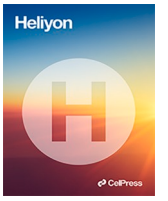
Heliyon 10 (2024) e24894

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Grey matter abnormalities in major depressive disorder patients with suicide attempts: A systematic review of age-specific differences

Ziwen Chen [a,1], Tao Xu [a,1], Qifu Li [b], Yunjie Shu [a], Xueli Zhou [a], Taipin Guo [b,**], Fanrong Liang [a,*]

[a] Department of Acupuncture and Moxibustion, Chengdu University of Traditional Chinese Medicine, Chengdu, China
[b] Department of Acupuncture and Moxibustion Rehabilitation, Yunnan University of Chinese Medicine, Kunming, China

ARTICLE INFO

Keywords:
Major depressive disorder
Suicidal attempt
Structural MRI
VBM

ABSTRACT

Background: Previous studies have reported alterations in brain structure in major depressive disorder (MDD) patients with suicide attempts. However, age-related changes in suicidal MDD patients remain unclear.

Methods: We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Embase, PubMed, and Web of Science were searched to identify relevant studies from inception to January 2023. All voxel-based and surface-based morphometry studies comparing suicidal MDD patients to MDD or healthy controls were included. Studies were then grouped by age range (old, middle-age, adolescent) and the commonalities and age-related structural brain alterations were summarized. The included studies were evaluated using the Newcastle-Ottawa Scale (NOS).

Results: A total of 17 studies met the inclusion criteria, including 3 of late-life depression (LLD) patients, 11 of middle-aged depression (MAD) patients, and 3 of adolescent depression (AOD) patients. The majority of studies had moderate to high NOS scores, indicating good quality. Patients in all three age groups exhibited extensive alterations in the lateral, medial, and orbital regions of the frontal lobes. Furthermore, suicidal MAD patients showed a specific decrease in the gray matter volume of the dorsolateral prefrontal cortex compared to suicidal LLD patients. Cortical thickness and left angular gyrus volume were decreased in suicidal MAD and suicidal LLD patients, but increased in suicidal AOD patients.

Conclusion: This systematic review summarizes structural brain changes in suicidal MDD patients at three age groups: elderly, middle-aged, and adolescent. These findings help elucidate the common circuitry of MDD related to suicide over the lifespan and highlight unique circuitry associated with different ages. These findings may help predict the risk of suicide in MDD patients at different ages.

* Corresponding author. Chengdu University of Traditional Chinese Medicine, Chengdu, China.
** Corresponding author. Yunnan University of Chinese Medicine, Kunming, China.
E-mail addresses: gtphncs@126.com (T. Guo), acuresearch@126.com (F. Liang).
[1] The authors contributed equally to this work as co-first authors.

https://doi.org/10.1016/j.heliyon.2024.e24894
Received 17 July 2023; Received in revised form 29 December 2023; Accepted 11 January 2024
Available online 23 January 2024

1. Introduction

Suicide has become a critical public health issue worldwide, with an estimated global incidence of 10.6 deaths per 100,000 individuals [1]. Psychiatric disorders, such as major depressive disorder (MDD), are known to significantly increase the risk of suicide [2–4]. Not only does suicide result in preventable loss of life, it also exerts a substantial impact on society. Current methods used to evaluate suicide rely heavily on interviews and questionnaires, such as the SAD PERSONS Scale [5], Columbia-Suicide Severity Rating Scale [6], and Beck Scale for Suicidal Ideation [7], which are largely based on subjective scoring. Obtaining reliable information can thus be challenging, especially when physical condition is poor. Thus, there is a need for more objective indicators to facilitate comprehensive assessment. Prior studies have shown that changes in biological markers can predict suicidal ideation. For example, MDD patients who have attempted suicide exhibit abnormally elevated levels of IL-6 and TNF-α, but abnormally lower levels of IL-2, compared to controls without suicide attempts (SA) [8–10]. Such evidence supports the hypothesis that individuals with suicidal tendencies may possess abnormal levels of pro-inflammatory cytokines. However, conventional neurochemical methods have failed to yield information regarding the precise location of abnormally altered targets *in vivo*.

Using magnetic resonance imaging (MRI) techniques, substantial efforts have been made to uncover the neural mechanisms underlying suicidal behavior through structural neuroimaging studies. Previous investigations have revealed an association between alterations in regional gray matter volume (GMV) and SA in individuals with MDD. Specifically, two comprehensive meta-analyses by the ENIGMA-MDD working group have reported distinct cortical and subcortical structural alterations in MDD patients with suicidal tendencies compared to controls, including smaller total intracranial and subcortical (especially thalamic) volumes, larger ventricular volumes, reduced thalamic and pallidum volumes, and decreased inferior parietal surface area [11,12]. These findings suggest the presence of neurobiological markers associated with suicidal behavior in individuals with depression. However, limited data availability has hindered the ability to draw clear conclusions. The findings of previous studies are largely constrained by heterogeneity, including differences in demographics, clinical characteristics, and research methodologies. Of particular note, age of MDD onset may be linked to distinct etiologies and yield diverse outcomes [13]. Cognitive and executive dysfunction have been identified as significant factors associated with increased susceptibility to suicide in late-life depression (LLD) patients [14], whereas, among adolescent depression (AOD) patients, suicide ideation and attempts are commonly linked to childhood maltreatment and neglect [15]. Although these findings suggest distinctive neurobiological changes and treatment strategies for AOD and LLD patients [16], few studies have considered age as a crucial variable for comparative analysis. A recent meta-analysis identified differences in frontoparietal, dorsal attention, and visual networks between LLD patients and middle-aged depression (MAD) patients [17], suggesting the existence of age-related changes in brain structure among individuals with MDD. However, it is still unknown whether there are general and age-specific changes in brain structure in MDD patients with suicidal ideation. Thus, a review of age-specific differences in brain structure is needed to further elucidate the neural mechanisms underlying suicidal behavior in individuals with MDD and may be of significant value for early prediction and care across various age groups.

2. Methods

This systematic review was prospectively registered with PROSPERO (registration No. CRD42022372476) and prepared in accordance with PRISMA guidelines for reviews and meta-analyses [18].

2.1. Data sources and search strategy

We conducted a literature search of three major electronic databases, namely Embase, PubMed, and Web of Science, for English articles published from inception to January 2023. The search terms were: (“depression” OR “depressive symptom*” OR “emotional depression” OR “major depressive disorder”); (“suicide” OR “suicidality” OR “suicidal ideation” OR “suicidal attempt”) and (“gray matter” OR “voxel-based morphometry” OR “VBM” OR “cortical thickness” OR “Freesurfer” OR “GMV” OR “gray matter volume”). The reference lists of reviews and included articles were also checked to identify relevant studies overlooked by the manual search. Additional information is provided in Supplementary Table 1.

2.2. Selection criteria

The inclusion criteria were as follows:

(1) neuroimaging studies that examined structural variation between suicidal MDD patients and MDD patients or healthy controls (HCs);
(2) MDD diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria;
(3) suicidality assessed by medical records or objective scales; and
(4) MRI magnet strength of 1.5 T or higher.

The exclusion criteria were:

(1) diagnosis with any other psychiatric disorder, such as anxiety disorders or schizophrenia;

(2) fewer than seven participants in any group; and
(3) systematic reviews, meta-analyses or letters.

To avoid duplication of data, if two studies were from the same data source, only the article with the most comprehensive information was included.

2.3. Study selection

After first removing duplicates using Endnote ×9, two researchers independently read the titles and abstracts of the identified studies to determine potentially eligible studies. Next, the two researchers read the full text of all articles and screened them according to the above selection criteria. Any discrepancies in the screening process were resolved by discussion with a third researcher.

2.4. Data extraction

All eligible studies were first categorized based on the average age of the participants. Following standard definitions in the literature [17], studies with an average age below 18 years were assigned to the AOD group, studies with an average age between 18 and 55 years were assigned to the MAD group, and studies with an average age over 55 years were assigned to the LLD group. After categorization, the following general information was extracted from each study: name of the first author, year of publication, country where the study was conducted, total sample size in each clinical group, neuroimaging technologies utilized, and neuroimaging results. Data extraction was supported by Endnote ×9 and Microsoft Excel 2010 to facilitate efficient compilation and sorting of the relevant data.

2.5. Quality assessment

We evaluated the quality of the included studies using a modified version of the Newcastle-Ottawa Scale (NOS) [19]. The NOS is scored out of 9 points based on responses to eight items: four items about study population selection (4 points), one item about comparability between groups (2 points), and three items about exposure factor measurement (3 points). Scores were interpreted as follows: 0–3 indicates low quality, 4–6 indicates medium quality, and 7–9 indicates high quality [20].

2.6. Data synthesis

To obtain reliable results, we analyzed the characteristics and quality of each study using bibliometric methods. We identified neuroimaging differences in suicidal MDD patients across age groups by synthesizing findings from multiple studies, drawing meaningful conclusions from patterns and trends in the data. These methods provide a thorough and nuanced understanding of neurobiological factors underlying suicidal behavior in MDD patients of different age groups.

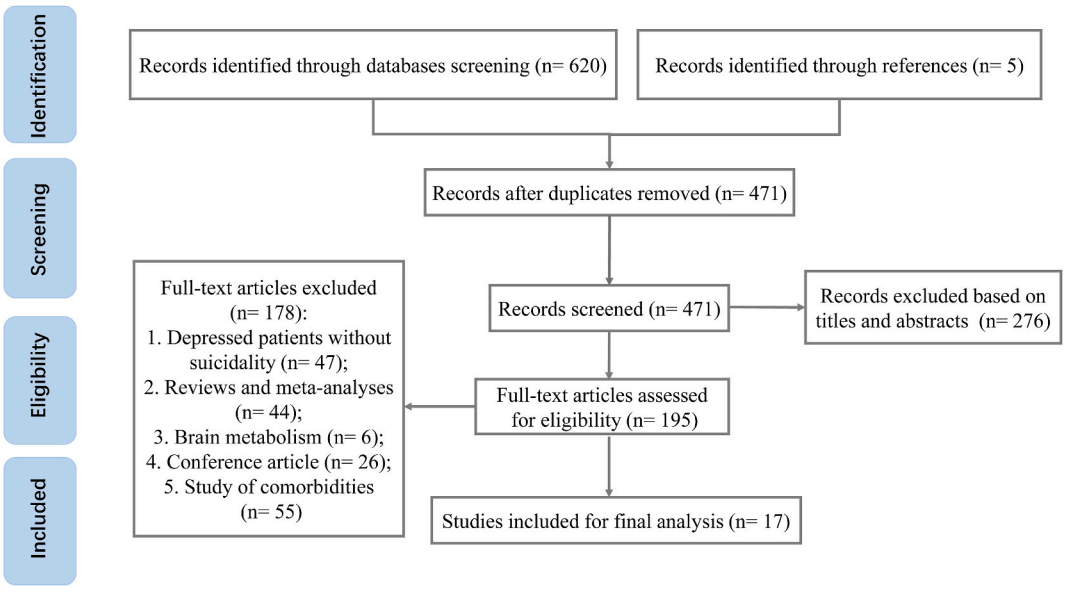


Fig. 1. The flow diagram of literature screening.

3. Results

3.1. Study characteristics

A total of 625 articles were obtained, of which 620 were identified by the database search and 5 were identified through a review of the references. Of these, 17 articles involving 1709 participants (n = 780 SA, n = 1046 MDD, and n = 911 HCs) ultimately met the inclusion criteria. The age groups of these studies were: 3 LLD [21–23] comparisons (n = 115 SA, n = 108 MDD, and n = 26 HCs), 11 MAD [24–34] comparisons (n = 313 SA, n = 481 MDD and n = 424 HCs), and 3 AOD [35–37] comparisons (n = 93 SA, n = 78 MDD and n = 71 HCs). Thirteen studies used voxel-based morphometry (VBM) while the remaining four studies used surface-based cortical thickness measures (conducted in Freesurfer). Most of the studies had moderate to high NOS scores, indicating they were of good quality. A flow chart of the study screening process is presented in Fig. 1, and characteristics of the included studies are shown in Table 1.

3.2. LLD patients with SA

As shown in Table 1, three [21–23] VBM studies examined differences between suicidal LLD patients and general LDD patients. The elderly patients included in these studies exhibited mean Mini-mental State Examination (MMSE) scores above 26, indicating normal cognitive and intellectual functioning. Several studies report alterations in the cerebral cortex and subcortical structures. Specifically, Eileen et al. [23] highlighted abnormalities in subcortical structures, notably heightened gray matter intensity in the basal ganglia that

Table 1
Descriptions of the included studies.

Author/Year/Country	Age	Groups			Diagnostic criteria	Suicide assessment	Scores of NOS	Antidepressant		
		SA	MDD	HC				SA	MDD	HC
Shao et al. (2022), China [21]	LLD	68	45	/	HAMD-17, HAMA, MMSE	BSS, SPS, TSII	8	13/68	10/45	/
Hwang et al. (2010), China [22]	LLD	27	43	26	DSM-IV, HAMD-17, MINI, MMSE	MRs	7	0/27	0/43	0/26
Eileen et al. (2001), the United States [23]	LLD	20	20	/	HAMD-17, MMSE	MRs	8	Not mentioned	Not mentioned	/
Wang et al. (2021), China [24]	MAD	41	44	52	DSM-IV , HAMD-17	BSS, C-SSRS	9	0/41	0/44	0/52
Zhang et al. (2020), China [25]	MAD	35	38	43	DSM-IV, HAMD-17	BSS	8	16/35	26/38	0/43
Yang et al. (2020), China [26]	MAD	68	119	103	DSM-IV, HAMD-17	NGASR	8	0/68	0/119	0/103
Wang et al. (2019), China [27]	MAD	38	60	60	DSM-IV, HAMD, YMRS	MRs	8	22/38	30/60	0/60
Mina et al. (2019), the United States [28]	MAD	25	66	/	DSM-IV, HAMD-17	BSS, C-SSRS	8	0/25	0/66	/
Lee et al. (2016), Korea [29]	MAD	19	19	/	DSM-IV, HAMD-17, CGI-S	BSS, BHS, BIS	7	18/19	18/19	/
Warren et al. (2015), the United States [30]	MAD	21	53	91	DSM-IV, MADRS, MINI	/	7	0/21	0/53	0/91
Romain et al. (2015), France [31]	MAD	24	39	/	DSM-IV, HAMD-17, MINI	MRs	8	19/24	30/39	/
Peng et al. (2014), China [32]	MAD	20	18	28	DSM-IV, HAMD-17, DAS, SDS	MRs	7	20/20	18/18	0/28
Wagner et al. (2012), Germany [33]	MAD	15	15	30	DSM-IV, HAMD-17, MINI	BDI	8	0/15	0/15	0/30
Monku et al. (2007), the United States [34]	MAD	7	10	17	DSM-IV, HAMD-17	MRs	8	0/7	0/10	0/17
Liu et al. (2021), China [35]	AOD	37	23	/	ICD-10	BSS	8	0/37	0/23	/
Anthony et al. (2021), France [36]	AOD	28	34	30	DSM-IV	BDI, SHQ	7	14/28	21/34	0/30
Lisa et al. (2015), the United States [37]	AOD	28	31	41	DSM-IV	SIQ, C-SSRS, BDI, SCARED	9	0/28	0/31	0/41

BDI: Beck Depression Inventory; BHS: the Beck Hopelessness Scale; BIS: the Barratt Impulsivity Scale; BSS: the Beck Scale for Suicidal Ideation; CGI-S: the Clinical Global Impression-Severity scale; C-SSRS: Columbia-suicide severity rating scale; DAS: Dysfunctional Attitude Scale; HAMD-17: the 17-item Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale; MADRS: Montgomery Asberg Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview; MMSE: Mini-Mental State Examination; MRs: Medical Records; NGASR: Nurses' Global Assessment of Suicide Risk Scale; SCARED: the Screen for Childhood Anxiety Related Emotional Disorders; SDS: Self-Rating Depression scale; SHQ: Suicide History Questionnaire (in house questionnaire); SIQ: the Suicidal Ideation Questionnaire; SPS: the SAD PERSONS Scale that assesses suicide potential; TSII: the Triggers of Suicidal Ideation Inventory; YMRS: Young Mania Rating Scale.

may be strongly associated with suicide attempts. Similarly, Hwang et al. [22] reported reduced GMV in the frontal, temporal, and parietal cortex as well as subcortical structures (especially the pallidum), and insula in LLD patients with SA compared to general depression patients. Shao et al. [21] examined structural changes in the cerebral cortex and found significant changes in the frontal cortex, particularly GMV changes in the orbital frontal cortex (OFC) and ventrolateral prefrontal cortex (VLPFC). Despite the relatively limited number of studies pertaining to LLD patients with SA, they typically report abnormal changes in the frontal cortex, including the orbital gyrus, medial and lateral regions (mainly VLPFC), and basal ganglia structures. Additional details are shown in Fig. 2a and Table 2.

3.3. MAD patients with SA

As shown in Fig. 2b and Tables 2 and 3, 11 studies [24–34] investigated structural brain changes in MAD patients with SA. Among these, eight studies compared differences between SA, MDD, and HC groups, while 3 studies compared differences between SA and MDD groups. The VBM approach was utilized in nine studies, whereas the FreeSurfer tool was used in two studies. The findings reveal structural brain alterations in suicidal MAD patients primarily within the fronto-parietal-temporal-limbic circuit, with the frontal lobe exhibiting abnormal changes in the orbital, medial, and lateral regions.

In the SA group compared with the HC group, Wang et al. [24] reported decreased gray matter density in the ventromedial prefrontal cortex (VMPFC), Zhang et al. [25] found a decreased GMV in the left and right dorsolateral prefrontal cortex (DLPFC) and right VLPFC, Wang et al. [27] identified reduced GMV in the ventral and medial prefrontal cortex (PFC), and Monku et al. [34] reported reduced GMV in the left and right OFC. Other significant findings include reduced GMV in the amygdala bilaterally [27], as well as decreased GMV in the right middle temporal gyrus, but increased GMV in the right parietal lobe [32].

Compared to the MAD group, the SA group also showed a decrease in GMV in the left and right DLPFC [25], ventral/medial PFC, amygdala [27], and right VLPFC [25], but with a greater decrease in volume. GMV decreases were also observed in the right inferior frontal orbital gyrus [26] and left angular gyrus [29]. Regarding cortical thickness, Warren et al. [30] reported a decrease in frontoparietal cortical thickness, while Wagner et al. [33] observed reduced cortical thickness in the left VLPFC and DLPFC. Limbic system abnormalities were predominantly observed within the basal ganglia. Wang et al. [24] identified increased gray matter density in the left striatum, which was correlated positively with the degree of suicidal ideation. Yang et al. [26] found reduced GMV in the left caudate nucleus, while other studies reported reduced GMV [32] and cortical thickness [33] in the cingulate gyrus.

One study reported increased GMV in the prefrontal and insula regions among individuals with high suicidal ideation compared to those with low suicidal ideation and general MDD, which is contrary to the majority of findings [28]. Another study [31] reported a significant reduction in GMV in the hippocampal region for patients with suicidal behavior within the last month. However, no differences were observed in patients whose last suicidal act occurred more than 1 month ago. This finding suggests the potential significance of the hippocampus in predicting acute suicidal behavior, although further studies with larger sample sizes are required to confirm this finding.

In summary, structural brain alterations observed in MAD patients with suicidality primarily involve the fronto-parietal-temporal-limbic circuit, with GMV reductions in the left and right DLPFC, ventral/medial PFC, amygdala, and right VLPFC were found both in SA vs. MAD and SA vs. HC group comparisons, with a greater degree of reduction in the first group than in the second.

3.4. AOD patients with SA

Three studies reported structural brain changes in suicidal AOD patients (see Fig. 2c and Table 2). Of these, two studies compared suicidal with general AOD patients and one study compared AOD with SA patients with HCs. In contrast to findings for the MAD and LLD groups with SA, AOD patients with SA exhibited increased GMV in the right middle frontal gyrus and left angular gyrus compared to AOD patients without SA [35]. However, they showed decreased GMV in the right superior temporal gyrus compared to HCs [37].

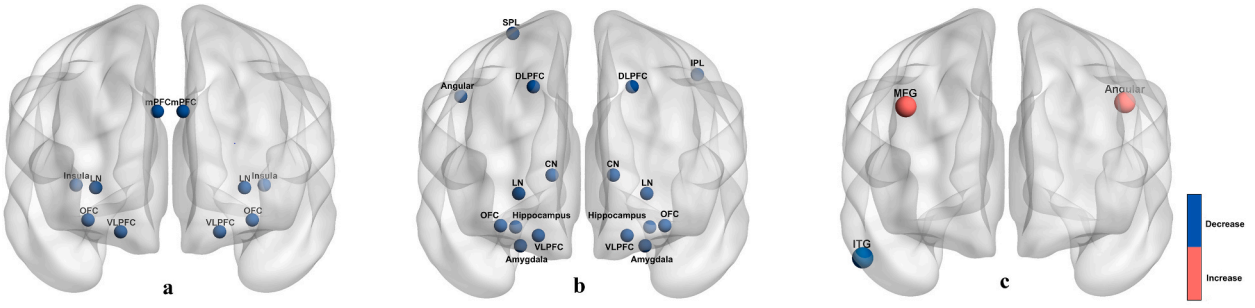


Fig. 2. (a) Gray matter changes in LLD patients with suicidality. (b) Gray matter changes in MAD patients with suicidality. (c) Grey matter changes in AOD patients with suicidality.
mPFC: medial prefrontal cortex; VLPFC: ventral lateral prefrontal cortex; LN: lentiform nucleus; OFC: orbitofrontal cortex; DLPFC: dorsal lateral prefrontal cortex; IPL: inferior parietal lobule; SPL: superior parietal lobule; CN: caudate nucleus; MFG: middle frontal gyrus; ITG: inferior temporal gyrus.

Table 2
Neuroimaging results of the included studies.

Age groups	Studies	Neuroimaging results
LLD patients with SA	Shao et al. (2022), China [21]	Decreased GMV in the default mode network and lateral PFC.
	Hwang et al. (2010), China [22]	Decreased GMV in insula and the posterior cingulate region.
	Eileen et al. (2001), the United States [23]	Subcortical gray matter hyperintensities.
MAD patients with SA	Wang et al. (2021), China [24]	Increased gray matter density in the left striatum of reward system.
	Zhang et al. (2020), China [25]	Decreased GMV in the left and right DLPFC and right VLPFC.
	Yang et al. (2020), China [26]	Decreased GMV in the right inferior frontal orbital gyrus and left caudate but increased in the left calcarine fissure.
	Wang et al. (2019), China [27]	Decreased GMV in the right and left amygdala, ventral/medial/dorsal PFC.
	Mina et al. (2019), the United States [28]	Increased GMV in the PFC and insula.
	Lee et al. (2016), Korea [29]	Decreased GMV in the left angular gyrus and right cerebellum.
	Warren et al. (2015), the United States [30]	Decreased cortical thickness in the left fronto-parietal regions and the insula.
	Romain et al. (2015), France [31]	Decreased GMV in the hippocampus.
	Peng et al. (2014), China [32]	Decreased GMV in the right middle temporal gyrus and increased in the right parietal lobe when compared to HCs; and decreased in the left limbic cingulate gyrus when compared with the group of non-suicidal MAD patients.
	Wagner et al. (2012), Germany [33]	Decreased cortical thickness in the left DLPFC, VLPFC and the anterior cingulate.
	Monku et al. (2007), the United States [34]	Decreased GMV in the right and left OFC when compared with HCs; increased in the right amygdala volumes when compared with non-suicidal MAD patients.
AOD with SA	Liu et al. (2021), China [35]	Increased GMV in the right middle frontal gyrus and left angular gyrus.
	Anthony et al. (2021), France [36]	Increased cortical thickness in the temporal cortices and right insula, and right putamen volume.
	Lisa et al. (2015), the United States [37]	Decreased GMV in the right superior temporal gyrus (BA38).

AOD: adolescent depression; DLPFC: dorsolateral prefrontal cortex; GMV: gray matter volume; LLD: late-life depression; MAD: middle-aged depression; MDD: major depressive disorder; OFC: orbital frontal cortex; PFC: prefrontal cortex; SA: suicide attempts; VLPFC: ventrolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex.

Table 3
Structural brain changes in the SA vs HC and SA vs MAD groups.

SA vs HC	GMV	Decreased: in the left and right DLPFC, OFC, ventral/medial PFC, amygdala; in the right VLPFC, the middle temporal gyrus; Increased: in the right parietal lobe.
	Gray Matter Density	Decreased: in the VMPFC.
SA vs MAD	GMV	Decreased: in the left and right DLPFC, ventral/medial PFC, amygdala, hippocampus; in the right VLPFC, inferior frontal orbital gyrus; in the left caudate, angular gyrus, limbic cingulate gyrus; Increased: in the PFC regions, insula and the right amygdala.
	Cortical Thickness	Decreased: in the left DLPFC, VLPFC, fronto-parietal regions, insula; and the anterior cingulate.
	Gray Matter Density	Increased: in the left striatum.

DLPFC: dorsolateral prefrontal cortex; GMV: gray matter volume; HC: healthy control; MAD: middle-aged depression; OFC: orbital frontal cortex; PFC: prefrontal cortex; SA: suicide attempts; VLPFC: ventrolateral prefrontal cortex; VMPFC: ventromedial prefrontal cortex.

Although no significant differences in cortical thickness were observed among the three groups, atypical maturation of specific cortical and subcortical areas was observed in the SA group (cortical thickness is generally negatively correlated with age, but showed a positive correlation in the SA group). This aberrant maturation may contribute to the heightened risk of suicide in this group [36].

4. Discussion

Given the increasing human and social costs of suicide, the need for biomarkers to predict and prevent suicidal behavior has become urgent. Neuroimaging techniques provide an excellent opportunity to understand structural and functional differences in the brain that underlie individual suicidal symptoms. By analyzing data from 17 studies encompassing 1709 participants (n = 780 SA, n = 1046 MDD, and n = 911 HCs), we present a review of structural brain changes in MDD patients with SA at three different age spans: elderly, middle-aged, and adolescent.

The majority of studies focused on the fronto-parietal-temporal-limbic circuit, showing a high degree of similarity alterations across

the three age groups. However, some studies reported age-specific alterations. For instance, both middle-aged and elderly patients exhibited abnormalities in the orbital, medial, and lateral regions of frontal lobes, but studies of elderly patients did not report any DLPFC volume abnormalities. Additionally, GMV in the left angular gyrus was found to decrease in middle-aged patients but increase in adolescent patients. Cortical thickness tended to decrease in middle-aged and older patients, but exhibited an abnormal increase in adolescent patients. We hypothesize that these differences may reflect specific changes in depressed patients with SA at different ages.

The frontal cortex is the highest level of neurodevelopment and the center of integrated emotional processing, involving executive function, emotional processing, and situational memory. Frontal cortex abnormalities were reported across all three age groups, particularly in the VLPFC and OFC. The VLPFC and OFC are known to play a crucial role in the transmission and regulation of non-reward and punishment signals [25,34]. Abnormalities in these areas are commonly associated with a lack of happiness in MDD patients [38]. Prior studies have reported that changes in VLPFC/OFC volume, combined with other gray matter features, can enhance sensitivity for detecting MDD patients at risk of suicide by 37 % [21]. Serotonin has also been extensively studied in relation to depressive suicide. Reduced serotonergic neurotransmission has been reported in suicide attempters, and central serotonergic abnormality appears to be specific to certain brain regions [39,40]. For instance, alterations in 5-HT1A and 5-HT2A receptor binding have been observed primarily in the ventral PFC of people who died by suicide [41]. Leyton et al. analyzed serotonin synthesis in suicide attempters and found abnormal tryptophan metabolism in the orbital and ventromedial PFC [42], which aligns with our findings. The DLPFC, which is involved in emotional judgments, tends to exhibit reduced volume in MDD patients with suicidal tendencies [43]. Transcranial magnetic stimulation of the DLPFC has been shown to significantly reduce suicidal ideation [44,45]. However, this treatment effect was not observed in older patients, which may be due to complex neuropathological changes in the brains of elderly patients involving multiple diseases, such as dementia and cerebrovascular disease. In elderly patients, depressive symptoms accompanied by suicidality may interact with other neuropathological changes, making it difficult to observe changes in the DLPFC. A neuroimaging study of cognitive executive dysfunction in elderly depressed patients revealed reduced DLPFC activation and decreased functional connectivity between the DLPFC and dorsal anterior cingulate cortex (dACC) during cognitive control network tasks. Importantly, this pattern of reduced functional connectivity persisted after antidepressant treatment [46]. It is worth noting that all elderly patients included in our study had MMSE scores above 26, indicating normal cognitive executive function, which may partially explain this discrepancy.

The angular gyrus, an integral component of the inferior parietal lobe, plays a crucial role in diverse functions including language and memory extraction [47]. Alterations in the structure and function of the angular gyrus have been shown to contribute to executive cognitive function decline, impaired emotional decision-making, sensory decline, memory deficits, and attention deficits, thereby augmenting the vulnerability of individuals suffering from MDD to SA. Consistent with the findings of the ENIGMA-MDD working group [12], our review identified reduced GMV in the left angular gyrus of suicidal MAD patients. Notably, this pattern contrasts sharply with the findings for suicidal AOD patients as well as a study of suicidal MAD patients with a younger average mean age (27.75 years) [32]. We propose that this difference may be influenced by distinct suicidal triggers. Among adolescents, suicidal ideation is largely influenced by factors such as education and interpersonal relationships, whereas physical illness and work-related stress are significant risk factors for suicide in middle-aged and older patients [48,49].

In general, there exists a notable negative correlation between age and mean cerebral cortex thickness [50]. Previous longitudinal studies involving healthy individuals have revealed that the most typical anatomical change in the adolescent brain is cortical thinning [51]. Cortical thinning during the aging process has also been observed in healthy adults [52]. Several studies have reported the impact of depression on cortical thickness, with depressed individuals showing a reduction in cortical thickness compared to healthy individuals [53,54]. Our review has further revealed that the cerebral cortex shrinks faster in suicidal middle-aged and older patients compared to general MDD patients [22,30,33] and shows atypical changes in suicidal adolescent patients [36]. As adolescents are in a stage characterized by substantial neurodevelopmental changes within a relatively short period [55], it is plausible that this opposing finding is due to variation in age among the included patients. Nevertheless, this observation may be valuable for diagnosis of adolescent patients with SA. However, given the limited number of studies and samples, a comprehensive longitudinal study with a larger sample size is warranted to validate any potential associations between SA and cortical thickness.

4.1. Limitations

This study is subject to several limitations. Firstly, there is a lack of sufficient research on subcortical structure and white matter changes in older adults and adolescents, which prevented us from performing a more comprehensive and specific review of structural changes across age groups. Additionally, most studies are cross-sectional and suffer from numerous confounding factors. For instance, some studies report contrasting results among patients with varying levels of suicidal ideation (e.g., those with suicidal thoughts only compared to those who have attempted suicide) [56], or among patients of different genders [57], which undermines the reliability of this study. Furthermore, the use of antidepressant medications can impact changes in brain structure [58]. As this review included medicated and non-medicated patients, and few studies reported the results of subgroup analysis, it is challenging to determine the influence of medication on the conclusions of this study. Future reviews could concentrate on longitudinal studies with more refined trial protocol designs, enabling insights into the trajectory of the disease and investigation of differences in imaging measures before and after pharmacological treatment and behavioral interventions to shed light on mechanisms and responses to treatment.

5. Conclusions

This review summarizes structural changes in the brains of suicidal MDD patients at three age groups (elderly, middle-aged, and

adolescents), emphasizing the importance of age in imaging studies. The findings shed light on the shared circuitry of suicidal MDD across the lifespan and highlight some circuitry specific to different age groups. To our knowledge, this is the first review of structural brain changes in suicidal MDD patients across age groups. The findings contribute to a deeper understanding of the neurobiological underpinnings of suicidal depression and provide valuable insights into the development of personalized treatment and prevention strategies across age groups.

Data availability statement

Data included in article/supp. Material/referenced in article.

Funding

The study was supported by the Key Project of Science and Technology Department of Sichuan Province (No. 2019YFS0081), the National Natural Science Foundation of China (82060900), the Youth Special of Yunnan Province Ten-thousand Plan (YNWR-QNBJ-2019-257) and the "Liang Fanrong Expert Workstation" of Yunnan Province - Yunnan Provincial Science and Technology Plan Project (202305AF150072).

CRediT authorship contribution statement

Ziwen Chen: Writing – review & editing, Writing – original draft, Conceptualization. **Tao Xu:** Methodology, Data curation. **Qifu Li:** Methodology, Data curation. **Yunjie Shu:** Supervision. **Xueli Zhou:** Supervision. **Taipin Guo:** Supervision. **Fanrong Liang:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e24894.

References

[1] Suicide Mortality Rate, WHO, 2018 at, http://apps.who.int/gho/data/node.sdg.3-4-viz-2?lang=en. (Accessed 10 December 2018).
[2] G. Zalsman, K. Hawton, D. Wasserman, K. van Heeringen, E. Arensman, et al., Suicide prevention strategies revisited: 10-year systematic review, Lancet Psychiatr. 3 (7) (2016) 646–659, https://doi.org/10.1016/S2215-0366(16)30030-X.
[3] J.D. Ribeiro, X. Huang, K.R. Fox, J.C. Franklin, Depression and hopelessness as risk factors for suicide ideation, attempts and death: meta-analysis of longitudinal studies, Br. J. Psychiatry 212 (5) (2018) 279–286, https://doi.org/10.1192/bjp.2018.27.
[4] J. Reis, R. Vieira, C. Portugal-Nunes, A. Coelho, R. Magalhães, et al., Suicidal ideation is associated with reduced functional connectivity and white matter integrity in drug-naïve patients with major depression, Front. Psychiatr. 13 (2022) 838111, https://doi.org/10.3389/fpsyt.2022.838111.
[5] W.M. Patterson, H.H. Dohn, J. Bird, G.A. Patterson, Evaluation of suicidal patients: the SAD PERSONS scale, Psychosomatics 24 (4) (1983) 343–345, https://doi.org/10.1016/S0033-3182(83)73213-5, 348-345.
[6] K. Posner, G.K. Brown, B. Stanley, D.A. Brent, K.V. Yershova, et al., The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults, Am. J. Psychiatr. 168 (12) (2011) 1266–1277, https://doi.org/10.1176/appi.ajp.2011.10111704.
[7] A.T. Beck, M. Kovacs, A. Weissman, Assessment of suicidal intention: the scale for suicide ideation, J. Consult. Clin. Psychol. 47 (2) (1979) 343–352, https://doi.org/10.1037//0022-006x.47.2.343.
[8] D. Lindqvist, S. Janelidze, P. Hagell, S. Erhardt, M. Samuelsson, et al., Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity, Biol. Psychiatr. 66 (3) (2009) 287–292, https://doi.org/10.1016/j.biopsych.2009.01.030.
[9] S. Janelidze, D. Mattei, Westrin Å, L. Träskman-Bendz, L. Brundin, Cytokine levels in the blood may distinguish suicide attempters from depressed patients, Brain Behav. Immun. 25 (2) (2011) 335–339, https://doi.org/10.1016/j.bbi.2010.10.010.
[10] D. Ducasse, E. Olié, S. Guillaume, S. Artéro, P. Courtet, A meta-analysis of cytokines in suicidal behavior, Brain Behav. Immun. 46 (2015) 203–211, https://doi.org/10.1016/j.bbi.2015.02.004.
[11] M.E. Rentería, L. Schmaal, D.P. Hibar, B. Couvy-Duchesne, L.T. Strike, et al., Subcortical brain structure and suicidal behaviour in major depressive disorder: a meta-analysis from the ENIGMA-MDD working group, Transl. Psychiatry 7 (5) (2017) e1116, https://doi.org/10.1038/tp.2017.84.
[12] A.I. Campos, P.M. Thompson, D.J. Veltman, E. Pozzi, L.S. van Veltzen, et al., Brain correlates of suicide attempt in 18,925 participants across 18 international cohorts, Biol. Psychiatr. 90 (4) (2021) 243–252, https://doi.org/10.1016/j.biopsych.2021.03.015.
[13] K.I. Salo, J. Scharfen, I.D. Wilden, R.I. Schubotz, H. Holling, Confining the concept of vascular depression to late-onset depression: a meta-analysis of MRI-defined hyperintensity burden in major depressive disorder and bipolar disorder, Front. Psychol. 10 (2019) 1–21, https://doi.org/10.3389/fpsyg.2019.01241.
[14] S. Richard-Devantoy, F. Jollant, F. Deguigne, G. Letourneau, Neurocognitive markers of suicide vulnerability in the elderly: a review, Geriatr Psychol Neuropsychiatr Vieil 11 (4) (2013) 367–378, https://doi.org/10.1684/pnv.2013.0442.
[15] E.T.C. Lippard, C.B. Nemeroff, The devastating clinical consequences of child abuse and neglect: increased disease vulnerability and poor treatment response in mood disorders, Am. J. Psychiatr. 177 (1) (2020) 20–36, https://doi.org/10.1176/appi.ajp.2019.19010020.
[16] S.L. Andersen, M.H. Teicher, Stress, sensitive periods and maturational events in adolescent depression, Trends Neurosci. 31 (4) (2008) 183–191, https://doi.org/10.1016/j.tins.2008.01.004.

[17] P. Zhukovsky, J.A.E. Anderson, G. Coughlan, B.H. Mulsant, A. Cipriani, et al., Coordinate-based network mapping of brain structure in major depressive disorder in younger and older adults: a systematic review and meta-analysis, Am. J. Psychiatr. 178 (12) (2021) 1119–1128, https://doi.org/10.1176/appi.ajp.2021.21010088.

[18] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Br. Med. J. 339 (2009) b2535, https://doi.org/10.1136/bmj.b2535.

[19] H.M. Al-Khazali, H. Ashina, A. Iljazi, Z. Al-Sayegh, R.B. Lipton, et al., Psychiatric sequelae following whiplash injury: a systematic review, Front. Psychiatr. 13 (2022) 814079, https://doi.org/10.3389/fpsyt.2022.814079.

[20] A. Griffin, I.C. Kenny, T.M. Comyns, The association between the acute: chronic workload ratio and injury and its application in team sports: a systematic review, Sports Med. 50 (3) (2020) 561–580, https://doi.org/10.1007/s40279-019-01218-2.

[21] R. Shao, M. Gao, C. Lin, C.M. Huang, H.L. Liu, et al., Multimodal neural evidence on the corticostriatal underpinning of suicidality in late-life depression, Biological psychiatry Cognitive neuroscience and neuroimaging 7 (9) (2022) 905–915, https://doi.org/10.1016/j.bpsc.2021.11.011.

[22] J.P. Hwang, T.W. Lee, S.J. Tsai, T.J. Chen, C.H. Yang, et al., Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry, J. Geriatr. Psychiatr. Neurol. 23 (3) (2010) 171–184, https://doi.org/10.1177/0891988710363713.

[23] E.P. Ahearn, K.R. Jamison, D.C. Steffens, F. Cassidy, J.M. Provenzale, et al., MRI correlates of suicide attempt history in unipolar depression, Biol. Psychiatr. 50 (4) (2001) 266–270, https://doi.org/10.1016/s0006-3223(01)01098-8.

[24] R. Wang, H. Ren, X.H. Tan, X.K. Li, Z.B. Yang, et al., Local structure and covariant network of reward system in young patients with depression, Chinese Journal of Medical Imaging 29 (12) (2021) 1177–1182.

[25] R. Zhang, S. Wei, M. Chang, X. Jiang, Y. Tang, et al., Dorsolateral and ventrolateral prefrontal cortex structural changes relative to suicidal ideation in patients with depression, Acta Neuropsychiatr. 32 (2) (2020) 84–91, https://doi.org/10.1017/neu.2019.45.

[26] Y. Yang, M.R. Chattun, R. Yan, K. Zhao, Y. Chen, et al., Atrophy of right inferior frontal orbital gyrus and frontoparietal functional connectivity abnormality in depressed suicide attempters, Brain Imaging Behav 14 (6) (2020) 2542–2552, https://doi.org/10.1007/s11682-019-00206-4.

[27] L. Wang, Y. Zhao, E.K. Edmiston, F.Y. Womer, R. Zhang, et al., Structural and functional abnormities of amygdala and prefrontal cortex in major depressive disorder with suicide attempts, Front. Psychiatr. 10 (2019) 923, https://doi.org/10.3389/fpsyt.2019.00923.

[28] M.M. Rizk, H. Rubin-Falcone, X. Lin, J.G. Keilp, J.M. Miller, et al., Gray matter volumetric study of major depression and suicidal behavior, Psychiatry Res. Neuroimaging. 283 (2019) 16–23, https://doi.org/10.1016/j.pscychresns.2018.11.007.

[29] Y.J. Lee, S. Kim, A.R. Gwak, S.J. Kim, S.G. Kang, et al., Decreased regional gray matter volume in suicide attempters compared to suicide non-attempters with major depressive disorders, Compr. Psychiatr. 67 (2016) 59–65, https://doi.org/10.1016/j.comppsych.2016.02.013.

[30] D.T. Warren, B. Boyd, D.R. McQuoid, K. Kudra, A. Saleh, et al., Widespread white matter but focal gray matter alterations in depressed individuals with thoughts of death, Progress in neuro-psychopharmacology & biological psychiatry 62 (2015) 22–28, https://doi.org/10.1016/j.pnpbp.2015.05.001.

[31] C. Romain, M. Chupin, C. Cury, C. Vandendrie, F. Gressier, et al., Depressed suicide attempters have smaller hippocampus than depressed patients without suicide attempts, J. Psychiatr. Res. 61 (2015) 13–18, https://doi.org/10.1016/j.jpsychires.2014.12.010.

[32] H. Peng, K. Wu, J. Li, H. Qi, S. Guo, et al., Increased suicide attempts in young depressed patients with abnormal temporal-parietal-limbic gray matter volume, J. Affect. Disord. 165 (2014) 69–73, https://doi.org/10.1016/j.jad.2014.04.046.

[33] G. Wagner, C.C. Schultz, K. Koch, C. Schachtzabel, H. Sauer, et al., Prefrontal cortical thickness in depressed patients with high-risk for suicidal behavior, J. Psychiatr. Res. 46 (11) (2012) 1449–1455, https://doi.org/10.1016/j.jpsychires.2012.07.013.

[34] E.S. Monkul, J.P. Hatch, M.A. Nicoletti, S. Spence, P. Brambilla, et al., Fronto-limbic brain structures in suicidal and non-suicidal female patients with major depressive disorder, Mol. Psychiatr. 12 (4) (2007) 360–366, https://doi.org/10.1038/sj.mp.4001919.

[35] S. Liu, H. Zhang, J.J. Zhu, C. Zhang, S.W. Hu, et al., Correlative study of brain structure and suicidal ideation in patients with early-onset depression, Chinese Journal of Behavioral Medicine and Brain Science 30 (5) (2021) 434–439, https://doi.org/10.3760/cma.j.cn371468-20201216-00068.

[36] J. Anthony, M.M. Chakravarty, M. Lepage, T.C. Ho, M.C. Geoffroy, et al., Brain cortical and subcortical morphology in adolescents with depression and a history of suicide attempt, J. Psychiatr. Neurosci. 46 (3) (2021) E347–E357, https://doi.org/10.1503/jpn.200198.

[37] A.P. Lisa, L. Ramos, A. Segreti, D.A. Brent, M.L. Phillips, Right superior temporal gyrus volume in adolescents with a history of suicide attempt, Br. J. Psychiatry 206 (4) (2015) 339–340, https://doi.org/10.1192/bjp.bp.114.151316.

[38] E.T. Rolls, A non-reward attractor theory of depression, Neurosci. Biobehav. Rev. 68 (2016) 47–58, https://doi.org/10.1016/j.neubiorev.2016.05.007.

[39] V. Arango, M.D. Underwood, M. Boldrini, H. Tamir, S.A. Kassir, et al., Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims, Neuropsychopharmacology 25 (6) (2001) 892–903, https://doi.org/10.1016/S0893-133X(01)00310-4.

[40] K.M. Malone, E.M. Corbitt, S. Li, J.J. Mann, Prolactin response to fenfluramine and suicide attempt lethality in major depression, Br. J. Psychiatry 168 (3) (1996) 324–329, https://doi.org/10.1192/bjp.168.3.324.

[41] V. Arango, M.D. Underwood, J.J. Mann, Postmortem findings in suicide victims. Implications for in vivo imaging studies, Ann. N. Y. Acad. Sci. 836 (1997) 269–287, https://doi.org/10.1111/j.1749-6632.1997.tb52365.x.

[42] M. Leyton, V. Paquette, P. Gravel, P. Rosa-Neto, F. Weston, et al., alpha-[11C]Methyl-L-tryptophan trapping in the orbital and ventral medial prefrontal cortex of suicide attempters, Eur. Neuropsychopharmacol 16 (3) (2006) 220–223, https://doi.org/10.1016/j.euroneuro.2005.09.006.

[43] E. Olie, Y. Ding, E. Le Bars, N.M. de Champfleur, T. Mura, et al., Processing of decision-making and social threat in patients with history of suicidal attempt: a neuroimaging replication study, Psychiatr. Res. 234 (2015) 369–377, https://doi.org/10.1016/j.pscychresns.2015.09.020.

[44] S. Desmyter, R. Duprat, C. Baeken, S. Bijttebier, K. van Heeringen, The acute effects of accelerated repetitive Transcranial Magnetic Stimulation on suicide risk in unipolar depression: preliminary results, Psychiatr. Danub. 26 (Suppl 1) (2014) 48–52.

[45] M.T. Berlim, F. Van den Eynde, S. Tovar-Perdomo, E. Chachamovich, A. Zangen, et al., Augmenting antidepressants with deep transcranial magnetic stimulation (DTMS) in treatment-resistant major depression, World J. Biol. Psychiatr. 15 (2014) 570–578, https://doi.org/10.3109/15622975.2014.925141.

[46] G.S. Alexopoulos, Mechanisms and treatment of late-life depression, Transl. Psychiatry 9 (1) (2019) 188, https://doi.org/10.1038/s41398-019-0514-6.

[47] G. Csifcsák, N.M. Boayue, O. Puonti, A. Thielscher, M. Mittner, Effects of transcranial direct current stimulation for treating depression: a modeling study, J. Affect. Disord. 234 (2018) 164–173, https://doi.org/10.1016/j.jad.2018.02.077.

[48] S.E. Jones, C. Pezzi, A. Rodriguez-Lainz, L. Whittle, Health risk behaviors by length of time in the United States among high school students in five sites, J. Immigr. Minority Health 18 (1) (2016) 150–160, https://doi.org/10.1007/s10903-014-0151-3.

[49] D.M. Harwood, K. Hawton, T. Hope, L. Harriss, R. Jacoby, Life problems and physical illness as risk factors for suicide in older people: a descriptive and case-control study, Psychol. Med. 36 (9) (2006) 1265–1274, https://doi.org/10.1017/s0033291706007872.

[50] D.H. Salat, R.L. Buckner, A.Z. Snyder, D.N. Greve, R.S. Desikan, et al., Thinning of the cerebral cortex in aging, Cerebr. Cortex 14 (7) (2004) 721–730, https://doi.org/10.1093/cercor/bhh032.

[51] C.K. Tamnes, M.M. Herting, A.L. Goddings, et al., Development of the cerebral cortex across adolescence: a multisample study of inter-related longitudinal changes in cortical volume, surface area, and thickness, J. Neurosci. 37 (12) (2017) 3402–3412, https://doi.org/10.1523/JNEUROSCI.3302-16.2017.

[52] A.B. Storsve, A.M. Fjell, C.K. Tamnes, et al., Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: regions of accelerating and decelerating change, J. Neurosci. 34 (25) (2014) 8488–8498, https://doi.org/10.1523/JNEUROSCI.0391-14.2014.

[53] D. Wei, K. Wang, J. Meng, et al., The reductions in the subcallosal region cortical volume and surface area in major depressive disorder across the adult life span, Psychol. Med. 50 (3) (2020) 422–430, https://doi.org/10.1017/S0033291719000230.

[54] T.B. Meier, W.C. Drevets, B.E. Wurfel, et al., Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder, Brain Behav. Immun. 53 (2016) 39–48, https://doi.org/10.1016/j.bbi.2015.11.003.

[55] E. Stefan, G.G. Noam, I.K. Lyoo, B.J. Kwon, M.A. Clark, et al., White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents, J. Am. Acad. Child Adolesc. Psychiatry 43 (6) (2004) 770–776, https://doi.org/10.1097/01.chi.0000120020.48166.93.

[56] Z. Jia, Y. Wang, X. Huang, W. Kuang, Q. Wu, et al., Impaired frontothalamic circuitry in suicidal patients with depression revealed by diffusion tensor imaging at 3.0 T, J. Psychiatr. Neurosci. : JPN 39 (3) (2014) 170–177, https://doi.org/10.1503/jpn.130023.
[57] Z. Jia, X. Huang, Q. Wu, T. Zhang, S. Lui, et al., High-field magnetic resonance imaging of suicidality in patients with major depressive disorder, Am. J. Psychiatr. 167 (11) (2010) 1381–1390, https://doi.org/10.1176/appi.ajp.2010.09101513.
[58] J. Liu, X. Xu, Q. Luo, Y. Luo, Y. Chen, S. Lui, M. Wu, H. Zhu, G.J. Kemp, Q. Gong, Brain grey matter volume alterations associated with antidepressant response in major depressive disorder, Sci. Rep. 7 (1) (2017) 10464, https://doi.org/10.1038/s41598-017-10676-5.