Commentary

Biological Psychiatry

Unraveling Circuit Mechanisms of Depression Remission and Relapse Vulnerability

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Major depressive disorder (MDD) is among the most prevalent and burdensome mood disorders, affecting more than 300 million people worldwide, and is the leading contributor to years of life lived with disability (1). Beyond the mystery of the neurobiological pathology underlying the clinical disturbances and behavioral deficits, the most important challenges in the clinical management of MDD are treatment and prevention. Currently, pharmacotherapy and psychotherapy are the most widely used treatment strategies for MDD. Unfortunately, only 30% of MDD patients gain remission after first-line therapies, and one-third of individuals are considered treatment resistant and fail to respond to at least two categories of antidepressant treatments. More seriously, a high rate of approximately 85% of patients with MDD who had recovered from an acute episode of major depression experienced recurrence, as reported in a prospective study with a 15-year follow-up (2). Over the past decades, with advances in neuroimaging techniques, considerable efforts have been made to explore the neural mechanism of the remission of MDD and to identify biomarkers to optimize treatment and improve the prognosis of this disorder (3).

In the current issue of *Biological Psychiatry*, Zhang *et al.* (4) present an example of how neuroimaging advances our understanding of the neural mechanisms of current and remitted MDD by combining cross-sectional and longitudinal experiments in a relatively large sample. In the cross-sectional study, 117 medication-naive patients with first-episode current depression, 45 remitted patients who had experienced only one episode of depression, and 102 healthy control subjects conducted an ecologically valid balloon analog risk task paradigm during a functional magnetic resonance imaging scan. Longitudinally, 26 patients with current MDD who experienced remission after 8 weeks of antidepressant treatment completed the same experiment a second time. Their task performance and brain activation were compared to distinguish the symptomatic state–dependent and persistent state–independent brain responses to negative decision outcomes from risky decision making. Zhang *et al.* demonstrated that compared with healthy controls, both current and remitted MDD patients exhibited higher brain activation in the ventral anterior cingulate cortex (vACC) in response to negative outcomes. However, hyper-responses in the amygdala were found only in the current MDD patients, and amygdala hyperactivity, but not vACC hyperactivity, was associated with depressive scale scores in current MDD patients. The subsequent longitudinal experiment confirmed the baseline finding that the hyperactivity in the amygdala resolved in the remitted MDD patients who had received 8 weeks of antidepressant treatment. These findings indicate that amygdala hyperactivity is a symptomatic state–dependent brain response pattern, while vACC hyperactivity is a persistent state–independent pattern in MDD. This kind of exploration is beneficial, as understanding the underpinning of differentiated neural mechanisms between current and remitted MDD patients not only enables the identification of biomarkers for effective treatment but also provides clues for preventing relapse.

A longitudinal design is particularly important for the identification of changes in brain activities that are linked to antidepressant treatment effects and the investigation of imaging biomarkers for treatment evaluation. The results of the longitudinal comparisons in the study by Zhang *et al.* (4) suggest that the hyper-response of the amygdala to a negative outcome can be modulated by selective serotonin (5-HT) reuptake inhibitors. The projections of 5-HT in the brain originate from the stem raphe nuclei, extending mainly to the cerebellum, subcortical nuclei, and prefrontal cortex. This pathway is involved in numerous physiological processes, particularly the regulation of emotions. The amygdala, as a critical node in the pathway, is closely associated with the processing of negative emotions and the experience of loss events and is prominently modulated by the neurotransmitter 5-HT, playing a key role in the development of depression symptoms. In addition to the hyper-response to negative outcomes shown in the study by Zhang *et al.*, numerous longitudinal studies have provided evidence that different imaging metrics of the amygdala can be modulated after antidepressant or neural stimulation treatment, including responses to different emotional tasks and intrinsic functional connectivity. These findings together suggest that the amygdala may serve as a state-dependent signature of the treatment response in patients with MDD. In addition to the amygdala, other brain regions and circuits can also be modulated during depressive remission. For example, the hyperconnectivity between the dorsolateral and medial prefrontal cortices is regulated after 8 weeks of antidepressant treatment using selective serotonin reuptake inhibitors, and its longitudinal changes are correlated with the reduction in depressive symptoms (5). At the network level, the default mode system relating to the processing of inner feelings, such as self-referential, autobiographical, and memory retrieval processes, is widely reported to be disrupted in MDD (6,7). The default mode system is also considered a potential network-based biomarker in that its connectivity profile is capable of classifying current and remitted MDD patients (7) and predicting follow-up treatment effects based on its baseline connectivity patterns (6).

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Another important issue is why many remitted MDD patients relapse and develop recurrent and even chronic major depression. The vACC has been documented as a critical node in the cortical-striatal-pallidal-thalamic network that is involved in emotion processing and modulation, as well as chronic stress. Hyperactivity, dysfunctional connectivity, neuronal and synaptic atrophy, and alterations in glutamate and 5-HT metabolism collectively suggest that the vACC is an important hallmark of MDD. Although the direct evidence was not proven by using longitudinal recurrence tracing in remitted MDD patients, Zhang *et al.* (4) provided evidence that the hyper-response in the vACC is persistent and cannot be modulated during antidepressant treatment. Thus, the abnormal activity in the vACC could be related to depression relapse. Using task-free functional magnetic resonance imaging data, one longitudinal study reported that intrinsic interhemispheric functional connectivity in the vACC distinguished the resilient MDD patients from the recurring episode patients and healthy control subjects but was not associated with residual depressive symptoms (8), which offers independent evidence for the nexus between the vACC and MDD relapse. Moreover, the vACC has been proposed as a potential intervention target in deep brain stimulation therapy for patients with treatment-resistant depression (9). Based upon localizing the left dorsolateral prefrontal cortex having the most negative functional connectivity with the vACC, a recently developed transcranial magnetic stimulation treatment protocol achieved a high remission rate of 90.5% in treatment-resistant patients with MDD (10). Notably, a clear and consistent conclusion is still limited due to the small sample size, high heterogeneity among the patients, and variability in the imaging analytic methodology.

There are several important issues to be further considered. First, the work of Zhang *et al.* (4) was based on the regional neural response to a risk decision task. The response of other cognitive domains to the task paradigm and the task-free functional connectivity of the amygdala and vACC relating to depression remission remain to be elucidated. Second, although the persistent hyper-response of the vACC in recurrent MDD patients was observed after escitalopram therapy in the study by Zhang *et al.*, whether vACC activity can be modulated by other kinds of antidepressants remains unclear. Third, there is high heterogeneity in both clinical symptoms and brain alterations among patients with MDD. A large variation in the hyper-response of the vACC may exist among different patients with remitted MDD. Thus, exploring individual differences and subtypes in MDD based on the fusion of neurobiological and clinical features would provide a distinguished understanding of biological mechanisms and facilitate the development of specific and effective intervention targets for different types of patients. Fourth, the human brain works as an integrated network in parallel to regional activation. Recent neuroimaging connectomics studies have suggested that MDD involves faulty wiring in both the functional and structural brain networks (3). Future studies scrutinizing the network connectivity patterns in MDD can provide insights into the specific circuit organization of these critical nodes that are associated with MDD remission. Finally, most of the MDD studies were based upon small research sample sizes, which limited the statistical power and reproducibility. The establishment of large-scale multimodal imaging cohort studies (6) could offer valuable resources and opportunities for elaborating on the neurobiological mechanisms underpinning depression remission and exploring valid biomarkers for treatment evaluations and the prevention of recurrence.

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Article Information

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