REVIEW

A Comprehensive Overview of the Role of Visual Cortex Malfunction in Depressive Disorders: Opportunities and Challenges

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Abstract Major depressive disorder (MDD) is a highly heterogeneous mental disorder, and its complex etiology and unclear mechanism are great obstacles to the diagnosis and treatment of the disease. Studies have shown that abnormal functions of the visual cortex have been reported in MDD patients, and the actions of several antidepressants coincide with improvements in the structure and synaptic functions of the visual cortex. In this review, we critically evaluate current evidence showing the involvement of the malfunctioning visual cortex in the pathophysiology and therapeutic process of depression. In addition, we discuss the molecular mechanisms of visual cortex dysfunction that may underlie the pathogenesis of MDD. Although the precise roles of visual cortex abnormalities in MDD remain uncertain, this undervalued brain region may become a novel area for the treatment of depressed patients.

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Introduction

Major depressive disorder (MDD) is the most common serious mental illness. According to the World Health Organization statistics, MDD will rank first in the global human disease burden in 2030 [1], and one-third of the annual global suicides are related to MDD [2]. In particular, the COVID-19 pandemic triggered a 28% increase in the prevalence of MDD globally [3].

The core brain regions associated with emotional disorders include the hippocampus, prefrontal lobe, amygdala, hypothalamus, and habenula [4, 5]. However, increasing evidence also shows that the visual cortex is associated with depression and antidepressant efficacy. In this manuscript, we review the research progress on visual cortex dysfunctions in patients with depression and animal models, based on different techniques and their correlation with depression and antidepressant efficacy. Through analyzing these research findings, we hope to present a new perspective on the role of the visual cortex in the occurrence and development of depression and antidepressant treatments.

Clinical Neuroimaging Studies of Visual Cortical Structure and Function in MDD

Neuroimaging is a helpful non-invasive tool with which to investigate mechanisms underlying depression. It provides anatomical and physiological information through structural imaging and functional imaging [6]. Combining the static and dynamic information from these imaging studies can

help to understand the complex pathophysiology of MDD (Fig. 1).

Structural Imaging of the Visual Cortex

As early as 2004, Sanacora et al. found that the grey matter volume (GMV) of the occipital lobe of MDD patients was significantly increased, while the total volume and white matter volume of the occipital lobe were significantly reduced compared with healthy controls (HCs) in a small sample as measured by structural magnetic resonance imaging (sMRI) [7]. An independent large sample sMRI study further found that the occipital cortex GMV of lifelong MDD patients is abnormally increased compared with non-lifelong MDD patients [8]. Support vector machine classifier analysis of sMRI data showed increased GMV in the bilateral superior marginal gyrus and occipital lobe of MDD patients, whereas increased GMV was found in the right dorsolateral prefrontal lobe of bipolar disorder (BD) patients. These structural differences can distinguish MDD and BD at the individual level with 75% accuracy [9]. However, a study found that young people who often witnessed domestic violence in childhood, as a high-risk group for depression, have decreased GMV and thickness of the visual cortex in adulthood, the bilateral secondary visual cortex and the left occipital pole being the most strongly affected [10].

An association study between patients with recurrent MDD and HCs showed that single nucleotide polymorphisms (SNPs) of two thyroid hormone transporter genes, rs496549, and rs479640, are associated with GMV in the left occipital cortex [11]. The Shanghai Mental Health Center analyzed the interaction of the tumor necrosis factor-α SNP, rs1799724, with voxel-based morphometry and structural covariance-based graph theory in 144 MDD patients and 111 HCs, and found that the interaction of rs1799724 is only localized to the visual cortex (right superior occipital gyrus), and the visual cortex volume of MDD patients is smaller than that of HCs [12]. An analysis of the transcriptome-based polygenic risk score (T-PRS) from a non-clinical sample of young adults with MDD and the Psychiatric Genomics Consortium-MDD genome-wide association analysis database demonstrated that T-PRS is associated with the severity of depression and hypergyrification in the temporal and occipital lobes of male MDD patients [13].

Occipital bending (OB) is an asymmetrical development of the occipital lobe where one lobe crosses the midline of the brain and wraps around the other lobe. This condition is three times more common in MDD patients than HCs and right OB is strongly correlated with major depression. MDD patients with right OB have a greater cortical thickness in three areas of the left occipital lobe (cuneus, lingual gyrus, and calcarine sulcus) and a 20% reduction in the size of the
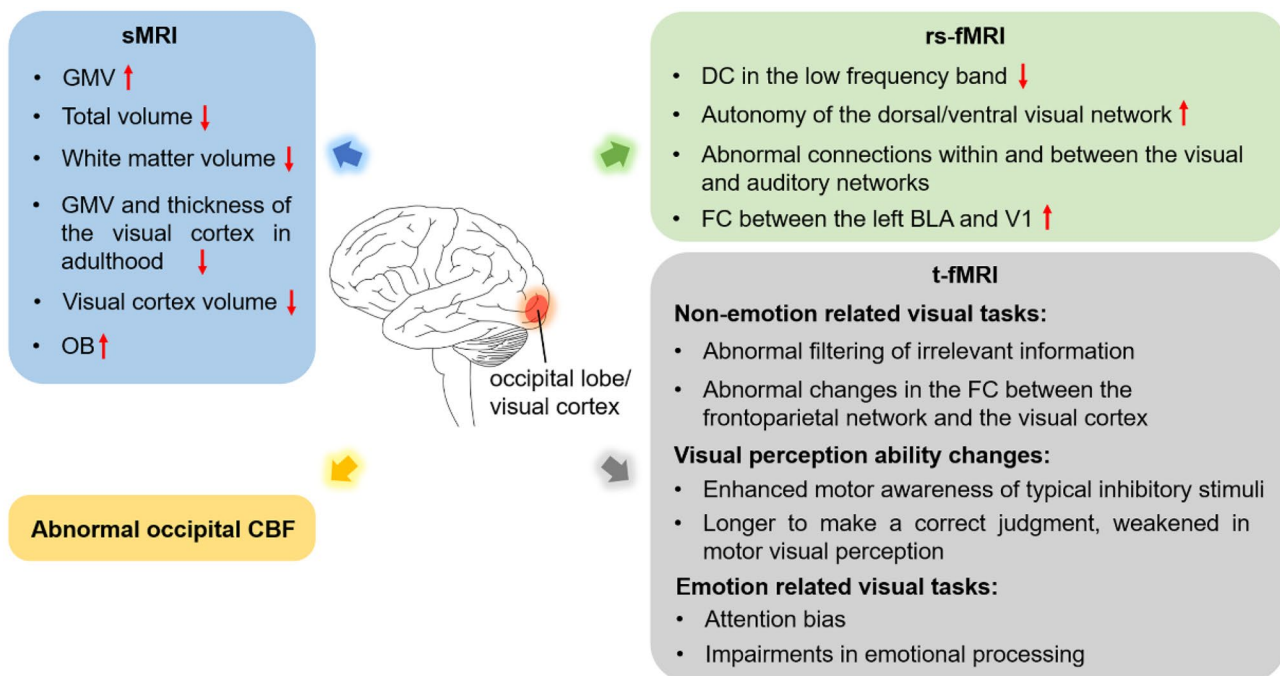

Fig. 1 Neuroimaging studies of visual cortical structure and function in depressed patients. The changes in the visual cortex in depressed patients are observed through structural and functional imaging. Red upward arrows indicate an increase; red downward arrows indicate a decrease. BLA, basolateral amygdala; CBF, cerebral blood flow; DC, degree centrality; FC, functional connectivity; GMV, grey matter volume; OB, occipital bending; rs-fMRI, resting-state functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging; t-fMRI, task-related functional magnetic resonance imaging; V1, primary visual cortex.

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bilateral lateral ventricles [14]. Taken together, these cortical structural differences, including GMV and OB, may suggest maladaptive visual cortical plasticity changes relating to depression.

Function Imaging of the Visual Cortex

Resting-State Functional Magnetic Resonance Imaging (rs-fMRI)

Comparison of the degree centrality (DC) in 10 different frequency subbands in the rs-fMRI blood oxygenation level-dependent (BOLD) fluctuation data showed that there are frequency-specific changes in the occipital lobe of MDD patients. The decreased DC in MDD patients is mainly concentrated in the occipital lobe in the low-frequency band [15]. The visual cortex can be divided into the ventral pathway for sensing shapes and the dorsal pathway for sensing spatial position [16]. In MDD patients, the dorsal visual pathway, involved in visuospatial processing, and the anterior/posterior parts of the right temporoparietal junction, involved in cognitive, emotional, and social processes, show interrupted resting-state functional connectivity [17]. Multivariable distance correlation between the dorsal attention network and the dorsal/ventral visual network was applied to quantify the connectivity between the networks in 86 drug-naive MDD patients and 73 HCs. It was found that the autonomy of the dorsal/ventral visual network in MDD patients was enhanced, that is a better, more economical, and efficient organization with enhanced independence and less external regulation by the attention network. These results showed functional dysconnectivity of the visual network in MDD patients that suggested a pathogenic role of visual systems [18].

A study based on rs-fMRI showed abnormal connections within and between the visual and auditory networks of MDD patients. The connectivity of the auditory networks, and visual components 2 (VC2) and 3 (VC3) in MDD patients are reduced. The connection between the auditory network and VC3 is weakened and the abnormal functional connectivity (FC) in the visual network is related to the clinical symptoms of MDD [19]. Depression in old age includes early-onset depression (EOD) and late-onset depression (LOD). Although the clinical symptoms of both are similar, the potential mechanism, treatment strategy, and clinical prognosis are different [20]. In a study evaluating the memory, executive function, and processing speed of 82 late-life depression (LLD) patients (40 EOD and 42 LOD patients) and 90 HCs, rs-fMRI, and Granger causality analysis found that the functional modularity and division are different for EOD and LOD patients, and the dorsal visual cortex region of interest is a potential specific node in module allocation [21].

MDD and post-traumatic stress disorder (PTSD) are highly comorbid [22], and up to 50% of PTSD patients are also diagnosed with MDD [23]. A study conducted interviews, symptom measurements, and rs-fMRI on 38 veterans who met the diagnostic criteria of depression/PTSD comorbidity. It was found that the FC between the left basolateral amygdala (BLA) and the primary visual cortex (V1) was increased in female patients, while the severity of depressive symptoms in men was related to an increased FC between the left BLA and bilateral occipital lobes [24].

Task-Related fMRI (t-fMRI)

Non-emotion Related Visual Tasks   Task-based functional MRI in response to visual stimuli has been applied extensively in patients with MDD. An fMRI study revealed that MDD patients show abnormal filtering of irrelevant information in the visual cortex and abnormal changes in the FC between the frontoparietal network and the visual cortex [25]. Other mental disorders are usually accompanied by depressive symptoms. In a study of schizophrenic patients, no significant activation of the middle occipital gyrus (MOG) was observed when they performed object perception-related tasks during fMRI, while both sides of the MOG were significantly activated in HCs. Depressive symptoms were significantly associated with increased activation of the right MOG, while anxiety was significantly associated with decreased activation [26]. BD usually alternates between depression and mania. The fMRI data showed that the visual cortical responses of patients in the depressive and manic states were reduced compared with patients in the healthy state and HCs, suggesting that abnormal visual processing may be one of the characteristics of BD [27].

Visual Perception Changes   A psychophysical visual motor processing task-based study showed that MDD patients have enhanced motor awareness of typical inhibitory stimuli compared with a control group, and the degree of spatial inhibition is related to the individual disease load [28]. The decline in spatial inhibition still exists after the patient has stopped medication for several months following clinical rehabilitation, indicating that the spatial inhibition of visual pathways may be a consequence of MDD and may last for a long time. This MDD-specific performance is related to stimulus characteristics (such as contrast, size, and presentation time) and is the result of changes in early visual processing rather than general defects or cognitive biases [28]. A recent study evaluated the motor visual perception of MDD patients by analyzing the results of their judgment of the direction of motion stimulated by a moving grating. The results showed that MDD patients took longer to make a correct judgment, and the weaker the peripheral

inhibition ability, the more severe the depression, which was manifested as a higher Hamilton depression score. This study suggested that MDD patients' ability to follow movements in the external world is significantly weakened [29]. Moreover, transcranial direct current stimulation (tDCS) of MDD patients receiving a single stimulation of the left dorsolateral prefrontal cortex (DLPFC) can also reverse the selective impairment of visual processing speed in these patients [30]. tDCS can stimulate the bilateral occipital lobe to induce long-term potentiation-like plasticity of the occipital lobe in HCs, which may be an important mechanism by which tDCS restores synaptic plasticity disorders of mental diseases, such as depression and schizophrenia [31].

Emotion-related Visual Tasks Attention Bias: Anxious individuals show a "vigilance-avoidance" pattern of attention towards threatening stimuli when both threatening and neutral stimuli are presented simultaneously, a phenomenon called "threat bias" [32]. A study by Barch's group screened 25 adolescents with and 27 without "threat avoidance" using a point detection task, and assessed brain responses to threatening and neutral faces by fMRI [33]. The results showed that the activity of several regions involved in early visual and face processing in the occipital, parietal, and temporal lobes is lower when adolescents with "threat avoidance" are presented with threatening and neutral faces [33]. Importantly, adolescents with a history of depression and/or anxiety exhibit reduced activity in these three brain regions regardless of the type of face presented. This study suggests that using attention training to change threat bias during adolescence may reduce anxiety/depression symptoms [33]. An emotional interference task-based fMRI study revealed that MDD adolescents show greater activation in the frontal cingulate gyrus and parietal occipital region when ignoring fear faces and neutral faces, that is, they need greater brain activation in cognitive control and visual attention. The authors suggested that attention bias towards negative emotions is one of the important characteristics of adolescent MDD [34]. In addition, a continuous attention task-based fMRI study showed that the activation of the occipital lobe decreases in adolescent MDD patients in the absence of reward [35]. Both adolescent and adult MDD patients have an impaired ability to selectively pay attention to negative emotions and inhibit negative stimuli. An emotional Go/No-Go task-based fMRI study reported that MDD adolescents have a decreased BOLD response in the right DLPFC and bilateral occipital lobe when "No-Go" targets and sad faces are presented, suggesting selective attention toward negative emotions and a reduced ability to suppress negative stimuli [36].

Impairments in Emotional Processing: The V1 region of MDD patients responds more strongly to emotional stimuli (happiness or sadness) than neutral stimuli [37] and the response of the right visual cortex to sadness predicts a good therapeutic effect of antidepressants [38]. A 7.0 T fMRI study showed no significant connection between V1 and the orbitofrontal cortex (OFC) in drug-naive female MDD patients, but significant positive regulation of the OFC-V1 pathway in HCs during a negative and neutral emotion image-viewing task, supporting the view that interruption of the effective connection between OFC and V1 may be closely related to the impairment of negative emotion processing and regulation in female MDD patients [39]. When MDD patients and HCs perform emotion regulation tasks, fMRI shows that the activity of the right amygdala and visual cortex in HCs are downregulated in negative emotional states, suggesting that there are obstacles in emotion regulation of the visual cortex in MDD patients [40].

By analyzing the activity pattern of the visual association area, the FC between the visual association area and prefrontal cortex, and the relationship between the visual association area and core clinical symptoms, a visual delayed recognition t-fMRI study revealed that MDD patients have connectivity interruption in the process of visual working memory updating, which is related to the retention of unrelated negative information, and could lead to persistent emotional abnormalities [41]. MDD patients show an overall decrease in the accuracy of performing emotional conflict tasks and reduced BOLD activity in the occipital region, which is responsible for face perception and emotional information processing. However, there is no difference in the response to fearful and happy faces [42]. Using alternating emotional and neutral visual stimuli, an fMRI study showed activation of the bilateral visual cortex during negative and neutral stimulation, but patients show stronger activation of the visual cortex and weaker activation of the left prefrontal cortex [43]. Patients with MDD and borderline personality disorder (BPD) differ in emotional regulation but are highly comorbid. A study that monitored HCs, MDD patients, and BPD/MDD comorbid patients by fMRI during emotional interference tasks showed that the visual cortex of BPD/MDD comorbid patients is more active during the activity [44]. However, additional studies are required to reveal the malleability of these structural correlates of attentional bias and emotional processing impairments and to determine whether this malleability is altered in patients suffering from depression. Together, these results may suggest maladaptive changes in visual cortical network plasticity that contribute to, and/or result from, depression.

The response of the right visual cortex to sadness stimuli predicts good therapeutic effects of antidepressants in MDD patients. A facial stimuli-task fMRI study showed that the severity of depression is positively correlated with the response of the right visual cortex to sad stimuli and negatively correlated with the response of the left visual cortex to happy stimuli in the early stage of treatment.

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After treatment, a decrease in the response of the right V1 to sad rather than happy stimuli is associated with a decrease in symptom scores [45]. In another study, two weeks of venlafaxine treatment increased the regional activity of the previously unresponsive right secondary visual cortex in MDD patients during the presentation of positive images under fMRI [46]. After receiving 14 sessions of cognitive behavioral therapy (CBT), MDD patients completed tasks including emotional response and emotional regulation under fMRI. Compared to the baseline before treatment, the down-regulation of BOLD activity in the precuneus, occipital lobe, and middle frontal gyrus predicts a better efficacy of CBT [47]. Interestingly, unconventional antidepressant treatments also have an impact on the visual cortex. In a double-blind placebo-controlled crossover trial, Furey's group found that the activation of the middle occipital lobe (MOC) in control participants was significantly enhanced compared to patients with depression at baseline before scopolamine treatment [48]. MDD patients at baseline only show activation of the bilateral MOC when performing facial emotional working memory rather than facial recognition tasks, and the degree of MOC activation is positively correlated with the curative effects of scopolamine [48]. This study proposed that the MOC is central to the curative effect of rapid-onset antidepressants such as scopolamine, revealing that the MOC may be the neural basis of depression or antidepressant effects [48]. In addition, a long-term follow-up fMRI study of alleviated patients showed that the reactivity of the visual cortex is inversely correlated with recurrence in these patients, including distress tolerance. Compared with HCs, MDD patients in remission show a more obvious trade-off in the reactivity between the medial prefrontal cortex and visual cortex than HCs. The reactivity difference score between the two brain regions can better predict the recurrence of depression [49].

It is worth noting that although the above studies found dysfunction of the visual cortex in MDD through different visual emotional tasks, none of them involved treatment in the visual cortex. Our group designed a randomized, double-blind, and controlled clinical trial in which we used near-infrared neuronavigation, based on magnetic resonance, and demonstrated for the first time the antidepressant effect of targeting the visual cortex with transcranial magnetic stimulation (rTMS). Based on this trial, we proposed that the abnormal neural activity of the visual cortex is not only involved in emotional regulation but is also associated with a disorder of information processing and processing of depression [50]. In addition, we found that five consecutive days of rTMS in the visual cortex can improve the symptoms of MDD patients and increase the expression of circulating RNA of the dymeclin (DYM) gene (circDYM) in the

plasma, and the expression of circDYM in MDD patients at baseline can effectively predict the efficacy of rTMS in the visual cortex [51].

Cerebral Blood Flow Changes

Studies have shown that the incidence of adolescent depression has increased sharply, the recurrence rate is high, and the functional prognosis is poor in child/adolescent MDD [52, 53]. As early as 1999, Bonte's group had found occipital lobe perfusion defects in adolescent MDD patients during regional cerebral blood flow (rCBF) single-photon emission computed tomography (SPECT) [54]. Two years later, the same research group compared the rCBF of children with MDD and healthy children and found that some adolescent MDD patients had a marked defect in occipital lobe posterior blood flow, and the defect was usually symmetrical, while other patients preferentially showed a right frontal lobe rCBF defect [55]. The reason for this difference is unclear, and follow-up research is needed to further explore the relationship between CBF and MDD in children/adolescents. The occipital CBF in adults with MDD is also abnormal. A retrospective study based on SPECT of 98 inpatients showed that MDD patients had decreased bilateral occipital CBF unrelated to age [56]. However, an abnormal increase of rCBF in the occipital cortex (bilateral B17, B19, and left B18) has been reported in unipolar MDD [57]. These contradictory results might be explained by the fact that the clinical presentation may be one of the influencing factors for rCBF in the occipital lobe of MDD patients. Psychological pain is one of the easily neglected symptoms of depression. In MDD patients with a high degree of psychological pain, the cerebral perfusion of the right DLPFC, occipital lobe, inferior frontal gyrus, and left inferior temporal gyrus is relatively increased, while the medullary perfusion is reduced [58].

Changes in Visual Cortical Neurotransmitters and Metabolism

The level of γ-aminobutyric acid (GABA) in the occipital lobe was first reported in 1999 to be 52% lower in patients with MDD than HCs [59]. Subsequently, a correlation between neurotransmitters and depression was consistently found in different populations. Intravenous injection of the selective serotonin reuptake inhibitor (SSRI), citalopram (10 mg), produced an increase of 35% in the relative GABA concentration in the occipital lobe, as measured by proton magnetic resonance spectroscopy (1H-MRS), suggesting a direct action of SSRIs on cortical GABA neurons rather than a secondary consequence of mood improvement [60]. 1H-MRS showed that the level of glutathione in the occipital lobe of adolescent MDD patients is lower than that

of healthy adolescents [61]. In addition to the decrease in GABA concentration [62], there is also an abnormal increase in the glutamate level in the occipital lobe of adult MDD patients [7, 63]. A study comparing the 1H-MRS data of patients with treatment-resistant depression (TRD) and non-TRD patients found that the level of GABA in the occipital lobe of TRD patients is 16.4% lower than that of non-TRD patients, suggesting that abnormality of the glutamate/glutamine/GABA cycle may be more serious in TRD patients [64]. Primary insomnia and MDD are closely associated in cross-sectional and longitudinal studies. 1H-MRS results showed that patients with primary insomnia have reduced GABA in the occipital lobe, similar to MDD patients [65]. It is worth noting that a recent study showed that patients with depression have abnormal visual motion, which is due to marked deficiencies in the concentrations of the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA in the brain area with sensory functions (the middle temporal lobe complex) [29]. Furthermore, studies have shown that the severity of anhedonia in MDD patients is negatively correlated with the level of glutathione in the occipital lobe, suggesting that there may be abnormal oxidative stress in the occipital lobe of MDD patients [66]. In addition, a study analyzing the postsynaptic brain GABA receptor of MDD patients with [^{123}I] iomazenil SPECT demonstrated that although the decrease in GABA level in the occipital lobe of MDD patients is reproducible, there is no significant abnormality in the postsynaptic GABA receptors of the occipital lobe [67].

Different antidepressant therapies have potentially different mechanisms, and their effects on the level of GABA in the occipital lobe are also different. Eleven MDD patients who took oral SSRI antidepressant treatment for 2 months showed significantly improved levels of GABA in the occipital lobe [68], while electroconvulsive therapy in 8 MDD patients tripled the concentration of GABA in the occipital lobe [69]. However, there was no significant change in GABA levels in the occipital lobe of MDD patients receiving 12 weeks of CBT [70]. A significant decrease in GABA levels in the occipital lobe also exists in recovered MDD patients, significantly correlating with the recurrence rate of depression [71], while glutamate and glutamine levels are significantly higher in recovered MDD and BD patients [72]. However, the finding of a low occipital GABA in MDD has been challenged. In 2015, Godlewska et al. combined 1H-MRS with ultrashort echo time "special" technology to measure the levels of GABA, glutamate, and glutathione in the occipital lobe of MDD patients [73]. This study found no significant difference between the levels of GABA and glutamate in the occipital lobe of MDD patients and HCs, but the level of glutathione in MDD patients was significantly lower than that in HCs [73]. After 6 weeks of SSRI treatment, the depressive symptoms of MDD patients improved,

but with no significant change in the GABA, glutamate, and glutathione levels [73].

As early as 1983, it was reported that the binding of imipramine in the occipital lobe of MDD patients was significantly reduced compared with HCs. The number of imipramine binding sites was reduced while receptor affinity remained normal [74]. In 2000, a small sample study found that treatment with the SSRI fluvoxamine can significantly improve the clinical symptoms of MDD patients and improve the uptake of [^{18}F] fluoro-ethyl-spiperone ([18F] FESP) in the frontal and occipital lobes [75]. The increased binding of [18F]FESP may reflect a modification in serotonin (5-HT) receptor 2 binding capacity secondary to changes in cortical 5-HT activity [75]. A resting positron emission computed tomography (PET) readouts study showed that 8 weeks of treatment with the SSRI antidepressant citalopram improved emotional symptoms and cognitive function while increasing glucose metabolism in the occipital lobe of LLD patients [76]. Similarly, acute citalopram (40 mg) treatment also clearly elevated glucose metabolism in the occipital lobe of LLD patients, and chronic treatment with citalopram for 8 weeks increased glucose metabolism in the left occipital lobe [77]. In addition, PET-CT results showed that 5-HT2a receptor binding potential in the occipital lobe of MDD patients with remission for at least 6 months increased by an average of 19% compared with HCs [78]. The binding potential was positively correlated with the dysfunctional attitude score of MDD patients during remission [78].

Clinical Neurophysiology Studies of the Visual Cortex

The steady-state visual evoked potential has been used to detect attention bias and the capacity of working memory (WM) has been evaluated before and after the induction of negative emotion. In the study by Woody et al., rMDD women (a subgroup of MDD with a higher risk for recurrence) showed difficulty in suppressing attention to all emotional disruptors before negative emotion induction. The strongest effect was seen with negative distractors (sad faces). Among all women with rMDD, lower WM ability indicates that it is more difficult to suppress attention to negative and neutral distractors [79].

Many studies have shown that ketamine has a rapid and efficient antidepressant effect [80]. A recent meta-analysis has shown that intravenous ketamine has a better antidepressant effect than nasal spray [81]. A randomized, single-blind, crossover study using magnetoencephalography (MEG) evaluated task-related high-frequency oscillations of the visual and motor cortices in 20 HCs after intravenous injection of 0.5 mg/kg ketamine and found that ketamine increased the visual cortex β and γ

band amplitude, but reduced the γ peak frequency [82]. Animal studies have shown that enhancement of the γ frequency band is associated with the disinhibition of cortical pyramidal cells [83]. Thus, regulation of the γ oscillation frequency by ketamine may underlie the basis of its rapid antidepressant effect and deserves further study. Ketamine can also quickly alleviate the depressive symptoms of patients with TRD. A double-blind, crossover, placebo-controlled study compared a single intravenous injection of ketamine hydrochloride (0.5 mg/kg) and a normal saline placebo in 19 untreated TRD patients and 15 HCs [84]. MEG data collected before and 6–9 h after injection showed that ketamine administration accelerated the transmission of GABA and N-methyl-D-aspartate in the early visual cortex (V1–V3), and led to direct and indirect changes in local inhibition of the early visual cortex and inferior frontal gyrus [84]. Moreover, reductions in depressive symptoms in TRD participants after treatment with ketamine are associated with faster α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid transmission and increased gain control of spiny stellate cells in the early visual cortex [84]. Although many 1H-MRS studies have shown that GABA concentration in the occipital lobe of MDD patients is significantly reduced, a MEG study of 19 female rMDD patients and 18 HCs showed no abnormality in the GABA system of both groups, but the early visual evoked response in the rMDD group was significantly impaired [85].

Clinical Histological and Molecular Biological Studies of the Visual Cortex

The reduced occipital lobe GABA level reported in 1H-MRS studies, although not found in MEG studies, is supported by histological examination. Using a three-dimensional cell counting probe on postmortem samples, a reduction in the density of calbindin-immunoreactive GABAergic neurons in layer II of the occipital lobe of MDD patients has been found [86]. Intriguingly, the size of these GABAergic neurons was unchanged in MDD patients compared to controls [86]. This study suggested that a deficit in cortical GABAergic interneurons may contribute to the lower GABA levels reported in neuroimaging studies of MDD patients.

A study using enzyme-linked immunosorbent assay in autopsy brain tissue samples showed that compared with drug-naive MDD patients and HCs, the level of brain-derived neurotrophic factor (BDNF) in the parietal cortex of treated MDD patients was significantly higher, while neurotrophic factor 3 levels in the parietal lobe, temporal occipital lobe, cingulate gyrus, thalamus, putamen, and caudate nucleus were also significantly increased [87]. This study revealed that antidepressant drugs mediate the changes in neural plasticity through the action of neurotrophic factor (NTF) [87]. These clinical studies suggest that GABAergic interneurons and NTF levels are altered in the visual cortex of depressed patients (Fig. 2). However, whether these abnormalities in the visual cortex are fundamentally involved in the etiology of MDD remains to be addressed.
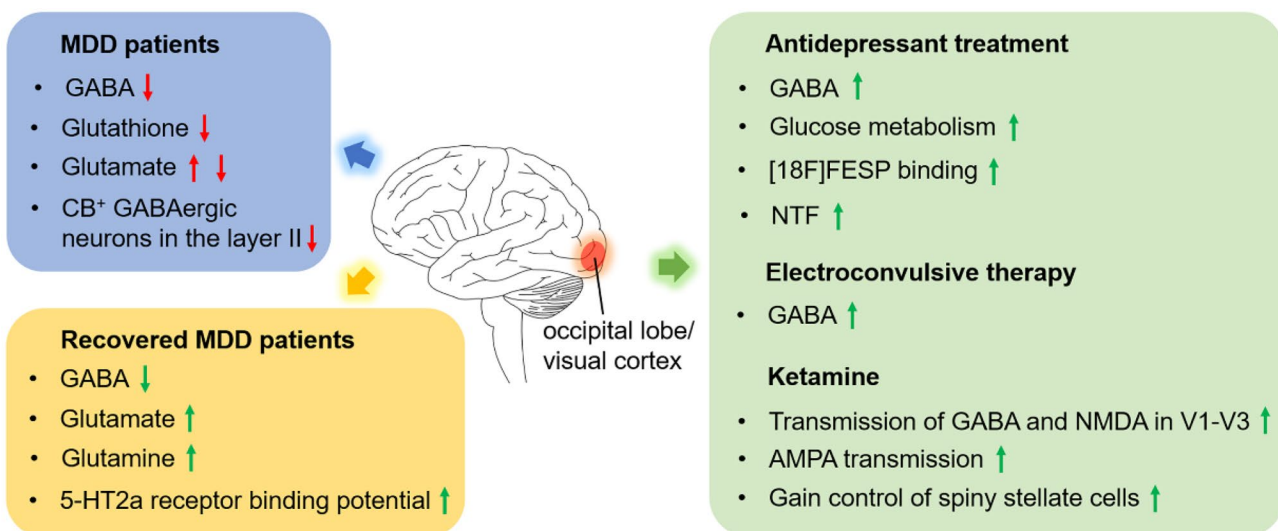

Fig. 2 Visual cortical neurotransmitter, metabolism, and molecular changes in depressed patients. The histological and molecular changes of the visual cortex in depressed patients or after antidepressant treatment. Red upward arrows indicate an increase in depression; red downward arrows indicate a decrease in depression; green upward arrows indicate an increase in recovered MDD or after therapy; green downward arrows indicate a decrease in recovered MDD or after therapy. 5-HT, serotonin; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CB, calbindin; [18F] FESP, [18F] fluoroethyl-spiperone; GABA, γ-aminobutyric acid; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; NTF, neurotrophic factor; V1, primary visual cortex; V3, visual association cortex.

Preclinical Studies

Animal models are valuable tools in which to explore mechanisms of visual cortical dysfunction in the context of depression (Fig. 3). Preclinical studies have shown that depression may lead to disorders of the sensory perception systems, including olfactory, auditory, visual, or gustatory [88]. Manganese-enhanced magnetic resonance imaging in mouse models of interferon-induced depression showed that the manganese uptake in the visual cortex was significantly lower than that in the control group, suggesting a dysfunction of the visual cortex [89]. In a rat depression model established by bilateral olfactory bulb resection, chronic administration of citalopram significantly diminished the regional cerebral glucose utilization [90]. Rs-fMRI showed that the regional homogeneity (ReHo) of the visual cortex in rats with chronic unpredictable mild stress (CUMS) was increased, while telmisartan, an adjuvant drug for MDD with memory impairment, reversed the abnormal changes of the visual cortex [91]. Based on ReHo analysis, the spontaneous activity of the visual cortex in CUMS mice is impaired and exercise significantly reduces CUMS-induced depression-like behaviors and increases the spontaneous activity in the visual cortex [92]. Male rats with both depression and erectile dysfunction are considered to have non-organic erectile dysfunction. fMRI in these animals indicated a central pathological mechanism of the visual cortex [93].

An imbalance of neuronal excitatory (E) and inhibitory (I) signals in the 5-HT system of the neocortical network can lead to serious neurological diseases, including MDD. Patch clamp studies have found that 5-HT in the visual cortex can regulate the balance of E-I signals, suggesting its role in multisynaptic sensory circuits [94]. Liu and coworkers established a new mouse model of early-life chronic mild stress without anxiety or depression-like behavior in adulthood and found that these mice showed normal maturation of visual acuity and orientation/direction selectivity, while their visual cortical neurons displayed lower spatial frequency and higher temporal frequency than control mice [95]. Thus, early adverse experiences may have a lasting effect on the visual development of mice in a sex-dependent manner [95]. Intake of the SSRI antidepressant fluoxetine for four weeks can restore the ocular dominant plasticity and promote the recovery of visual function in adult amblyopic rats. These effects are accompanied by decreased inhibition in the cortex and increased BDNF expression in the visual cortex [96].

Fragile X pre-mutation phenotypes include anxiety, depression, social phobia, and memory defects. Mouse models of this condition have abnormal morphology in the pyramidal neurons of layer II/III of V1, resulting in abnormal synaptic circuits. This may be a fragile X-related characteristic lesion of the nervous system [97]. The orphan nuclear receptor gene *Nurr1* is involved in the differentiation, maturation, and
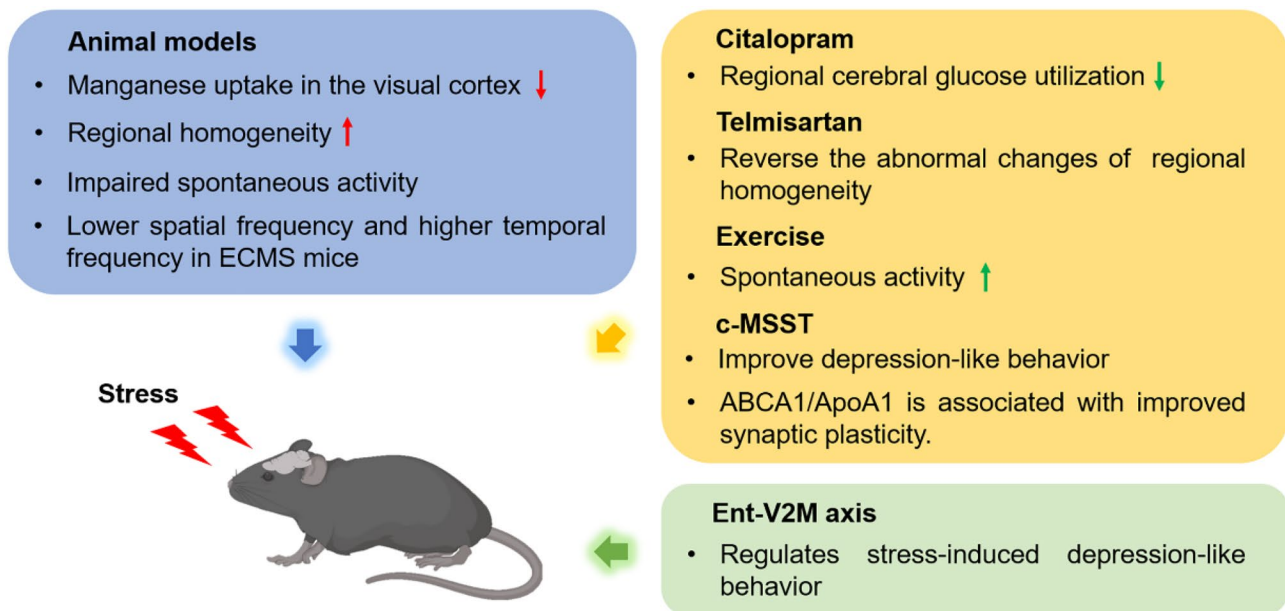

Fig. 3 Visual cortical dysfunction in animal models of depression. The changes of neuronal activity, metabolism, synaptic plasticity, and neural circuits in the visual cortex in depressive animal models or after antidepressant treatment. Red upward arrows indicate an increase in animal models; red downward arrows indicate a decrease in animal models; green upward arrows indicate an increase after therapy; green downward arrows indicate a decrease after therapy. ABCA1, ATP-binding cassette transporter A1; ApoA1, apolipoprotein A1; c-MSST, combined magnetic stimulation system treatment; ECMS, early-life chronic mild stress; Ent, entorhinal cortex; V2M, secondary visual cortex.

maintenance of dopaminergic neurons. When healthy adult mice are forced to swim, the expression of *Nurr1* is upregulated rapidly and widely throughout the brain at 30 min or 3 h later, including the primary and secondary visual cortices, suggesting that the visual cortex is involved in the stress response through the *Nurr1* gene [98].

In 2022, our research group independently developed a new precision magnetic stimulation technology, combined magnetic stimulation system treatment (c-MSST), and treated the left V1 regions in two mouse models of depression, CUMS and lipopolysaccharide-induced. The magnetoelectrical effect generated significant improvement in depression-like behavior over five days. We also analyzed the disease/efficacy-related protein, apolipoprotein A1 (ApoA1), and its interacting protein, ATP binding cassette transporter A1 (ABCA1), in the V1 region by high-throughput omics technology, and demonstrated that ABCA1/ApoA1 is associated with improved synaptic plasticity in the visual cortex at multiple levels, thus contributing to antidepressant efficacy [99].

Neural Circuit Research in Depressive Animal Models

In a mouse model of depression induced by long-term exposure to aversive stimuli or chronic social failure stress, light therapy can improve depression-like behavior with observable changes in synapses connecting the retina and the lateral habenula [100]. Although the study did not evaluate the role of the visual cortex in the antidepressant effect of light therapy, as the most important cerebral cortex for receiving and processing visual information, its role deserves further study.

It is worth noting that a new study in 2022 showed that neurons in layer 5A of the mouse entorhinal cortex (Ent) independently project to the medial area of the secondary visual cortex (V2M). Chronic social frustration stress is widely used to induce depression-like animal models with two phenotypes: stress-resistant and stress-sensitive. In stress-sensitive mice, the activity of neurons in layer 5A of the Ent is significantly decreased. Inhibition of the Ent-V2M pathway induces depression-like behavior in stress-resistant mice, while activation of this pathway in stress-sensitive mice significantly alleviates depression-like behavior. These results show that the Ent-V2M axis plays an important role in stress-induced depression-like behavior [101].

Conclusion

The etiology and mechanism of depression are complex. It is urgent to deeply explore the pathophysiological mechanism of depression. We believe that the importance of MDD visual cortical disorders is seriously underestimated. This review summarizes abnormalities in visual cortical structures and perfusion, information filtering, visual processing, spatial inhibition, motor visual perception, attention bias hypotheses such as visual emotion processing disorder, abnormalities in neurotransmitter levels, metabolism of the visual cortex, the connection of visual grid function, synaptic plasticity, and neural circuits. Clinical and preclinical findings suggest that the alterations of the visual cortex structure and function are closely associated with depression-related emotions, and antidepressants can change the electrophysiological characteristics and neurotransmitters of the visual cortex, thus extending our present insights of the possibility of visual cortical abnormalities in the pathogenesis and antidepressant mechanism of depression.

Although more and more evidence shows a relationship between MDD and visual cortex disorders, the research is still in its infancy, with many problems and limitations. First, most studies are small-sample clinical trials, and only a few clinical studies have used longitudinal designs, which may have a certain false positive rate and lead to partially contradictory results. Prospective and large-scale clinical trials should be designed to obtain more accurate results. Longitudinal studies are needed to evaluate how changes in clinical phenotype affect imaging or neurophysiological findings. Second, there is no unified standard for the design of visual tasks for participants, so consistent and comparable results are difficult to obtain. Optimizing visual tasks and finding the corresponding representation of different types of visual disorders and MDD are the key problems to be solved in the future. Third, at present, there are only a few studies directly targeting the visual cortex. In the future, techniques such as rTMS, theta burst stimulation, or c-MSST can be used to directly intervene in the visual cortex. Viral vectors or nanomaterials can be used to deliver drugs to the visual cortex, so as to find direct evidence of the involvement of the visual cortex in MDD and develop new intervention strategies. Finally, current studies on the visual cortex remain superficial. Most of the studies involve the whole occipital lobe and the visual cortex. In addition, it remains unclear whether positive findings are consequences and/or causes of depression. The possible interaction between different cell types in the visual cortex is a new research direction worthy of further exploration. Exploring the molecular mechanisms of depression to discover more effective, rapid, and precise targets for antidepressant drugs will become a new hot spot in the field of depression research. Identification of baseline biomarkers that predict and monitor the treatment response in MDD patients will provide important tools for personalized medicine.

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