NeuroImage: Clinical 38 (2023) 103403

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Altered gray matter volumes and plasma IL-6 level in major depressive disorder patients with suicidal ideation

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ARTICLE INFO

Keywords:
Suicidal ideation
Major depressive disorder
Gray matter volumes
IL-6

ABSTRACT

Backgrounds: Suicidal ideation (SI) is one of the most serious consequences of major depressive disorder (MDD). Understanding the unique mechanism of MDD with SI (MDD + S) is crucial for treatment development. While abundant research has studied MDD, past studies have not reached a consensus on the mechanism of MDD + S. The study aimed to investigate the abnormalities of the gray matter volumes (GMVs) and plasma IL-6 level in MDD + S to further reveal the mechanism of MDD + S.

Methods: We tested the plasma IL-6 level using Luminex multifactor assays and collected the Structural Magnetic Resonance Imaging (SMRI) data from 34 healthy controls (HCs), 36 MDD patients without SI (MDD − S) and 34 MDD + S patients. We performed a partial correlation between the GMVs of the brain regions with significant differences and plasma IL-6 level with age, sex, medication, scores of HAMD-17 and HAMA as the covariates.

Results: Compared with HCs and MDD − S, MDD + S had significantly decreased GMVs in the left cerebellum Crus I/II and significantly increased plasma IL-6 level; compared with HCs, both the MDD + S and MDD − S had significantly decreased GMVs in right precentral and postcentral gyri. No significant correlation was found between the GMVs and the plasma IL-6 level in the MDD + S and MDD − S, respectively. While the GMVs of the right precentral and postcentral gyri negatively correlated with the level of IL-6 in the whole MDD ($r = -0.28$, $P = 0.03$). The GMVs of the left cerebellum Crus I/II ($r = -0.47$, $P = 0.02$), and the right precentral and postcentral gyri ($r = -0.42$, $P = 0.04$) negatively correlated with the level of IL-6 in HCs.

Conclusion: The altered GMVs and the plasma IL-6 level may provide a scientific basis to understand the pathophysiological mechanisms of MDD + S.

1. Introduction

Suicide is one of the most serious consequences of major depressive disorder (MDD). More than 90% of suicide victims and suicide attempters are accompanied by at least one axis I mental disorder, the most common of which is MDD, accounting for 56%–87% (Rihmer, 2007). Furthermore, suicide is associated with the number of depressive episodes (McGirr et al., 2008) and the severity of depression (Holma et al., 2010) in MDD patients. As the starting point of the whole suicide process, suicidal ideation (SI) is one of the predictors to distinguish suicide attempters from suicide non-attempters (Park et al., 2017). MDD patients with SI (MDD + S) had been reported to have significantly poorer health-related quality of life, greater work productivity loss and daily activity impairment, and higher healthcare resource utilization compared to MDD patients without SI (MDD − S) and the healthy controls (HCs) (Jaffe et al., 2019). Furthermore, MDD + S had higher unmet

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https://doi.org/10.1016/j.nicl.2023.103403
Received 12 September 2022; Received in revised form 7 April 2023; Accepted 8 April 2023
Available online 11 April 2023

medical need and therapy difficulties than the general MDD population (Kern et al., 2021). Therefore, it is meaningful to explore the mechanism of SI in MDD.

Structural magnetic resonance imaging (SMRI) is used to explore the changes in gray matter in vivo (Yousaf et al., 2018). Many findings about the impaired gray matter volumes (GMVs) in MDD + S have been reported. For example, previous studies had shown that the reductions of GMVs in the bilateral caudate nucleus, right nucleus accumbens (Ho et al., 2021), dorsal striatum (Ho et al., 2018), the lingual gyrus (Wang et al., 2021), right insula (Ge et al., 2021), bilateral dorsolateral prefrontal cortex and right ventrolateral prefrontal cortex (Zhang et al., 2020) were related to SI in MDD patients. In addition, gray matter thickness, an indicator related to GMVs, also found a specific change in MDD + S. For example, Taylor. et al. found that compared with MDD − S, the thickness of gray matter cortex in the frontal lobe, temporal lobe, parietal lobe, and the insular lobe of the left hemisphere reduced in MDD + S (Taylor et al., 2015). To sum up, the study of GMVs detected the subtle changes in brain structure which may be a promising method to explore the potential neuroimaging mechanism of MDD + S.

In addition to the studies of GMVs, the studies of inflammatory cytokines also found changes of MDD + S. Cytokines including interleukin (ILs), tumor necrosis factor (TNF), colony stimulating factor, transforming growth factor, interference factor are small molecular proteins with extensive biological activities secreted by various immune cells (Liu et al., 2021a). Smith found that major depressive episode was related to the excessive secretion of cytokines such as IL-1 by macrophages for the first time in 1991 (Smith, 1991). In the past two decades, more and more evidence supported that MDD is related to abnormal cytokine levels (Adler et al., 2008; Miller et al., 2009). A *meta*-analysis further proposed IL-6 is a crucial cytokine participating the pathogenesis and maintenance of depression (Dowlati et al., 2010). Furthermore, in the study of suicide-related cytokines, the most consistent result is that the level of IL-6 is significantly increased in suicidal people (Ganança et al., 2016), MDD + S patients also showed accordant significantly increased level of IL-6. For example, a study found that plasma IL-6 level in MDD patients with high SI was significantly higher than MDD patients with low SI and HCs (O'Donovan et al., 2013). MDD + S also had significantly higher IL-6 level than MDD − S (Karlović et al., 2012). It has also been reported that the level of IL-6 in cerebrospinal fluid was positively correlated with SI in MDD patients (Martinez et al., 2012). Also, the IL-6 level of MDD patients with a history of suicide attempts was significantly higher than HCs and MDD patients without a history of suicide attempts (Janelidze et al., 2011). In summary, MDD + S may have abnormal immunology.

Additionally, the levels of peripheral cytokines are proved to have a relationship with the decreased GMVs in the brain. Peripheral inflammatory cytokines can cross the blood–brain barrier and enter the central nervous system through a variety of pathways (Banks, 2005; Banks and Erickson, 2010; Ek et al., 2001). Cytokines only function on target cells with their receptors (Vitkovic et al., 2000), and expression of cytokine receptors are found both on the cells and protrusions of human brain neurons (Boka et al., 1994), which are the major component of the gray matter and in neurons in different brain regions of rats (Cheng et al., 1994). Animal experiments have also shown that IL-6 can significantly inhibit the development of neuronal dendrites (Gilmore et al., 2004), and prenatal exposure to IL-6 will lead to neuronal deletion in adult rats (Samuelsson et al., 2006). We thus speculate that peripheral cytokines may enter the central nervous system through the blood–brain barrier and may affect neurons, which in turn may lead to changes in the GMVs in the brain. Previous studies have also confirmed that the level of peripheral cytokines is related to the change of GMVs. For example, in the geriatric HCs, increased peripheral blood IL-6 level negatively correlated with the GMVs in the hippocampus (Karoly et al., 2021; Marsland et al., 2008), medial prefrontal cortex, and right cerebellar posterior lobe (Marsland et al., 2008). In the study of affective disorders, IL-6 was found to be related to the more pervasive reduced GMVs in bipolar disorder patients compared with unipolar depression (Chen et al., 2019). In other neuropsychiatric disorders, genetically determined IL-6 was associated with GMVs in the middle temporal cortex, inferior temporal, fusiform and potentially affects areas implicated in schizophrenia and autism (Williams et al., 2022) and the serum level of IL-6 was associated with the GMVs of right lingual gyrus in schizophrenia patients (Wu et al., 2019). Thus, it is important to consider the role that cytokines play in the changed GMVs of subjects. However, to our knowledge, there is no study to detect the changes by using GMVs combined with IL-6 level in MDD + S. Therefore, herein we combine the methods of neuroimaging and immunology to explore the changes of GMVs and plasma IL-6 level and the relationship between them in MDD + S, further to explore the pathogenesis of SI in MDD patients and provide a new perspective for exploring the mechanism of SI in MDD.

2. Materials and methods

2.1. Subjects

A total of 104 participants aged 18–50 were included in this study, including 34 HCs, 36 MDD − S, and 34 MDD + S. The HCs group was recruited through advertising, and all MDD patients were from the Department of Psychiatry, the First Affiliated Hospital of China Medical University. All participants were informed of the purpose and content of the experiment in detail. They were voluntarily participated, and signed a written informed consent form. The study was authorized by the Institutional Review Board of the First Affiliated Hospital of China Medical University.

HCs had no history of Axial I disorders or Axial II disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) themselves or their first-degree relatives; and no SI or suicidal behavior. MDD patients met the criteria of MDD in DSM-IV and were diagnosed by professionally trained psychiatrists through Structured Clinical Interviews for DSM-IV (SCID) and determined whether the participants were enrolled. Hamilton Depression Scale-17 items (HAMD-17) (Hamilton, 1960) is an international scale used to evaluate the severity of depression in MDD patients. Of 17 items, the item "suicide" is related to SI. The Cronbach's alpha of HAMD-17 is 0.897 which means the reliability can be trusted. Then according to the grouping criteria of a previous study (Levey et al., 2016), that is, whether the HAMD-17 suicide score was 0, MDD patients were divided into MDD − S and MDD + S. HAMD-17 and Hamilton Anxiety Scale (HAMA) (Hamilton, 1959) were used to quantify the severity of symptoms in participants over the past week. All scales were evaluated by researchers who passed consistency training.

Subjects were excluded if they had abuse or dependence on drugs, alcohol, and other substances; or accompanied by a history of diseases that may cause changes in brain structure, such as hypertension, diabetes, or tumor metastatic diseases, as well as diseases that affect cytokine levels such as influenza; or history of neurological abnormalities, including head trauma (clearly $\geq$ 5 min of loss of consciousness), seizures, cerebrovascular diseases, and neurodegenerative diseases or any magnetic resonance imaging (MRI) contraindications.

2.2. MRI acquisition

All subjects underwent head MRI scanning at the Department of Radiology, The First Affiliated Hospital of China Medical University, and the scanning machine was the GE Signa HDX 3.0 T scanner. The scanning parameters are as follows: 3D-T1 high-resolution structure imaging adopts a three-dimensional rapid scrambled gradient echo sequence (3D-FSPGR) sequence, and the scanning parameters are: repetition time (TR) = 7.1 ms, echo time (TE) = 3.15 ms, flip angle of 13°, image matrix = 240 × 240, field of view (FOV) = 240 × 240 mm^2, 176 slices of 1 mm with 1 mm gap, the voxel size = 1 mm^3, the scanning time is 8min22s.

3D-MRI preprocess: In this study, voxel-based morphometry (VBM)

was used to conduct a direct comparative study of changes in GMVs in the MDD + S, the MDD − S, and the HCs. The pre-processing is carried out on Matlab 2011a software, using the VBM8 software package which is under the Statistical Parametric Mapping (SPM8) software, and the specific steps mainly conclude magnetic field correction, tissue segmentation and spatial standardization. After the image space is standardized, according to the default parameters of the VBM8 software package, it is adjusted to the Montreal Neurological Institute (MNI) space, and then resampled to 1.5 mm^3 isotropic voxels; then the GMVs of the subject is adjusted, using nonlinear transformations, so that the voxel value becomes the local tissue relative volume after the individual brain size correction. Finally, the image data is Gaussian smoothed at 8 mm^3 full width at half maximum (FWHM). The final image is used for statistical analysis of voxel-wise levels.

2.3. Plasma IL-6 analysis

A professional nurse collected four ml elbow vein blood from the subjects in an EDTA anticoagulant tube at every weekend from 10 a.m. to 2p.m. We mixed the blood well, and performed a 2000 rpm, 10 min centrifugation process, after which we collected and stored the plasma in a refrigerator at −80 °C for testing. The plasma IL-6 level was measured by the immunoassay (Human Magnetic Luminex Assay, Human Premixed Multi-Analyte Kit, R&D Systems, Inc., Minneapolis, MN, USA). In this process, a Human magnetic premixed microparticle cocktail of antibodies (Kit Lot Number L141975) was used to magnetically label the samples.

2.4. Statistical analyses

The pre-processed 3D brain image data was analyzed by Data Processing Assistant for Brain Imaging (DPABI) software under Matlab software platform, and the GMVs of the three groups of samples was statistically analyzed by analysis of covariance (ANCOVA) using age and sex as covariates, and the brain area was automatically labeled by anatomy (Anatomical Automatic Labeling, AAL) template for identification. Then, the GRF (Gaussian Random Field) method was used to correct, after the correction, the *P*-value of each cluster < 0.05 (GMVs single voxel $P < 0.005$) was statistically significant. The mean value of GMVs of each cluster is extracted without Marsbar toolbox for subsequent post hoc ($P < 0.05$, Bonferroni correction) and correlation analysis ($P < 0.05$).

IBM SPSS Statistics (version 22.0, Armonk, NY, USA) for Windows was used to analyze the demographic and clinical data of the subjects. The independent samples *t*-test was utilized to compare the duration of illness between MDD + S and MDD − S. One-way analysis of variance (ANOVA) was used to compare age, education years, total scores of HAMD-17 and HAMA among MDD + S, MDD − S, and HCs. Additionally, Chi-square tests were adopted to compare differences in gender and medication status. ANCOVA was used to compare IL-6 level and GMVs among the three groups using age, sex, medication, total HAMD-17 scores, and total HAMA scores as covariates. Partial correlation analysis was used to analyze the correlation between GMVs and the IL-6 level in the MDD + S (age, sex, medication, total HAMD-17 scores, and total HAMA scores as covariates) to determine whether the increased IL-6 level was associated with the change of gray matter structure in MDD + S. We also analyze the relationships between severity of clinical symptoms (scores of HAMD-17 and HAMA) and IL-6 level, as well as GMVs in MDD + S by using the partial correlation analysis with age, sex and medication as covariates. We also use partial correlation analysis to analyze the correlation between GMVs and the IL-6 level in the MDD (age, sex, medication, total HAMD-17 scores, and total HAMA scores as covariates) and in medication-free patients (age, sex, total HAMD-17 scores, and total HAMA scores as covariates).

3. Results

3.1. Demographic and clinical data analysis

There was no significant difference in age, gender, and educational years among the three groups. There was no significant difference in the duration of illness and medication status between the two subgroups of MDD. There were significant differences in HAMD-17 and HAMA scores among the three groups. *Post-hoc* analysis showed that the HAMD-17 and HAMA scores of MDD + S were significantly higher than those of MDD − S and HCs ($P < 0.05$, Bonferroni correction) (Table 1). The results of medication-free subjects were summarized in Supplementary material Table 6.

3.2. GMVs findings

Among MDD + S, MDD − S, and HCs groups, significant GMVs differences were found in the left cerebellum, including the left Crus I/II, and the right cerebrum, including the right precentral and postcentral gyri ($P < 0.005$, GRF correction) (Table 2, Fig. 1). *Post-hoc* analyses revealed that compared to MDD − S and HCs, MDD + S showed significantly decreased GMVs in the left cerebellum Crus I/II ($P < 0.05$, $\eta^2 = 0.15$, $df = 82$, Bonferroni correction). Compared to HCs, both MDD + S and MDD − S groups showed significantly reduced GMVs in the right precentral and postcentral gyri ($P < 0.05$, $\eta^2 = 0.09$, $df = 82$, Bonferroni correction), and there were no significant differences between the two subgroups of MDD (Fig. 2). The results of medication-free subjects were summarized in Supplementary material Table 7, Fig. 1 and Fig. 2.

3.3. Plasma IL-6 level analysis

For plasma IL-6 level, there was a significant difference in IL-6 level ($F = 25.41$, $P < 0.001$, $df = 82$) among these three groups. *Post-hoc* analysis found significantly increased IL-6 level in MDD + S compared to MDD − S and HCs ($P < 0.05$, Bonferroni correction) (Table 1). The results of medication-free subjects were summarized in Supplementary material Table 6 and Section 3.3.

3.4. Correlation between the GMVs and the plasma IL-6 level

No regions showed a correlation between the plasma IL-6 level and the GMVs in MDD + S and MDD − S (Table 3). While the GMVs of the right precentral and postcentral gyri negatively correlated with the level of IL-6 in the whole MDD ($r = -0.28$, $P = 0.03$, $df = 61$, Fig. 3). The GMVs of the left cerebellum Crus I/II, and the right precentral and postcentral gyri negatively correlated with the level of IL-6 in HCs (Table 3). The results of the medication-free patients were summarized in Supplementary material 3.4. The robust regression result of MDD + S was summarized in Supplementary material Section 4.

3.5. Correlation between the severity of clinical symptoms and gray matter volumes

No correlations between the severity of clinical symptoms and GMVs were found in MDD + S, MDD − S and HCs (Table 4).

3.6. Correlation between the severity of clinical symptoms and IL-6 level

No correlations between the severity of clinical symptoms and IL-6 level were found in MDD + S, MDD − S and HCs (Table 5).

4. Discussion

In this study, we found that MDD + S exhibited significantly reduced GMVs in the left cerebellum Crus I/II and increased IL-6 level compared with HCs and MDD − S. Furthermore, the GMVs of the right precentral

Table 1
Demographic and clinical characteristics and IL-6 level of subjects.

Variables	HCs (n = 34)	MDD − S (n = 36)	MDD + S (n = 34)	$F/t/\chi^2$	*P*	*ES*	*Post-hoc comparison (Bonferroni), P*		
							HCs vs MDD − S	HCs vs MDD + S	MDD − S vs MDD + S
Characteristics									
Age, years	30.71 ± 7.69	27.97 ± 8.47	27.71 ± 8.01	1.45	0.24	0.03	0.48	0.39	1.00
Male/Female	13/21	14/22	15/19	0.30	0.86	0.05	NA	NA	NA
Education, years	15.46 ± 3.11	13.81 ± 3.36	14.53 ± 3.27	2.22	0.11	0.04	0.11	0.26	0.99
Duration of illness, months	NA	30.57 ± 45.26	31.31 ± 56.86	−0.06	0.85	−0.01	NA	NA	NA
Medication use	NA	26 (72.2%)	24(70.6)	0.02	0.88	0.02	NA	NA	NA
Antidepressants	NA	26 (72.2%)	24(70.6%)	0.02	0.88	0.02	NA	NA	NA
Antipsychotics	NA	1(2.8%)	1(2.9%)	0.00	0.97	0.01	NA	NA	NA
HAMD-17 scores	1.12 ± 1.67	9.67 ± 6.24	19.88 ± 6.99	98.77	<0.001*	0.66	<0.001*	<0.001*	<0.001*
HAMA scores	0.79 ± 1.41	8.47 ± 6.27	19.00 ± 9.31	66.70	<0.001*	0.57	<0.001*	<0.001*	<0.001*
Cytokine (pg/ml)									
IL-6	0.97 ± 0.05	1.16 ± 0.03	1.45 ± 0.04	25.41	<0.001*	0.59	<0.001*	<0.001*	<0.001*
TIV	1458.02 ± 22.97	1428.87 ± 18.48	1457.09 ± 18.87	0.77	0.47	0.02	0.37	0.97	0.26

Data are presented as number (%) or mean ± standard deviation.
Note: MDD, major depressive disorder; n, number of subjects; HCs, healthy controls; MDD + S, MDD patients with suicidal ideation; MDD − S, MDD patients without suicidal ideation; HAMD-17, 17-item Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Rating Scale; * Significant level at $P < 0.05$; NA, not applicable; vs, versus; ES, effect size; TIV, total intracranial volume.

Table 2
Differences of GMVs among MDD + S, MDD − S and HCs.

Cluster	Region	Voxels	Peak MNI coordinates			*F* values	*P*
			X	Y	Z		
A	Left cerebellum Crus I Left cerebellum Crus II	932	−26	−69	−18	4.28	< 0.05*
B	Right precentral gyrus Right postcentral gyrus	611	24	−29	71	3.28	< 0.05*

Note: GMVs, gray matter volumes; MNI, Montreal Neurological Institute; * Significant at $P < 0.05$, post hoc analysis is the Bonferroni correction.

and postcentral gyri was significantly reduced in MDD patients compared to HCs and there was no significant difference between the two subgroups of MDD. Though we failed to find a significant correlation between the brain regions and plasma IL-6 level in MDD + S and MDD − S, the negative correlation in the whole MDD group was observed. Overall, we studied MDD + S from neuroimaging and peripheral immune perspectives, and preliminary discovered the specific alterations of the population, suggesting abnormal GMVs and IL-6 level involve in the biological underpinning of SI in MDD.

Significantly reduced GMVs in the left cerebellum Crus I/II was specific to MDD + S in this study. It is a pity that we did not find any evidence indicating that the left cerebellum Crus I/II has concern with MDD + S. However, we found two studies that had demonstrated that the GMVs of the cerebellum was significantly reduced in MDD patients with suicide attempts compared to MDD patients without suicide attempts (Hwang et al., 2010; Lee et al., 2016). Most of the people who has suicide attempts have SI, so the two studies can indirectly reflect the changes in the brain region of MDD + S, indicating that changes in the GMVs of cerebellum may be related to MDD + S. Abnormalities in cerebellar function and structure are associated with depression (Lai and Wu, 2016; Smith et al., 2002) and negative emotions (Lupo et al., 2015) such as anger (Park et al., 2010) and fear (Baumann and Mattingley, 2012) which may be associated with SI (Preston et al., 2021; Wilks et al., 2019). Therefore, we speculate that the decrease in the GMVs in the left cerebellum Crus I/II in MDD + S patients may be related to SI by influencing the ability to deal with negative emotions such as anger and fear. Since there are few similar studies, more studies are needed in the future to validate this result.

In the present study, the IL-6 level in MDD + S is significantly higher than MDD − S and HCs. IL-6 is a cytokine with neurodegenerative function (Morales et al., 2010). By searching the literature, we found that IL-6 may lead to suicide in MDD patients through imbalance in the serotonin system (Oquendo et al., 2014; Vaswani et al., 2003; Zhang et al., 2001), activation of the kynurenine metabolic pathway (Bay-Richter et al., 2015; Erhardt et al., 2013; Sublette et al., 2011), and vitamin D deficiency (Grudet et al., 2014; Umhau et al., 2013; Zhang et al., 2012). Furthermore, in MDD patients, Kim et al. found that elevated plasma IL-6 levels in women were associated with SI in MDD (Kim et al., 2021). However, Gabbay et al. found no significant difference in plasma IL-6 level in adolescent MDD + S compared with adolescent MDD − S (Gabbay et al., 2009). This is inconsistent with our findings, which may be due to reasons such as the different ages of the study population.

In this study, no changes in the GMVs were found to be associated with plasma IL-6 level in MDD + S. To our knowledge, limited studies have explored the correlations between the two indicators in MDD + S, and only several studies detected the correlations in the MDD patients and HCs, respectively. MDD patients exhibited smaller hippocampal volumes and increased IL-6 concentration, and further regression analysis implied an inverse effect of IL-6 concentration on the volume of hippocampus (Frodl et al., 2012). Lu et al. investigated MDD patients with and without anhedonia, they addressed that anhedonia subgroup had specifically association between elevated IL-6 levels and reduced GMVs of the left putamen (Lu et al., 2022). The results along with our findings indicate that the change of gray matter and peripheral IL-6 level are interrelated factors in the pathophysiological mechanisms of MDD. While in the drug-naïve, first-episode MDD patients, it was found that changes in the prefrontal lobe network in MDD patients were significantly associated with serum TNF-α levels (Kakeda et al., 2020). A genetic study revealed that a genetic variation, which can increase TNF-α expression selectively, affects the GMVs of the visual cortex among the MDD (Zhou et al., 2018). In the geriatric HCs, elevated peripheral blood IL-6 level negatively affected GMVs in the hippocampus (Karoly et al., 2021; Marsland et al., 2008), medial prefrontal cortex, and right

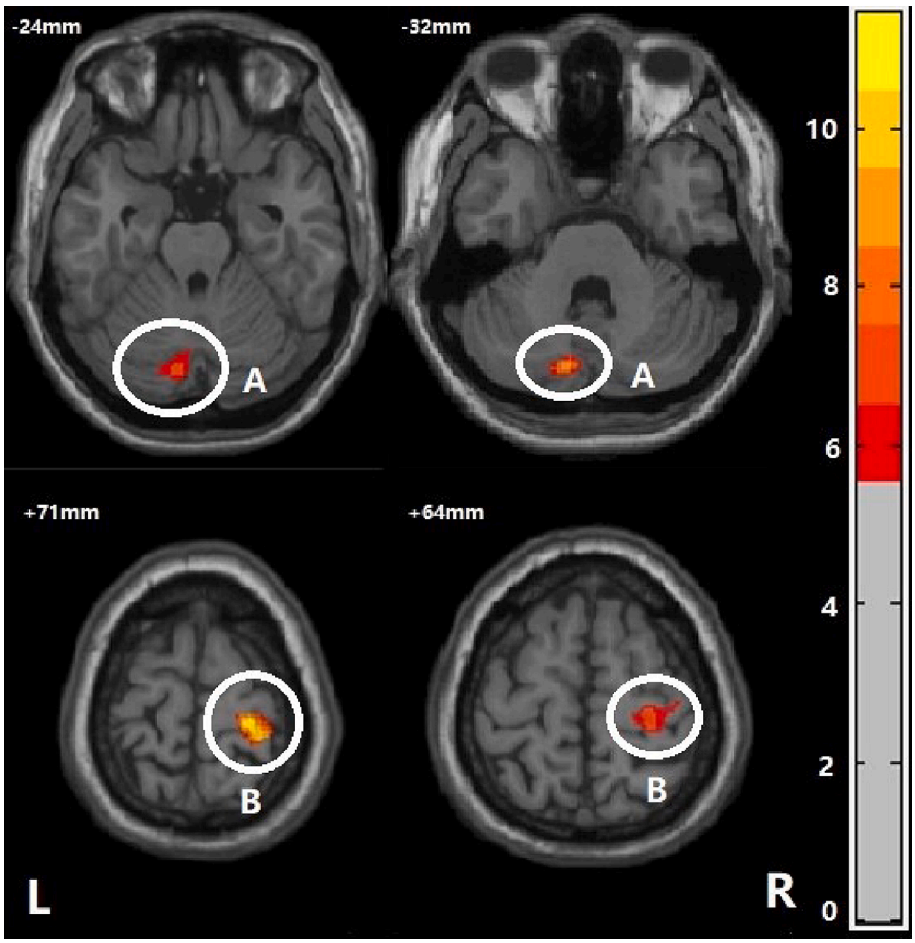

Fig. 1. Regions showing GMVs differences among the MDD + S, MDD − S, and HCs groups. Note: A, the left cerebellum Crus I/II; B, the right precentral gyrus, the right postcentral gyrus. The number is z-coordinate; The color bar is the range of F-values; L, left; R, right.

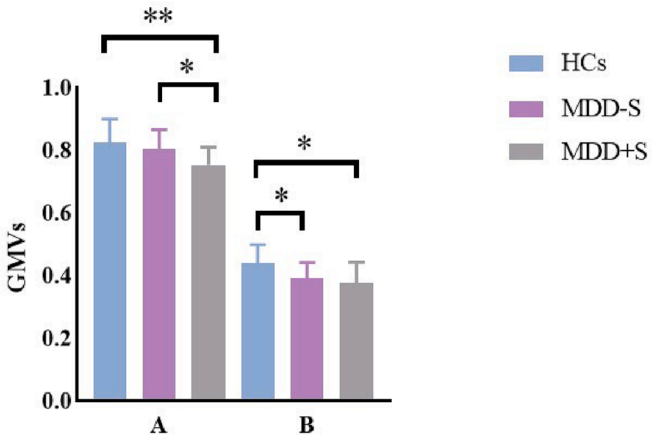

Fig. 2. GMVs of each cluster in the MDD + S, MDD − S, and HCs groups. Note: GMVs, gray matter volumes; A, the left cerebellum Crus I/II; B, the right precentral and postcentral gyri; MDD, major depressive disorder; HCs, healthy controls; MDD + S, MDD patients with suicidal ideation; MDD − S, MDD patients without suicidal ideation; * $P < 0.05$; ** $P < 0.01$.

cerebellar posterior lobe (Marsland et al., 2008). The possible reasons for the inconsistent results may be due to the different subjects, sample size, image methods, cytokines, age ranges and the different definitions of suicidality in the published studies (e.g., history of suicide attempts and their number, or the more subtle suicidal intention or ideation). However, Zhu et al. reported that it is uncertain whether the increase of cytokine levels in the central nervous system is parallel to those in the peripheral blood (Zhu et al., 2004), which suggest that the cytokine levels in the peripheral blood may be independent of the reduction of the GMVs. Therefore, it is difficult to accurately infer the relationship between them in MDD, especially in MDD + S. Future studies should pay more attention to MDD + S and provide more evidence for the underlying mechanism of the MDD + S. The correlation observed across MDD but not in MDD + S may be a power issue, and therefore more sample of MDD + S should be enrolled in to enhance the statistical validity. Due to the small number of studies on MDD + S populations and the negative results, we discussed the relationship of SI with GMV and IL-6, expecting to find some evidence. Changes of GMVs in several cortical and subcortical structures were linked to SI (Wang et al., 2021). Besides, the decreased GMVs of dorsal striatum predicted self-associations with death, namely the implicit SI (Ho et al., 2018). A large sample study enrolling adult depression and anxiety disorders manifested IL-6 may be a mediation factor in the relationship of sleep disturbance and SI (Dolsen et al., 2021). The study hints that the IL-6 may play a mediation role, which cannot probe by directly correlation analysis.

In addition, we found that the decreased GMVs in the right precentral and postcentral gyri may play a role in the pathological mechanism of MDD. A study had shown that the precentral gyrus is associated with somatic symptoms and cognitive impairment in MDD patients (Geng et al., 2019). The precentral and postcentral gyri belong to the somatic motor and somatic sensory regions of the brain, and abnormal functioning of these areas can lead to somatic discomfort in MDD patients (Liu et al., 2021b). It has also been reported that the precentral gyrus is

Table 3
Correlation Between the GMVs and the plasma IL-6 level.

	MDD + S			MDD − S			HCs		
	r	*P*	*df*	*r*	*P*	*df*	*r*	*P*	*df*
GMVA vs IL-6	0.26	0.17	27	−0.07	0.72	27	−0.47	0.02*	22
GMVB vs IL-6	−0.12	0.54	27	0.07	0.71	27	−0.42	0.04*	22

Note: GMVs, gray matter volumes; GMVA, the left cerebellum Crus I/II; GMVB, the right precentral and postcentral gyri; MDD, major depressive disorder; HCs, healthy controls; MDD + S, MDD patients with suicidal ideation; MDD − S, MDD patients without suicidal ideation; *r*, correlation coefficient; *df*, degrees of freedom; * $P < 0.05$.

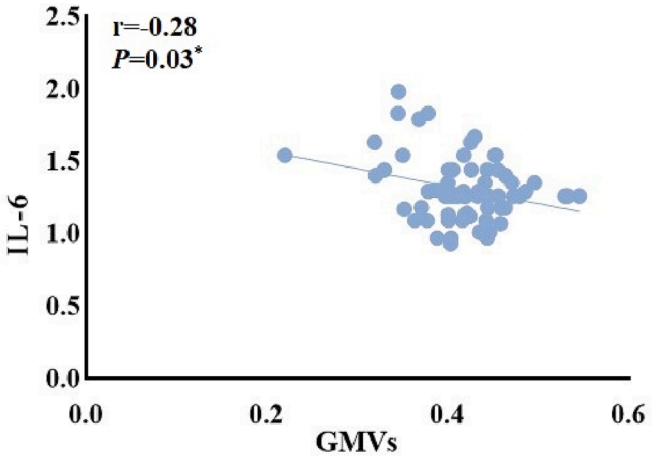

Fig. 3. Correlation between the GMVs and the plasma IL-6 level in the whole MDD group. Note: GMVs, gray matter volumes; * $P < 0.05$.

associated with cognitive function in HCs (Genon et al., 2018). Both somatic symptoms (Shim et al., 2020) and impairment of cognitive function (Hammen, 2018) are risk factors of MDD. Therefore, we speculate that the reduction of the GMVs in the precentral and postcentral gyri may be involved in the neuroimaging mechanism of MDD. Through the search of literature, we did not find studies on SMRI of the precentral and postcentral gyri, however, the Functional Magnetic Resonance Imaging (FMRI) found the above regions were related to MDD. For example, Liu et al. found that the reduction of local consistency and low-frequency amplitude of the bilateral precentral and bilateral postcentral gyri were inversely correlated with the severity of somatic symptoms and depressive symptoms in patients with MDD (Liu et al., 2021b). There is also evidence that the local consistency and low-frequency amplitude of the right precentral and postcentral gyri in MDD patients were also significantly reduced (Liang et al., 2020). The above evidence confirms our finding that the right precentral and postcentral gyri may have association with the pathological mechanism of MDD. We also found that the GMVs decreased gradually from HCs to MDD − S to MDD + S. Our findings may support the idea that decreased GMVs occur in a graded manner, i.e., MDD + S < MDD − S < HCs.

4.1. Limitation

The limitation of this study is that the sample size is small, and it may be that for this reason, no correlation between the changes of GMVs in the brain and plasma IL-6 level has been found in MDD + S, and future studies will require larger samples to continue to explore this issue. The age range is wide in the current sample. According to the grouping criteria of a previous study (Wei et al., 2020), we regrouped two age groups (early adulthood:18–30 years old; middle adulthood:31–50 years old) to explore the possible influence of age on GMVs and plasma IL-6 level, and no significant differences between the two groups were observed (Table 1, Table 2 and Table 3 in the Supplementary materials). Some of the participants were treated with drugs, which may have an impact on the results of the study. Thus, we compared the GMVs and plasma IL-6 level between medication use and medication-free in MDD + S and MDD − S groups respectively, and found no statistical differences between the medication use and medication-free groups (Table 4 and Table 5 in the Supplementary materials). Also, the assay standard range and sensitivity are crucial for testing the plasma interleukins. As a result, future studies need to expand the sample size, or treat the drug-naïve MDD patients as participants, to exclude the effects of the drug, and implement more high-sensitivity assay to observe subtle changes of SI in MDD patients.

4.2. Conclusion

In conclusion, our findings suggest that MDD + S may have specific and much more aberrant neuroimaging and immunologic changes in comparison with MDD − S. It may provide a scientific basis to understand the potential mechanisms of MDD + S and calls for attention to the suicidal ideation in MDD patients.

Table 5
Correlation Between the Severity of Clinical Symptoms and IL-6 Level.

	MDD + S			MDD − S			HCs		
	r	*P*	*df*	*r*	*P*	*df*	*r*	*P*	*df*
IL-6 vs HAMD	0.01	0.95	29	0.12	0.53	29	0.07	0.75	22
IL-6 vs HAMA	0.07	0.71	29	0.07	0.70	29	0.21	0.32	22

Note: MDD, major depressive disorder; HCs, healthy controls; MDD + S, MDD patients with suicidal ideation; MDD − S, MDD patients without suicidal ideation; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Rating Scale; *r*, correlation coefficient; *df*, degrees of freedom; * $P < 0.05$.

Table 4
Correlation Between the Severity of Clinical Symptoms and Gray Matter Volumes.

	MDD + S			MDD − S			HCs		
	r	*P*	*df*	*r*	*P*	*df*	*r*	*P*	*df*
GMVA vs HAMD	0.12	0.51	29	0.03	0.88	29	−0.20	0.34	22
GMVA vs HAMA	0.12	0.54	29	0.14	0.45	29	−0.26	0.22	22
GMVB vs HAMD	0.14	0.50	29	−0.03	0.87	29	0.07	0.76	22
GMVB vs HAMA	−0.004	0.98	29	0.03	0.89	29	0.07	0.75	22

Note: GMVs, gray matter volumes; GMVA, the left cerebellum Crus I/II; GMVB, the right precentral and postcentral gyri; MDD, major depressive disorder; HCs, healthy controls; MDD + S, MDD patients with suicidal ideation; MDD − S, MDD patients without suicidal ideation; HAMD, Hamilton Rating Scale for Depression; HAMA, Hamilton Anxiety Rating Scale; *r*, correlation coefficient; *df*, degrees of freedom; * $P < 0.05$.

Author contributions

Yingrui Guo: data collection, study design, data analysis and manuscript writing. Xiaowei Jiang: data collection, study design and manuscript writing. Linna Jia and Yue Zhu: data collection and manuscript writing. Xinyu Han: data analysis. Yifan Wu, Wen Liu, Wenhui Zhao, Huaqian Zhu, Dahai Wang, Zhaoyuan Tu, Yifang Zhou and Qikun Sun: data collection. Feng Wu and Lingtao Kong: recruited the patients, confirmed the diagnosis, and acquired the funding. Yanqing Tang: obtained funding and supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This work was supported by grants from the National Key R&D Program of China (grant numbers 2018YFC1311600 and 2016YFC1306900 to Yanqing Tang); the Liaoning Revitalization Talents Program (grant number XLYC1808036 to Yanqing Tang); the Natural Science Foundation of Liaoning Province (grant number 2020-MS-176 to Xiaowei Jiang); the National Key R&D Program "Science and Technology Winter Olympics" (grant number 2021YFF0306503 to Feng Wu); the Joint Fund of National Natural Science Foundation of China (grant number U1808204 to Feng Wu), and the Natural Science Foundation of Liaoning Province (grant number 2019-MS-05 to Feng Wu).

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.

Data availability

The data that has been used is confidential.

Acknowledgements

The authors thank all participants in the study, as well as investigators involved in conducting the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103403.

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