Received: 13 December 2023 | Revised: 9 April 2024 | Accepted: 17 April 2024

DOI: 10.1002/hbm.26702

REVIEW ARTICLE

WILEY

Structural and functional brain alterations in subthreshold depression: A multimodal coordinate-based meta-analysis

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 31700995; The Humanity and Social Science Youth Foundation of Ministry of Education of China, Grant/Award Number: 17YJC190011

Abstract

Imaging studies of subthreshold depression (StD) have reported structural and functional abnormalities in a variety of spatially diverse brain regions. However, there is no consensus among different studies. In the present study, we applied a multimodal meta-analytic approach, the Activation Likelihood Estimation (ALE), to test the hypothesis that StD exhibits spatially convergent structural and functional brain abnormalities compared to healthy controls. A total of 31 articles with 25 experiments were included, collectively representing 1001 subjects with StD. We found consistent differences between StD and healthy controls mainly in the left insula across studies with various neuroimaging methods. Further exploratory analyses found structural atrophy and decreased functional activities in the right pallidum and thalamus in StD, and abnormal spontaneous activity converged to the middle frontal gyrus. Coordinate-based meta-analysis found spatially convergent structural and functional impairments in StD. These findings provide novel insights for understanding the neural underpinnings of subthreshold depression and enlighten the potential targets for its early screening and therapeutic interventions in the future.

KEYWORDS
activation likelihood estimation, functional magnetic resonance imaging, meta-analysis, multimodal, subthreshold depression, voxel-based morphometry

1 | INTRODUCTION

Subthreshold depression (StD) (also referred to as subclinical depression, subsyndromal depression, or mild depression) is found to be a threatening precursor and a risk factor for major depressive disorder (MDD) (Zhang et al., 2023). StD presents two to four criterion depressive symptoms for 2 weeks or longer (Rodríguez et al., 2012), but does not meet the diagnostic criteria for MDD.

Depression has been a significant public health issue and a great health service burden (Liu et al., 2020). The same is true for subthreshold depression due to the population's higher prevalence rate than major depression (Kroenke, 2017; Topuzoğlu et al., 2015). Studies have consistently demonstrated that individuals with subthreshold depression are more likely to develop major depression (Lee et al., 2019; Tuithof et al., 2018). Adolescents with subthreshold depression experience significant impairment and have striking similarities to adolescents with MDD, and have also been found to be at risk for developing other disorders, including dysthymia, social phobia, anxiety disorders, and suicidality (Klein et al., 2009; Pietrzak et al., 2013; Scott et al., 2021).

A rising amount of research has called for psychiatric disorders, including depressive disorders, to be viewed as a spectrum rather than categorically (Bakker, 2019; Krueger et al., 2018; Noyes et al., 2022).

From the spectrum perspective, depressive disorders are acknowledged to exist along a spectrum of increasing severity (McElroy et al., 2021). Therefore, subthreshold depression might be a suitable model for understanding the pathophysiological mechanisms of depression, contributing to the development of tailored treatments for patients at different stages of depression. Subthreshold depression is of clinical importance. The latest reviews explore the effects of the psychological treatment and nonpharmacological interventions for subthreshold depression (Cuijpers et al., 2014; Cuijpers et al., 2021; He et al., 2022), and one network meta-analysis compares the efficacy of multiple therapies (Jiang et al., 2021). To provide new insights into the clinical treatment selection of subthreshold depression and facilitate the development and application of early prevention and intervention, there is a great need for a clear understanding of its neurobiology.

In pursuit of elucidating the neurobiological underpinnings of StD, numerous neuroimaging studies have investigated localized abnormalities of the brain structure and function, using voxel-based morphometry (VBM), resting-state and task-based functional magnetic resonance imaging (rs-fMRI and t-fMRI), and positron emission tomography (PET). Albeit these studies have deepened our understanding of the neural correlates of StD, they have often yielded conflicting and heterogeneous results. For example, compared with controls, StD subjects showed increased voxel-wise regional homogeneity (ReHo) in the bilateral middle frontal gyrus (MFG), superior frontal gyrus (SFG), precentral gyrus, right precuneus and left hippocampus, and increased amplitude of low-frequency fluctuation (ALFF) in the right precuneus and left MFG (B. Zhang et al., 2021; 2022). However, another study found that StD subjects displayed higher ReHo only in the bilateral insula and right dorsolateral prefrontal cortex (DLPFC), while lower ReHo in the right orbitofrontal cortex (OFC), left DLPFC, left postcentral gyrus (PCG), left MFG and inferior temporal gyri (Ma et al., 2013). In addition, structural neuroimaging studies have variably reported structural abnormalities in StD, including decreased grey matter volume (GMV) in right inferior parietal lobule, bilateral medial prefrontal cortex, right precentral gyrus, ventromedial prefrontal, rostral anterior cingulate cortices, bilateral globus pallidus, precentral gyrus and caudates; as well as increased GMV in the left thalamus, amygdala, right medial prefrontal cortex, posterior cingulate cortex, and precuneus (Hayakawa et al., 2013; Li et al., 2015; J. Li et al., 2017; Taki et al., 2005).

In the context of these inconsistent findings, coordinate-based meta-analysis (CBMA), a well-established family of methods that holds a prominent position in neuroimaging research (Samartsidis et al., 2017), offers a valuable approach to evaluating convergent spatial findings of previously published neuroimaging studies (Müller et al., 2018; Tahmasian et al., 2019). Coordinate-based meta-analysis is applicable to multiple types of imaging data, including task activation (Wang et al., 2023), voxel-based morphometry (VBM) (Spindler et al., 2022), diffusion tensor imaging (Z. Zhang et al., 2021), and resting-state fMRI measures (ReHo or ALFF) (Yuan et al., 2022).

The most popular coordinate-based meta-analytic method is activation or anatomic likelihood estimation (ALE). It identifies spatial convergence of reported findings based entirely on location and only applies to data obtained from the whole brain and with coordinates or statistic images in standard anatomical space (Eickhoff et al., 2012; Fox et al., 2014). Although traditionally ALE has been employed in single-modality meta-analysis, it can flexibly integrate research findings across various imaging methods, thereby enabling a comprehensive assessment of disease-related effects. For instance, a couple of neuropsychiatric diseases-related meta-analyses have utilized this multimodal approach and resulted in robust findings: anorexia nervosa (Su et al., 2021), borderline personality disorder (Schulze et al., 2016), major depressive disorder (Gray et al., 2020), treatment-resistant depression (Miola et al., 2023), bipolar disorder (Cattarinussi et al., 2019), and anxiety disorder and chronic pain (Brandl et al., 2022).

Up to date, a CBMA focusing on the neural substrates of subthreshold depression, in particular, is still lacking. The present study aims to obtain the overall brain imaging characteristics of individuals diagnosed with subthreshold depression by integrating multimodal data. Additionally, it aims to portray the distinctive outcomes yielded by various brain imaging methods.

Here, we employed the ALE method on the reported brain differences of people with StD and healthy individuals derived from whole-brain structural and functional neuroimaging studies to assess the spatial convergence of brain alterations in subthreshold depression across published literature. We hypothesized that subthreshold depression would demonstrate brain alterations detectable across neuroimaging paradigms, mainly manifested as localized convergence of gray/white matter changes and increased and decreased brain function in individuals with subthreshold depression relative to control subjects.

2 | METHODS

2.1 | Literature search

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Page et al., 2021), we searched the following database: PubMed, Web of Science, Embase for studies published until January 2023, using these keywords: [“minor depression” OR “subthreshold depress*” OR “subclinical depress*” OR “subsyndromal depress*”] AND [“fMRI” OR “functional Magnetic Resonance Imaging” OR “PET” OR “Positron-Emission Tomography” OR “voxel-based morphometry” OR “VBM” OR “neuroimaging”].

2.2 | Literature screening

After removing duplicated records across databases, a total of 168 unique records were screened by two authors (J.Y.L., H.J.L.) double-blindly. Literature screening includes titles and abstracts, followed by full-text screening.

A study was included in the meta-analysis if it met the following criteria: (1) subjects were grouped in subthreshold depression with

clear-cut inclusion and exclusion criteria (e.g., presence of least two DSM depressive symptoms for at least 2 weeks, one symptom of depressed mood, no MDD or minor depression); (2) subjects with subthreshold depression were compared to healthy controls (HC); (3) whole-brain structural or functional differences were assessed using rs-fMRI, t-fMRI, VBM, DTI, or PET, and analysis was not limited to region of interest (ROI) or small volume corrected (SVC), as these would violate ALE methods assumption and lead to inflated significance (Tahmasian et al., 2019); (4) whole-brain coordinates in either Talairach or Montreal Neurological Institute (MNI) space can be acquired from the literature or Supplementary Materials, or provided by authors upon request; (5) no animal study; (6) participants did not receive treatment yet; and (7) the study was published in English and peer-reviewed journals.

Notably, considering heterogeneous definitions of StD damage the meaning of meta-analysis, thus we carefully screened the inclusion criteria for StD in the included studies to ensure that they met the operational definition by Volz et al. (2022).

2.3 | Data extraction

Two authors (J.Y.L., H.J.L.) coded study characteristics double-blindly. The extracted data consisted of bibliographic information (e.g., first author and year), demographic (e.g., sample size, age, sex ratio) and clinical status, methodological details (e.g., imaging modality, task name, analysis approach, method of smoothing), assessment of StD, and the peak coordinates of between-group experiments reported in each study.

Pooling the data from overlapping samples in ALE meta-analyses leads to erroneous results by incorrectly amplifying the influence of that sample (Turkeltaub et al., 2012). Therefore, we were very careful to prevent convergence between analyses conducted on (partially) overlapping samples within and between papers. We reviewed the included studies for signs of overlap with other studies by examining their team members, recruitment interval, and sample demographics. In such cases, We merged their data to ensure that in all analyses, each sample is only represented by one experiment in ALE analyses.

2.4 | ALE meta-analysis

We followed the principles of activation likelihood estimation (ALE) (Eickhoff et al., 2009; Eickhoff et al., 2012). The most recent version of GingerALE (3.0.2) was used (www.brainmap.org/ale) to compare coordinates compiled from multiple articles, calculate the degree of overlap, and produce clusters most statistically likely to become active across studies. Coordinates reported in Talairach space were transformed into MNI space by Lancaster's transformation (Lancaster et al., 2007), so all the experiments are in the same reference space. Imported foci were modeled as three-dimensional Gaussian spatial probability distributions using a full-width at half-maximum (FWHM) kernel estimated based on the sample size of the corresponding experiment. Next, a union map of all modeled activation maps for each experiment was generated, and above-chance spatial convergence was tested with various available thresholding options. We followed the ALE best practices (Müller et al., 2018; Tahmasian et al., 2019), and corrected the results using cluster-level inference of $p < .05$ with a cluster-forming threshold of $p < .001$ and conducted 1000 permutation test to distinguish between true convergence of foci and random clustering. Then, we performed separate ALE meta-analyses for different neuroimaging methods. In the primary analysis, the coordinates of all included studies were pooled to conduct an all-effects meta-analysis to investigate all the brain alterations and identify a neurobiological signature of StD, where neuroimaging changes colocalize.

2.5 | Exploratory analyses

In the exploratory meta-analyses, to perform complementary analyses on more homogeneous subsections of the data, we split the experiments by the direction of effect (HC > StD or StD > HC) and imaging modalities (rs-fMRI, t-fMRI, or VBM/DTI).

Given that the ALE primarily focuses on evaluating the convergence of significant findings in the neuroimaging literature, it lacks sensitivity towards unpublished null results. To assess the robustness of identified clusters against potential publication bias, we performed the Fail-Safe N (FSN) method adapted for ALE analyses as described by Acar et al. (2018). By adding the noise (randomly generated study coordinates) to the meta-analysis, the amount of noise study is FSN value before the results are changed.

3 | RESULTS

3.1 | Study selection and characteristics

A flow chart illustrating the detailed study selection process is depicted in Figure 1. Ultimately, 31 articles with 25 experiments (after overlap removal) comprising results from 1001 subthreshold depressed subjects were included in this meta-analysis. The number of experiments included in each modality was as follows: rs-fMRI (13), s-MRI (7, 5 VBM, 1 DTI, 1 cortical thickness), and t-fMRI (11). The more detailed information about each study is shown in Table 1.

3.2 | Coordinate-based meta-analysis (CBMA) results

3.2.1 | All-effects analysis

As illustrated in Figure 2, combining all multimodal coordinates and obtaining 222 foci from 25 experiments, the all-effects meta-analysis

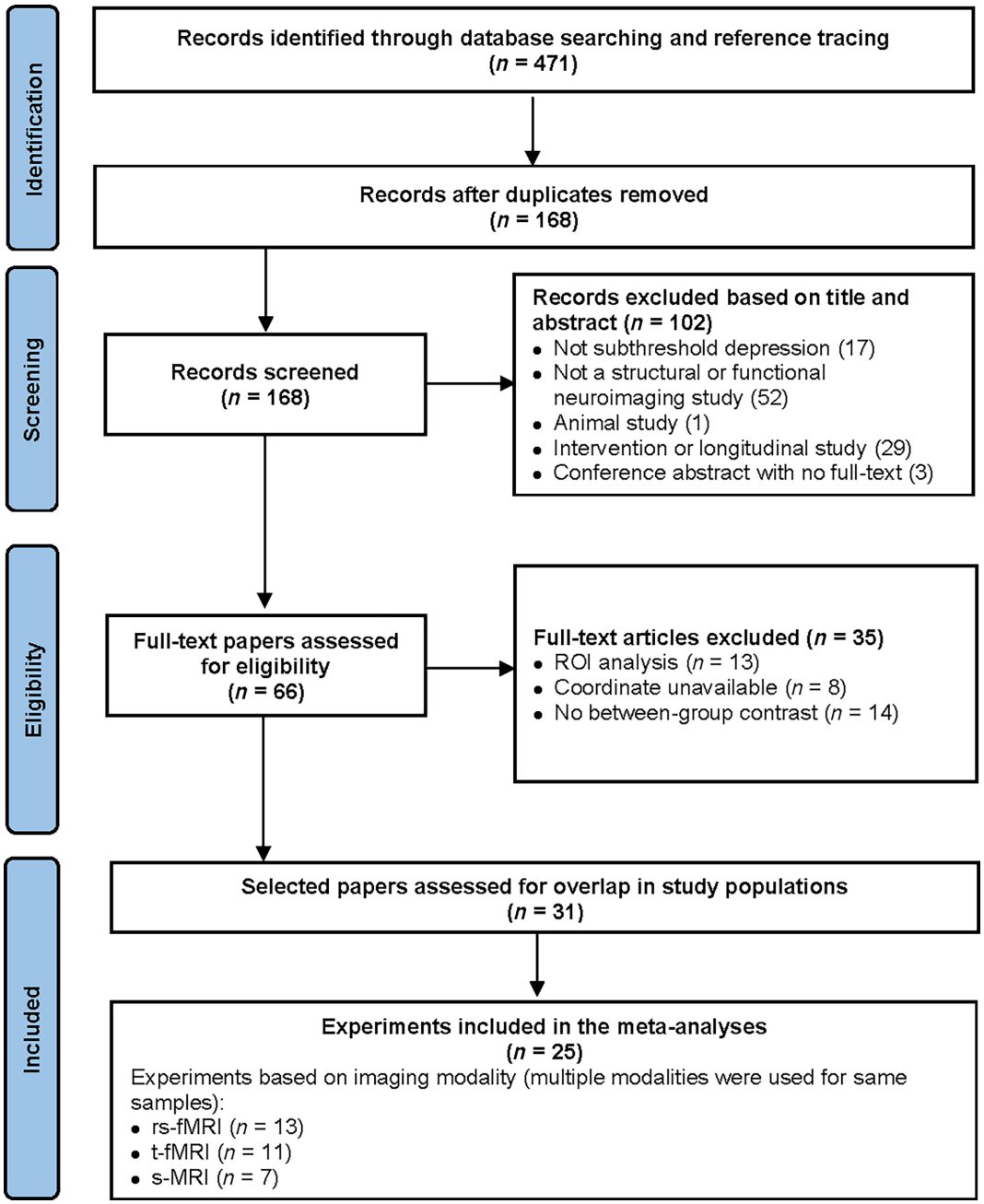

FIGURE 1 Flow chart of study selection for a meta-analysis of neuroimaging studies in subthreshold depression. ROI: region of interest; rs-fMRI: resting-state functional magnetic resonance imaging; s-MRI: structural magnetic resonance imaging; t-fMRI: task-based functional magnetic resonance imaging.

results showed that insula is a single region demonstrating convergent abnormality in StD compared to HC. The peak coordinates, the cluster sizes, and associated ALE values are reported in Table 2.

3.2.2 | Exploratory analysis

Considering the direction of effects, we pooled over 17 experiments reflecting increases (i.e., StD > HC), and 21 experiments representing decreases (i.e., HC > StD) separately.

Compared to HC, significantly decreased activation (i.e., when resting-state or task) or smaller grey matter volume was found for the thalamus and pallidum in StD. Whereas StD > HC did not show significant regional convergence.

In the separate analysis for each neuroimaging modality, only the resting-state fMRI resulted in a significant cluster in the middle frontal gyrus. The detailed information is shown in Table 2. Regarding the robustness of the results, the FSN of extra noise that must be added to each meta-analysis so that the discovered clusters no longer converge is listed in last column of Table 2.

TABLE 1 Characteristics of studies included in the meta-analysis.

Author, year	Participants (female), *n*		Mean age ± SD, year		Inclusion criteria	Modality	Task/methods	FWHM of smoothing kernel (mm)
	StD	HC	StD	HC				
(B. Zhang et al., 2022)	26 (16)	33 (17)	19.69 ± 1.73	19.18 ± 0.87	BDI-II	rs-fMRI	ReHo	6
(Yang et al., 2022)	26 (16)	33 (17)	19.65 ± 1.77	19.24 ± 0.94	BDI-II > 13 (total score, 14–28)	rs-fMRI	FC	6
(Huang et al., 2021)	38 (21)	32 (21)	29.84 ± 6.83	28.13 ± 9.68	PHQ-9 ≥ 5	rs-fMRI	ALFF	4
(B. Zhang et al., 2021)	26 (16)	33 (17)	19.69 ± 1.73	19.18 ± 0.87	BDI-II > 10	rs-fMRI	ALFF; ReHo; FC	6
(Peng et al., 2020)	59 (30)	59 (31)	20.12 ± 1.39	19.95 ± 1.42	BDI: mild (score of 14–18) or moderate (score of 19–29) depressive symptoms, with a mean score of 17.52 ± 3.43	rs-fMRI	FC	6
(Zhu et al., 2019)	34 (23)	40 (19)	19.91 ± 1.64	19.70 ± 0.85	BDI-II > 13	rs-fMRI	Functional networks	6
(Hwang et al., 2016)	57 (42)	79 (54)	32.25 ± 15.62	29.52 ± 14.32	CES-D ≥ 16; HAMD7-17	rs-fMRI	Default mode network functional connectivity	5
(Li et al., 2016)	41 (41)	26 (26)	20.27 ± 0.89	20.35 ± 1.32	BDI-II ≥ 14 at the two-stage assessment	rs-fMRI	ALFF	8
(Gao et al., 2016)	37 (23)	34 (19)	19.81 ± 1.56	19.29 ± 1.00	BDI-II > 13	rs-fMRI	Degree Centrality	6
(Hwang et al., 2015)	57 (42)	76 (53)	32.25 ± 15.62	29.86 ± 14.49	CES-D ≥ 16; HAMD7-17	rs-fMRI	FC	6
(Zhu et al., 2014)	19 (12)	18 (10)	66.50 ± 5.70	66.40 ± 3.90	CES-D ≥ 8	rs-fMRI	FC	4
(Li et al., 2014)	19 (12)	18 (10)	66.50 ± 5.70	66.40 ± 3.90	CES-D ≥ 8	rs-fMRI	ALFF; FC	4
(Ma et al., 2013)	19 (12)	18 (10)	66.50 ± 5.70	66.40 ± 3.90	CES-D ≥ 8	rs-fMRI	ReHo	4
(Bi et al., 2022)	33 (23)	30 (17)	20.73 ± 2.20	20.23 ± 1.70	BDI-II > 13	t-fMRI	Effort-based decision-making Task	6
(S. Zhang et al., 2022)	42 (26)	32 (25)	22.19 ± 1.97	21.50 ± 3.13	CES-D > 16 and BDI-II > 14 at two assessments	t-fMRI	Passive Viewing Task	6
(Yun et al., 2022)	21 (9)	23 (10)	24.33 ± 3.04	24.65 ± 2.87	(1) depressive mood or (2) loss of interest or pleasure over the last 2 weeks. DSM-5 2–4	t-fMRI	Simon Task	6
(He et al., 2020)	22 (12)	25 (12)	19.50 ± 1.63	19.32 ± 1.38	BDI-II > 13	t-fMRI	Social Judgement Task	6
(Yang et al., 2020)	18	20	20.56 ± 1.10	20.35 ± 1.31	BDI-II ≥ 14 twice	t-fMRI	TNT paradigm	8
(H. Li et al., 2017)	40 (40)	25 (25)	20.28 ± 0.85	20.32 ± 1.46	BDI-II ≥ 14 (two stages)	t-fMRI	Dot-Probe Task	6
(Dedovic et al., 2016)	22 (10)	26 (14)	21.90 ± 2.50		10 ≤ BDI-II ≤ 18	t-fMRI	Dot-Probe Task	6
(Mori et al., 2016)	15 (9)	15 (7)	18.50 ± 0.60	19.10 ± 0.70	BDI-II ≥ 10	t-fMRI	Monetary Incentive Delay Task	8
(Stringaris et al., 2015)	101 (66)	123 (90)	14.50 ± 0.40	14.40 ± 0.40	Three or more depressive symptoms, including at least one core symptom and at least two other DSM-IV depressive symptoms, without fulfilling criteria for clinical depression in terms of duration, number of symptoms, or impact on functioning in the past 4 weeks	t-fMRI	Monetary Incentive Delay Task	5
(Dedovic et al., 2014)	23 (11)	26 (14)	21.90 ± 2.50		10 ≤ BDI-II ≤ 18	t-fMRI	Montreal Imaging Stress Task	6
(Modinos et al., 2013)	17 (10)	17 (10)	20.50 ± 2.40	20.70 ± 2.30	BDI-II 11–19	t-fMRI	Passive Viewing Task	8

(Continues)

TABLE 1 (Continued)

Author, year	Participants (female), *n*		Mean age ± SD, year		Inclusion criteria	Modality	Task/methods	FWHM of smoothing kernel (mm)
	StD	HC	StD	HC				
(Vulser et al., 2018)	96 (62)	336 (217)	14.47 ± 0.38	14.41 ± 0.40	Three or more depressive symptoms, including at least one core symptom and at least two other DSM-IV depressive symptoms, without fulfilling criteria for clinical depression in terms of duration, number of symptoms, or impact on functioning in the past 4 weeks	s-MRI	Fractional anisotropy	10
(J. Li et al., 2017)	57 (42)	76 (53)	NA	NA	CES-D ≥ 16; HAMD 7—17	s-MRI	GMV	10
(Vulser et al., 2015)	119 (78)	461 (303)	14.45 ± 0.36	14.40 ± 0.41	Three or more depressive symptoms, including at least one core symptom and at least two other DSM-IV depressive symptoms, without fulfilling criteria for clinical depression in terms of duration, number of symptoms, or impact on functioning in the past 4 weeks	s-MRI	GMV, WMV	10
(Li et al., 2015)	42 (42)	30 (30)	20.26 ± 0.89	20.20 ± 1.30	BDI-II ≥ 14 (two stages)	s-MRI	GMV, WMV	10
(Kumar et al., 2014)	16 (9)	16 (9)	76.25 ± 7.54	75.06 ± 5.42	HAMD 8—14	s-MRI	Cortical thinning	NA
(Hayakawa et al., 2013)	21 (12)	21 (12)	51.00 ± 7.50	51.50 ± 6.90	CES-D ≥ 16	s-MRI	GMV	10
(Taki et al., 2005)	13	(Male)	55 (Male)	72.92 ± 1.71	72.38 ± 1.30		GDS ≥ 15; MMSE ≥ 22	s-MRI
GMV	12							

Abbreviations: ALFF, amplitude of low-frequency fluctuation; FC, functional connectivity; FWHM, full-width at half-maximum; GMV, grey matter volume; HC, healthy control; ReHo, regional homogeneity; rs-fMRI, resting-state functional magnetic resonance imaging; SD, Standard Deviation; s-MRI, structural magnetic resonance imaging; StD, subthreshold depression; t-fMRI, task-based functional magnetic resonance imaging; WMV, white matter volume.

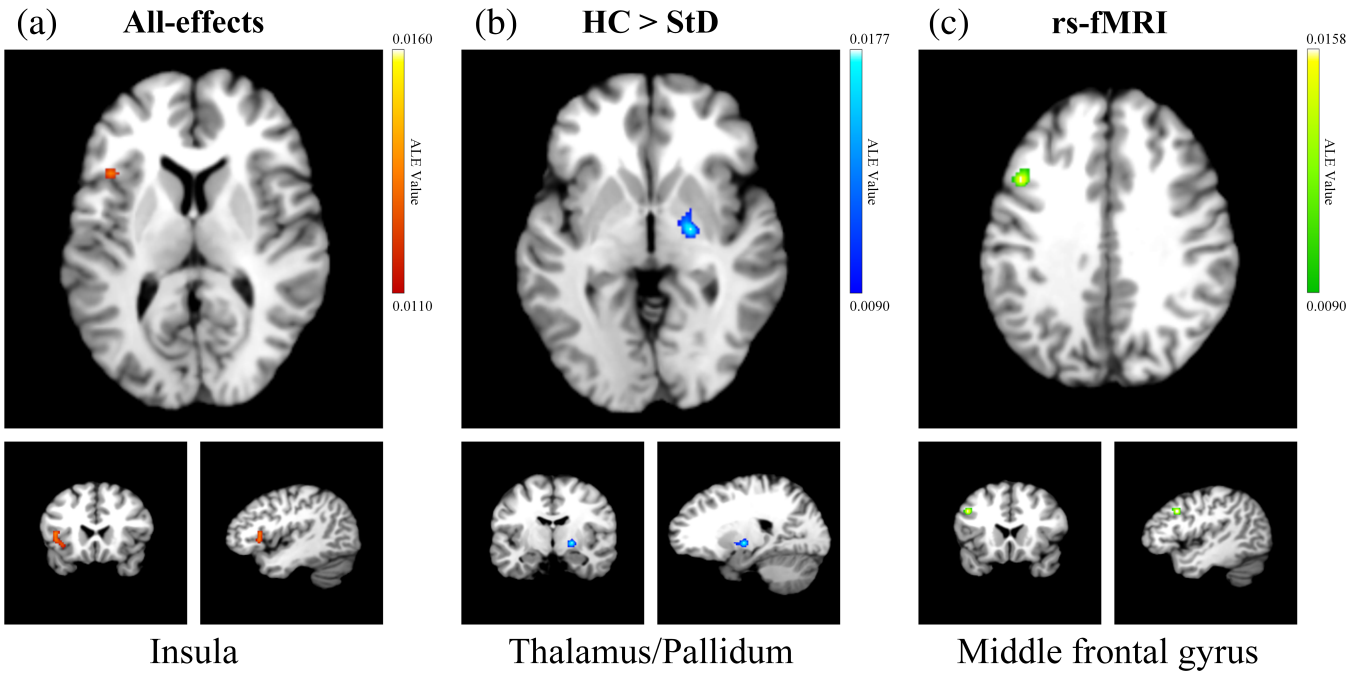

FIGURE 2 Results of the meta-analyses. (a) Brain difference between StD and HC from all experiments with different modalities (red); (b) Structural atrophy or decreased functional activities in StD compared to HC (blue); (c) Resting-state functional activity difference between StD and HC (green). HC, healthy controls; rs-fMRI, resting-state functional magnetic resonance imaging; StD, subthreshold depression. This image was created with Mango (v4.1., http://ric.uthscsa.edu/mango/).

TABLE 2 Results of ALE meta-analyses after cluster-level FWE correction for multiple comparisons.

Analysis	Cluster	Cluster size (mm^3)	Anatomical region	BA	Hemisphere	Peak MNI coordinates			ALE value	Fail-safe N (%)
						x	*y*	*z*		
All-effects										
	1	808	Insula	13	Left	−42	18	10	0.0160	7 (28)
	1		Insula	45	Left	−42	18	4	0.0156	
	1		Claustrum/insula	13	Left	−34	20	−2	0.0151	
Subgroup										
StD > HC										
	No sig.									
HC > StD										
	1	720	Thalamus		Right	20	−10	0	0.0177	5 (23.8)
	1		Pallidum		Right	16	−2	−6	0.0106	
Modality										
rs-fMRI										
	1	504	Middle Frontal Gyrus	9	Left	−44	16	34	0.0158	2 (15.4)
t-fMRI										
	No sig.									
s-MRI										
	No sig.									

Abbreviations: BA: Brodmann area; MNI: Montreal Neurological Institute; no sig.: no significant results after correction for multiple comparisons; StD: subthreshold depression; HC: healthy control; rs-fMRI: resting-state functional magnetic resonance imaging; s-MRI: structural magnetic resonance imaging; t-fMRI: task-based functional magnetic resonance imaging.

4 | DISCUSSION

The need to better describe the human brain alterations in subthreshold depression has long been acknowledged, whereby meta-analyses serve as a crucial tool for consolidating evidence. To our knowledge, the present work provides the first comprehensive assessment of multimodal imaging data to investigate the convergence of findings in subthreshold depression. Identification of convergent brain abnormalities across structural and functional data sets supports our hypothesis for the co-localization of disease effects in StD.

The present meta-analysis indicated clusters encompassing the left insula, right thalamus, right pallidum, and middle frontal gyrus, corroborating the prominent role of these functions and structures in StD. Furthermore, our methods of pooling multimodal data, separating single modalities and exploring different directions, deepened our understanding of the neuropathology of StD.

4.1 | All-effects analysis

The coordinates of all included studies across imaging modalities (s-MRI, rs-fMRI, and t-fMRI) were pooled to conduct an all-effects meta-analysis. The results showed one large cluster located in the left insula. Identification of consistent structural and functional abnormality within the insula in this meta-analysis is a potentially important finding for subthreshold depression research.

A brain system known as the salience network, with key nodes in the insular cortices, is central in detecting behaviorally relevant stimuli and coordinating neural resources. Emerging evidence suggests that atypical engagement of specific insula subdivisions within the salience network is a feature of many neuropsychiatric disorders (Uddin, 2015). The insula, engaged in the perception of emotions and monitoring the continuous internal emotional state of the body (Harvey et al., 2007), is regarded to be an essential neurological correlate of the core symptoms of MDD (Stratmann et al., 2014).

The latest study, using the causal structural covariance network method, finds that the GMV reduction in MDD originated from the right insula with a greater duration of illness. It revealed that the right insula was the prominent node projecting positive causal influences (i.e., GMV decrease) to the frontal lobe, temporal lobe, postcentral gyrus, putamen, and precuneus (Lu et al., 2023). As the precursor period of MDD, subthreshold depression is similarly associated with progressive brain structural alterations. Some studies also find the brain structural changes in StD. Compared to healthy controls, the young StD patients show a significant grey matter volume (GMV) decrease in the left insula and right putamen (J. Li et al., 2017). Depressive and anxious symptoms in late-life depression are also linked to reduced insula volumes (Laird et al., 2019).

These abnormal functional alterations in StD were also found in rs-fMRI studies. Compared to controls, StD displayed higher ReHo in the bilateral insula and right DLPFC (Ma et al., 2013), as well as the increased ALFF in the anterior portion of the dorsal ACC (adACC), which also displayed decreased functional connectivity (FC) with the anterior insula, thalamus, and putamen (Li et al., 2014). Hwang et al. (2015) found a significant resting-state FC decrease within the cognitive control network (CNN), especially between DLPFC and the insula in StD subjects, and further found FC between the default mode network (DMN) and left insula is enhanced in StD, which might reflect self-compensation for the lowered reward function of the left insula (Hwang et al., 2016). All these findings represented impaired cognitive control and salience detection in StD, and the insula played a central role (Cole & Schneider, 2007; Manoliu et al., 2014).

Insula is also a part of the affective network and has functional interconnections to regions associated with the experience of emotion (Wager et al., 2008). Reduced connectivity between the bilateral amygdala and the left insula within the affective network is one of the distinguishing features of MDD (Veer et al., 2010). Similarly, individuals with StD exhibited decreased functional connectivity between the left amygdala and the left insula (Peng et al., 2020), which means reduced amygdala–insula functional connectivity at rest might play a central role in maladaptation of emotion processing and autonomic regulation in StD.

A resting-state fMRI study found that attentional bias modification training significantly reduced ALFF of the right anterior insula (AI) and right middle frontal gyrus, which showed greater ALFF than healthy controls before training (Li et al., 2016). It may shed light on the therapeutic interventions for StD, though the effect of attentional bias modification training is inconsistent to a large extent (Li et al., 2023).

The insula has been given specific roles in various tasks that span a wide range of cognitive and affective processes. During the passive viewing task, StD showed a decreased activation in the left insula and a significantly increased functional connectivity between the superior frontal gyrus (SFG) and insula, pallidum, and caudate (Modinos et al., 2013; S. Zhang et al., 2022). Consistently, individuals with StD exhibit diminished insula responses and positive connectivity between the insula and ventral lateral prefrontal cortex (VLPFC) in consuming social loss (He et al., 2019). However, faced with significant financial loss, greater functional activation of the left insula in StD is found (Yun et al., 2022). These suggest that neural alterations in subthreshold depression are associated with the processing of conflict control against loss, mainly characterized by dysfunction within the *social pain network*, particularly the insula. Further studies that examine the functional activation patterns at the insula are warranted.

In common with impaired motivational effort decision-making and self-relevant processing in depressive individuals (Hobbs et al., 2021; Horne et al., 2021), StD displayed blunted activity in the bilateral anterior insula and right putamen-left dorsolateral prefrontal cortex functional connectivity when choosing to exert effort for themselves, while greater activation in the bilateral anterior insula when choosing to exert effort for others (Bi et al., 2022).

Note that, though numerous researchers have found significant effects of bilateral insula in StD, the left and right insula are connected to distinct networks and carry out diverse functions (Menon & Uddin, 2010; Wang et al., 2020). A latest study found left–right insula thickness difference and left insula thickness significantly predicted

MDD risk in middle-aged to older adults, but right insula thickness did not (Jones et al., 2019).

Considering the important role of the left anterior insula in social affect (Uddin et al., 2017) and emotion regulation, it might be an important identifying indicator of major depression. There was a significant and robust volume reduction of the left insular cortex and grey matter volume in MDD (Schnellbächer et al., 2022; Sprengelmeyer et al., 2011; Takahashi et al., 2010; Zhang et al., 2016). Patients with MDD has also shown decreased functional connectivity in the left insula (Guo et al., 2015; Veer et al., 2010), which would disrupt the function of the fronto-limbic circuit and result in social withdrawal. In consistent with these findings, our results also emphasize the left insula as a region of specific interest in StD. And the investigation of both structural and functional alterations, as well as lateralization of the insula in StD, warrants further exploration in future.

We also found some researches have linked the insula to interventions in schizophrenia and depression. One month of music intervention could facilitate improvement of the insular FC in schizophrenia (He et al., 2018). Individuals in the early course of schizophrenia showed changes in the functional connectivity between the resting-state brain network and the insula as well as the dorsolateral prefrontal cortex after receiving cognitive enhancement therapy (CET) (Eack et al., 2016). Increased fMRI brain response to interoception in anterior insula was found after mindfulness training in anxiety or depressed patients (Datko et al., 2022). And even in general population, short-term mindfulness meditation enhanced cerebral blood flow (CBF) in left ACC and insula (Tang et al., 2015). In short, the improvement in mindfulness were accompanied by functional alterations in the insula (Mooneyham et al., 2017; Mrazek et al., 2016).

Especially, after modified electroconvulsive therapy, there were structural changes in the insula, manifested as enhanced GMV in bilateral posterior insula in schizophrenia (Jiang et al., 2019). Therefore, the future study could scrutinize potential alterations within the insula concerning the efficacy of these interventions in StD.

4.2 | Convergence of different direction

Coordinates were assigned to two categories based on the directionality of findings to avoid conclusions opposed to the original studies enhancing each other in the ALE analysis (Sundermann et al., 2014). Direction-specific CBMAs only found a large cluster in the HC > StD comparison, while there was no significant convergence in StD > HC.

StD showed decreased GMV in the orbitofrontal cortex, left temporal gyrus, bilateral globus pallidus, and precentral gyrus (J. Li et al., 2017; Zhang et al., 2020). Previous studies suggested that the volumetric reduction in the globus pallidus in depressed individuals (Griffiths et al., 2015) is associated with reduced awareness of the causal efficacy of goal-directed actions. The pallidum is also an essential part of the affective network (including the amygdala, temporal poles), which plays a vital role in identifying MMD, StD, and HC (B. Zhang et al., 2022). The severity of depressive symptoms was associated with reduced gray matter volume in the orbitofrontal cortex, anterior cingulate, thalamus, superior temporal gyrus/temporal pole, superior frontal gyrus and the bilateral globus pallidus (J. Li et al., 2017; Webb et al., 2014).

Cortico-striatal-pallidal-thalamic (CSPT) circuits are highly organized and integrated to support diverse motor, cognitive, and emotional processes (Haber & Calzavara, 2009). A meta-analysis found abnormalities in CSPT have been implicated in MDD, and late-life depression (LLD) tended to be associated with smaller volumes in circumscribed frontal and subcortical structures, especially in thalamus (Bora et al., 2012). Abnormalities in CSPT might be the neural mechanism of subthreshold depression that needs to be explored in more studies in the future.

4.3 | Convergence of imaging modalities

In the separate meta-analyses for each modality approach, only the rs-fMRI studies converged on a single cluster in the middle frontal gyrus, showing a functional alteration between StD and HC that contributed by three experiments. Compared to HC, increased ReHo and ALFF in the middle frontal gyrus were found in StD (B. Zhang et al., 2021; 2022), and the middle frontal gyrus also showed an elevated degree centrality of the brain network (Gao et al., 2016). However, one included study reported the opposite result: elderly StD subjects display lower ReHo in the left middle frontal (Ma et al., 2013), probably due to the heterogeneity of subjects and inclusion criteria.

In addition, one study using dynamic casual modeling found that medicated depressed patients had significantly reduced effective connectivity from the anterior insula to the MFG (Kandilarova et al., 2018). Our results also suggest a possible intrinsic link between the MFG and the insula.

Notably, though studies based on t-fMRI failed to get a significantly convergent result, reduced activations in the MFG when StD performed a passive viewing task (S. Zhang et al., 2022), stronger activity in the MFG during suppressing neutral and negative stimuli (Yang et al., 2020), and increased activation during gain anticipation (Mori et al., 2016) we documented. It implies that MFG is a core area that influences social, emotional, and cognitive functioning, and its abnormality is closely related to subthreshold depression.

It also suggests the potential for improved convergence of resting-state data compared to task-activated and structure data. The lack of convergence might be partially caused by confounders introduced through inconsistency in various tasks' procedures.

However, the number of single modality experiments is relatively small, so the conclusions would be cautiously drawn.

Of note, our study was limited by the recruiting and reporting methods employed at the individual study level. Although there are subtle differences in the definition of subthreshold depression across studies, mainly in the operational definition of subthreshold depression and the inclusion criteria for subjects, there is still an essential consistency among different studies. Twenty-eight studies (87.5% of the total) use the standard self-reported scales, such as the Centre for

Epidemiological Studies Depression Scale-Revised (CESD), Beck Depression Inventory (BDI-II), or Brief Patient Health Questionnaire Mood Scale (PHQ-9) to identify depressive symptoms and the exclusion of DSM-IV MDD. Four studies use clinical structural interviews.

Consistent with Volz's proposal (Volz et al., 2022), to achieve consensus on the definition of subthreshold depression, we recommend that:

- Presence of at least two DSM depressive symptoms for at least 2 weeks, one symptom of depressed mood, no major depressive disorder or minor depression.
- Brief Patient Health Questionnaire Mood Scale (PHQ-9) between five and nine, CES-D at least 16 and/or BDI-II at least 14.
- Montgomery-Ăsberg Depression Rating Scale (MADRS) between 10 and 18 (for 2 weeks).

Adopting more standardized and consistent definitions of StD can lead to more homogeneous study populations, further improve the interpretation of findings at the individual study level, and promote more meaningful investigations at the meta-analytic level.

We believe that hypotheses confirmed by this meta-analysis should be regarded as providing direction for further primary data studies rather than as established conclusions.

5 | LIMITATIONS

This study has several limitations that should be considered when interpreting the results. First, ALE analyses with few experiments are unstable and can be largely influenced by a single experiment (Eickhoff et al., 2016). Therefore, the exploratory analysis results with various modalities separately may be underpowered. Notably, with more neuroimaging studies on StD published, an updated meta-analysis would be able to undertake additional subgroup analyses and identify modal-specific convergence across more homogenous data. Second, it is significant to highlight the controversy about multimodal CBMAs due to the differences among the various imaging modalities. However, from the technical perspective, the results from any imaging modality that provides stereotaxic coordinates in a standard reference space for the peak locations of those clusters that became significant in a voxel-wise whole-brain analysis are readily includable in a CBMA (Tahmasian et al., 2018). Inherent to all meta-analytic approaches, it requires a trade-off between the power or generalizability of the findings versus the homogeneity of the included experiments. Third, the ALE approach is not sensitive to non-significant results and thus susceptible to publication bias. To address this issue, we performed the Fail-Safe N method for each identified clusters and most clusters show stability and robustness against additional noise studies. Fourth, our study focused on specific imaging modalities and abnormal brain changes among individuals with subthreshold depression, and these conclusions may not generalize to other samples like MDD. A meta-analysis concentrating on the abnormal brain connections reported the thalamus as the causal hub of intervention in patients with major depressive disorder (Yang et al., 2023). Finally, as previously discussed, demographic characteristics such as age (adolescents, adults or the elderly), inclusion criteria or measures of StD, and depression severity may act as potential confounding factors. Accordingly, testing of subgroups based on more standardized definition would have provided more clinically meaningful findings and the clinical heterogeneity of StD warrants further investigation in neuroimaging studies.

6 | CONCLUSIONS

By summarizing studies across modalities to date, this meta-analysis demonstrated that subthreshold depression exhibited a concordance of structural and functional brain alterations in the insula, which is consistent with dysfunction in major depression, likely reflecting subthreshold depression existing on a spectrum with major depressive disorder. Moreover, resting-state functional abnormality in the middle frontal gyrus may also play a significant role in subthreshold depression. These results may contribute to the understanding of the neuropathologic mechanism in subthreshold depression and provide additional potential targets for therapeutic intervention. Finally, a well-recognized, unique definition of subthreshold depression is still lacking. A more precise and valid definition is needed for future studies, which recruit more homogenous populations and aim better to characterize the behavioral and neural features of subthreshold depression.

AUTHOR CONTRIBUTIONS

J.Y.L. and H.J.L. formed the idea and designed the study. J.Y.L. and H.J.L. contributed to the literature search and data extraction based on suggestions from Y.L. J.Y.L. performed the analyses. J.Y.L. drafted the manuscript, S.R.K., Y.L., Y.D.W., and H.J.L. revised and approved the article.

ACKNOWLEDGMENTS

This study was supported by the National Natural Science Foundation of China (31700995); The Humanity and Social Science Youth Foundation of Ministry of Education of China (17YJC190011).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Li, J., Kuang, S., Liu, Y., Wu, Y., & Li, H. (2024). Structural and functional brain alterations in subthreshold depression: A multimodal coordinate-based meta-analysis. *Human Brain Mapping*, *45*(7), e26702. https://doi.org/10.1002/hbm.26702