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Gray matter volume reduction in orbitofrontal cortex correlated with plasma glial cell line-derived neurotrophic factor (GDNF) levels within major depressive disorder

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ABSTRACT

Background: Major depressive disorder (MDD) is a severe mental disorder characterized by reduced gray matter volume (GMV). To date, the pathogenesis of MDD remains unclear, but neurotrophic factors play an essential role in the pathophysiological alterations of MDD during disease development. In particular, plasma glial cell line-derived neurotrophic factor (GDNF) has been suggested as a potential biomarker that may be associated with disease activity and neurological progression in MDD. Our study investigated whether plasma GDNF levels in MDD patients and healthy controls (HCs) are correlated with GMV alterations.

Methods: We studied 54 MDD patients and 48 HCs. The effect of different diagnoses on whole-brain GMV was investigated using ANOVA (Analysis of Variance). The threshold of significance was $p < 0.05$, and Gaussian random-field (GRF) correction for error was used. All analyses were controlled for covariates such as ethnicity, handedness, age, and gender that could affect GMV.

Result: Compared with the HC group, the GMV in the MDD group was significantly reduced in the right inferior orbitofrontal cortex (OFC), and plasma GDNF levels were significantly higher in the MDD group than in the HC group. In the right inferior OFC, the GDNF levels were positively correlated with GMV reduction in the MDD group, whereas in the HC group, a negative correlation was observed between GDNF levels and GMV reduction.

Conclusion: Although increased production of GDNF in MDD may help repair neural damage in brain regions associated with brain disease, its repairing effects may be interfered with and hindered by underlying neuro-inflammatory processes.

1. Introduction

There is evidence that major depressive disorder (MDD) is linked to abnormally low gray matter volume (GMV) in various brain regions, such as the hippocampus, cingulate gyrus, frontal lobe, occipital lobe, temporal lobe, insula, and striatum (Kim et al., 2019; Schmaal et al., 2017; Meng et al., 2020; Fossati et al., 2004; Duman and Monteggia, 2006; Du et al., 2012; Stratmann et al., 2014; Lloyd et al., 2004). Moreover, researchers have found that MDD patients had less GMV in the frontal lobes (Bora et al., 2012), especially in the prefrontal cortex (PFC) (Czeh and Nagy, 2018), which was smaller than in healthy controls (HCs) (Grieve et al., 2013; Ansell et al., 2012; Nakano et al., 2014). The PFC is located in the anterior part of the frontal lobe and is considered to be one of the most complex anatomical and functional structures in the mammalian brain. The primary function of the PFC involves attention, planning, and decision-making, which occur mainly through the dynamic interaction of two parallel networks of the PFC—the "execution" network and the "limbic" network (Abernathy et al., 2010). The prefrontal neocortical and limbic archicortical network is dysregulated in MDD (Bennett, 2011; Bennett, 2010).

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According to functional magnetic resonance imaging (fMRI) studies, this disorder is mainly manifested by reduced activity in the PFC (Taylor and Liberzon, 2007). A functional near-infrared spectroscopy (fNIRS) study found that impaired processing of emotional faces in patients with mood disorders may be associated with abnormal functioning of the right PFC (Manelis et al., 2019). Another study revealed that MDD patients had significantly lower functional connectivity strength (FCS) in the bilateral PFC compared to the HC group (Shi et al., 2020). Zhang et al. (Zhang et al., 2018) observed that MDD patients had decreased GMV and local brain function in the PFC. An additional study found that the mean GMV of the PFC was abnormally reduced in subjects with MDD, irrespective of their treatment status or current mood state (Drevets et al., 1997). An early *meta*-analysis reported that frontal regions show the most significant reduction in MDD (Koolschijn et al., 2009), particularly in the anterior cingulate cortex (ACC) and bilateral orbitofrontal cortex (OFC) (Gray et al., 2020). In the largest structural MRI (sMRI) study ever performed, adults with MDD showed cortical gray matter thinning in the ACC and OFC compared with controls (Schmaal et al., 2017). Importantly, structural abnormalities of the ACC and OFC occurred early in MDD and affected regions that are crucial to the regulation of negative emotions, value representation, and self-referential processing (Hiser and Koenigs, 2018). A five-year prospective study evaluating MDD mothers and never-depressed daughters found lower cortical thickness in the right medial OFC to be one of the neurological features predictive of first-onset MDD (Foland-Ross et al., 2015). There is substantial heterogeneity in MDD; therefore, studies linking structural abnormalities to a more homogeneous biological phenotype of depression may provide key findings (Pizzagalli and Roberts, 2022).

Previous studies found that the gray matter abnormalities in the OFC play a crucial role in MDD, where it receives input from visual (Barbas, 1988), gustatory (Rolls and Baylis, 1994), olfactory (Carmichael et al., 1994), and somatosensory cortices (Ongür and Price, 1991) 2000). Sensory and emotional information from the thalamus, olfactory system, and amygdala are relayed in the OFC and then transmitted to the striatum and PFC (Rolls, 2019). Cognitive dysfunction in depression is related to the complexity of the right OFC (Schmitt et al., 2021). Imaging and neuropathological studies have shown that MDD patients do exhibit several types of OFC abnormalities (Ongür and Price, 1991) 2000). An autopsy study found that patients with MDD have smaller neurons in the medial OFC and reduced cortical thickness (Rajkowska et al., 1999), and one fMRI study showed a significant reduction in OFC activation in MDD patients compared with the HC group during a working memory task (Rose et al., 2006). An sMRI study showed smaller OFC volumes in patients with MDD in the remission period (Bremner et al., 2002). The studies mentioned above suggest that the reduction and dysfunction of GMV in the OFC may be related to the pathophysiology of MDD in adults.

The reduction in GMV and atrophy of gray matter morphology in patients with MDD may be due to excessive neural loss (apoptosis) and altered regulation of neurotrophic processes (Fossati et al., 2004; Czeh and Nagy, 2018; Rajkowska, 2003). In recent years, an essential neurotrophic factor (NTF) closely related to MDD, the glial cell line-derived neurotrophic factor (GDNF) (Brunoni et al., 2015; Skibinska et al., 2017), has been identified. GDNF is a secreted protein that belongs to one of the NTFs (Oppenheim et al., 1995). It can promote the survival of dopaminergic neurons, support motor neurons, nourish sympathetic and parasympathetic neurons, and influence synaptic efficiency and neuroplasticity (Mesulam, 1999). A target-derived trophic factor, GDNF, has been found to be essential for the survival of primary sensory neurons (Erickson et al., 2001). It was found to protect neurons from excitotoxicity-induced cell death and ischemic injury and to have a protective effect on hippocampal neurons and ischemic cortical areas (Curcio et al., 2015). It has also been suggested that GDNF may be a potential biomarker for disease activity and neurological progression in MDD (Blizniewska-Kowalska et al., 2021). A comparative post-mortem study showed that GDNF concentrations were significantly increased in the parietal cortex of depression patients (Michel et al., 2008), and affective symptoms of depression, such as mood regulation, are influenced heavily by parietal structures (Anderson et al., 2004; Price, 1999). Increased GDNF synthesis may be a feature of acute mood episodes (Rosa et al., 2006). Wang et al. (Wang et al., 2011) found that plasma GDNF levels were significantly higher in patients with late-onset MDD than in controls. Age and severity of clinical depression symptoms play a critical role in the expression of GDNF in MDD patients, according to our previous study (Sun et al., 2019).

No studies have investigated the possible link between GDNF and GMV in MDD yet. Based on the current status of the research, we hypothesize that patients with MDD may exhibit abnormal plasma GDNF levels and reduced GMV in the PFC compared with HCs, and there may be a correlation between GMV alterations in the PFC and plasma GDNF levels.

2. Methods

2.1. Participants and clinical measures

Data for all subjects in this study were collected at the First Affiliated Hospital of China Medical University from 2013 to 2019. The patient group was drawn from patients with MDD aged 18–45 years ($n = 54$) attending the psychiatric outpatient clinic of the First Affiliated Hospital of China Medical University. Of these, 22 (40.7%) were in depression state and the remaining 32 (59.3%) were in remission state. 36 (66.7%) patients were taking a sedative, mood stabilizers, antidepressants, or antipsychotics at the time of scanning, while 18 (33.3%) patients were not taking any of these medications. A case–control design was used, with 48 HCs, aged 18–45 years, recruited from the community by advertisement. Two experienced psychiatrists confirmed the diagnosis of the MDD patient group based on the Structured Clinical Interview for DSM-IV (SCID) (above 18 years). Patients were excluded if they had a history of other DSM-IV Axis I disorders, including schizophrenia, bipolar disorder, substance abuse, anxiety disorders, and eating disorders. Determined by their detailed family history, participants in the HCs did not have any current or lifetime Axis I disorder or history of psychiatric, mood, or other Axis I disorders in their first-degree relatives. Participants in all groups were excluded if they had dementia or other significant medical conditions, including hypertension, diabetes, autoimmune diseases, infectious diseases within one month, and a history of head injury. A psychiatrist assessed the severity of the subjects' depression and anxiety using the 17-item Hamilton rating scale for depression (HAMD-17) and Hamilton anxiety scale (HAMA). All subjects voluntarily signed a written informed consent form after they had become familiar with the entire study procedure. The study protocol was approved by the Medical Research Ethics Committee of the First Affiliated Hospital of China Medical University and was performed in accordance with the Declaration of Helsinki.

2.2. Image acquisition and processing

The MRI scans were performed at the Department of Radiology of the First Affiliated Hospital of China Medical University, using a Signa HDx 3.0 T superconducting MRI scanner from General Electric (USA) with a standard 8-channel phased-array head orthogonal coil. All subjects had their heads fixed with foam and wore earplugs to reduce noise. Diffusion tensor imaging and high-resolution sMRI scans were performed after the localization scans, during which the subjects were kept at rest: supine, eyes closed, and quiet without thinking. The scan parameters were as follows: the structural image was taken using a three dimensional-fast spoiled gradient-echo (3D-FSPGR) T1-weighted sequence with a repetition time (TR) = 7.1 ms, echo time (TE) = 3.2 ms, flip angle = 13°, image matrix = 240 × 240, field of view = 240 mm × 240 mm, number of slices = 176, slice thickness = 1 mm, without gap, and voxel size =

1.0 mm^3, and the scanning time was 8 m 22 s.

3D MRI pre-processing: In this study, the voxel-based morphometry (VBM8) toolbox (https://dbm.neuro.uni-jena.de/vbm8/) implemented in Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK. https://www.fil.ion.ucl.ac.uk/spm/software/spm8/),was used to quantify the changes in brain GMV for direct comparison between the MDD and HC groups. Preprocessing was performed using the VBM8 toolkit in the Matlab-based SPM8 software and consisted mainly of correcting the magnetic field, segmenting the organization, and spatial normalization steps. The image space was normalized to Montreal Neurological Institute (MNI) space according to the default parameters of the VBM8 toolkit and resampled to 1.5 mm isotropic voxels. The GMV of the subjects were adjusted by nonlinear transformation so that the voxel values became the relative volumes of local tissue after individual brain size correction. Finally, the image data were Gaussian smoothed with a full width at half maximum (FWHM) of 8 mm^3. The final images were used for statistical analysis at the voxel-wise level.

The pre-processed image data were statistically analyzed with the Matlab platform using the Data Processing Assistant for Brain Imaging (DPABI) V5.0 software package. The GMV values of the MDD group and the HC group were statistically analyzed by a two-sample *t*-test, and the differential brain regions between two groups were identified by the Anatomical Automatic Labeling (AAL) template. The Gaussian random field (GRF) method was used for comparison correction, and the differences were considered statistically significant at $p < 0.05$ (GRF corrected) for each cluster of differential brain regions. The GMV values of the clusters shown differences between MDD group and HC group were extracted using ROI signal extractor. Bivariate Pearson correlation analyses were performed in MDD group to assess the correlation of HAMD-17 scores and other clinical and demographic characteristics of the participants with GMV values of the clusters.

2.3. Measurements of GDNF

After collection, the samples were centrifuged at 2000 rpm/min for 10 min, and the plasma was stored in aliquots in a refrigerator at − 80 °C until assayed. With the same Luminex instrument， plasma GDNF concentrations were determined by magnetic Luminex analysis according to the manufacturer's instructions. According to the manufacturer's recommendations, plasma GDNF concentrations were adjusted by protein concentration. All assays were performed twice using duplicate kits by the same operator, who was blinded to the clinical grouping of the subjects.

2.4. Statistical analysis

All statistical analyses were performed using SPSS Statistics version 22 (IBM, Armonk, NY, USA). Box plots and the one-sample Shapiro—Wilk test were used to examine whether there were outliers in GDNF concentrations and whether GDNF concentrations and GMV values were conformed to a normal distribution. Differences in gender between the MDD and HC groups were tested using Chi-square tests. Differences in age, GDNF concentrations, and GMV values between the MDD and HC groups were tested using independent samples *t* tests.

MDD and HC groups were compared using bivariate Pearson correlation analysis of GDNF values and GMV at differential brain region. All *p*-values were two-tailed, and *p*-values < 0.05 were considered significant.

3. Results

3.1. Demographics and clinical profile

The clinical and demographic characteristics of the participants are shown in Table.1. There were no statistically significant differences in age at scan ($t = 1.02$, $p = 0.310$), gender ($\chi = 1.47$, $p = 0.140$) between the two groups. The MDD group had significantly higher GDNF levels than the HC group ($p = 0.033$, Table 1).

Table 1
Clinical and demographic characteristics of the groups. MDD, major depressive disorder; HC, healthy control; n = Number of subjects. SD, Standard Deviation; Values are expressed as Mean ± SD; HAMD-17, 17-item Hamilton Depression rating scale; F, female; M, male; HAMA, 17-item Hamilton Anxiety rating scale; GDNF, glial cell line-derived neurotrophic factor. $p < 0.05$ was considered statistically significant.

	MDD (n = 54) Mean ± SD	HC (n = 48) Mean ± SD	t/χ	*p*
Age at scan(years)	29.30 ± 8.39	27.67 ± 7.66	1.02	0.310
Gender(F/M)	42/12	31/17	1.47	0.140
Duration of illness (months)	26.63 ± 47.3	——		
HAMD-17	15.87 ± 9.11	——		
HAMA	15.39 ± 10.74	——		
GDNF(pg/ml)	1.85 ± 0.45	1.67 ± 0.45	2.164	0.033

3.2. GMV findings

A comparison between the MDD group and the HC group showed that patients had reduced GMV in the region of the right inferior orbitofrontal gyrus (AAL90, MNI coordinates 43.5, 40.5, −16.5; voxel size: 664, *t*-value: 3.390, $p < 0.05$ (GRF corrected)) (Fig. 1). No statistical differences were found in GMV between the drug-using group and drug-naive group. In the MDD group, there was a significant correlation between GMV and disease duration (r = -0.281, $p = 0.040$); there was no significant correlation between GMV and age (r = -0.134, $p = 0.333$), the HAMD-17 scores (r = -0.003, $p = 0.981$), or the HAMA scores (r = -0.111, $p = 0.422$).

3.3. Plasma GDNF findings

GDNF levels were significantly higher in the MDD group than in the HC group ($p = 0.033$) (Fig. 2). No statistical differences were found in GDNF between the drug-using group and drug-naive group ($p = 0.336$). There was no significant correlation between GDNF levels and age (r = 0.151, $p = 0.275$), disease duration (r = 0.081, $p = 0.558$), the HAMD-17 scores (r = 0.019, $p = 0.889$), or the HAMA scores (r = -0.010, $p = 0.942$).

3.4. Correlation between the reduction of GMVs and the plasma GDNF levels

The MDD group showed a positive correlation between GDNF levels and GMV (r = 0.274, $p = 0.045$), while a negative correlation between GDNF and GMV was observed in the HC group (r = -0.339, $p = 0.018$) (Fig. 3).

4. Discussion

In this study, we found that MDD patients showed a diffuse reduction in GMV in the right inferior OFC, and they had higher plasma GDNF levels than HCs. In the MDD group, the lower the GDNF levels, the smaller the GMV in the right inferior OFC. To our knowledge, this is the first study to explore the relationship between whole-brain GMV and plasma GDNF levels in patients with MDD.

Numerous studies have found that patients with MDD have abnormally reduced GMV in the frontal brain regions (Kim et al., 2019; Schmaal et al., 2017; Meng et al., 2020; Fossati et al., 2004; Duman and Monteggia, 2006; Du et al., 2012; Stratmann et al., 2014; Lloyd et al., 2004; Bora et al., 2012), especially in the OFC, where the GMV is significantly smaller than that of HCs (Lai et al., 2000; Zhao et al., 2017;

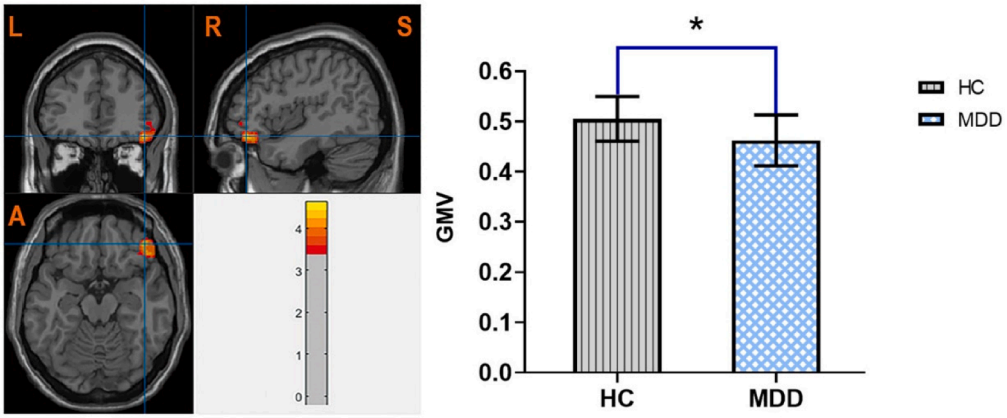

Fig. 1. Gray matter areas show significant differences between MDD and HCs. The orange areas are the locations of brain areas where the GMV differs between the two groups. The color bar is the range of *t*-values. (AAL90, MNI coordinates: x = 43.5, y = 40.5, z = − 16.5; voxel size: 664, *t*-value: 3.390, $p < 0.05$ (GRF corrected)). L, left; R, right; A, anterior; S, superior. HC, healthy control; MDD, major depressive disorder. GMV, gray matter volume. *$p < 0.05$ was considered statistically significant. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

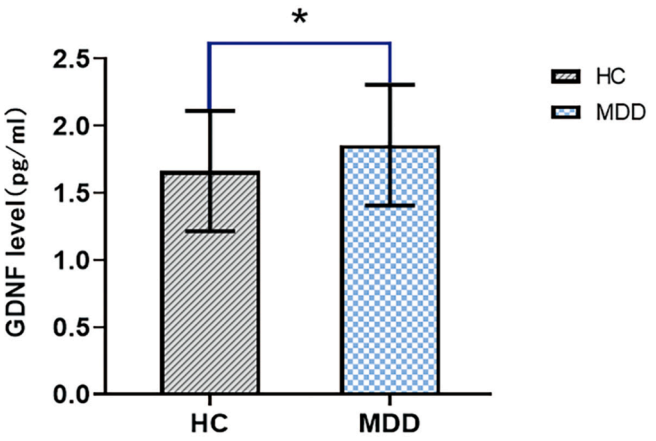

Fig. 2. Higher plasma GDNF levels in the MDD group compared with the HC group (MDD 1.85 ± 0.45 pg/ml, HC 1.67 ± 0.45 pg/ml, $p = 0.033$). GDNF, glial cell line-derived neurotrophic factor. *$p < 0.05$ was considered statistically significant.

Ballmaier et al., 2004), which further confirms our findings. The OFC is located in the corticomotor and ventral premotor areas of the PFC and is primarily involved in cognitive functions, where individuals make choices or avoid risks. It can integrate external stimuli with internal states and regulate higher cognitive functions such as reward prediction, working memory, risky decision-making, emotion regulation, and other neural activities (Stalnaker et al., 2015; Rudebeck and Rich, 2018). Impaired negative emotion regulation in MDD patients is associated with the right OFC (Qin et al., 2014). In a *meta*-analysis of whole-brain functional neuroimaging, non-psychotic disorders such as depression were found to manifest as abnormal activation in the right anterior insula/prefrontal ventral lateral cortex and right intraparietal sulcus (McTeague et al., 2017). Decreased functional connectivity (FC) between the medial OFC, parahippocampal gyrus, and middle temporal lobe results in the failure of reward-related information to reach the hippocampus, i.e., reward-related pleasant emotions cannot be transmitted to hippocampal storage, and pleasant experiences are absent from memory, resulting in clinical symptoms such as pleasure deficit and diminished interest. The lateral OFC receives information from the non-reward/punishment system and processes it abnormally, the precuneus processes mainly self-relevant information, and the middle temporal gyrus is associated with visual information processing, with enhanced FC between them leading to negative self-perception and misrecognition of face emotions (Cheng et al., 2016). Another sMRI study has shown a decrease in OFC surface area in adolescents with MDD and a decrease in OFC thickness early in the disease in adults (Schmaal et al., 2017). These structural abnormalities may be due to the delayed maturation of neurons in the developing central nervous system, reduced dendritic growth, branching, and synaptic number, and the inability to transmit relevant signals to and from the OFC, resulting in

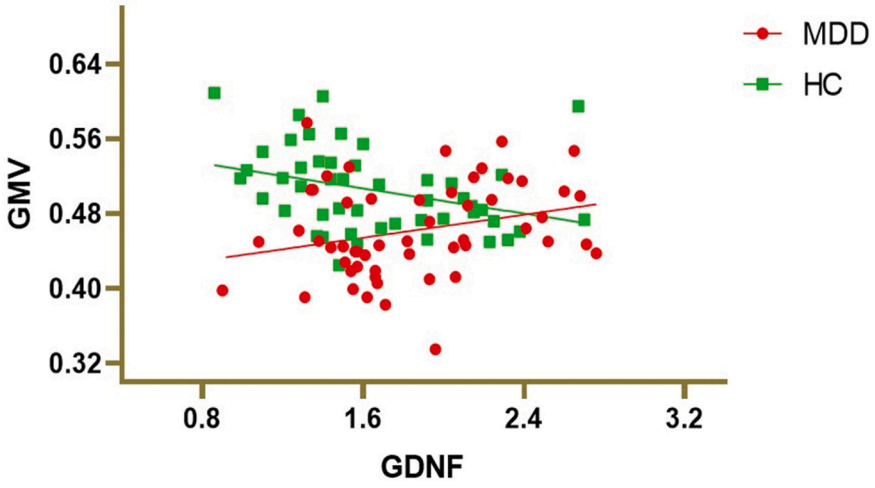

Fig. 3. Effect of GDNF levels on GMV in MDD and HCs. The MDD group showed a positive correlation between GDNF levels and GMV reduction (r = 0.274, $p = 0.045$), while a negative correlation between GDNF and GMV reduction was observed in the HC group (r = − 0.339, $p = 0.018$). $p < 0.05$ was considered statistically significant.

functional abnormalities (Lai et al., 2000). We also found that in the MDD group, disease duration was negatively correlated with GMV, which was consistent with the findings of Lampe et al. (Lampe et al., 2003).

Our study found significantly elevated GDNF levels in MDD patients compared with the HC group. However, there have been conflicting studies on peripheral blood GDNF levels in MDD patients, with either high or low values of GDNF found at both the serum and plasma levels (Wang et al., 2011; Sun et al., 2019; de Azevedo et al., 2014; Zhang et al., 2008; Takebayashi et al., 2006; Lin and Tseng, 2015; Otsuki et al., 2008). Our results are consistent with a study reporting high plasma GDNF levels in MDD (Wang et al., 2011), which confirms our hypothesis and also suggests that elevated GDNF levels may be a biomarker for MDD disease (Blizniewska-Kowalska et al., 2021). It is unclear whether this is a pathological or a compensatory mechanism. This result is consistent with a previous study on higher serum GDNF levels during acute manic and depressive episodes in patients with bipolar disorder (Rosa et al., 2006). In addition, a previous study had similar findings and noted that GDNF concentrations in the parietal cortex were significantly higher in depressed patients than in matched controls (Michel et al., 2008). The neurotrophic effects of GDNF are potent on various brain neurons and can help reduce the effects of oxidative stress (Gratacòs et al., 2001). Meanwhile, oxidative stress plays an important role in the pathogenesis of MDD (Gałecki et al., 2009). Therefore, we tentatively hypothesized that elevated GDNF levels may be associated with disturbances in the oxidative and antioxidant homeostasis system.

There remains a critical link between GDNF levels in the central nervous system and those in the peripheral blood—the blood–brain barrier (BBB). Although an early study did not support the idea that GDNF could cross the BBB (Kastin et al., 2003), several later studies in animals and humans found that the BBB may become dysfunctional and hyperpermeable in the presence of stress, inflammation, pain, or infection (Bittner et al., 2014; Li et al., 2014). It has also been found that increased susceptibility of astrocytes during the progression of depression may exacerbate BBB dysfunction (Wu et al., 2021). Although there is no direct evidence that the permeability of the BBB is increased enough for GDNF to pass through in depressed patients, one study has shown that chronic pain increases the levels of inflammatory cytokines (IL-8) and leads to opposite changes in GDNF levels at the brain and peripheral levels, with increased levels of GDNF in the cerebrospinal fluid but not in the peripheral blood and decreased levels of GDNF in peripheral blood (Lundborg et al., 2010). This phenomenon may be due to the extracerebral production of GDNF entering the central nervous system through the dysregulated BBB and repairing damaged neurons in MDD patients (Lin and Tseng, 2015). In addition, the increase in GDNF in the cerebrospinal fluid may be due to the restorative effect of GDNF on dysregulated BBB function, and the interaction between dysregulated BBB and neurotrophic factors in the pathogenesis of depression needs to be further investigated (Yosef and Ubogu, 2012).

Finally, we also found that the GMV of MDD patients in the right inferior OFC was positively correlated with plasma GDNF levels. We speculated that the increase of GDNF levels may be to repair the neural damage in the brain that occurred in MDD patients, which seems to imply that pharmacological or non-pharmacological treatments targeting plasma GDNF could alter the gray matter in local brain regions to some extent.

5. Limitations

First, despite our efforts to demonstrate the role of disease markers of peripheral GDNF in depression and MDD, we did not investigate whether plasma GDNF levels changed in subjects after antidepressant treatment. After eight weeks of antidepressant therapy, serum GDNF levels increased significantly in MDD patients who were significantly lower before treatment (Zhang et al., 2008). Additionally, the medication given during the disease may affect the results of MRI measurements of the brain, as one animal study found an increase in GMV in the left middle frontal gyrus and right OFC in the MDD group after eight weeks of fluoxetine treatment (Kong et al., 2014). Second, all subjects included in this study were recruited from a single center and consisted of a single ethnic group, thus increasing the potential for population stratification and limiting the generalizability of the findings. Finally, whether the disease recurs or not also has an effect on patient gray matter. One study examining the relationship between cortical changes and recurrence in MDD patients found a significant decrease in the insula and dorsolateral prefrontal GMV in the group of patients with relapsed MDD; in contrast, in the group without relapse, there were no significant changes in GMV in these regions (Zhang et al., 2016; Zaremba et al., 2018). Our study did not strictly distinguish between patients with first-onset and relapsed MDD.

6. Conclusion

We innovatively explored the relationship between plasma GDNF levels and GMV in MDD patients and HCs. We found that plasma GDNF levels in MDD patients were positively correlated with GMV reduction in the right inferior OFC, suggesting that increased production of GDNF in MDD patients may help prevent and repair disease-related neurological damage. Still, its effects may be interfered with by an underlying neuroinflammatory process, a mechanism that is unclear and requires further study, and our findings may provide new ideas for the treatment of depression.

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 authors do not have permission to share data.

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Author contributions

Yifan Wu: data collection, study design, data analysis and manuscript writing. Lingtao Kong: data collection, study design and manuscript writing. Anqi Yang, Kaiqi Xin, Yihui Lu, Xintong Yan, Wen Liu, Yue Zhu, Xiaowei Jiang, Yingrui Guo and Qikun Sun: data collection. Feng Wu and Lingtao Kong: recruited the patients, confirmed the diagnosis, and acquired the funding. Yanqing Tang, Xiaowei Jiang and Feng Wu: obtained funding and supervised the study. All authors contributed to manuscript revision, read, and approved the submitted version.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Abernathy, K., Chandler, L.J., Woodward, J.J., 2010. Alcohol and the prefrontal cortex. In: Functional Plasticity and Genetic Variation: Insights into the Neurobiology of Alcoholism, pp. 289–320.

Anderson, A., Oquendo, M., Parsey, R., Milak, M., Campbell, C., Mann, J., 2004. Regional brain responses to serotonin in major depressive disorder. J. Affect. Disord. 82 (3), 411–417.

Ansell, E.B., Rando, K., Tuit, K., Guarnaccia, J., Sinha, R., 2012. Cumulative adversity and smaller gray matter volume in medial prefrontal, anterior cingulate, and insula regions. Biol. Psychiatry 72 (1), 57–64.

Ballmaier, M., Toga, A., Blanton, R., Sowell, E., Lavretsky, H., Peterson, J., Pham, D., Kumar, A., 2004. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. Am. J. Psychiatry 161 (1), 99–108.

Barbas, H., 1988. Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. J. Comp. Neurol. 276 (3), 313–342.

Bennett, M., 2010. Synapse regression in depression: the role of 5-HT receptors in modulating NMDA receptor function and synaptic plasticity. Aust. N. Z. J. Psychiatry 44 (4), 301–308.

Bennett, M.R., 2011. The prefrontal-limbic network in depression: Modulation by hypothalamus, basal ganglia and midbrain. Prog. Neurobiol. 93 (4), 468–487.

Bittner, S., Ruck, T., Fernandez-Orth, J., Meuth, S.G., 2014. TREK-king the blood-brain-barrier. J. Neuroimmune Pharmacol. 9 (3), 293–301.

Bliznіewska-Kowalska, K., Galecki, P., Szemraj, J., Talarowska, M., 2021. Expression of Selected Genes Involved in Neurogenesis in the Etiopathogenesis of Depressive Disorders. J Pers Med 11 (3).

Bora, E., Fornito, A., Pantelis, C., Yucel, M., 2012. Gray matter abnormalities in Major Depressive Disorder: a meta-analysis of voxel based morphometry studies. J. Affect. Disord. 138 (1–2), 9–18.

Bremner, J., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., Staib, L., Charney, D., 2002. Reduced volume of orbitofrontal cortex in major depression. Biol. Psychiatry 51 (4), 273–279.

Brunoni, A., Machado-Vieira, R., Zarate, C., Vieira, E., Valiengo, L., Benseñor, I., Lotufo, P., Gattaz, W., Teixeira, A., 2015. Assessment of non-BDNF neurotrophins and GDNF levels after depression treatment with sertraline and transcranial direct current stimulation in a factorial, randomized, sham-controlled trial (SELECT-TDCS): an exploratory analysis. Prog. Neuropsychopharmacol. Biol. Psychiatry 56, 91–96.

Carmichael, S., Clugnet, M., Price, J., 1994. Central olfactory connections in the macaque monkey. J. Comp. Neurol. 346 (3), 403–434.

Cheng, W., Rolls, E., Qiu, J., Liu, W., Tang, Y., Huang, C., Wang, X., Zhang, J., Lin, W., Zheng, L., et al., 2016. Medial reward and lateral non-reward orbitofrontal cortex circuits change in opposite directions in depression. Brain J. Neurol. 139, 3296–3309.

Curcio, M., Salazar, I.L., Inacio, A.R., Duarte, E.P., Canzoniero, L.M., Duarte, C.B., 2015. Brain ischemia downregulates the neuroprotective GDNF-Ret signaling by a calpain-dependent mechanism in cultured hippocampal neurons. Cell Death Dis. 6, e1645.

Czeh, B., Nagy, S.A., 2018. Clinical Findings Documenting Cellular and Molecular Abnormalities of Glia in Depressive Disorders. Front. Mol. Neurosci. 11, 56.

de Azevedo, C.T., Mondin, T.C., Wiener, C.D., Marques, M.B., Fucolo Bde, A., Pinheiro, R. T., de Souza, L.D., da Silva, R.A., Jansen, K., Oses, J.P., 2014. Neurotrophic factors, clinical features and gender differences in depression. Neurochem. Res. 39 (8), 1571–1578.

Drevets, W., Price, J., Simpson, J., Todd, R., Reich, T., Vannier, M., Raichle, M., 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 386 (6627), 824–827.

Du, M.Y., Wu, Q.Z., Yue, Q., Li, J., Liao, Y., Kuang, W.H., Huang, X.Q., Chan, R.C., Mechelli, A., Gong, Q.Y., 2012. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 36 (1), 11–16.

Duman, R., Monteggia, L., 2006. A neurotrophic model for stress-related mood disorders. Biol. Psychiatry 59 (12), 1116–1127.

Erickson, J., Brosenitsch, T., Katz, D., 2001. Brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor are required simultaneously for survival of dopaminergic primary sensory neurons in vivo. J. Neurosci. 21 (2), 581–589.

Foland-Ross, L.C., Sacchet, M.D., Prasad, G., Gilbert, B., Thompson, P.M., Gotlib, I.H., 2015. Cortical thickness predicts the first onset of major depression in adolescence. Int. J. Dev. Neurosci. 46, 125–131.

Fossati, P., Radtchenko, A., Boyer, P., 2004. Neuroplasticity: from MRI to depressive symptoms. In: European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, pp. S503–510.

Gałecki, P., Szemraj, J., Bieńkiewicz, M., Florkowski, A., Gałecka, E., 2009. Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. Pharmacol. Rep. 61 (3), 436–447.

Gratacòs, E., Pérez-Navarro, E., Tolosa, E., Arenas, E., Alberch, J., 2001. Neuroprotection of striatal neurons against kainate excitotoxicity by neurotrophins and GDNF family members. J. Neurochem. 78 (6), 1287–1296.

Gray, J.P., Muller, V.I., Eickhoff, S.B., Fox, P.T., 2020. Multimodal abnormalities of brain structure and function in major depressive disorder: A meta-analysis of neuroimaging studies. Am. J. Psychiatry 177 (5), 422–434.

Grieve, S.M., Korgaonkar, M.S., Koslow, S.H., Gordon, E., Williams, L.M., 2013. Widespread reductions in gray matter volume in depression. Neuroimage Clin 3, 332–339.

Hiser, J., Koenigs, M., 2018. The multifaceted role of the ventromedial prefrontal cortex in emotion, decision making, social cognition, and psychopathology. Biol. Psychiatry 83 (8), 638–647.

Kastin, A.J., Akerstrom, V., Pan, W., 2003. Glial cell line-derived neurotrophic factor does not enter normal mouse brain. Neurosci. Lett. 340 (3), 239–241.

Kim, J.H., Suh, S.I., Lee, H.J., Lee, J.H., Lee, M.S., 2019. Cortical and subcortical gray matter alterations in first-episode drug-naive adolescents with major depressive disorder. Neuroreport 30 (17), 1172–1178.

Kong, L., Wu, F., Tang, Y., Ren, L., Kong, D., Liu, Y., Xu, K., Wang, F., 2014. Frontal-subcortical volumetric deficits in single episode, medication-naive depressed patients and the effects of 8 weeks fluoxetine treatment: a VBM-DARTEL study. PLoS One 9 (1), e79055.

Koolschijn, P.C., van Haren, N.E., Lensvelt-Mulders, G.J., Hulshoff Pol, H.E., Kahn, R.S., 2009. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Hum. Brain Mapp. 30 (11), 3719–3735.

Lai, T., Payne, M., Byrum, C., Steffens, D., Krishnan, K., 2000. Reduction of orbital frontal cortex volume in geriatric depression. Biol. Psychiatry 48 (10), 971–975.

Lampe, I.K., Hulshoff Pol, H.E., Janssen, J., Schnack, H.G., Kahn, R.S., Heeren, T.J., 2003. Association of depression duration with reduction of global cerebral gray matter volume in female patients with recurrent major depressive disorder. Am. J. Psychiatry 160 (11), 2052–2054.

Li, X., Wilder-Smith, C., Kan, M., Lu, J., Cao, Y., Wong, R., 2014. Combat-training stress in soldiers increases S100B, a marker of increased blood-brain-barrier permeability, and induces immune activation. Neuro Endocrinol. Lett. 35 (1), 58–63.

Lin, P.Y., Tseng, P.T., 2015. Decreased glial cell line-derived neurotrophic factor levels in patients with depression: a meta-analytic study. J. Psychiatr. Res. 63, 20–27.

Lloyd, A., Ferrier, I., Barber, R., Gholkar, A., Young, A., O'Brien, J., 2004. Hippocampal volume change in depression: late- and early-onset illness compared. Br. J. Psychiatry J. Ment. Sci. 184, 488–495.

Lundborg, C., Hahn-Zoric, M., Biber, B., Hansson, E., 2010. Glial cell line-derived neurotrophic factor is increased in cerebrospinal fluid but decreased in blood during long-term pain. J. Neuroimmunol. 220 (1–2), 108–113.

Manelis, A., Huppert, T., Rodgers, E., Swartz, H., Phillips, M., 2019. The role of the right prefrontal cortex in recognition of facial emotional expressions in depressed individuals: fNIRS study. J. Affect. Disord. 258, 151–158.

McTeague, L., Huemer, J., Carreon, D., Jiang, Y., Eickhoff, S., Etkin, A., 2017. Identification of Common Neural Circuit Disruptions in Cognitive Control Across Psychiatric Disorders. Am. J. Psychiatry 174 (7), 676–685.

Meng, Q., Zhang, A., Cao, X., Sun, N., Li, X., Zhang, Y., Wang, Y., 2020. Brain Imaging Study on the Pathogenesis of Depression & Therapeutic Effect of Selective Serotonin Reuptake Inhibitors. Psychiatry Investig. 17 (7), 688–694.

Mesulam, M., 1999. Neuroplasticity failure in Alzheimer's disease: bridging the gap between plaques and tangles. Neuron 24 (3), 521–529.

Michel, T., Frangou, S., Camara, S., Thiemeyer, D., Jecel, J., Tatschner, T., Zoechling, R., Grünblatt, E., 2008. Altered glial cell line-derived neurotrophic factor (GDNF) concentrations in the brain of patients with depressive disorder: a comparative post-mortem study. Eur. Psychiatry 23 (6), 413–420.

Nakano, M., Matsuo, K., Nakashima, M., Matsubara, T., Harada, K., Egashira, K., Masaki, H., Takahashi, K., Watanabe, Y., 2014. Gray matter volume and rapid decision-making in major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 51–56.

Ongür, D., Price, J., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cerebral Cortex (New York, NY : 1991) 10 (3), 206–219.

Oppenheim, R., Houenou, L., Johnson, J., Lin, L., Li, L., Lo, A., Newsome, A., Prevette, D., Wang, S., 1995. Developing motor neurons rescued from programmed and axotomy-induced cell death by GDNF. Nature 373 (6512), 344–346.

Otsuki, K., Uchida, S., Watanuki, T., Wakabayashi, Y., Fujimoto, M., Matsubara, T., Funato, H., Watanabe, Y., 2008. Altered expression of neurotrophic factors in patients with major depression. J. Psychiatr. Res. 42 (14), 1145–1153.

Pizzagalli, D.A., Roberts, A.C., 2022. Prefrontal cortex and depression. Neuropsychopharmacology 47 (1), 225–246.

Price, J., 1999. Prefrontal cortical networks related to visceral function and mood. Ann. N. Y. Acad. Sci. 877, 383–396.

Qin, J., Wei, M., Liu, H., Yan, R., Luo, G., Yao, Z., Lu, Q., 2014. Abnormal brain anatomical topological organization of the cognitive-emotional and the frontoparietal circuitry in major depressive disorder. Magn. Reson. Med. 72 (5), 1397–1407.

Rajkowska, G., 2003. Depression: what we can learn from postmortem studies. Neuroscientist 9 (4), 273–284.

Rajkowska, G., Miguel-Hidalgo, J., Wei, J., Dilley, G., Pittman, S., Meltzer, H., Overholser, J., Roth, B., Stockmeier, C., 1999. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol. Psychiatry 45 (9), 1085–1098.

Rolls, E., 2019. Taste and smell processing in the brain. Handb. Clin. Neurol. 164, 97–118.

Rolls, E., Baylis, L., 1994. Gustatory, olfactory, and visual convergence within the primate orbitofrontal cortex. J. Neurosci. 14 (9), 5437–5452.
Rosa, A., Frey, B., Andreazza, A., Ceresér, K., Cunha, A., Quevedo, J., Santin, A., Gottfried, C., Gonçalves, C., Vieta, E., et al., 2006. Increased serum glial cell line-derived neurotrophic factor immunocontent during manic and depressive episodes in individuals with bipolar disorder. Neurosci. Lett. 407 (2), 146–150.
Rose, E., Simonotto, E., Ebmeier, K., 2006. Limbic over-activity in depression during preserved performance on the n-back task. Neuroimage 29 (1), 203–215.
Rudebeck, P.H., Rich, E.L., 2018. Orbitofrontal cortex. Curr. Biol. 28 (18), R1083–R1088.
Schmaal, L., Hibar, D., Sämann, P., Hall, G., Baune, B., Jahanshad, N., Cheung, J., van Erp, T., Bos, D., Ikram, M., et al., 2017. Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Mol. Psychiatry 22 (6), 900–909.
Schmitt, S., Meller, T., Stein, F., Brosch, K., Ringwald, K., Pfarr, J.K., Bordin, C., Peusch, N., Steinstrater, O., Grotegerd, D., et al., 2021. Effects of polygenic risk for major mental disorders and cross-disorder on cortical complexity. Psychol. Med. 1–12.
Shi, Y., Li, J., Feng, Z., Xie, H., Duan, J., Chen, F., Yang, H., 2020. Abnormal functional connectivity strength in first-episode, drug-naive adult patients with major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 97, 109759.
Skibinska, M., Kapelski, P., Pawlak, J., Rajewska-Rager, A., Dmitrzak-Weglarz, M., Szczepankiewicz, A., Czerski, P., Twarowska-Hauser, J., 2017. Glial Cell Line-Derived Neurotrophic Factor (GDNF) serum level in women with schizophrenia and depression, correlation with clinical and metabolic parameters. Psychiatry Res. 256, 396–402.
Stalnaker, T., Cooch, N., Schoenbaum, G., 2015. What the orbitofrontal cortex does not do. Nat. Neurosci. 18 (5), 620–627.
Stratmann, M., Konrad, C., Kugel, H., Krug, A., Schoning, S., Ohrmann, P., Uhlmann, C., Postert, C., Suslow, T., Heindel, W., et al., 2014. Insular and hippocampal gray matter volume reductions in patients with major depressive disorder. PLoS One 9 (7), e102692.
Sun, J., Kong, L., Wu, F., Wei, Y., Zhu, Y., Yin, Z., Deng, X., Jiang, X., Tang, Y., Wang, F., 2019. Decreased plasma glial cell line-derived neurotrophic factor level in major depressive disorder is associated with age and clinical severity. J. Affect. Disord. 245, 602–607.
Takebayashi, M., Hisaoka, K., Nishida, A., Tsuchioka, M., Miyoshi, I., Kozuru, T., Hikasa, S., Okamoto, Y., Shinno, H., Morinobu, S., et al., 2006. Decreased levels of whole blood glial cell line-derived neurotrophic factor (GDNF) in remitted patients with mood disorders. Int. J. Neuropsychopharmacol. 9 (5), 607–612.
Taylor, S., Liberzon, I., 2007. Neural correlates of emotion regulation in psychopathology. Trends Cogn. Sci. 11 (10), 413–418.
Wang, X., Hou, Z., Yuan, Y., Hou, G., Liu, Y., Li, H., Zhang, Z., 2011. Association study between plasma GDNF and cognitive function in late-onset depression. J. Affect. Disord. 132 (3), 418–421.
Wu, S., Yin, Y., Du, L., 2021. Blood-brain barrier dysfunction in the pathogenesis of major depressive disorder. Cell. Mol. Neurobiol.
Yosef, N., Ubogu, E., 2012. GDNF restores human blood-nerve barrier function via RET tyrosine kinase-mediated cytoskeletal reorganization. Microvasc. Res. 83 (3), 298–310.
Zaremba, D., Dohm, K., Redlich, R., Grotegerd, D., Strojny, R., Meinert, S., Burger, C., Enneking, V., Forster, K., Repple, J., et al., 2018. Association of brain cortical changes with relapse in patients with major depressive disorder. JAMA Psychiat. 75 (5), 484–492.
Zhang, H., Li, L., Wu, M., Chen, Z., Hu, X., Chen, Y., Zhu, H., Jia, Z., Gong, Q., 2016. Brain gray matter alterations in first episodes of depression: A meta-analysis of whole-brain studies. Neurosci. Biobehav. Rev. 60, 43–50.
Zhang, F.F., Peng, W., Sweeney, J.A., Jia, Z.Y., Gong, Q.Y., 2018. Brain structure alterations in depression: Psychoradiological evidence. CNS Neurosci. Ther. 24 (11), 994–1003.
Zhang, X., Zhang, Z., Xie, C., Xi, G., Zhou, H., Zhang, Y., Sha, W., 2008. Effect of treatment on serum glial cell line-derived neurotrophic factor in depressed patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 32 (3), 886–890.
Zhao, Y., Chen, L., Zhang, W., Xiao, Y., Shah, C., Zhu, H., Yuan, M., Sun, H., Yue, Q., Jia, Z., et al., 2017. Gray matter abnormalities in non-comorbid medication-naive patients with major depressive disorder or social anxiety disorder. EBioMedicine 21, 228–235.