/S genotype
Taylor et al (2005)[29]	5-HTTLPR	MDD135 HC 83	LL/LS/SS	51/21 39/24	68.7 ± 6.4 71.5 ± 7.9	sMRI, 1.5T	Late-onset depressed patients with LL genotype had significantly smaller right hippocampal volumes than did L/L early-onset depressed patients or L/L control subjects
Eker et al (2011)[27]	5-HTTLPR	MDD 44 HC 43	LL/LS/SS	33/11 27/16	33.6 ± 9.5 30.4 ± 6.7	sMRI, 1.5T	Hippocampal volumes of S/S homozygous depressed patients were smaller compared to healthy controls in both hemispheres
Frodl et al (2010)[28]	5-HTTLPR	MDD 24 HC 27	S-allele, L-allele	18/9 13/11	43.8 ± 11.9 41.9 ± 13.2	sMRI, 1.5T	Patients carrying the risk S-allele developed smaller hippocampal volumes when they had a history of emotional neglect compared with patients who only had one risk factor (environmental or genetic)
Alexopoulos et al (2009)[53]	5-HTTLPR	MDD 37 HC 27	LL/S carriers		S, 72.7 ± 6.6 LL, 67.6 ± 5.6 S, 70.5 ± 7.1 LL, 73.3 ± 5.3	sMRI, DTI, 1.5T	Depressed S-allele carriers had lower FA in multiple frontolimbic and in some subcortical and posterior areas demonstrated clusters of reduced FA in the dorsolateral prefrontal dorsal and rostral anterior cingulate, posterior cingulate, medial prefrontal regions, and thalamus, compared to depressed L homozygotes
Taylor et al (2007)[34]	5HTTLPR ApoE ε4	MDD 226 HC 144	LL/LS/SS No e4/e4	150/76 100/44	70.0 ± 7.4 70.3 ± 6.5	sMRI, 1.5T	There was no association between gray matter lesion measures or 5HTTLPR genotype and OFC volume; subjects who were APOE e4-allele positive exhibited larger OFC volumes; in secondary analyses, this finding was limited to the nondepressed group

(Continues)

TABLE 1 (Continued)

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Kostic et al (2016)[55]	HTTLPR BDNF COMT	MDD 77 HC 66	High/intermediate/low-frequency SNP	46/31 35/31	44.6 ± 10.6 45.4 ± 10.8	sMRI, DTI, 1.5T	Compared to controls, hfSP patients showed thinning of the middle frontal cortex bilaterally, left frontal pole, and right lateral occipital cortex, and smaller hippocampal volume bilaterally; both hfSP and lfSP patient groups showed thinning of the left inferior parietal cortex and reduced WM integrity of the corpus callosum. Compared to patients, hfSP controls showed greater integrity of the fronto-occipital cortices and corpus callosum
Jaworska et al (2016)[32]	HTTLPR BDNF	MDD 43 HC 15		26/17 8/7	30.3 ± 8.1 36.6 ± 11.1	sMRI, 3.0T	In the MDD group, larger left thalamus and putamen volumes were observed in LA/LA homozygotes
Phillips et al (2015)[26]	HTTLPR NET HTR1A HTR2A COMT BDNF	MDD 26 HC 27	LL/LS/SS TT/TC/CC CC/CG/GG TT/TC/CC ValVal/ValMet/MetMet ValVal/ValMet/MetMet	18/8 18/9	46.0 ± 10.4 45.4 ± 10.7	sMRI, 1.5T	The NET and 5-HT1A polymorphisms appear to have similar effects on hippocampal volume in patients and controls, while the 5-HTTLPR polymorphism differentially affects hippocampal volume in the presence of depression. There was no association between the 5-HT2A, COMT, and BDNF SNPs and hippocampal volume
Cole et al (2011)[24]	5-HTTLPR BDNF	MDD 84 HC 111	S or Lg carriers/LaLa Met carriers/ValVal	57/27 56/55	48.82 ± 8.93 33.00 ± 9.23	sMRI, 1.5T	Hippocampal volume normalized by intracranial volume (ICV) showed no significant difference between 5HTTLPR S-allele carriers and L/L homozygotes or between BDNF Met-allele carriers and Val/Val homozygotes in the group of healthy individuals; there was no significant difference in normalized HCV between 5HTTLPR or between the BDNF Val66Met genotypes in MDD patients, although there was a relationship between BDNF Val66Met and ICV
Legge et al (2015)[22]	BDNF	MDD 79 HC 74	Met carrier/ValVal	52/27 40/34	49.09 ± 8.96 50.92 ± 7.82	sMRI, 1.5T	Met-allele carriers showed reduced caudal middle frontal thickness in both study groups; MDD patients carrying Met showed the greatest reduction in anterior cingulate and rostral middle frontal region surface area
Ide et al (2015)[21]	BDNF	MDD 38 HC 42	Met carrier/Val-Val	21/17 18/24	48.9 ± 17.2 40.5 ± 11.3	sMRI, 3.0T	Among the Met carriers, the volume of the left middle frontal gyrus was significantly smaller for MDD patients than for the HS
Cardoner et al (2013)[17]	BDNF	MDD 37	Met carrier/Val-Val	11/11 5/10	60 ± 8 56 ± 7	sMRI, 1.5T	Met66 carriers: GM volume reduction in the left hippocampus; right orbitofrontal cortex volume increase
Kanellopoulos et al (2011)[20]	BDNF	MDD 33 HC 23	Met carrier/Val-Val	21/12 14/9	72.3 ± 6.8 70.7 ± 5.7	sMRI, 1.5T	Elderly MDD BDNF val/val homozygotes had significantly higher right hippocampal volumes compared with nondepressed val/val subjects
Frodl et al (2007)[18]	BDNF	MDD 60 HC 60	ValVal/ValMet/MetMet	29/31 29/31	44.2 ± 11.8 41.6 ± 12.3	sMRI, 1.5T,	Patients had significantly smaller hippocampal volumes compared with controls; significantly smaller hippocampal volumes were observed for patients and for controls carrying the allele Met BDNF compared with subjects homozygous for the allele Val BDNF

(Continues)

TABLE 1 (Continued)

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Jessen et al (2009)[25]	BDNF	MDD 79 HC 84	Met carrier/ ValVal	52/27 40/44	48.2 ± 12.8 43.9 ± 8.7	sMRI, 1.5T	The hippocampal volumes of patients were significantly smaller than those of the participants compared
Carballedo et al (2012)[52]	BDNF	MDD 37 HC 42	Met/Val allele	25/12 25/17	40.4 ± 10.3 36.3 ± 13.0	sMRI, DTI, 3.0T	Patients carrying the BDNF met-allele had smaller fractional anisotropy (FA) in the UF compared to those patients homozygous for val-allele and compared to healthy subjects carrying the met-allele; larger FA was detectable in the left rostral cingulum for met-allele carriers when compared to val/val-allele carriers
Gonul et al (2010)[19]	BDNF	MDD 33 HC 40	Met carriers/ ValVal	8/25 17/23	33.9 ± 9.9 29.8 ± 6.4	sMRI, 1.5T	Among Val homozygotes, depressed patients had significantly smaller left hippocampal volumes compared to controls
Carballedo et al (2013)[16]	BDNF	MDD 62 HC 71	Met carriers/ ValVal	38/24 44/27	41.8 ± 11.1 38.4 ± 13.5	sMRI, 3.0T	Met-allele carriers in our samples showed significantly smaller hippocampal volumes when they did have a history of childhood adversity, both in patients and in controls
Kim et al (2002)[36]	ApoE ε4	MDD 45	Noncarrier/ carriers	25/11 8/1	68.72 ± 1.14 64.25 ± 2.45	sMRI, 1.5T	Compared with 36 depressed subjects without an apolipoprotein E ε4-allele, 9 subjects with at least one APOE ε4-allele showed significant decline in hippocampal volume, particularly in the right hippocampus
Qiu et al (2009)[35]	ApoE ε4	MDD52 HC 31	Non-ApoE ε4/ ApoE ε4	34/18 21/10	64.7 ± 4.5 68.9 ± 5.9	sMRI, 3.0T	The depressed patients with one apoE E4 show more pronounced shape inward compression in the anterior CA1 than the depressed patients without the apoE E4 when compared with the healthy controls without the apoE E4
Yuan et al (2010)[42]	ApoE ε4	MDD 37	Noncarrier/ carriers	16/9 8/4	69.91 ± 6.9 69.14 ± 6.0	sMRI, 1.5T	The volumes of right medial frontal gyrus, left middle frontal gyrus and left inferior occipital gyrus were significantly smaller in RLOD patients with ApoE ε4-allele carriers as compared to ApoE ε4-allele noncarriers
Watanabe et al (2015)[45]	COMT	MDD 30 HC 48	ValVal/ValMet	13/17 12/36		sMRI, 3.0T	Among the Val/Met individuals, the volume of the bilateral caudate was significantly smaller for MDD patients than for HS; in the Val/Val individuals, the caudate volume was comparable between MDD patients and HS
Pan et al (2009)[56]	COMT MTHFR	MDD 170 HC 83	ValVal/ValMet/ MetMet TT/CT/CC	112/58 61/22	69.4 ± 7.5 69.8 ± 5.6	sMRI, 1.5T	After controlling for covariates, depressed subjects with MTHFR C/C, both the right putamen and left putamen have smaller volumes as the number of COMT 158Val increases; the left putamen volumes of depressed subjects with COMT Met/Met are smaller as the number of MTHFR 677T increases compared to nondepressed subjects
Inkster et al (2010)[44]	GSK3β gene	MDD 134 HC 144		94/48 92/52	49.2 ± 13.4 50.0 ± 12.1	sMRI, 1.5T	We observed associations for polymorphisms in 8/13 canonical Wnt pathway genes and 5/10 GSK3β substrate genes, predominantly in the temporolateral and medial prefrontal cortices
Inkster et al (2009)[40]	GSK3β	MDD 134 HC 143	15 GSK3β SNP	84/48 91/52	49.3 ± 13.4 49.9 ± 12.1	sMRI, 1.5T	The most significant associations were found for rs6438552, a putative functional intronic SNP that showed 3 significant GM clusters in the right and left superior temporal gyri and the right hippocampus; a significant SNP MDD status interaction was observed for the effect on GM volumes in the right hippocampus and superior temporal gyri

(Continues)

TABLE 1 (Continued)

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Ueda et al (2016)[43]	NET	MDD 30 HC 48	G1287A T-182C	13/17 13/35	44.3 ± 13.0 41.2 ± 11.4	sMRI, 3.0T	A significant genotype (G1287A)-diagnosis interaction was found in the left dorsolateral prefrontal cortex
Han et al (2017)[41]	TPH-2	MDD 113 HC 86	GG/T-allele	90/23 59/27	42.78 ± 1.07 39.23 ± 1.46	sMRI, 3.0T	A significant genotype-by-diagnosis interaction for the local gyrification index in the right rostral anterior cingulate cortex
Dannlowski et al (2015)[37]	NCAN	MDD 171 HC 512	GG/A-allele	105/66 289/223	MDD AG/AA: 38.6 ± 12.5 GG: 38.7 ± 11.5 HC AG/AA: 33.9 ± 12.8 GG: 33.1 ± 11.3	sMRI, 3.0T	Risk (A)-allele carriers showed reduced amygdalar and hippocampal gray matter volumes in both cohorts with a remarkable spatial overlap; in the combined sample (MDD + HC groups), genotype effects observed for the amygdala and hippocampus survived correction for entire brain volume and also observed in the left orbitofrontal cortex and the cerebellum/fusiform gyrus
Stacey et al (2014)[48]	DISC1	MDD 171 HC 512	rs3738401 rs6675281 rs821616	105/66 289/223	38.6 ± 11.7 33.3 ± 11.7	sMRI, 3.0T	Region-of-interest analyses failed to reveal DISC1-associated morphological changes in the hippocampus, ACC, or striatum in MDD patients and healthy controls
Cole et al (2013)[49]	FTO	MDD 81 HC 69	TT/G carriers	54/27 38/31	48.56 ± 9.19 51.19 ± 7.99	sMRI, 1.5T	Significant effects of BMI were observed across widespread brain regions, indicating reductions in predominantly subcortical and white matter areas associated with increased BMI
Taylor et al (2012)[38]	AGTR1	MDD 257 HC 116	rs2638363; rs10935724; rs1492103; rs718858; rs12721331; rs2675511; rs389566; rs12695902; rs385338; rs5182	166/91 83/33	70.8 ± 7.1 72.7 ± 6.7	sMRI, 1.5T	Although hyperintense lesion volume did not significantly differ by any htSNP, dlPFC and hippocampus volumes differed significantly for several htSNPs; intriguingly, for those htSNPs differing significantly for both dlPFC and hippocampus volumes, the variant associated with smaller dlPFC volume was associated with larger hippocampal volume
Bermingham et al (2012)[39]	BICCI-1	MDD 44 HC 44	CC/T carriers	28/16 27/17	MDD T carriers 45.8 ± 9.3 CC 40.0 ± 10.3 HC T carriers 36.6 ± 11.8 CC 35.5 ± 13.4	sMRI, 3.0T	Right hippocampal bodies of patients and controls without a history of ELA and who carry the protective T-allele of BICC1 were significantly larger compared with those participants homozygous for the major C-allele of BICC1; MDD patients with ELA, who carry the T-allele, had smaller hippocampal head volumes compared with MDD patients without ELA
Zhang et al (2016)[51]	SLC6A15	MDD 86 HC 64	GG/A carriers	68/18 43/21	44.34 ± 12.34 41.69 ± 14.58	sMRI, DTI, 3.0T	MDD patients with the A-allele showed reduced FA values for the left PHC than did healthy controls with the A-allele

(Continues)

TABLE 1 (Continued)

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Hou et al (2010)[46]	ACE I/D	MDD 31	II/D carriers	7/4 14/6	71.1 ± 4.3 70.4 ± 4.2	sMRI, 1.5T	D-allele carriers exhibited significantly smaller white matter volumes of right superior frontal gyrus (SFG) and right anterior cingulate gyrus (ACG), but had larger volumes of left middle temporal gyrus (MTG) and right middle occipital gyrus (MOG) than I homozygotes
Hong et al (2009)[50]	MTHFR	MDD 178 HC 85	CC/CT/TT	116/62 58/17	69.9 ± 7.7 70.0 ± 5.7	sMRI, 1.5T	We found no statistically significant genotype-depression interaction
Won et al (2016)[54]	BclI C/G	MDD 42 HC 52	CC/G carriers	41/11 32/20	42.29 ± 12.35 42.73 ± 15.00	sMRI, DTI, 3.0T	MDD patients of the BclI minor (G-) allele carrier group showed significant alterations in left hippocampal shape and decreased FA values of the left parahippocampal cingulum compared to BclI minor (G-) allele carrier HCs
Han et al (2017)[47]	TESC	MDD 105 HC 85	TT/C carriers	86/19 60/25	43.1 ± 11.40 39.98 ± 13.49	sMRI, DTI, 3.0T	Significant interactive effects of rs7294919 and MDD in the volumes of the dentate gyrus and CA4; the methylation of CpG3 was significantly correlated with right PHC integrity in the MDD group

(5-HTTLPR: 12 studies, BDNF: 11 studies, ApoE ε4: 4 studies, COMT: 3 studies, NET: 2 studies, GSK3β: 2 studies). The other genes (TPH-2, HTR1A, HTR2A, NCAN, DISC1, FTO, AGTR1, BICCI-1, ACE, and MTHFR) were investigated in a single study.

3.2.1 | Genetic-neuroimaging association using VBM/ROI methods

The most frequently investigated genetic variants in relation to brain structures were BDNF and 5-HTTLPR genes. Several genetic-neuroimaging studies found that there were significant genotype (BDNF Val66Met)-diagnosis interactions in the hippocampus,[16-20] the orbitofrontal cortex,[17] the anterior cingulate, and the middle frontal regions.[21,22] However, some studies failed to verify the relationship between BDNF Val66Met polymorphisms and the hippocampus.[23-26] There were also some discrepant findings on the relationship between brain structural abnormalities and 5-HTTLPR genotypes. Numerous studies found effects of 5-HTTLPR genotype on the hippocampus,[26-29] the caudate nucleus,[30,31] the thalamus, and the putamen.[32] However, other studies did not find significant 5-HTTLPR genotype-diagnosis interactions in the hippocampus,[24,31,33] the amygdala,[31] or the orbitofrontal cortex.[34]

Hippocampal alterations were associated with genetic variants in ApoE ε4,[35,36] NCAN,[37] AGTR1,[38] BICCI-1,[39] GSK3β,[40] and TESC genes.[41] The significant associations between morphological alterations in prefrontal regions were observed for variants in ApoE ε4,[34,42] NET,[43] and GSK3β genes.[44] There was a significant genotype-diagnosis interaction in COMT,[45] ACE,[46] and TPH-2 genes.[47] Other studies failed to find reliable associations between brain structure and DISC1,[48] FTO,[49] 5-HT2A,[26] and MTHFR[50] genes.

3.2.2 | Synergistic effect of genetic polymorphisms on structural imaging

Two studies investigated multiple gene effects on brain structure in MDD patients. One study examined the impact of the BDNF, COMT, and SERT genes on both gray matter and white matter.[55] Another study focused on COMT/MTHFR polymorphisms and the putamen.[56] Kostic et al[55] found that MDD patients with all three risk polymorphisms showed structural alterations in fronto-occipital regions. Pan et al[56] observed that MDD patients who were MTHFR C homozygotes had smaller volumes of the bilateral putamina when they harbored increased numbers of COMT 158 Val polymorphism. In the same study, compared to HCs, MDD patients who were COMT Met homozygotes had smaller left putaminal volumes as the number of MTHFR 677T copies increased.

3.3 | Genetic-neuroimaging association using DTI methods

Studies using DTI methods have established associations between structural integrity of white matter in MDD patients and genetic

TABLE 2 Studies investigating the association between genetic polymorphisms and brain structure in MDD using functional magnetic resonance imaging (MRI)

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Cui et al (2016)[62]	LHPP	MDD 45 HC 115	CC/T carriers	32/13 66/49	27.13 ± 12.65 33.96 ± 14.25	rs-fMRI, 3.0T	The T carrier group showed increased ALFF in the left superior temporal gyrus; significant diagnosis × genotype interaction was noted in the bilateral lingual gyri, bilateral dorsal lateral prefrontal cortex (dlPFC), and left medial prefrontal cortex (mPFC)
Yin et al (2015)[58]	BDNF	MDD 26 HC 33	Met−/Met+	18/8 19/14	MDD: Met− 68.50 ± 6.99 Met+ 66.89 ± 5.43 HC: Met− 64.56 ± 10.05 Met+ 65.45 ± 6.19	rs-fMRI, 1.5T	BDNF Met-allele mainly decreased bilateral positive HFC with the cerebellum; The interaction between LOD and BDNF Met-allele primarily influenced the bilateral HFC with the temporal cortex and dorsal nexus
Shu et al (2014)[57]	APOE ε4	MDD 31 HC 29	No e4/e4	20/11 16/13	MDD: No e4 68.60 ± 4.73 e4 66.73 ± 3.52 HC: No e4 71.81 ± 3.81 e4 70.14 ± 4.88	rs-fMRI, 1.5T	When both factors coexisted, the left HFC network was significantly disrupted in the dorsal anterior cingulate cortex and increased in somatomotor and occipital regions; the extent of network alterations was linked to inferior cognitive performances in RGD patients and APOE ε4 carriers
Chen et al (2012)[61]	DAOA	MDD 53 HC 46	Ten SNPs			rs-fMRI, 3.0T	Six clusters in the cerebellum, right middle frontal gyrus and left middle temporal gyrus showed genotypic association between altered ReHo and rs2391191; the main effects of rs2391191 genotypes were found in the right culmen and right middle frontal gyrus.; the left uvula and left middle temporal gyrus showed a genotypes × disease status interaction
Wang et al (2012)[60]	ACE I/D	MDD 26 HC 24	II/D carriers	17/9 11/13	MDD: II 66.1 ± 2.5 D carriers 68.9 ± 5.0 HC: II 73.6 ± 3.7 D carriers 69.9 ± 4.0	rs-fMRI, 1.5T	There were significant interactions between disease and genotype at two clusters: left superior temporal gyrus/middle temporal gyrus and left cerebellum; there was a significant positive correlation between the functional connection of PCC-left cerebellum crus I and the CFT-delayed recall test scores in RGD group ACE-D-allele carriers
Liu et al (2014)[116]	GSK3β	MDD 88 HC 55	CC/TT/TC	37/51 27/28	31.56 ± 9.97 29.71 ± 7.49	rs-fMRI, 3.0T	Compared with CC carriers, T-allele carriers with MDD showed increased nodal centralities in many brain regions—mainly the limbic system, thalamus, and parts of the parietal, temporal, occipital, and frontal regions
Tozzi et al (2016)[74]	FKBP5	MDD 40 HC 43	CC/T carriers	27/13 27/16	MDD: CC 37.8 ± 9.91 T carriers 45.35 ± 10.74 HC: CC 36.43 ± 14.65 T carriers 36.00 ± 12.32	Task-fMRI, 3.0T	Patients carrying the high-risk allele, compared with patients not carrying it, showed reduced activity in the rolandic operculum, Heschl gyrus, insula, parahippocampal gyrus, posterior cingulate cortex, and inferior frontal gyrus; increased MD; and reduced FA measures in many of these regions

(Continues)

TABLE 2 (Continued)

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Guo et al (2014)[76]	5-HT2A MAOA	MDD 72 HC 70	TT/TC/CC; H/L	43/29 42/28	43.9 ± 10.7 44.1 ± 10.9	Task-fMRI, 1.5T	The activation intensity in right frontal middle gyrus of patients with CC genotype increased obviously compared with TT and TC genotype patient groups and TT genotype control group; the activation intensity in right frontal middle gyrus and left frontal inferior gyrus of patients with MAOA high-activity genotype increased obviously compared with patient and control groups with MAOA low-activity genotype
Backes et al (2014)[75]	CACNA1C	MDD 40 HC 40	GG/A carriers	21/19 21/19	MDD: GG 35.11 ± 11.77 A carriers 37.86 ± 9.99 HC: GG 32.63 ± 11.55 A carriers 32.95 ± 11.24	Task-fMRI, 3.0T	MDD with A-allele: increased task-related activation in the left middle/inferior frontal gyrus and the bilateral cerebellum (vs MDD with GG); MDD with A-allele: enhanced functional coupling between left middle/inferior and right superior/middle frontal gyri (vs MDD with GG)
Wu et al (2013)[59]	ApoE ε4	MDD 33 HC 33	No e4/e4	20/13 17/16	68.09 ± 4.56 71.48 ± 4.18	rs-fMRI, Task-fMRI, 1.5T	The FCs of the remitted late-onset depression patients without APOE4 were significantly increased in the resting state, but the remitted late-onset depression patients who carried APOE4 showed a trend toward decreased FCs
Domschke et al (2013)[71]	PCLO	MDD89 HC 29	Carriers/noncarriers	51/31 22/14	37.5 ± 10.1 39.3 ± 10.6	Task-fMRI, 3.0T	Depressed risk allele carriers showed significant lower activity relative to nonrisk allele carriers in the striatum, an effect which was absent in healthy controls; amygdala response during processing new positive words vs known words was blunted in healthy PCLO+ carriers and in MDD patients irrespective of the genotype
Costafreda et al (2013)[70]	5-HTTLPR	MDD 67 HC 49	Biallelic: LL/LS/SS; triallelic: LaLa/S or Lg/SS	43/24 26/23	49.6 ± 8.5 51.6 ± 6.3	Task-fMRI, 1.5T	Increased amygdala activity was associated with 5-HTTLPR genotype in low transcription allele carriers as well as with a diagnosis of depression; there were no interaction effects between genotype and diagnosis in amygdala activity or connectivity
Woudstra et al (2012)[63]	PCLO	MDD118 HC 41	PCLO+/PCLO−	71/39 31/18	38.17 ± 10.7 37.9 ± 10.2	Task-fMRI, 3.0 T	During processing of fearful faces, the PCLO risk allele was associated with increased amygdala activation in MDD patients only
Hsu et al (2012)[64]	CRHR1	MDD 16 HC 83	GG/A carriers	11/5 38/45		Task-fMRI, 3.0T	Among GG homozygotes, BOLD signal in the subgenual cingulate was greater in MDD patients (n = 9) compared to controls (n = 33); conversely, among A carriers, BOLD signal was smaller in MDD patients (n = 7) compared to controls (n = 50) in the hypothalamus, bilateral amygdala, and left nucleus accumbens

(Continues)

TABLE 2 (Continued)

Author	Candidate gene	Subjects, n	Genetic polymorphism	Female:male	Age [mean ± SD]	Methods	Main findings
Bermingham et al (2012)[39]	BICCI	MDD 44 HC 44	CC/T carriers	28/16 27/17	MDD T carriers 45.8 ± 9.3 CC 40.0 ± 10.3 HC T carriers 36.6 ± 11.8 CC 35.5 ± 13.4	Task-fMRI, 3.0T	fMRI showed that patients and controls carrying the protective T-allele of BICC1 activate the emotion regulation system significantly more compared with those participants homozygous for the major C-allele
Domschke et al (2010)[65]	NPY	MDD 35	TT/CT/CC	24/11	37.3 ± 12.6	Task-fMRI, 3.0T	The rs16147 C-allele was further associated with stronger bilateral amygdala activation in response to threatening faces in an allele-dose fashion
Baune et al (2010)[66]	IL1β	MDD 32	rs16944 rs1143634 rs1143643	22/10	37.8 ± 12.5	Task-fMRI, 3.0T	The number of G-alleles in both SNPs (rs16944 and rs1143643) was associated with reduced responsiveness of the amygdala and ACC to emotional stimulation
Lee et al (2009)[67]	TPH1	MDD 26	CC/A carriers	26/0	50.3 ± 5.9	Task-fMRI, 1.5T	A significant association between A-allele of the TPH1 A218C polymorphism and neural activations in response to negative facial stimuli; subjects with the A-allele of the TPH1 A218C polymorphism showed greater brain activity in the bilateral amygdala under the sad vs the neutral condition compared with subjects homozygous for the C- allele
Friedel et al (2009)[73]	5-HTTLPR	MDD 21 HC 21	LL/LS/SS (S = Lg + S)	5/16 6/15	40 ± 10; 38 ± 12	Task-fMRI, 1.5T	While in healthy controls, prefrontal (BA10) activation and BA10-amygdala coupling increased with the number of 5-HTT low-expression risk alleles, this effect was abolished, and even reversed, in patients with MDD
Dannlowski et al (2008)[72]	MAOAu-VNTR	MDD 34 HC 31	Low risk/high risk	23/11 18/13	36.9 ± 12.6 37.0 ± 11.5	Task-fMRI, 3.0T	Amygdala-prefrontal connectivity was significantly reduced in depressed patients and carriers of the higher active MAOA risk alleles (MAOA-H)
Dannlowski et al (2007)[68]	5-HTTLPR, 5-HT1A	MDD 27	SaSa/SaLg/ SaLa/LaLg/ LaLaGG/CG/ CC	20/7	36.7 ± 12.5	Task-fMRI, 3.0T	Risk allele carriers (5-HT1A-1019C/G: GG and CG; 5-HTTLPR/5-HTT-rs25531: SaSa, SaLg, SaLa, and LaLg) for either gene showed significantly increased bilateral amygdala activation in response to emotional stimuli, implicating an additive effect of both genotypes
Opmeer et al (2013)[94]	COMT	MDD 97 HC 28	MetMet/ MetVal/ValVal MetMet/ MetVal/Val			Task-fMRI, 3.0T	During emotional processing, there was an effect of genotype in a cluster including the amygdala and hippocampus
Dannlowski et al (2008b)[120]	5-HTTLPR	MDD 35 HC 31	LaLa/LgLa/SLa/ SLg/SS	18/10 15/13	38.6 ± 12.2 36.8 ± 12.2	Task-fMRI, 3.0T	Risk allele carriers (S or LG) demonstrated increased amygdala reactivity to masked emotional faces

variants of SLC6A15,[51] BDNF,[52] 5-HTTLPR,[53] BclI C/G,[54] and TESC genes.[41] Variants in SLC6A15 and BclI C/G genes were found to be associated with abnormalities of the parahippocampal cingulum, and variants in the BDNF gene were found to have a significant association with fiber tracts connecting hippocampus and amygdala.[52] Furthermore, Alexopoulos et al[53] suggested that fractional anisotropy (FA) values in frontolimbic and subcortical and posterior areas were significantly decreased in 5-HTTLPR S-allele carriers with depression.

3.4 | Association of genetic polymorphisms with functional MRI

Twenty-one studies used fMRI to investigate the association between genetic-neuroimaging and 15 risk candidate genes. Two of these studies investigated the synergistic effect of 5-HTR2A and MAOA, and 5-HTTLPR and 5-HTR1A. Three of 15 risk candidate genes were investigated in replication studies (5-HTTLPR: 3 studies; ApoE ε4: 2 studies; PCLO: 2 studies). The other genes (BDNF, BICCI-1, ACE, DAOA, CACNA1C, LHPP, FKPB5, CRHR1, NPY, IL1 β, TPH1, MAOA) were investigated in a single study.

3.4.1 | Genetic-neuroimaging association using rs-fMRI

In studies using rs-fMRI, genetic polymorphisms (LHPP, BDNF, APOE ε4, DAOA, and ACE I/D genes) were associated with particular patterns of brain activity in MDD patients. Alterations in hippocampal functional connectivity networks were associated with genetic variants in BDNF and APOE ε4 genes.[57,58] Associations between APOE ε4 and ACE genes and functional connectivity of a default-mode network have also been reported.[59,60] An association between the DAOA gene and activity was found in left uvula of cerebellum and left middle temporal gyrus among people with MDD,[61] and significant LHPP genotype-diagnosis effects existed in the bilateral dorsal lateral frontal cortex and left medial prefrontal gyrus in another study.[62]

3.4.2 | Genetic-neuroimaging association using task-fMRI

In functional genetic-neuroimaging studies of MDD patients using task-fMRI, the most frequently reported regional brain activation was for the amygdala. Amygdalar activation alterations have been found to be associated with genetic variants in PCLO,[63] CRHR1,[64] NPY,[65] IL1β,[66] TPH1,[67] 5-HTTLPR, and 5-HT1A genes[68,69] during emotion processing. However, other studies have failed to provide evidence implicating the PCLO or 5-HTTLPR genes.[70,71] MDD patients with an MAOA H-allele showed significantly lower amygdala-prefrontal connectivity,[72] but not in those with 5-HTTLPR genetic variants.[70,73]

Other studies have reported significant genotype-diagnosis interaction effects on emotional regulation systems for FKBP5,[74] CACNA1C,[75] CRHR1,[64] and BICCI[39] genes. The remaining studies showed decreased activation of the striatum with a PCLO risk allele, decreased activation of right frontal middle gyrus in a 5-HT2A T-allele, or decreased connectivity of amygdala-prefrontal circuitry with the MAOA H-allele.

3.4.3 | Synergistic effects of genetic polymorphisms on functional imaging

Two studies have investigated the synergistic effects of genetic polymorphisms on functional neuroimaging in MDD patients during emotional processing tasks, including the 5-HT2A and MAOA genes,[76] and the 5-HTTLPR and 5-HT1A genes.[69] Significant synergistic effects were observed in MDD patients with both 5-HT2A CC and MAOA H-allele who had the highest negative activation intensity in the right frontal middle gyrus during an emotional recognition task.[76] Dannlowski et al[68] found that bilateral amygdalar activation during emotional processing significantly increased with the number of risk alleles (5-HT1A G-allele, 5-HTTLPR S- and L_G-allele).

4 | DISCUSSION

In this systematic review, we aimed at elucidating the effects of genetic variants on structural and functional neuroimaging in MDD. Numerous genetic-neuroimaging studies strengthen our understanding of the functional effects of genetic polymorphisms on brain imaging alterations in MDD. Given that genetic polymorphisms are implicated in some common hypotheses of the pathogenesis of MDD, we categorize these candidate genes into monoaminergic genes, HPA axis-related genes, BDNF genes, glutamatergic genes, and other genes (RAS system-related genes, APOE ε4 gene, and GSK3β gene).

4.1 | Association of monoaminergic genes with neuroimaging

The monoamine-deficiency hypothesis suggests that monoaminergic neurotransmitters (serotonin and epinephrine) are involved in the pathophysiology of MDD and are associated with antidepressant response.[77-79] Monoaminergic genes play critical roles in brain morphology and activation via regulating the function of monoaminergic neurotransmitters.

4.1.1 | Genetic-neuroimaging association in serotonergic genes

Serotonergic genes associated with neuroimaging alterations were those encoding serotonin biosynthesis enzymes: tryptophan hydroxylase-1 (TPH1) and tryptophan hydroxylase-2 (TPH2) genes; serotonin receptors: serotonin receptor 1A (HTR1A) and serotonin receptor 2A (HTR2A) genes; and serotonin transporter: serotonin transporter polymorphism (5-HTTLPR/SLC6A4) gene.

Both TPH1 and TPH2 genes encode TPH, which is the rate-limiting enzyme in the biosynthesis of 5-HT.[80,81] Depressed patients with TPH2 G homozygosity showed abnormal functional connectivity in the anterior cingulate cortex.[47] A potential explanation for this is that the expression of TPH2 polymorphism is related to serotonin levels in the cingulate cortex.[82] Consistent with this, one study[67] found a significant association between TPH1 polymorphism and bilateral amygdalar activity in MDD patients.

The G-variant of 5-HTR1A-1019C/G depresses 5-HT_{1A} autoreceptor expression and reduces serotonergic neurotransmitters in limbic brain regions, including the hippocampus and the amygdala.[83] The HTR2A gene encodes the 5-HT_{2A} receptor, which is an inhibitory receptor that reduces the excitability of the neuron after stimulation. HTR1A polymorphisms affect the number and shape of dendritic spines in the hippocampus via regulating 5-HT_{1A} receptor activation.[84] Consistent with this, homozygosity for the HTR1A G-allele carriers has been shown to be associated with significantly increased hippocampal volumes and bilateral amygdala activation relative to C-allele carriers.[26,85] Significant interaction effects between HTR2A polymorphisms and diagnosis were found during right frontal middle gyrus activation.[76] This finding is in line with a previous study that reported that the 5-HT_{2A} receptor, but not 5-HT_{1A} receptor, had higher concentrations on the prefrontal cortex.[86]

The triallelic 5-HTTLPR gene (Lg-allele, La-allele, and S-allele) regulates the level of serotonin transporter transcription and serotonin neurotransmission. The LaLa genotype has been shown to have a higher level of 5-HTT transcription expression and serotonin reuptake than S'-allele (Lg- or S-allele).[87] Several studies have focused on the effects of the 5-HTTLPR S'-allele on hippocampal volumes, but this association is still controversial: smaller volumes,[26-28] larger volumes,[11] and even unchanged volumes[24,31-33] have been reported. The discrepancies between studies seem to be supported by the suggestion that 5-HTTLPR polymorphisms may moderate the potential effects of stress on the hippocampus and amygdala, as well as on the other brain regions.[28,88] Stress alters neuronal plasticity, suppresses neuronal proliferation, and changes neuronal morphology in brain regions such as the dentate gyrus and CA3 regions of the hippocampus.[89] These findings provide some indication that structural and functional neuroimaging alteration may be mediated by stress.[13]

4.1.2 | Genetic-neuroimaging association in the norepinephrinergic gene

The norepinephrine transporter (NET) gene is located on the chromosome 16q12.2, whose encoding protein regulates norepinephrine reuptake by the presynaptic terminal.[90] The NET/SLC6A2 genotype (G1287A) has been associated with dorsolateral prefrontal cortex volume[43] and hippocampal volume.[26] A previous study found that a NET G/G genotype had lower norepinephrine levels.[91] Hence, abnormal brain morphology may result from abnormal level of norepinephrine, which plays a critical role in neuronal differentiation, neurogenesis, and neurodegeneration.[92]

4.1.3 | Genetic-neuroimaging association in MAOA and COMT genes

The catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAOA) genes are involved in the metabolic activity of monoamines in the brain. COMT polymorphisms affect its enzyme activity, which in turn regulates monoamine metabolism. The MAOA gene regulates the biosynthesis of MAOA, which affects the level of monoamine neurotransmitters in the brain.[93] Significant interaction effects of COMT genotype-diagnosis were observed in the right caudate and inferior frontal gyrus in two studies.[45,94] Depressed patients with MAOA polymorphisms showed abnormal amygdala-prefrontal connectivity and activation.[72,76] As mentioned above, the low level of norepinephrine leads to abnormalities of neuronal differentiation, resulting in abnormal brain morphology and activation.[92]

Based on these findings, structural and functional imaging alterations would be predisposing traits and endophenotypes for the development of MDD.[12]

4.2 | Association of BDNF genes with neuroimaging

Brain-derived neurotrophic factor is involved in synaptic plasticity and neurogenesis in the brain, which may play a critical role in the pathophysiology of depression.[95] A single-nucleotide polymorphism (rs6265) in the BDNF gene produces an amino acid substitution (valine to methionine) at codon 66 (Val66Met), which affects the intracellular packaging and decreases the activity-dependent secretion of BDNF.[95] The effect of BDNF genetic variations on brain structure and function is mainly focused on the hippocampal and frontal regions.

Several studies found that depressed subjects who are Met carriers had significantly smaller hippocampal volumes.[16-18] However, this finding was not evident or even reversed in other studies.[19-21,24-26,32] A previous meta-analysis found that there is no association between hippocampal volumes and a BDNF Val66Met polymorphism.[96] Another meta-analysis reported that there was a significant interaction between life stress and BDNF polymorphisms in depression,[97] suggesting that life stress may contribute to hippocampal volume alterations in depression. The BDNF gene and the hippocampus are highly sensitive to stress, which can induce dendritic retraction and neuronal body loss in the hippocampus.[98] In summary, the association between BDNF Val66Met polymorphisms and hippocampal volumes in MDD patients remains inconclusive and needs to be elucidated in future research.

Major depressive disorder patients with the Met-allele have been found to have significantly smaller caudal middle frontal thickness,[22] reduced rostral middle frontal and anterior cingulate surface area[22], smaller left middle frontal gyrus volume,[21] and higher right orbitofrontal cortex volume[17] than controls. However, Jaworska et al[32] reported an inconsistent finding in that there were no significant BDNF genotype-diagnosis interaction

effects on frontal, cingulate, and temporal cortical thickness. As mentioned above, stress can cause dendritic retraction and induce brain atrophy. These effects were also observed in anterior cingulate, medial and lateral prefrontal cortices, and orbitofrontal cortex.[98,99]

4.3 | Association of HPA axis-related genes with neuroimaging

Evidence indicates that the hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the development of MDD and responses to adverse life experiences.[100,101] Both FKBP5 and CRHR1 are involved in the regulation of the HPA-negative feedback loop. FKBP5 genes were shown to regulate glucocorticoid receptor sensitivity by reducing nuclear translocation and hormone-binding affinity of glucocorticoid receptors.[102] CRHR1 genetic variants may influence the function of the neural circuit, which was associated with stress-related MDD.

In this systematic review, neuroimaging alteration in MDD was found to be associated with FK506-binding protein 51 (FKBP5) and corticotropin-releasing hormone receptor 1 (CRHR1) genes.[64,74] The dysfunction of glucocorticoid receptor and endogenous glucocorticoid levels impair the HPA axis feedback inhibition in depressed patients. Abnormal glucocorticoid levels can inhibit neural proliferation and encourage dendritic atrophy, which in turn causes brain structural and functional alterations.[103] Therefore, FKBP5 and CRHR1 genes are associated with neuroimaging abnormalities in MDD by impairment of the function of HPA axis.

4.4 | Association of glutamatergic genes with neuroimaging

In this review, neuroimaging alterations were found to be associated with two glutamatergic genes: D-amino acid oxidase activator (DAOA) and SLC6A15. The expression of the DAOA gene may influence the functioning of NMDA-type glutamate receptors by degrading the D-serine metabolism, which in turn leads to glutamate dysfunction.[104,105] The SLC6A15 gene encodes a sodium-dependent branched-chain amino acid transporter, which regulates the expression of glutamate receptors and influences glutamate synthesis.[106] Studies have revealed that glutamate dysfunction, glutamate receptor abnormalities, and glutamate excitotoxicity may be possible pathophysiological mechanisms of MDD.[107] The DAOA rs2391191-diagnosis interaction effects may contribute to the abnormality of regional homogeneity in depressed patients.[61] Zhang et al (2016) found that depressed patients with a SLC6A15 A-allele had decreased FA values for the left parahippocampal cingulum than HCs with the same genotypes. Another study revealed that SLC6A15 polymorphisms were associated with specific brain region alterations in healthy subjects, suggesting a potential mechanism leading to susceptibility to MDD.[108] Based on these findings, DAOA and SLC6A15 genes may contribute to genetic risks for neuroimaging alterations in MDD.

4.5 | Genetic-neuroimaging association in other genes

Our systematic review found that some genes in the renin-angiotensin-aldosterone system (RAA system) were significantly associated with neuroimaging alterations in MDD patients. The other most frequently studied genes (at least 3 studies) with significant genetic-neuroimaging association were the APOE ε4 and GSK3β genes.

4.5.1 | Association of RAS system-related genes with neuroimaging

Recent evidence indicates that the RAA system may be involved in the pathophysiology of MDD and be a potential target for depression treatment.[109,110] Diverse studies have found that neuroimaging alterations in MDD were associated with angiotensin-converting enzyme insertion/deletion (ACE I/D) and type 1 angiotensin II receptor (AGTR1) genes. ACE-D carriers showed significantly smaller anterior cingulate gyrus volumes and larger middle temporal gyrus volumes,[46] as well as decreased default-mode network activity in remitted geriatric depression.[60] A similar pattern was observed in AGTR1 polymorphisms in that genetic variation was associated with frontotemporal morphology.[38] ACE D-allele downregulates ACE expression, which in turn modulates the level of angiotensin II.[111] The AGTR1 gene encodes the primary angiotensin II receptor.[112] Both of them are involved in the regulation of angiotensin II. Vian et al[110] proposed that angiotensin II and its receptors, a key part of the RAS system, may be involved in the regulation of neuroinflammation and the HPA axis. Hence, the effects of AGTR1 and ACE I/D genes on neuroimaging may have been mediated by other factors.

4.5.2 | Association of the APOE ε4 gene with neuroimaging

While the ApoE ε4-allele is known to be a genetic risk factor for Alzheimer's disease, its association with depression remains inconclusive.[113] Geriatric depressed patients with an ApoE ε4-allele show abnormal hippocampal morphology[35,36] and functional networks,[57] as well as abnormal functional connectivity in the DMN.[59] The association between ApoE ε4 and depression is predominantly observed among older people. Although the mechanisms underlying this relationship remain unclear, geriatric depression on those with the ApoE ε4-allele may be an early manifestation of the Alzheimer's disease.

4.5.3 | Association of the GSK3β gene with neuroimaging

Abnormally active glycogen synthase kinase-3beta (GSK3β) may contribute to the pathophysiology of MDD[114] and affect antidepressant responses.[115] Several studies revealed that GSK3β genetic variants were associated with morphological alteration in hippocampus and the temporal lobe,[40] as well as medial prefrontal cortices,[44] and also abnormal functional brain activity in the thalamus and parts of the occipital and

parietal regions.[116] Loss of neuronal GSK3β is involved in impairment of hippocampal proliferation and alteration of dendritic spine morphology, which results in high vulnerability to depression-like behavior in rat brains.[114,117] These findings suggest that GSK3β polymorphisms and their interaction with major depression may result in altered topological organization of brain structural and functional networks.

4.6 | Synergistic effects of genes in neuroimaging

As noted above, serotonergic genes and MAOA polymorphisms can regulate serotonin levels in the brain, implying that neuroimaging alteration can possibly be partly ascribed to the synergistic effects of numerous genetic variants. A synergistic effect on neuroimaging alteration was observed in COMT and MTHFR,[56] 5-HTR2A and MAOA,[76] and 5-HTTLPR and 5-HTR1A[69] polymorphisms, as well as 5-HTTLPR, BDNF, and COMT polymorphisms.[55]

COMT polymorphism regulates the expression of COMT enzyme, which influences monoamine neurotransmitter levels.[118] Pan et al[56] found that the interaction between the MTHFR genotype and COMT genotype was associated with putamen volumes, whereas neither genetic variant independently affected brain morphology. A similar pattern was observed in 5-HTR1A and 5-HTTLPR genetic variants in that depressed patients with both genotypes showed the highest amygdalar activity during emotional processing.[69] The cumulative effects of 5-HTTLPR, BDNF Val66Met, and COMT polymorphisms were observed in fronto-occipital cortices and corpus callosum.[55] Another study reported that depressed patients with both a 5-HTR2A CC-allele and MAOA-H genotype had the strongest negative activation in the right frontal middle gyrus.[76] A possible explanation for this is that 5-HTR1A, 5-HTR2A, and 5-HTTLPR genetic variants are engaged in the regulation of serotonin levels in the brain, while MAOA polymorphisms are involved in the catabolism of serotonin. Susceptibility genes alone exert small effects on brain morphology, but the synergistic effects of numerous genes may result in neuroimaging alteration.[8]

4.7 | Limitations

Some limitations of this systematic review must be considered when interpreting these findings. The most important is the methodological discrepancies across included studies. Some studies did not include HC subjects, and the effects of risk genes on neuroimaging were compared between MDD patients with and without risk genetic variants, but not healthy subjects with risk genetic variants. On the other hand, some studies conducted multiple comparisons among 2 × 2 genotype-and-disease interaction. Another limitation is the discrepancy of demographic characteristics, such as mood status, the age of depressed patients, the duration of illness, and the use of antidepressants. For example, hippocampal volume alterations were mediated by early-life stress, duration of illness, and antidepressant treatment. Lastly, the imaging methods varied across included studies. For example, some studies used whole-brain-analysis methods to investigate morphological alterations in the brain, while others used ROI-based analysis.

5 | CONCLUSIONS

This systematic review indicates that genetic-neuroimaging studies may provide new insights into MDD. Abnormalities of vital brain regions involved in neural circuits may contribute to the susceptibility to MDD. Although precise mechanisms of genetic-neuroimaging association are yet to be elucidated, genetic variations may produce endophenotypes of MDD by mediating morphological and functional brain alterations. Furthermore, we found that the effects of genetic variants on neuroimaging may inform some hypotheses related to the pathophysiology of MDD, such as the monoamine-deficiency hypothesis, the glutamatergic hypothesis, and the neurotrophic hypothesis. However, some studies of candidate genes showed inconsistent findings that were not replicated in other studies. Therefore, further research is needed to focus on the field of genetic-neuroimaging connectomics in MDD.

CONFLICT OF INTEREST

No conflict of interests are reported.

ORCID

Dai-Hui Peng http://orcid.org/0000-0003-4338-967X

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