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RESEARCH ARTICLE

Altered cerebral activities and functional connectivity in depression: a systematic review of fMRI studies

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***Background*: As one of the leading causes of global disability, major depressive disorder (MDD) places a noticeable burden on individuals and society. Despite the great expectation on finding accurate biomarkers and effective treatment targets of MDD, studies in applying functional magnetic resonance imaging (fMRI) are still faced with challenges, including the representational ambiguity, small sample size, low statistical power, relatively high false positive rates, *etc*. Thus, reviewing studies with solid methodology may help achieve a consensus on the pathology of MDD.**

***Methods*: In this systematic review, we screened fMRI studies on MDD through strict criteria to focus on reliable studies with sufficient sample size, adequate control of head motion, and a proper multiple comparison control strategy.**

***Results*: We found consistent evidence regarding the dysfunction within and among the default mode network (DMN), the frontoparietal network (FPN), and other brain regions. However, controversy remains, probably due to the heterogeneity of participants and data processing strategies.**

***Conclusion*: Future studies are recommended to apply a comprehensive set of neuro-behavioral measurements, consider the heterogeneity of MDD patients and other potentially confounding factors, apply surface-based neuroscientific network fMRI approaches, and advance research transparency and open science by applying state-of-the-art pipelines along with open data sharing.**

Keywords: depression; resting-state fMRI; task-based fMRI; default mode network; frontoparietal network

Author summary: Major depressive disorder (MDD) is a prevalent disorder and places noticeable societal burdens, however, findings of objective biomarkers in previous researches were inconsistent. In this systematic review, to detect more reproducible MDD-specific brain circuits, fMRI studies on MDD are screened by strict criteria that carefully minimize the effect of fMRI methodology issues. Though dysfunction in the default mode network (DMN) and the frontoparietal network (FPN) was repeatedly reported, heterogeneity remains in the included studies. Based on these findings, we highlight the necessity of considering some specific potentially confounding factors in future fMRI studies on MDD.

INTRODUCTION

Major depressive disorder (MDD) is a prevalent disorder and places noticeable societal burdens [1]. For the recent 20 years, it has been stably listed in the leading 20 causes of global disability across ages and genders, which account for 37% of the total disability caused by mental disorders [2]. Despite the burgeoning methodological advances of neuroimaging, the current diagnosis approach of MDD is mainly based on the clinical interview or patient rating scales, which is associated with high rates of misdiagnosis [3]. Recent advances in neuroimaging techniques have made it possible to leverage the brain's functional architecture towards the objective biomarker of MDD. With advantages of simpleness, non-invasiveness, safety, and relatively high spatial and temporal resolutions [4], functional magnetic resonance imaging (fMRI) method, especially resting-state fMRI (R-fMRI) method, has enabled to depict of dynamic maps of the brain and carry great expectations on finding biomarkers and effective treatment targets of MDD.

Unfortunately, though a large number of studies have been conducted, few consensuses have been reached on the neural mechanism of depression. Several challenges for fMRI studies have been noted, including between-subject and within-subject variability, the representational ambiguity, small sample size, low statistical power, relatively high false positive rates, and lack of consistency in data preprocessing procedures and statistical analysis [5–8]. For instance, the challenge of small sample size has been proposed to dampen the reliability of the fMRI results directly. Moreover, the between-participant variability that significantly impacts the reliability of fMRI studies is limited by the measurement and the experimental design, especially in task-based fMRI studies [8].

To deal with the current challenges in fMRI studies, researchers have highlighted a couple of recommendations on the designs of study, preprocessing pipelines, and strategies to correct multiple comparisons. These recommendations included performing adequate confound regression strategies [9–11] and multiple comparison correction, enlarging the sample size, and openly data sharing [12–14]. Chen and his colleagues assessed the test-retest reliability of fMRI studies and found studies with small sample sizes (< 40 per group) are not well reliable [14]. Head motions of subjects in an MRI scanner can produce artifacts, leading to results not caused by the "real" intrinsic brain functions [15,16]. Thus, adequate head motion corrections should be included to get reliable results. Eklund *et al.* reported that the liberal thresholding strategies commonly used in the field of neuroimaging could cause high false positive rates [17], which emphasized the significance of the effective multiple comparison correction, such as permutation test with threshold-free cluster enhancement (TFCE) and false discovery rate (FDR) based correction [14,18,19]. Moreover, within-subjects designs, paired repetitive measurements, and meta-analyses have also been noted as effective ways to reduce the false positivity in brain imaging studies [12,20].

Therefore, it is clear that adequate sample size, confound regression strategies, and strict enough threshold for the multiple comparison correction are important and necessary. In the present systematic review, we screened studies according to the criteria such as sufficient sample size (*i.e.*, more than 40 participants per group according to the findings of our previous study [14]), proper head motion correction, appropriate correction strategies for multiple comparisons (*e.g.,* FWE correction with voxel-wise $P < 0.001$ and cluster-wise $P < 0.05$ or permutation test with TFCE, FDR correction with $q < 0.05$). Through this strict screening for studies, we intend to focus on more reliable studies in this review and to get more reproducible and reliable results with less false positivity to some extent. We aim to reach a consensus on the key brain circuits in MDD. Finally, we also intended to raise some suggestions and directions for further fMRI studies on MDD.

RESULTS

General information

In the first step for article identification in PubMed, 1,012 papers were obtained and fed into the next screening procedures. After the first screening of titles and abstracts, most review and comment articles, the structural MRI studies, and the studies not focusing on MDD were excluded, with 462 lefts. Then, the full texts of these fMRI studies on depression were read through and screened by the relatively strict criteria (see materials and methods) for their qualities, leaving a final sample of 39 studies (Table 1), of which 25 were R-fMRI studies, 17 were task-based fMRI (included 9 meta-analysis studies [49–51,53,55–59] and 3 multi-modality studies with both resting-state and task-based fMRI [36,46,56]). Note that some multi-modality studies only reported significant results regarding one modality (*i.e.*, resting-state or task-based fMRI), so they were listed in only one result table.

Most of the early MRI studies on depression were structural MRI studies, in which the earliest one found in this searching was published in 1993 [60]. The recent 10 years have witnessed the rise of fMRI studies and multi-modality studies (the earliest fMRI study included

Table 1 A summary of all the included articles

Study	Group	Sample size	Realignment	Strategy to control multiple comparisons
Demenescu *et al*. 2011 [21]	HCs	56	SPM5 realignment	q_FDR < 0.05
	MDD	59		
	Anxiety disorders	57		
	Depression-anxiety co-morbidity	66		
van Tol *et al*. 2011 [22]	Outpatients with MDD	65	SPM5 realignment; excluded when movement > 3 mm	P_FWE < 0.05
	MDD with comorbid anxiety	82		
	Anxiety disorders without MDD	64		
	HCs	63		
Bermingham *et al*. 2012 [23]	MDD	44	SPM8 realignment; excluded when movement > 4.8 mm (one slice thickness)	P_FWE_wholebrain < 0.05
	HCs	44		
Yang *et al*. 2015 [24]	MDD	50	Excluded when movement > 2 mm in x, y, or z and 2° of angular motion	P_Alphasim_Monte_Carlo < 0.001
	HCs	50		
Gollier-Briant *et al*. 2016 [25]	Healthy adolescents	685 (368 girls)	SPM8 realignment	P_FWE < 0.05
Posner *et al*. 2016 [26]	High family risk	57	SPM8 realignment	q_FDR < 0.05
	Low family risk	47		
Casement *et al*. 2016 [27]	Longitudinal study from age 9–13	123	SPM8 realignment	P_Alphasim < 0.05
Hermesdorf *et al*. 2016 [28]	MDD	368	DPARSF 2.3 realignment	P_Alphasim_Monte_Carlo < 0.05 (p < 0.01 for single voxel)
	HCs	461		
Davey *et al*. 2017 [29]	MDD	71	SPM12 realignment; excluded movement > 2 mm or 2°	P_FWE_whole_brain < 0.05
	HCs	88		
Yüksel *et al*. 2017 [30]	Healthy subjects with MDD risk scores	107	SPM8 realignment	P_Monte_Carlo_whole_brain < 0.05 (cluster level)
Ye *et al*. 2017 [31]	First-episode and untreated MDD patients	69	DPARSF realignment	P_AlphaSim < 0.001 with more than 6 voxels of cluster size
	HCs	81		
Pan *et al*. 2017 [32]	No MDD at follow-up	529	Yes (used AFNI, version 2011_12_21_1014, and the FMRIB Software Library, version 5.0)	P_Bonferroni < 0.05/55 = 0.00091
	MDD at follow-up	56		
Admon *et al*. 2017 [33]	Unmedicated depressed participants	46	SPM12 realignment	P_FWE_whole_brain < 0.05
	HCs	43		
Lopez *et al*. 2018 [34]	MDD-Hx	58	Six head realignment parameters	q_FDR < 0.05 (for a given seed)
	No MDD-Hx	85		
Mehta *et al*. 2018 [35]	MDD patients	48	Yes	P_AFNI_3dClustsim < 0.05
Qi *et al*. 2018 [36]	MDD patients	81	SPM8 INRIalign	q_FDR < 0.05
	HCs	123		
Tokuda *et al*. 2018 [37]	MDD patients	67	SPM8 Realignment	P_ Bonferroni < 0.05
	HCs	67		
Tu *et al*. 2018 [38]	MDD outpatient	76	SPM8 Realignment	q_FDR < 0.05
Wang *et al*. 2019 [39]	MDD patients	55	DPABI realignment; excluded movement > 2 mm or 2°	P_GRF_voxel < 0.001; P_GRF_cluster < 0.05
	HCs	40		
Fitzgerald *et al*. 2019 [40]	GAD patients	47	SPM8 Realignment	P_FWE < 0.05
	SAD patients	78		
	MDD patients	49		

(*continued*)

Study	Group	Sample size	Realignment	Strategy to control multiple comparisons
Xia *et al.* 2019 [41]	MDD patients	709	SPM12 realignment	q_FDR < 0.05; P_Bonferroni < 0.05;
	HCs	725		
Yao *et al.* 2019 [42]	MDD patients	55	SPM8 realignment	q_FDR <0.05
	HCs	71		
Chin Fatt *et al.* 2020 [43]	Sertraline arm of depression	139	SPM8 realignment	P_Multiple Comparison < 0.05
	Placebo arm of depression	140		
Zhu *et al.* 2020 [44]	MDD with NSE	42	SPM12 realignment	P_FWE < 0.05 (cluster level)
	MDD with LSE	54		
Hilland *et al.* 2020 [45]	Previous depression with placebo	70	FMRIB Software Library version (FSL version 6.00)	TFCE with 5000 permutations; and FSL FEAT correction with p (cluster) < 0.05
	Previous depression with ABM training	64		
Korgaonkar *et al.* 2020 [46]	MDD patients	163	Yes	q_FDR < 0.05
	HCs	62		
Rupprechter *et al.* 2020 [47]	MDD patients	130	SPM12 realignment	P_whole_brain_corrected < 0.001
	HCs	345		
Yang *et al.* 2020 [48]	MDD with NSE	42	DPABI realignment	P_FWE < 0.05
	MDD with LSE	54		
Graham *et al.* 2013[a] [49]	MDD patients	566	/	q_FDR < 0.05
	HCs	599		
Groenewold *et al.* 2013[a] [50]	MDD patients	795	/	q_FDR < 0.05 or P_uncorrected < 0.001
	HCs	792		
Zhang *et al.* 2013[a] [51]	MDD patients	341	/	q_FDR < 0.05
	HCs	367		
Iwabuchi *et al.* 2015[a] [52]	MDD patients	225	/	P < 0.005
	HCs	230		
Wang *et al.* 2015[a] [53]	MDD patients	160	/	P < 0.005
	HCs	203		
Zhong *et al.* 2016[a] [54]	MDD patients	457	/	P < 0.001
	HCs	451		
Wang *et al.* 2017[a] [55]	First-episode drug-naïve MDD patients	VBM: 471; ALFF: 261	/	P < 0.005
	HCs	VBM: 521; ALFF: 278		
Kambeitz *et al.* 2017[a] [56]	MDD patients	912	/	P < 0.005
	HCs	894		
Zhou *et al.* 2017[a] [57]	MDD patients	438	/	P < 0.001
	HCs	421		
Keren *et al.* 2018[a] [58]	MDD patients or non-depressed subjects at-risk of MDD	653	/	P < 0.005
	Depression on continuum	503		
	HCs	828		
Sha *et al.* 2018[a] [59]	Patients across 11 brain disorders	6683 (817 depressive disorder patients)	/	P_FDR/GRF < 0.05
	HCs	6692		

[a] Meta-analysis (a threshold of uncorrected P < 0.005 was also accepted for meta-analytic studies). Abbreviations: MDD (major depressive disorder), HCs (healthy control subjects), MDD-Hx (history of MDD), GAD (generalized anxiety disorder), SAD (social anxiety disorder), NSE (normal sleep efficiency), LSE (low sleep efficiency); VBM (voxel-based morphometry), ALFF (amplitude of low-frequency fluctuations), FWE (family-wise error), FDR (false discovery rate), TFCE (thresholdfree cluster enhancement).

in this review was published in 2011 [22], see Table 1). Among studies reviewed here, a meta-analysis examined multiple neuroimaging methods and reported the lower sensitivity and specificity of structural MRI and task-based fMRI methods than R-fMRI in the differentiation of MDD patients from healthy control subjects (HCs) [56], which may occur due to the introduction of the potential complexity from task design and manipulation in measuring dynamic brain functions and which implies the advantages of R-fMRI in identifying neuroimaging markers for MDD [61].

Table 1 shows that SPM [62], DPABI [63], FSL [64], and AFNI [65], realignment tools are most commonly used in the literature. All the included studies have applied head motion corrections, but some omitted key details regarding the nuisance covariates regression they applied. For example, simply "realignment" or "applying head motion correction" was declared in the methods section without further description. Moreover, a large proportion of studies were excluded due to the small sample size and inadequate multiple comparison strategies.

Results from R-fMRI studies

Altered spontaneous functional activities in MDD

Nine R-fMRI studies reported the abnormal functional metric values in MDD patients vs. HCs, including the regional homogeneity (ReHo), the amplitude of low-frequency fluctuations (ALFF), and the fractional amplitude of low-frequency fluctuations (fALFF) (Table 2).

Four studies reported abnormally increased ReHo values in the left precuneus, the inferior frontal gyrus (IFG), and the medial prefrontal cortex (MPFC), as well as abnormally decreased ReHo values in the left putamen, the right postcentral gyrus (poCG), the right poCG and the lingual gyrus (LG) in patients with MDD [24,41,48,52]. Three studies reported abnormally increased ALFF in the IFG, the supplementary motor area (SMA), the left parahippocampal gyrus (PHG), the left anterior cingulate cortex (ACC), and the left superior temporal gyrus (STG) and abnormally decreased activation in the orbitofrontal cortices (OFC), the left cerebellum and the left middle temporal gyrus (MTG) [41,55,57]. Three studies reported abnormally increased fALFF in the visual cortex (VC), as well as abnormally decreased fALFF in the cuneus, the thalamus, MTG, the hippocampus, PHG, the amygdala, the dorsolateral prefrontal cortex (dlPFC), the insula, ACC, the superior frontal gyrus (SFG) and the inferior parietal lobule (IPL) [36,44,57].

Among these findings, abnormally decreased ALFF and fALFF in MTG [44,57] and reduced ReHo in poCG [41,48] were reported convergently. Furthermore, altered spontaneous activities in PHG and ACC were reported, albeit in opposite directions [36,55,57].

Altered resting-state functional connectivity in MDD

Fourteen studies reported abnormal functional connectivity in the resting state (Table 3), in which most of them performed the seed-based analysis except one applied the voxel-mirrored homotopic connectivity

Table 2 Altered spontaneous functional activities in local brain regions of MDD reported by R-fMRI studies

Study	Metric	Principal findings	
		Finding of altered increasing activity	Finding of altered decreasing activity
Yang *et al.* 2015 [24]	ReHo	Left precuneus	Left putamen
Qi *et al.* 2018 [36]	fALFF	VC	Hippocampus, PHG, amygdala, dlPFC, insula, ACC and IPL
Xia *et al.* 2019 [41]	ALFF, ReHo	IFG (ALFF)	Right poCG (ReHo)
Yang *et al.* 2020 [48]	ReHo		Left and right LG, right poCG
Zhu *et al.* 2020 [44]	fALFF		Right cuneus, thalamus, and MTG (in LSE)
Iwabuchi *et al.* 2015[a] [52]	ReHo	MPFC	
Zhong *et al.* 2016[a] [54]	ReHo, ALFF, fALFF	Putamen and anterior precuneus	MTG, STG, dlPFC, LG, PCC, posterior precuneus, fusiform and occipital areas
Wang *et al.* 2017[a] [55]	ALFF	Bilateral SMA and left PHG	Bilateral OFC
Zhou *et al.* 2017[a] [57]	ALFF, fALFF	Left ACC (ALFF), left STG (ALFF)	Left cerebellum (ALFF), left MTG (ALFF), right SFG (fALFF)

[a] Meta-analysis. Abbreviations: ReHo (regional homogeneity), ALFF (amplitude of low-frequency fluctuations), fALFF (fractional amplitude of low-frequency fluctuations), VC (visual cortex), PHG (parahippocampal gyrus), dlPFC (dorsolateral prefrontal cortex), ACC (anterior cingulate cortex), IPL (inferior parietal lobule), IFG (inferior frontal gyrus), poCG (postcentral gyrus), LG (lingual gyrus), MTG (middle temporal gyrus), MPFC (medial prefrontal cortex), PCC (posterior cingulate cortex), SMA (supplementary motor area), OFC (orbitofrontal cortex), STG (superior temporal gyrus), SFG (superior frontal gyrus), LSE (low sleep efficacy group).

Table 3 Altered functional connectivity findings reported by R-fMRI studies on MDD

Study	Method	Principal findings	
		Findings of altered increasing connectivity	Findings of altered decreasing connectivity
Hermesdorf *et al*. 2016 [28]	VMHC		STG, insula, and precuneus
Posner *et al*. 2016 [26]	ICA	Precuneus/PCC and left LPC	Bilateral anterior portion of dlPFC
Pan *et al.* 2017 [32]	Seed-based analysis: 11 ROIs in the valuation system	Left VS	
Ye *et al*. 2017 [31]	Seed-based analysis: amygdala	Left amygdala with the PFC, right amygdala with the left poCG, left PCC, left uncus, right STG, right prCG, right SOG, right insula and right uncus	Left amygdala with the left IPL, right MFG, right IPL, right insula, right CBPL and right CBT; right amygdala with the left IFG, left MFG, left temporal pole and bilateral CBPL.
Lopez *et al*. 2018 [34]	Seed-based analysis: amygdala, dlPFC	dlFC with dACC	
Mehta *et al.* 2018 [35]	Seed-based analysis: amygdala		Right amygdala and vmPFC (increasing plasma C-reactive protein)
Tokuda *et al.* 2018 [37]	Seed-based analysis: 78 ROIs across 14 brain networks		Right AG with other areas within DMN
Tu *et al.* 2018 [38]	ICA, PPI	Positive modulatory interactions in the auditory network	Negative modulatory interactions in DMN
Sha *et al*. 2018[a] [59]	Modularity analysis: WMD, PC of nodes across 7 networks	VN	DMN, FPN
Wang *et al.* 2019 [39]	Seed-based analysis: hypothalamus		Bilateral hypothalamus with the right insula, STG, IFG, and Rolandic operculum
Yao *et al.* 2019 [42]	Seed-based analysis: 90 ROIs across 14 brain networks		SOG, STG
Yang *et al*. 2020 [48]	Functional connectivity strength analysis	Left AG	
Zhu *et al*. 2020 [44]	Seed-based analysis: cuneus		Right cuneus to right LTC (LES)
Chin Fatt *et al*. 2020 [43]	Seed-based analysis: a 100-brain-region parcellation and hippocampus, VS, thalamus, and amygdala parcellations across 7 brain networks	Within the DMN, between-network connectivity of the DMN and ECN	Between-network hippocampal connectivity

[a] Meta-analysis. Abbreviations: VMHC (voxel-mirrored homotopic connectivity), ICA (independent component analysis), ROI (region of interest), PPI (physiophysiological interaction) STG (superior temporal gyrus), PCC (posterior cingulate cortex), LPC (lateral parietal cortex), dlPFC (dorsolateral prefrontal cortex), VS (ventral striatum), poCG (postcentral gyrus), prCG (precentral gyrus), SOG (superior occipital gyrus), IPL(inferior parietal lobule), MFG (top frontal gyrus), CBPL (cerebellum posterior lobe), CBT (cerebellar tonsil), IFG (inferior frontal gyrus), dACC (dorsal anterior cingulate cortex), vmPFC (ventral medial prefrontal cortex), AG(angular gyrus), DMN (default mode network), VN (visual network), FPN (frontoparietal network), LTC (lateral temporal cortex), ECN (executive control networks); LSE (low sleep efficacy group); WMD(within-module degree), PC (participant coefficient).

(VMHC) [28], and two performed the independent component analysis (ICA) [26,38].

Decreased VMHC was found in STG, the insula, and the precuneus [28]. In ICA studies, abnormally increased functional connectivity was found between the precuneus/posterior cingulate cortex (PCC) and the left lateral parietal cortex (LPC), and the abnormally decreased coupling was found between the bilateral anterior portion of dlPFC [26,38]. In the seed-based analysis, the most common region of interest (ROI) is the amygdala. The abnormally increased connectivity was found between the amygdala and the prefrontal cortex, the precentral gyrus (prCG), poCG, PCC, the uncus, STG, the superior occipital gyrus (SOG), and the insula [31,34,43]. Moreover, abnormally decreased connectivity was found between the amygdala and IPL, the middle frontal gyrus (MFG), the insula, the cerebellum posterior lobe (CBPL), the cerebellar tonsil, IFG, the temporal pole, and the ventromedial prefrontal cortex (vmPFC) [31,35,43]. As for studies with multiple ROIs across brain networks, abnormally increased connectivity within the reward network and the default mode network (DMN) as well as between DMN and the executive control network was reported [32,43,48]. Meanwhile, abnormally decreased within DMN connectivity, within-network superior occipital and superior temporal connectivity, and between-network hippocampal connectivity was reported [37,42,43,59].

Among these findings, though the increased and decreased connectivity within or between networks were

reported, DMN was the most involved brain network in MDD, suggesting not only the limited statical power but the complex neuropathobiology underlying the interactions of DMN and other confounding factors. One recent study investigated the DMN functional connectivity in a large sample of 1,300 depressed patients and 1,128 HCs and then found a significantly decreased functional connectivity within DMN in recurrent MDD *vs*. HCs as well as recurrent MDD *vs*. first-episode drug-naïve MDD patients. Furthermore, this effect was associated with medication usage rather than MDD duration [66]. Moreover, the abnormal connectivity between the amygdala and the insula, the precuneus, PCC, IPL, and CBPL was reported in more than one study.

Results from task-based fMRI studies

Altered activations in local brain regions of MDD

Fourteen task-based fMRI studies reported abnormal activations in local brain regions in patients with MDD (Table 4). Tasks in these studies can be roughly classified into three categories: the emotional processing tasks (including the angry faces processing task and the emotion regulation task), the reward learning and valuation tasks (including the reward guessing task, the monetary reward tasks, probabilistic selection task, the probabilistic reward task, and other reward-related tasks) and the cognitive tasks (including the working memory tasks and the Tower of London paradigm).

In the studies performing the emotional processing tasks [21,25,40,45,50], abnormally increased activations were found in the right ventrolateral prefrontal cortex (vlPFC), OFC, the bilateral MTG, STG, and MFG in dlPFC, the amygdala, the striatum, the parahippocampal, the cerebellar, the fusiform and ACC, and abnormally decreased activation was found in the dACC. In the studies performing the reward learning and valuation tasks [27,33,47,51,58], abnormally increased activation

Table 4 Altered activations in local brain regions of MDD reported by task-based fMRI studies

Study	Task	Principal findings	
		Findings of altered increasing activation	Findings of altered decreasing activation
Demenescu *et al*. 2011 [21]	Emotional faces processing task	dlPFC	
van Tol *et al.* 2011 [22]	Tower of London paradigm	Left dlPFC	
Casement *et al*. 2016 [27]	Reward guessing task	dmPFC	
Gollier-Briant *et al*. 2016 [25]	Angry faces processing task	Right vlPFC, OFC, MFG in the dlPFC and in the bilateral MTG and STG	
Yüksel *et al.* 2017 [30]	Working memory *n*-back task (0-back, 2-back and 3-back)		Bilateral MOG, bilateral MFG, right prCG, bilateral cerebellum, left IPL
Admon *et al*. 2017 [33]	Monetary incentive delay task, Probabilistic selection task		Striatum
Fitzgerald *et al*. 2019 [40]	Block-design reappraisal-based Emotion regulation task		dACC
Rupprechter *et al*. 2020 [47]	Probabilistic reward learning task		NAcc
Hilland *et al*. 2020 [45]	Emotion regulation task	ACC and amygdala (MDD without ABM training)	
Groenewold *et al.* 2013[a] [50]	Emotional processing tasks	Amygdala, striatum, parahippocampal, cerebellar, fusiform and ACC (negative stimuli)	Amygdala, striatum, parahippocampal, cerebellar, fusiform and ACC (positive stimuli)
Graham *et al.* 2013[a] [49]	Emotional, cognitive and other tasks	Bilateral MTG, left IFC, left sgACC, left prCG, left thalamus, left MFG;	Right MFG, right parahippocampus, left IFC, bilateral caudate, right STG, MTG, right aACC, right insula, right amygdala and left occipital regions
Zhang *et al.* 2013[a] [51]	Money reward tasks and emotion processing tasks	MFG and dACC	Caudate
Wang *et al.* 2015[a] [53]	Working memory tasks	Left IFC and MFC, left prCG, left insula, right STG and right SG	Right prCG, right precuneus and right insula
Keren *et al.* 2018[a] [58]	Reward-related tasks		Caudate, putamen and globus pallidus

[a] Meta-analysis. Abbreviations: MDD (major depressive disorder), ABM (attentional bias modification), dlPFC (dorsolateral prefrontal cortex), dmPFC (dorsal medial prefrontal cortex), vlPFC (ventral lateral prefrontal cortex), OFC (orbitofrontal cortex), MFG (top frontal gyrus), MTG (top temporal gyrus), STG (superior temporal gyrus), MOG (top occipital gyri), prCG (precentral gyrus), IPL (inferior parietal lobule), ACC (anterior cingulate cortex), dACC (dorsal anterior cingulate cortex), sgACC (subgenual anterior cingulate), NAcc (nucleus accumbens), IFC (inferior frontal cortex), poCG (postcentral gyrus), SG (supramarginal gyrus).

was found in the dorsal medial prefrontal cortex (dmPFC) and MFG. Abnormally decreased activations were found in the striatum and the nucleus accumbens (NAcc), the caudate, the putamen, and the globus pallidus. In the studies performing the cognitive tasks [22,30,53], abnormally increased activation was found in the left dlPFC, and abnormally decreased activations were found in the middle occipital gyri (MOG), MFG, the right prCG, the cerebellum, and the left IPL. Moreover, a meta-analysis [53] reviewed the altered brain responses to working memory loads in MDD patients *vs*. HCs and reported the increased activations in the left IFG and MFG, the left prCG, the left insula, the right STG, and the right supramarginal gyrus (SG) and the decreased activations in the right prCG, the right precuneus, and the right insula.

In sum, studies on working memory generally reported the decreased activation in the right prCG. With both cognitive tasks and emotional processing tasks, researchers generally found altered activations in dlPFC and STG.

Altered functional connectivity during tasks in MDD

Five task-based fMRI studies reported the altered functional connectivity in patients with MDD (Table 5). Tasks performed in the five studies can be roughly classified into four categories, three of which are the same as the above-mentioned tasks: the emotion processing tasks (including the emotion regulation task, conscious and non-conscious emotional faces processing tasks), the reward learning and valuation tasks (including the monetary incentive delay task, probabilistic selection task, and the probabilistic reward learning task), and the cognitive tasks (including the external attention task, the auditory oddball task, the continuous performance task, and the Go-No Go task). Moreover, the self-appraisal task is classified into the fourth category as self-perception and self-understanding.

In studies performing the emotion processing tasks, decreased functional connectivity between the amygdala and vlPFC in patients with MDD was reported [40]. In studies with the reward learning and valuation tasks, decreased connectivity between the prefrontal cortex and the ventral striatum (VS) as well as between NAcc and the midcingulate cortex (MCC) was reported [33,47]. In the study of Korgaonkar *et al*. [46], cognitive and emotion processing abilities were assessed through 5 fMRI tasks, and decreased DMN–FPN connectivity was observed in MDD non-remitters. And in the study with self-appraisal task, the negative modulatory effect of the medial prefrontal cortex (mPFC) on IPL was reported [29].

DISCUSSION

Due to the lack of consensus and reproducibility in fMRI studies on MDD, a growing body of literature has highlighted the methodological issues in neuroimaging research. According to these studies, we screened previous fMRI studies on MDD using criteria including sample size, preprocessing pipelines, and multiple comparison correction strategies. Contrary to our assumptions, after screening the previous studies with the above-mentioned criteria, both convergent and contradicted results were reported. Here, we focused on those convergent findings and discussed some implications accordingly.

Table 5 Altered functional connectivity during tasks in MDD

Study	Task	Principal findings	
		Findings of altered increasing connectivity	Findings of altered decreasing connectivity
Davey *et al.* 2017 [29]	Self-appraisal task, external attention task	MPFC negatively modulates IPL	
Fitzgerald *et al.* 2019 [40]	Block-design reappraisal-based Emotion Regulation Task		Amygdala with vlPFC
Korgaonkar *et al*. 2020 [46]	iSPOT-D study protocol with 5 fMRI tasks: auditory oddball task, continuous performance task, Go-NoGo task, conscious and non-conscious emotional faces processing tasks		Between DMN and FPN
Rupprechter *et al*. 2020 [47]	Probabilistic reward learning task		PFC with VS
Admon *et al.* 2017[a] [33]	Monetary incentive delay task; Probabilistic selection task		NACc and midcingulate cortex

[a] Meta-analysis. Abbreviations: iSPOT-D (International Study to Predict Optimized Treatment for Depression), mPFC (medial prefrontal cortex), IPL (inferior parietal lobule), vlPFC (ventral lateral prefrontal cortex), DMN (default mode network), FPN (frontoparietal network), PFC (prefrontal cortex), VS (ventral striatum), NAcc (nucleus accumbens), MCC (midcingulate cortex).

Dysfunctions of brain regions and networks in MDD

Evidence from the R-fMRI studies reviewed here suggests that the alterations in DMN (especially in ACC, PCC, and the precuneus) and its couplings with other brain networks may play an important role in the pathology of MDD. As a key node of DMN, convergent dysfunction of the precuneus regarding abnormal regional activities and functional connectivity [26] in MDD patients versus HCs in resting-state were reported. The precuneus dysfunction has been found in several different mental disorders, even in migraines [67,68]. Thus the dysfunction of the precuneus may be a generalized functional marker across mental disorders. It has been proposed that DMN underlies the self-referential process and the negative rumination in MDD [69–72]. It is also found that the hyper-connectivity within DMN may predict the better outcomes of sertraline treatment [43], which was consistent with the recent study reporting the decreased functional connectivity within DMN in recurrent MDD patients [66]. To sum up, these studies implicated that DMN may be a potential biomarker of MDD and a possible target for future MDD treatment.

We found that task-based fMRI studies get some convergent results about cognitive and emotional processing. Specifically, the hyperactivity in dlPFC and altered functional connectivity between DMN and FPN, especially dlPFC, were reported in studies applying paradigms with both cognitive or emotional stimuli. These findings align with previous studies indicating the recruitment of dlPFC in emotion regulation [73]. Specifically, dlPFC has been repetitively reported for blunted activity in R-fMRI studies and proved as an effective target for the TMS treatment of MDD [74]. Of note, dlPFC was a key node of the FPN, which underlies executive and control functions [75]. FPN does not generate emotions directly but may underlie the reappraisal and reactive processes regarding emotions. Emotion regulation is identified as a process with conscious or non-conscious strategies to change the initial emotional reaction, especially negative emotions [76]. Regulating strategies can impact the generation and reactivity to emotions at different time points [77]. Thus, the causal relationship between cognition and emotion yields a confounding pattern asking for further examinations.

Caveats for future fMRI studies on MDD

We also observed inconsistency among these results. For example, both decreased and increased spontaneous activities in the PHG and ACC were reported [36,55,57]. And both increased and decreased functional connectivity between the amygdala and the insula, as well as within- and between-network connectivity regarding DMN was reported [28,31,43,78]. Issues including the lack of integrative assessments and interpretations of MDD, differences in experimental design, data acquisition and preprocessing procedures, the mixture of the heterogeneous participant populations, and inappropriate methodologies to depict the anatomical and functional brain may lead to such inconsistency in R-fMRI studies.

It is not surprising that task-based fMRI studies yielded such inconsistent results, given the differences in the psychological processes they investigated. In previous studies, these processes were commonly investigated by three sets of paradigms, which correspond to three functional systems according to the research domain criteria (RDoC) [79,80] framework: the emotion processing tasks, the reward learning and valuation tasks and the cognitive tasks. The cognitive tasks mainly assess the working memory and attention, which corresponds to the cognitive system. The reward learning and valuation tasks mainly assess the learning and valuating ability to rewards, which corresponds to the positive valence system. The emotion processing tasks mainly assessed the responses to threats and loss, which are closely related to the negative valence system [81]. Note that these psychological functions were investigated separately in most previous MDD studies lacking integrative assessments and interpretations. However, as a disorde characterized by a constellation of behavioral, emotional, and cognitive symptoms [82], MDD is posited to involve dysfunctions in many aspects of cognitive and emotional processes including inhibitory processes, deficits in working memory, rumination and reappraisal [83]. This suggests that applying a carefully selected and comprehensive set of neurobehavioral measurements that covers multiple psychological functions may shed new light on depression research.

Furthermore, the lack of convergent results across previous fMRI studies investigating the same cognitive or emotional function indicates that differences in experimental design and data acquisition procedures may also contribute to inconsistency [84]. For example, in task-based studies included in the current review, working memory was tested by different versions of *n*-back tasks (*e.g.*, continuous performance task, or *n*-back tasks that consist of conditions of 0-back, 2-back, and 3-back), mental arithmetic tasks, Tower of London tasks and other paradigms. In these experiments, participants were instructed to respond to different stimuli, such as

letters or numbers [30,46,53]. Even in R-fMRI studies, the MRI data were acquired on different scanners, with different parameters and prompted for subjects (eyes open or closed), and through different scan durations, followed by various pre-processing workflows [28,32,36,44]. The absence of a "gold standard" for the data acquisition in R-fMRI studies may lead to the recent replicability and reproducibility crises as well as difficulties in interpreting this inconsistency [85,86]. Some researchers have raised the discussion of replicability issues and called for disciplines to advance research transparency and open science [87,88]. In practice, we have initiated the REST-meta-MDD Project with a standardized MRI data sharing and preprocessing protocol based on data processing assistant for resting-state fMRI (DPARSF) [89] and achieved preliminary success in open data sharing and collaborative research [66].

One other possible contribution to the inconsistency of previous fMRI studies on MDD is the heterogeneity of the investigated populations [84] regarding medications, treatment outcomes, onset ages, and subtypes (*e.g.*, melancholic vs. atypical MDD) [90]. Therefore, future studies on MDD should carefully divide the MDD samples into subgroups according to these confounding factors so that a clearer understanding of the relationships between representations of fMRI brain alternations and MDD can be obtained.

Finally, the functional systems of the human brain have features of an intricate network with multiple temporal and spatial levels, which are largely distributed/embedded on the intrinsic two-dimensional structure of the cortical surface [91,92]. The network neuroscientific approach provided efficient new ways to map, analyze and model the elements and interactions of neurobiological systems as a graph [93]. There have been fMRI studies [94,95] using the network and graph theory analysis that shows some altered functional locations in line with the voxel-wise metrics, including Reho, ALFF, and fALFF and functional connectivity strength findings. For example, Long and his colleagues find local changes in the default-mode, sensorimotor and subcortical areas using a novel dynamic network-based approach [94]. What's more, in order to properly understand the brain functional systems, it is necessary to obtain an accurate and explicit representation of the cortical surface considering its topology of a 2-D sheet and a highly folded geometry. The surface-based fMRI approach is a principled way to achieve this goal, which was reported to be nearly three times better than the traditional volume-based approaches in special localization of cortical areas [96]. However, most previous studies are still based on traditional voxel-wise metrics (*e.g.*, Reho, ALFF, and fALFF) and functional connectivity. Future studies could leverage a surface-based network neuroscientific approach to advance understanding the brain dysfunctions in depressions from a more integrative perspective.

Limitations

Despite the strict criteria we applied, controversy still existed in the remaining studies. Due to the limited number of papers included in the present review, we did not further group studies according to factors such as age, race, severity of disease, or medication usage. Moreover, we note that graph theory metrics can depict the brain as a complex networked system and be worth considering. However, findings from graph theory studies may need to be interpreted in a more sophisticated framework and thus are out of the scope of the current review.

CONCLUSION

In this systematic review, we found that MDD was consistently characterized by abnormalities within the DMN and the FPN, as well as altered connectivity between them and other brain networks. However, highly inconsistent results remained, probably due to issues including the lack of integrative assessments and interpretations of MDD, differences in experimental design and data acquisition procedures, the mixture of the heterogeneous participant populations, and the relatively inappropriate methodologies to depict the anatomical and functional brain. Apart from a sufficient sample size, adequate head motion artifact correction, and multiple comparison correction strategies, future studies are recommended to perform a comprehensive set of neuro-behavioral measurements, consider the heterogeneity of MDD patients and other potentially confounding factors, apply surface-based neuroscientific network fMRI approaches and advance research transparency and open science by movements including developing state-of-the-art pipeline with open data sharing.

MATERIALS AND METHODS

Literature search strategy

Studies that are electronically published until June 10th, 2020, were searched in PubMed (Fig.1). The search terms are "((English [Language]) AND ((MRI [Title/Abstract]) OR (fMRI [Title/Abstract]))) AND ((depression [Title/Abstract]) OR (depressive disorder [Title/Abstract]))". The filter of PubMed was used to constrain the article types of the searching results, which

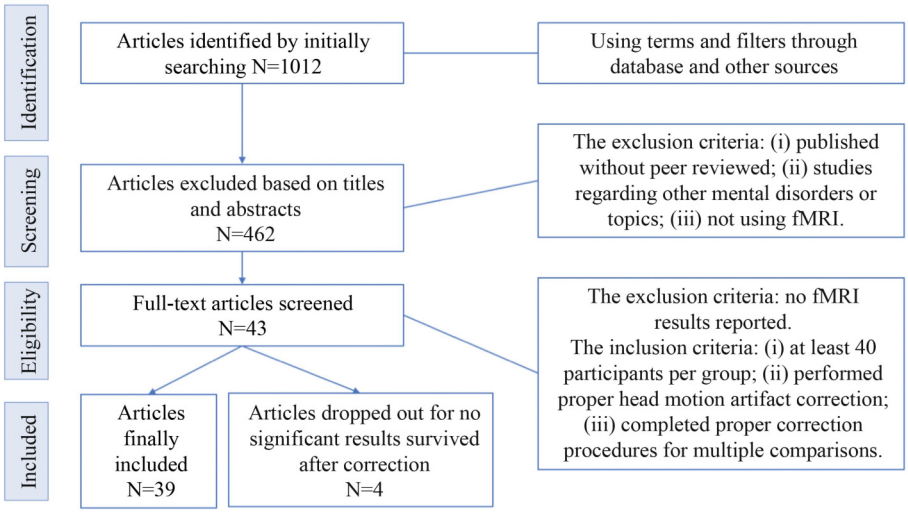

Figure 1. Flowchart of literature screening.

could exclude the nonscientific papers, such as news, books, and documents. Moreover, the reference lists of the included articles were also screened.

Inclusion and exclusion criteria

We reviewed the titles and abstracts to exclude studies that are not fMRI studies on MDD, systematic reviews, and commentary articles. Then the following exclusion criteria were applied: (i) publications that have not been peer-reviewed; (ii) studies regarding other mental diseases, such as post-traumatic stress disorder (PTSD) or bipolar disorders. (iii) studies based solely on the structural MRI or diffusion MRI. (iv) studies reporting no fMRI findings; (v) studies focusing on topics other than the human brain, such as genetics or gut-brain axis.

To ensure the quality of the included studies, we further applied additional methodological criteria: (i) at least 40 participants per group; (ii) performed proper head motion artifact correction; (iii) with proper correction for multiple comparisons, *e.g.*, FWE-based or FDR-based. Except for the permutation test with TFCE, the accepted thresholds for other FWE-based correction are voxel-wise $P < 0.001$ with cluster-wise $P < 0.05$, and for FDR-based correction $q < 0.05$.

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The authors Xue-Ying Li, Xiao Chen and Chao-Gan Yan declare that they have no conflict of interest.

This article does not contain any studies with human or animal materials performed by any of the authors.

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