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Exploration of brain imaging biomarkers in subthreshold depression patients across different ages: an ALE meta-analysis based on MRI studies

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Abstract

Background Structural neuroimaging findings in Subthreshold depression (StD) patients at different ages are highly heterogeneous. This study aims to investigate the pathophysiology of StD across different ages.

Methods Literature searches for MRI studies of StD were conducted in 11 databases, including PubMed and Embase, from database inception to June 18, 2024. An activation likelihood estimation (ALE) meta-analysis was performed on the studies across different ages.

Results A total of 24 studies were included. The results revealed that the significant convergent brain regions in StD patients across different ages were primarily located within the frontostriatal circuit. Age-related differences were observed. For adolescent patients, the significant convergent brain regions were the caudate, putamen, anterior cingulate cortex (ACC), and medial frontal gyrus (MFG). For young adult patients, the significant convergent brain regions were the inferior frontal gyrus, parahippocampal gyrus, insula, putamen, claustrum, and medial globus pallidus. For middle-aged and older patients, the significant convergent brain regions were the ACC, the MFG, and the superior frontal gyrus.

Conclusions This study revealed that abnormalities in the frontostriatal circuit were neuroimaging features common in StD patients across different ages. Additionally, unique different brain regions were identified between age groups. These findings elucidated the mechanisms of StD and provided a theoretical basis for its prevention and treatment.

Keywords Activation likelihood estimation, Different ages, Frontostriatal circuit, Magnetic resonance imaging, Meta-analysis, Subthreshold depression

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Introduction

Major depressive disorder (MDD) is the leading cause of global disability and a primary contributor to suicides, with over 300 million people affected worldwide annually [1]. Depressive disorders were gradually considered as a spectrum of increasing severity [2]. Subthreshold depression (StD), an early stage of MDD, has affected nearly 11.04% of the global population [3–5]. StD negatively affected the quality of life in the long term and predisposed individuals to other clinical comorbidities, with a 2.95 times higher risk of progressing to MDD [5–7]. Therefore, understanding the pathophysiology of StD might allow better treatment of patients at different stages of depression, including MDD. Despite decades of research in psychiatry and cognitive neuroscience, the pathophysiology of StD remains unclear, limiting its early and rapid identification.

Neuroimaging approaches comprised a vital method to investigate the neurobiological mechanisms in StD. Several studies have reported that patients with StD exhibited abnormalities in both brain structure and function [8–11]. A recent study based on activation likelihood estimation (ALE) analysis found that the abnormal brain regions in StD were primarily concentrated in the left insula, right thalamus, right pallidum, and middle frontal gyrus [12]. These findings provided insights into the pathogenesis and early prevention of StD.

The structure and function of the central nervous system were not static but changed with advancing age. As a result of neurobiological processes such as synaptogenesis, myelination, and synaptic pruning, the adolescent brain undergoes complex and lasting changes in its structure and function [13, 14]. A pronounced age-related decline in the central nervous system was observed in older individuals when compared to younger individuals. The interconnections between the frontal cortex and the subcortex were significantly reduced after the age of 40–50 years [15, 16].

Notably, imaging abnormalities varied among StD patients of different ages. For example, in terms of brain structure, adolescent StD patients showed decreased gray matter volume in the bilateral caudate and right anterior cingulate cortex (ACC) [17]; in contrast, decreased gray matter volume in elderly StD patients was observed in the hippocampus [18]. Regarding brain function, older StD patients showed decreased ReHo values in the left middle frontal gyrus [19], while young StD patients exhibited significantly increased ReHo values in the same region [9]. Previous studies have analyzed the neuroimaging characteristics of StD in the entire population [12, 20], but not those across different ages. Therefore, it is crucial to conduct an ALE meta-analysis of StD MRI studies across different ages to clarify the pathophysiology of StD.

In this study, we conducted an ALE meta-analysis of the scientific literature to identify significant convergent brain regions at different ages. We expected that common and different clusters would be observed across adolescents, young adults, and middle-aged and older adults with StD. Identifying the unique features of StD at different life stages could provide a hypothesis base for the dynamic changes of StD across the lifespan. Meanwhile, the common features might contribute to capturing the core brain circuit during the development of StD. Our findings intended to provide important clinical guidance for the early diagnosis, identification, and prevention of StD.

Data and methods

Search strategy

The protocol was registered in PROSPERO and followed the PRISMA guidelines (PROSPERO-ID CRD42022374135). A literature search in eight international databases (PubMed, Medline, Web of Science, EMBASE, EBSCOhost, APA, SinoMed databases and the Cochrane Library) and three Chinese databases (CNKI, Wan Fang and VIP) was performed using these search terms: ("minor depression" OR "subclinical depression" OR "subsyndromal depression" OR "subthreshold Depression" OR "subthreshold depressive symptoms" OR "subclinical depressive conditions") AND TS=("imaging" OR "MRI" OR "PET" OR "SPECT" OR "fMRI" OR "functional MRI"). The search was conducted across the entire period until June 18, 2024, and resulted in 1248 articles. Grey literature like theses and dissertations, was also included in the search.

The age categories were defined as follows: according to the definition in the Medium-and Long-term Youth Development Plan (2016–2025) [21], Medical Subject Headings Database, and the standard for healthy Chinese older adults (2022) [22], the study population was divided into three groups: adolescents (13–18 years), young adults (19–35 years), and middle-aged and older adults (45 years and above).

Inclusion and exclusion criteria

Studies were included based on the following criteria: (i) including subjects with subthreshold depression (as defined in DSM-V or any prior DSM) and healthy control; (ii) neuroimaging method: structural MRI or functional MRI; (iii) performing whole-brain analysis. Exclusion criteria were as follows: (i) studies focusing on depression exclusively in the context of another specified psychiatric or neurological condition such as bipolar disorder, traumatic brain injury, eating disorder(s), post-traumatic stress disorder, mild cognitive impairment, dementia; (ii) the coordinates were not in standard space (i.e., MNI or Talairach); (iii) analysis only based on

ROI-to-ROI or seed-to-ROI connectivity; (iv) did not report the differences between StD patients and controls; (v) Full text unavailable.

Literature screening and data extraction

Two reviewers (YD.H. & ZY.L.) independently assessed the records. After removing duplicate studies, they first screened the titles and abstracts for relevance. Studies that passed this initial screening were then evaluated in full text to determine their eligibility for inclusion in the study. For any discrepancies in the title/abstract screening or full-text evaluation, a dual review was conducted, and disagreements were resolved by a third reviewer (L.C.). The data collected were as follows: (i) title, author, and publication date, (ii) individual characteristics (numbers, average age, depression measure for each group), (iii) Brain-related data (modality, brain area, hemisphere, full width at half maximum).

To assess inter-rater reliability, we used Cohen's κ coefficient, which measured the agreement between reviewers beyond what would be expected by chance [23]. Cohen's κ can be categorized into 5 levels (scale: 0.01–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, 0.81–0.99 = almost perfect) [24]. Cohen's κ was calculated based on the difference between observed inclusion/exclusion ratings across studies and the probability of expected agreement due to change. For the title/abstract screening stage, Cohen's κ was 0.832 (almost perfect agreement). For the full-text evaluation stage, Cohen's κ was 0.897 (almost perfect agreement). These two Cohen's κ indicated high levels of inclusion/exclusion agreement between reviewers.

Quality assessment

Twenty-four studies were included ultimately and reviewed independently by two team members (YD.H. & ZY.L.). Any disagreements were resolved through consensus discussions, with a third member (L.C.) adjudicating when necessary.

Studies assessed the risk of bias in individual studies have been performed using 9 quality criteria, following the approach of Wolters et al. [25]. Detailed criteria included: (a) inclusion/exclusion procedure, and patient demographics; (b) MRI procedure and patient instructions; (c) spatial normalization; (d) determination of the regions of interest (As the literature included in the analysis was based on whole-brain analyses, this item was not applicable); (e) reproducibility of the analysis; (f) statistical tests for substantiation of results; (g) correction for multiple measurements; (h) figures and tables; (i) quality control measures. Each item was rated at 0, 0.5, or 1 point. Based on the total score, each study can be categorized into 3 levels: good (≥ 7.5), fair (4-7.5), or poor (≤ 4). Based on the total score, each study can be categorized into 3 levels: good (≥ 7.5), fair (4-7.5), or poor (≤ 4). After a third member (L.C.) adjudicating, 15 were of high quality, 9 were of moderate quality, and 0 were of poor quality (Table S1 in supplementary materials). The average score was 7.48 ± 0.67 (Mean ± SD).

To better assess the consistency between the two reviewers, we used Cohen's κ coefficient to evaluate inter-rater reliability and Cohen's κ was 0.814 (almost perfect agreement), indicating that high levels of quality assessment agreement between reviewers.

Statistical analysis

This study performed exploratory coordinate-based meta-analyses [26] to extract the difference coordinates between StD and healthy controls (HCs). ALE analysis was conducted based on GingerALE software v 3.0.2 (https://brainmap.org/ale/). Before the main analysis, the coordinates reported in Talairach space were converted to MNI standard space via the GingerALE convert tool icbm2tal transformation [27]. Two of the included studies were reported in the Talairach standard space [28, 29]. Then, the coordinates and sample size of each study were collected and input GingerALE for meta-analysis. Then, ALE maps were created by calculating the union of activation probabilities across experiments for each voxel. According to the GingerALE manual and the recommendations for neuroimaging meta-analysis, the cluster-forming threshold was set at $P < 0.001$ uncorrected, and the cluster-level inference threshold was set at 0.05 [26, 30]. This method assessed the significance of cluster sizes, thereby providing a more robust approach to identifying significant brain activity patterns. Research by Eickhoff et al. has shown that when using this conventional uncorrected threshold, outcomes from randomized and analytical inference methods yield comparable results [31].

Results

A total of 24 studies were included in this meta-analysis, search strategy was shown in Fig. 1. The total sample size was 2877 participants (1711 in the StD and 1166 in the HCs), including 1236 adolescents, 755 young adults, and 835 middle-aged and older adults. Additional characteristics of the included studies were detailed in Table 1.

Total effects analysis

In adolescents with StD, compared to the HCs, significant convergent brain regions were concentrated in the bilateral caudate, left medial frontal gyrus (MFG), left putamen, and right ACC (Table 2; Fig. 2A).

In young adults with StD, compared to the HCs, significant convergent brain regions were focused in the right claustrum, inferior frontal gyrus (IFG), insula, medial

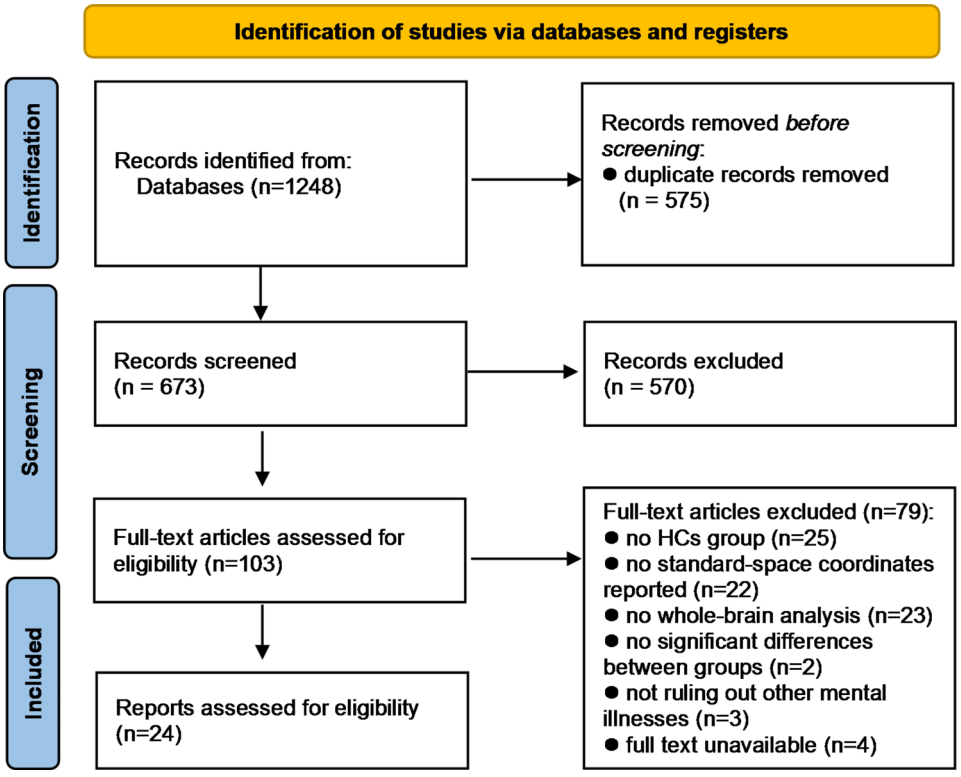

Fig. 1 Flowchart of studies identification

globus pallidus (MGP), parahippocampal gyrus (PHG) and putamen (Table 2; Fig. 2B).

In middle-aged and older adults, compared to the HCs, significant convergent brain regions were focused in the bilateral ACC, left MFG, and left superior frontal gyrus (SFG) (Table 2; Fig. 2C).

Subgroup analyses

Considering the direction of the overall effect, we conducted subgroup analyses for upward trends (i.e., StD > HCs) and downward trends (i.e., StD < HCs) across different ages.

In adolescents with StD, all included studies reported a downward trend. Compared to the HCs, adolescents with StD showed reduced functional activation or decreased gray matter volume in the bilateral caudate, left MFG and putamen, and right ACC (Table 3; Fig. 2A).

In young adults with StD, there was increased functional activation or larger gray matter volume in the right caudate, claustrum, insula, PHG, and Putamen. No significantly convergent brain regions were found in the StD < HCs (Table 3; Fig. 2D).

In middle-aged and older adults, StD showed increased functional activation or larger gray matter volume in the left insula and right claustrum (Table 3; Fig. 2E), and decreased functional activation or smaller gray matter volume in the bilateral ACC, left SFG, and MFG (Table 3; Fig. 2F).

Discussion

This study utilized ALE analysis to elucidate the neuroimaging characteristics of StD patients across different ages. The meta-analysis demonstrated that the significantly convergent brain regions among StD patients were primarily localized within the frontostriatal circuit. Specifically, adolescent patients showed significant convergence in the left MFG, right ACC, bilateral caudate, and right putamen. In young adult patients, significantly convergent brain regions were concentrated in the right IFG, PHG, insula, claustrum, putamen, and MGP. For middle-aged and older patients, significantly convergent brain regions were concentrated in the left SFG and MFG, and bilateral ACC. Subgroup analyses showed that the subcortex of the adolescent groups showed decreased volume or activation. In contrast, young adults and middle-aged/older groups showed compensatory increases in gray matter volume or activation. In addition, the compensatory increases in the middle-aged and older groups were less than those in the young adults.

The frontostriatal circuit plays a crucial role in reward-seeking behavior and is sensitive to chronic stress [32]. Recent research published in Nature has confirmed that individuals with depression exhibit expansive alterations

Table 1 Characteristics of included studies

No.	Studies	Age range	Modality	StD		HC		Depression measure	FWHM
				N	Age($\bar{X}$±SD)	*N*	Age($\bar{X}$±SD)		
1	Stringaris et al. 2015 [8]	Adolescents	task-related fMRI	101	14.5 ± 0.4	123	14.4 ± 0.4	DAWBA	5
2	Vulser et al. 2015 [17]	Adolescents	sMRI	119	14.45 ± 0.36	461	14.40 ± 0.41	DAWBA	10
3	Vulser et al. 2018 [56]	Adolescents	sMRI	96	14.47 ± 0.38	336	14.41 ± 0.40	DAWBA	10
4	Modinos et al.2013 [57]	Young	task-related fMRI	17	20.5 ± 2.4	17	20.7 ± 2.3	BDI	8
5	Dedovic et al. 2014 [58]	Young	task-related fMRI	23	Total sample age only 21.9 ± 2.5	26	Total sample age only 21.9 ± 2.5	BDI	6
6	Li et al. 2015 [59]	Young	sMRI	42	20.26 ± 0.89	30	20.20 ± 1.3	BDI	10
7	Dedovic et al. 2016 [60]	Young	task-related fMRI	22	Total sample age only 21.9 ± 2.5	26	Total sample age only 21.9 ± 2.5	BDI	6
8	Gao et al. 2016 [61]	Young	rs-fMRI	37	19.81 ± 1.56	34	19.29 ± 1.001	BDI	6
9	Li et al. 2016 [62]	Young	rs-fMRI	41	20.27 ± 0.89	26	20.35 ± 1.32	BDI	6
10	Mori et al. 2016 [63]	Young	task-related fMRI	15	18.5 ± 0.6	15	19.1 ± 0.7	BDI	8
11	Li Jing et al. 2017 [64]	Young, Middle-aged	sMRI	Young: 51 Middle-aged: 25	Young: 20.63 ± 1.89 Middle-aged: 49.2 ± 10.25	Young: 34 Middle-aged: 23	Young: 20.29 ± 1.40 Middle-aged: 49.91 ± 8.44	CES-D, HAMD	10
12	Yang et al. 2020 [65]	Young	task-related fMRI	23	20.56 ± 1.10	21	20.35 ± 1.31	BDI	8
13	Huang et al. 2021 [66]	Young	rs-fMRI	38	29.84 ± 6.83	32	28.13 ± 9.68	PHQ-9	4
14	Zhang Bo et al. 2021 [9]	Young	rs-fMRI	26	19.69 ± 1.73	33	19.18 ± 0.87	BDI, HAMD	6
15	Bi et al. 2022 [67]	Young	task-related fMRI	33	20.73 ± 2.20	30	20.23 ± 1.70	BDI	6
16	Yun et al. 2022 [10]	Young	task-related fMRI	21	24.33 ± 3.04	23	24.65 ± 2.87	MINI-International Neuropsychiatric Interview	6
17	Zhang Bo et al. 2022 [11]	Young	rs-fMRI	26	19.69 ± 1.73	33	19.18 ± 0.87	BDI, HAMD	6
18	Zhang Shu et al. 2022 [68]	Young	rs-fMRI	42	22.19 ± 1.97	32	21.5 ± 3.13	CES-D, BDI	6
19	Huang et al. 2024 [52]	Young	rs-fMRI	44	30.66 ± 7.45	34	31.50 ± 10.72	PHQ-9	6
20	Shen et al. 2024 [69]	Young	rs-fMRI	44	30.66 ± 7.45	34	31.50 ± 10.72	PHQ-9	6
21	Hayakawa et al. 2013 [28]	Middle-aged	sMRI	21	51.0 ± 7.5	21	51.5 ± 6.9	CES-D	10
22	Taki et al. 2005 [29]	Older	sMRI	13	72.92 ± 1.71	55	72.38 ± 1.60	GDS	12
23	Ma et al. 2013 [19]	Older	rs-fMRI	19	66.5 ± 5.70	19	66.4 ± 3.9	CES-D	4
24	Touron et al. 2022 [18]	Older	sMRI	age-well: 77 ADNI: 134	age-well: 68.45 ± 3.63 ADNI: 73.66 ± 6.32	age-well: 58 ADNI: 118	age-well: 69.41 ± 3.91 ADNI: 73.35 ± 5.69	age-well: MADRS ANDI: GDS	8

StD: Subthreshold Depression; HC: Healthy control; BDI: Beck Depression Inventory; CES-D: Center for Epidemiological Studies Depression Scale; DAWBA: Development and Well-Being Assessment; DSM-IV: the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DTI: Diffusion tensor imaging; fMRI: functional magnetic resonance imaging; FWHM: full width at half maximum; GDS: geriatric depression scale; HAMD: Hamilton Rating Scale for Depression; MADRS-S: Montgomery Asberg Depression Rating Scale; PHQ-9: Patient Health Questionnaire-9; rs-fMRI: resting-state functional magnetic resonance imaging

in the connectivity of the frontostriatal circuit, which were associated with loss of interest and anxiety [33]. Additionally, mood-state-dependent connectivity changes in the frontostriatal circuit appeared early in life and could predict future anhedonia symptoms [33]. Differently, the subcortex of the adolescent groups showed decreased volume or activation, while young adults and middle-aged/older groups showed compensatory increases in gray matter volume or activation. In

Table 2 Total effect of StD patients at different ages

Lable	MNI space			ALE	*P*	Z
	x	y	z			
Adolescents						
Left Medial Frontal Gyrus	-12	50	6	0.0110	< 0.001	4.343
Left Caudate	-6	18	2	0.0114	< 0.001	4.592
	-12	14	-2	0.0114	< 0.001	4.592
Left Putamen	-18	8	-8	0.0108	< 0.001	4.160
Right Anterior Cingulate Cortex	4	36	0	0.0106	< 0.001	3.931
	14	30	14	0.0106	< 0.001	3.887
Right Caudate	6	20	2	0.0110	< 0.001	4.343
	12	20	-4	0.0108	< 0.001	4.159
	12	12	-10	0.0100	< 0.001	3.783
Young Adults						
Right Claustrum	32	16	-12	0.0106	< 0.001	3.257
	32	18	-4	0.0104	< 0.001	3.221
Right Inferior Frontal Gyrus	48	30	0	0.0108	< 0.001	3.299
	44	24	2	0.0100	< 0.001	3.136
Right Insula	40	-6	10	0.0099	< 0.001	3.096
	42	12	12	0.0097	0.001	3.055
	34	28	2	0.0092	0.002	2.893
Right Medial Globus Pallidus	16	-6	-2	0.0107	< 0.001	3.270
Right Parahippocampal Gyrus	28	2	-26	0.0153	< 0.001	3.955
	22	-12	-30	0.0099	0.001	3.081
Right Putamen	26	6	-4	0.0201	< 0.001	4.753
	30	-12	-6	0.0104	< 0.001	3.230
	30	-4	2	0.0101	< 0.001	3.139
	28	-2	-14	0.0095	0.001	3.005
Middle-aged and older adults						
Left Anterior Cingulate Cortex	0	46	8	0.0096	< 0.001	3.780
Left Medial Frontal Gyrus	-4	64	14	0.0098	< 0.001	3.850
	-4	62	10	0.0096	< 0.001	3.795
Left Superior Frontal Gyrus	0	62	20	0.0097	< 0.001	3.829
Right Anterior Cingulate Cortex	2	46	-6	0.0093	< 0.001	3.670

addition, the compensatory increases in the middle-aged and older groups were less than those in the young adults.

During adolescence, the thickness of the frontal cortex undergoes a more rapid reduction, while the volume of the caudate and putamen gradually decreases with age until reaching a plateau in adulthood [34, 35]. The results of this study indicated that adolescents with StD demonstrate decreased gray matter volume or reduced functional activation in the frontostriatal circuit, including the left MFG, left putamen, bilateral caudate, and right ACC. It could be postulated that StD might accelerate the atrophy or reduce functional activation in the frontostriatal circuit in adolescents. Epidemiological data showed that adolescents had the highest prevalence of StD compared to other age groups [5], suggesting a higher susceptibility to depressive emotions for adolescents. This susceptibility might be linked to factors such as academic pressure, genetic predisposition, family conflicts, and hormonal changes [36, 37].

In this study, subcortical brain regions, such as the caudate and putamen, showed reduced total effects in adolescents with StD. In contrast, these effects were increased in young adults and middle-aged and older patients with StD. We hypothesized that young adults and middle-aged and older patients would experience compensatory increases in the convergent brain regions. Compensatory increases in gray matter volume or functional activation of subcortical brain regions have already been observed in previous studies [12, 20]. However, the ongoing development of myelination in the central nervous system during adolescence might have limited their emotional regulation [38]. It might contribute to the absence of compensatory mechanisms observed in this age group.

In this study, the significant convergent brain regions in middle-aged and older StD patients were concentrated in the cortex such as the frontal lobe and ACC, with no findings reported in the subcortex. Compared to younger adults, the elderly showed more pronounced activation

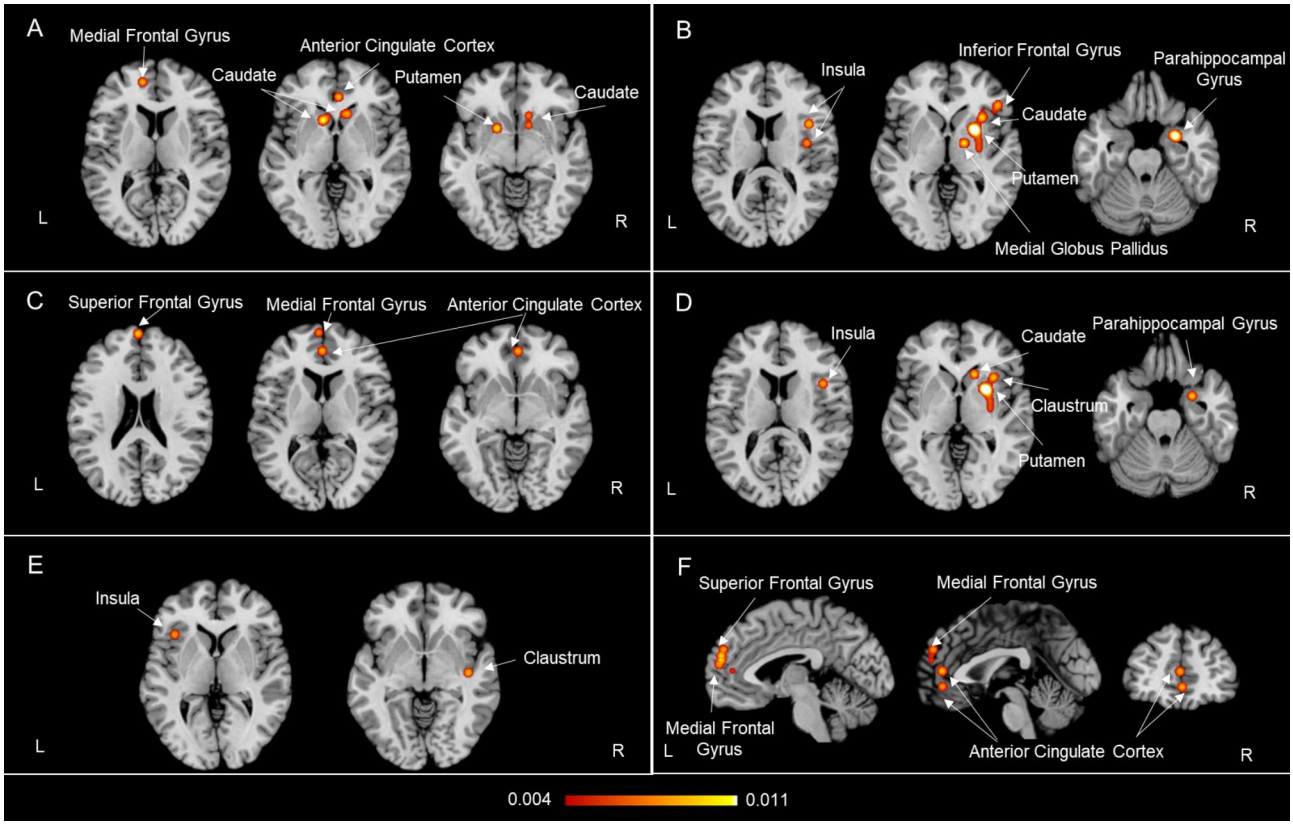

Fig. 2 Significant convergent brain regions in StD patients. **A**: Total effect of StD patients in adolescents. Since all included studies indicated a downward trend, it also represented total effect "decrease" (StD < HC) in adolescents. **B**: Total effect of StD patients in young adults. **C**: Total effect of StD patients in middle-aged and older adults. D: Total effect "increase" (StD > HC) in young adults. E: Total effect "increase" (StD > HC) in middle-aged and older adults. F: Total effect "decrease" (StD < HC) in middle-aged and older adults

in the cortex when performing emotion regulation tasks, such as the left frontal lobe [39] and dorsal ACC [40]. Karl et al. summarized that the brain regions involved in emotion regulation changed with age, specifically moving from the subcortex in younger individuals to the cortex in the elderly [41]. Meanwhile, only two convergent brain regions (the insula and claustrum) showed reduced overall effects in middle-aged and older patients, fewer than in young adult patients. We speculated that middle-aged and older patients might rely on fewer brain regions for emotion regulation. As life experience increased, older adults tended to employ more effective strategies to regulate emotions than younger people [42]. Besides, these changes might be related to physiological and pathological factors associated with biological aging, including decreases in gray and white matter volume, inflammation, vascular dysfunction, and metabolic abnormalities [43, 44]. Further studies are needed to investigate compensatory mechanisms in middle-aged and older adults with StD.

In the subgroup analysis, middle-aged and older StD patients showed smaller gray matter volume or decreased functional activation in the frontal lobe and the ACC, while showing larger gray matter volume or increased functional activation in the insula and claustrum. This might be related to neurodegeneration and cognitive aging. As individuals entered middle age and advanced into older adulthood, the volume of gray and white matter in the brain gradually decreased [45]. Smaller volume in the frontal cortex has been observed in older adults with depression [46]. Moreover, the frontal lobe and ACC, as critical regions for cognition, are particularly affected during cognitive aging [47, 48]. The capacity for emotion regulation in the frontal lobe and ACC was limited in middle-aged and older StD patients due to the influence of neurodegeneration and cognitive aging. This made it challenging for these regions to compensate as effectively as the insula and claustrum.

Variability in the types of depression measures used across age groups might impact the comparability and interpretation of our findings. According to DSM-V or any prior DSM, subthreshold depression (StD) was diagnosed based on fewer than five symptoms of depression lasting at least two weeks, without meeting the criteria for Major Depressive Disorder (MDD) [49]. All included StD patients in our study met this diagnostic criterion.

Table 3 Total effect "increase" (StD > HC) or "decrease" (StD > HC) of StD patients at different ages

Lable	MNI space			ALE	*P*	Z
	x	y	z			
Adolescents (StD < HC)						
Left Medial Frontal Gyrus	-12	50	6	0.0110	< 0.001	4.343
Left Caudate	-6	18	2	0.0114	< 0.001	4.592
	-12	14	-2	0.0114	< 0.001	4.592
Left Putamen	-18	8	-8	0.0108	< 0.001	4.160
Right Anterior Cingulate Cortex	4	36	0	0.0106	< 0.001	3.931
	14	30	14	0.0106	< 0.001	3.887
Right Caudate	6	20	2	0.0110	< 0.001	4.343
	12	20	-4	0.0108	< 0.001	4.159
	12	12	-10	0.0100	< 0.001	3.783
Young Adults (StD > HC)						
Right Caudate	16	20	-2	0.0092	< 0.001	3.155
Right Claustrum	34	18	-2	0.0095	< 0.001	3.310
Right Insula	42	12	12	0.0097	< 0.001	3.356
	44	22	4	0.0088	0.001	3.031
Right Parahippocampal Gyrus	26	2	-26	0.0099	< 0.001	3.408
Right Putamen	26	6	-4	0.0201	< 0.001	5.103
	30	-12	-6	0.0104	< 0.001	3.552
	30	-4	2	0.0100	< 0.001	3.421
	28	-2	-14	0.0095	< 0.001	3.301
Middle-aged and older adults (StD > HC)						
Left Insula	-39	21	0	0.0089	< 0.001	3.840
Right Claustrum	42	-15	-6	0.0092	< 0.001	4.130
Middle-aged and older adults (StD < HC)						
Left Anterior Cingulate Cortex	0	46	8	0.0096	< 0.001	3.810
Left Medial Frontal Gyrus	-6	58	14	0.0102	< 0.001	3.900
	-4	56	18	0.0102	< 0.001	3.900
	-4	56	22	0.0102	< 0.001	3.900
Left Superior Frontal Gyrus	-2	54	28	0.0102	< 0.001	3.900
Right Anterior Cingulate Cortex	2	46	-6	0.0093	< 0.001	3.740

StD: Subthreshold Depression; HC: Healthy control

Besides, depressive symptom assessments were primarily conducted using standard self-reported scales. Specifically:

(1)For adolescents: all studies (100%) used self-reported scales.

(2)For young adults: one study used a clinical structured interview, while the rest (94.12%) used self-reported scales or combined these with clinical interviews.

(3)For middle-aged and older adults, all studies (100%) used self-reported scales or combined these with clinical interviews.

While the diagnostic criteria for StD were consistent and depressive symptoms assessments were primarily consistent across studies, the lack of assessments based on clinically structured interviews might make it challenging to compare neuroimaging characteristics across different ages and determine the impact of methodological differences. Future research should investigate this issue further to clarify the specific effects of these variations.

An important area for further exploration was the impact of psychotherapeutic and counseling interventions on individuals with subthreshold depression (StD). Some evidence suggested that interventions like TMS could improve depressive symptoms and influence brain function [50, 51]. In contrast, Huang et al. [52] found that although aerobic training significantly improved depressive symptoms in StD patients, it did not result in significant differences in degree centrality values compared to healthy controls. Given the limited number of studies and the scarcity of research incorporating healthy controls, the specific effects of these interventions on neuroimaging characteristics remained underexplored. Future research should prioritize comprehensive investigations, including robust control groups and longitudinal designs, to better understand how psychotherapeutic and counseling interventions affect both symptomatology and brain function in StD.

Our study identified key brain regions that converge across different age groups in StD patients, providing

crucial guidance for selecting targets in non-invasive brain stimulation (NIBS). NIBS is an effective treatment for depression, with high-frequency rTMS on the left dorsolateral prefrontal cortex (DLPFC) achieving Level A evidence [53, 54]. By revealing age-related changes in the frontostriatal circuit, our research has deepened the understanding of brain structure and function. In the future, this evidence might help identify age-specific targets and design personalized treatment plans for StD patients. It might provide a theoretical reference for optimizing clinical outcomes and improving therapeutic efficacy.

Furthermore, this study has certain limitations. Firstly, coordinate-based meta-analysis assumed that each voxel in the brain had an equal chance of being activated. However, seed-based analyses might introduce selection bias, potentially exaggerating the importance of specific brain regions [26]. Consequently, this study exclusively included articles that conducted whole-brain analyses. This would facilitate a more comprehensive understanding of the neuroimaging characteristics of StD patients across different ages, thereby providing evidence for more targeted identification of biomarkers in StD patients. Secondly, our study conducted a coordinate-based meta-analysis (CBMA) to integrate significant peak coordinates from various imaging modalities. This approach minimized modality-specific signal differences (e.g., scaling, heteroscedasticity, and smoothness) and reduced the influence of statistical choices (e.g. thresholding procedures and significance levels) [55]. On the other hand, combining different modalities helped to enlarge the number of studies to increase the power to detect smaller effects and enhance analytical robustness, providing stronger evidence for generalization across experiments and analytical procedures [55]. Thirdly, potential confounding factors such as gender, diagnostic criteria, and geographic region require further investigation in future studies. This would facilitate a more comprehensive understanding of the neuroimaging characteristics of StD patients across different ages, thereby providing evidence for more targeted identification of biomarkers in StD patients.

In conclusion, our study has identified unique features of StD at different life stages, partly revealing its dynamic impact on neurodevelopment across the lifespan. Meanwhile, the neuroimaging characteristics of StD supported the critical role of the frontostriatal circuit. Further studies were needed for the frontostriatal circuit on the progression of StD and other depressive disorders. Our findings potentially provided valuable insights for the early diagnosis, identification, and prevention of StD.

Abbreviations

MDD	Major depressive disorder
StD	Subthreshold depression
ALE	Activation likelihood estimation
ACC	Anterior cingulate cortex
HCs	Healthy controls
IFG	Inferior frontal gyrus
MGP	Medial globus pallidus
PHG	Parahippocampal gyrus
SFG	Superior frontal gyrus

Supplementary Information

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Supplementary Material 1

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Author contributions

Writing - Original draft, review & editing, formal analysis and visualization: BR.Z. & ZH.L. Writing - Original draft, review & editing and visualization: YZ.H. Investigation and data curation: YD.H., ZY.L. & L.C. Writing – Original review & editing: C.L., & RJ.Y. Project administration and supervision: LF.Y. Project administration, funding acquisition, supervision, and writing - review & editing: JS.W. All authors approved the final version of the manuscript. BR.Z., ZH.L. & YZ.H. Contributed equally and shared the first authorship. LF.Y and JS.W. were co-corresponding authors.

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Data availability

The data used for this meta-analysis are publicly available in the research studies. The full dataset can be requested from the corresponding author at a reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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