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Cognitive Changes and Brain Structural Plasticity under Long-Term Negative Emotions: Research Progress and Causal Controversies

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Abstract. Depression, fear, and anxiety are typical negative emotions. If these emotions persist for a long time, they can lead to cognitive biases and physical discomfort. Two common clinical subtypes are generalized anxiety disorder (GAD) and major depressive disorder (MDD). Whether these emotions causally affect structural plasticity and neural circuit function—and if so, how—remains an open question. Prior work has combined brain imaging, non-invasive brain stimulation (including Repetitive Transcranial Magnetic Stimulation), and drug intervention data to map the structural and circuit changes linked to different negative emotions. The prefrontal-amygdala circuit appears central to negative emotion processing, yet the brain changes linked to depression, anxiety, and fear differ. Because cross-sectional studies capture only one time point, they cannot resolve causality—brain abnormalities may be pre-existing traits, or they may emerge secondarily from persistent emotions. Non-invasive brain stimulation and pharmacological interventions can modulate neural circuits, which supports their potential as interventions. A single scan gives only a snapshot. It cannot show whether negative emotions reshape the brain over time, or whether pre-existing brain features shape those emotions. Longitudinal tracking of the same individuals across multiple time points, with control groups for comparison, would help clarify it.

Keywords: Depression, anxiety, fear, brain structural plasticity, neural circuits

1. Introduction

In today's highly competitive society, anxiety, depression, and fear have become common psychological experiences anxiety, depression, fear and many other negative emotions have become common psychological experiences among the general population, and various groups have begun to pay more and more attention to their own mental health. Persistent negative emotions do not simply stay at the level of feeling, but may also compress brain neurons to further change the brain structure. Therefore, exploring the impact of negative emotions on brain structure has become an important starting point for understanding the psychological dilemma of modern society, and also

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provides a physiological basis for the clinical aspects of neuroscience. The breakthrough in scientific instrument technology has given academic research an operable tool. With the help of brain imaging technologies such as nuclear magnetic resonance imaging, it is confirmed that the emotional state is closely related to the neural structure and functional plasticity of the brain.

Evidence on this topic remains limited because the relevant fields are still developing. Whether long-term negative emotions affect the brain structure or different brain structures cause people to fall into negative emotions for a long time, at present, there are not enough experimental research results to clearly confirm the causal relationship between the two.

This article will summarize the changes in the brain structure under some studies from the three typical negative emotions of anxiety, depression and fear to prove that "negative emotions affect the brain structure", and explain why the relevant changes in brain structure can cause brain damage. It provides a theoretical basis for subsequent efforts to regulate emotions and maintain brain health.

2. Depression

Depression can leave individuals in a prolonged state of self-denial and low mood, and may be accompanied by insomnia, diarrhea, mental retardation and other conditions. Without timely intervention, these symptoms may trigger a vicious cycle, which can impair the physiological structure of the brain (most structural changes are reversible).

Compared with ordinary people, Patients with major depressive disorder show hyperactivation of the Hypothalamic–Pituitary–Adrenal Axis axis and elevated glucocorticoid concentrations in the blood, which causes neurotoxicity due to excessive activation of the prefrontal cortex of ordinary people (especially the dorsal lateral frontal lobe Dorsolateral Prefrontal Cortex (dlPFC), the medial frontal lobe vm-PFC). This neurotoxicity causes neuronal atrophy and substantial synaptic loss, resulting in a significant decrease in prefrontal gray matter volume.

The electroencephalogram (EEG) in the resting state indicates that patients with depression may exhibit asymmetry in the activity of the frontal lobe [1]. This difference in neural activity can be combined with phenomena such as weakened responses to positive stimuli, decreased interest, reduced pleasure experiences, and decreased performance in other functions in these patients. The left hemisphere of the brain is responsible for processing positive emotional information, and the right hemisphere of the brain is responsible for processing negative emotional information. If there is excessive negative information to be processed for a long time, the right hemisphere's emotional-processing system may become overloaded by the sustained demand. However, the left hemisphere of the brain hardly needs to work, and this difference will directly stimulate the prefrontal structure of the brain. Under the condition that the forehead of the brain of most depressed patients is asymmetrical, it has been confirmed that depression does affect the structure of the brain.

After frontal lobe injury, the amygdala cannot get enough inhibition and regulation from the frontal lobe. In the depressive emotional mechanism discussed in this article, the amygdala is mainly involved in the identification and processing of external emotional stimuli, so its activity changes may directly affect the individual's response to negative emotional information. At present, when the inhibitory and regulating effects of the frontal lobe on the amygdala are weakened, the amygdala may show a stronger response to negative stimuli, making it easier for individuals to have persistent or enhanced negative emotional experiences.

In a study of children and adolescent patients with depressive disorder, it was found that the amygdala-related functional connection may be abnormal [2]. For example, the connection between the amygdala and the cingulate gyrus, parahippocampal gyrus, middle temporal gyrus and other areas weaker than that observed in healthy controls. In the face of negative emotional feelings that

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weaken the inhibitory effect of the frontal lobe on the amygdala due to persistent excessive depression information, it is more difficult for people to control their instinctive impulses rationally in the face of negative stimuli, and there is no way to correct the wrong cognition, so they fall into a vicious circle again.

3. Anxiety

Most studies of brain structure in anxiety disorders report abnormalities in the prefrontal-limbic circuit, but there is currently no unified conclusion regarding the direction of gray matter changes or the affected brain regions. Zhu et al. found abnormal gray matter volume in multiple brain regions of generalized anxiety disorder (GAD) patients, and some indicators correlated with treatment efficacy [3]. Baseline brain structure may predict treatment response. In addition, the magnitude of gray-matter deviation could serve as a candidate indicator for impaired brain-plasticity levels [3]. However, such correlations are affected by the severity of initial symptoms, and baseline symptom variables need to be controlled in studies to verify their independent predictive value [3]. Yu et al. compared healthy controls with patients who had GAD or major depressive disorder (MDD) [4]. Both GAD and MDD showed overlapping brain changes: more gray matter in the left putamen, but less in the left middle frontal gyrus and postcentral gyrus [4]. Only the MDD group showed a decrease in right superior frontal gyrus gray matter. This decrease was positively correlated with symptom severity, which suggests that the right superior frontal gyrus is specifically involved in depression [4]. Anxiety-associated structural abnormalities are focused in the circuits related to worry and alertness [4].

Zhang et al. synthesized Repetitive Transcranial Magnetic Stimulation (rTMS) findings in GAD and highlighted the frequent co-occurrence of structural reorganization and functional connectivity remodeling [5]. Functional changes may therefore indirectly reflect altered brain plasticity [5]. At the same time, they cautioned against assuming a causal link between treatment and structural recovery [5]. Most studies, however, collect imaging data only once. It therefore remains unknown whether pre-existing structural features predict treatment outcomes, or whether treatment-induced effects alter brain structure [5]. Gray-matter measurements may potentially be complicated by pharmacological drugs [5]. The observed "recovery" should therefore be interpreted cautiously in biological terms [5].

There are inherent limits to cross-sectional studies. They are unable to identify whether anatomical abnormalities are secondary changes brought on by chronic worry or pre-existing predispositions [3-5]. The separation of anxiety-specific neural markers is further complicated by the high comorbidity of depression and anxiety, and cross-sectional data cannot establish the causative direction of cross-disease brain alterations. In their pediatric sample, Gold et al. proposed that adolescents' prefrontal-limbic circuits are undergoing a crucial growth stage [6]. This process may be susceptible to anxiety-related factors, which could lead to a series of structural alterations in the brain [6]. Longitudinal cohort studies are still required to validate this concept [6]. Future studies should distinguish between experience-dependent alterations, compensatory remodeling, and baseline predisposition characteristics using multi-time-point imaging, multi-group control designs, and follow-up of high-risk populations [3-6]. Future study will focus on elucidating the conditions and timing of the bidirectional dynamic link between anxiety and brain structure [3-6].

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4. Fear

Abnormal fear cognition is widely documented to be closely linked to altered brain structural plasticity and neural circuit dysfunction. The abnormal fear cognition referred to in this article includes threat recognition bias, enhanced fear generalization, impaired extinction, and persistent fear memory, all of which are inseparable from changes in brain structural plasticity and dysfunction in neural circuit functions. On the one hand, existing evidence links structural changes in key regions of the fear circuit to abnormal fear cognition. This line of evidence further indicates that the structural characteristics of key brain regions are associated with abnormal fear cognition, but whether they constitute a direct neural basis still needs to be determined by combining longitudinal and intervention results from both human and rodent studies. On the other hand, the development of non-invasive brain stimulation and drug interventions also provides experimental evidence for the improvement of abnormal fear cognition.

Clem and Schiller separated extinction from reconsolidation by asking what happens to the original fear trace [7]. In extinction, that trace survives; a new safety memory is formed, and Ventromedial Prefrontal Cortex (vmPFC) activity helps suppress fear expression. In reconsolidation, the trace itself is modified, but only after retrieval makes it labile and open to updating. Amygdala–vmPFC plasticity is required for both, yet the two procedures engage it differently. Retrieval conditions, intervention timing, and memory strength therefore determine which route is available and how stable the result is. These two routes can coexist, which makes single-mechanism accounts of fear-memory regulation incomplete.

Borgomaneri et al. re-analyzed human Transcranial Direct Current Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS) fear-extinction experiments [8]. Prefrontal stimulation reduced return of fear in some protocols. The effect was not uniform; stimulation type, polarity or frequency, and timing changed the outcome. Zhang , in a master's thesis, reviewed non-invasive stimulation and identified the visual cortex as a separate target; because intrusive memories and fear generalization were measured under different tasks and time windows, they should not be pooled [9]. Zhou examined a pharmacological route: losartan, an angiotensin II receptor antagonist, altered amygdala-prefrontal activity and fear responses [10]. Prefrontal tDCS/TMS and losartan can change fear-related prefrontal-amygdala activity. Whether this neural change helps patients remains untested; at least in the studies reviewed here, samples were small, protocols diverged, and none reported fewer intrusive memories or less fear generalization [8-10].

All four papers deal with fear circuitry, but they ask different questions. Clem and Schiller traced how extinction and reconsolidation handle the original fear trace [7]. Extinction keeps that trace and builds a new safety memory; reconsolidation changes the trace itself, but only after retrieval makes it labile. Borgomaneri et al. combined tDCS and TMS fear-extinction studies [8]. Prefrontal stimulation weakened return of fear in some protocols, but not all. Polarity, frequency, and timing moderated the result. In a master's thesis, Zhang examined non-prefrontal targets and included the visual cortex [9]. Intrusive memories and fear generalization were analyzed separately because they were measured under different tasks and time windows. Zhou moved to pharmacology: losartan changed amygdala–prefrontal activity and fear responses [10]. Brain structure and function are often linked to abnormal fear cognition. These four papers test that link in different ways, but none alone shows how the changes produce abnormal fear cognition.

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5. Conclusion

Long-term negative emotions do more than alter mood; they can change cognition and reshape brain structure. This review focuses on three such emotions—fear, depression, and anxiety—and compares their neural mechanisms. Fear is perhaps the best-characterized case. Maladaptive fear cognition tracks with plasticity-related changes in the amygdala-prefrontal cortex circuit, and work on extinction and reconsolidation has given interventions a useful theoretical base. Depression is less straightforward. HPA-axis hyperactivation may contribute to prefrontal gray-matter atrophy and hemispheric asymmetry, and it also appears to weaken inhibitory control over the amygdala; the result can be a self-sustaining loop. Anxiety, meanwhile, is marked mainly by structural abnormalities in the prefrontal-limbic circuit, though it shares several neural alterations with depression. What remains unresolved is the direction and causal timing of gray-matter changes—whether they come first, follow later, or simply co-occur. To address this, future studies should follow longitudinal cohorts with repeated assessments, separate pure anxiety, pure depression, and comorbid samples, and accelerate clinical translation of non-invasive brain stimulation and pharmacological treatments. These studies can be integrated across the mechanism, intervention, and translation levels.

Author contribution

All the authors contributed equally and their names were listed in alphabetical order.

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