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Progress in research on effects of chronic stress on brain structure and function

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Abstract:

As a cumulative and persistent form of stress, chronic stress has been shown to have a profound impact on the structure and function of the human brain. This article reviews the neurobiological mechanisms of chronic stress acting on the brain and its key role in mood and cognitive dysfunction. Long-term activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to sustained elevation of cortisol, disrupting negative feedback regulation and causing neurotoxic damage to key brain regions such as the hippocampus and prefrontal cortex. At the same time, chronic stress can interfere with the neurotransmitter system, especially the dopamine and serotonin pathways, leading to emotional instability, anhedonia, and decreased cognitive flexibility. In addition, synaptic plasticity and functional remodeling of neural networks are also significantly affected, manifested by inhibition of long-term enhancement (LTP), abnormal enhancement of long-term inhibition (LTD), decreased synaptic connectivity, and dysregulation of emotion-cognitive circuits. These mechanisms interact to form a vicious circle that increases the risk of depression, anxiety disorders, and mental illnesses such as post-traumatic stress disorder (PTSD). A deeper understanding of the neural mechanisms of chronic stress not only helps to reveal the brain's adaptation and dysregulation response to stress, but also provides a theoretical basis for early intervention, biomarker identification and treatment strategy development.

Keywords: Chronic stress; Hypothalamic-pituitary-adrenal (HPA) axis; Cortisol; Hippocampus.

1. Introduction

Nowadays, many people from all over the stages of age are suffering chronic stress in some degrees. Scientists are exploring the relationship between chronic stress and the structure and function of the human brain, with stress stemming from diverse sources such as social pressure and employment problems [1]. This progress let human beings know more about the system and regulation of human brains under the

chronic stress, which indicates that people will have a better live and control more about their own body by learning how the body system works under such great living pressure and what kind of influence will occur when body suffer large amount of pressure [1]. Therefore, studying chronic stress provides important insights into both the adaptive and maladaptive responses of the brain.

Recent advances in neuroscience and neuroimaging techniques have deepened our understanding of how chronic stress affects brain circuits [2]. Chronic stress, characterized by its cumulative and persistent nature, exerts multifaceted effects on the brain, particularly in the hippocampus and amygdala, where structural and functional disruptions underlie deficits in emotion, memory, and cognition [2]. Moreover, the effects of chronic stress on the brain are not only limited to the structural level, but also involve changes at the functional level [3]. In addition, chronic stress is also closely related to the mechanism of various mental illnesses, such as depression, anxiety disorders, and post-traumatic stress disorder (PTSD) [3]. The occurrence of these diseases is closely related to changes in neurotransmitters, neurotransmitter receptors, and neuroplasticity in the brain [4]. Future research should also focus on identifying biomarkers that can predict individual vulnerability to stress-related brain changes [5].

In recent years, the impact of chronic stress on brain structure and function has emerged as a significant interdisciplinary research topic. Beyond directly affecting mood, memory, and cognitive function, chronic stress influences overall bodily health through complex neuroendocrine regulatory networks. For instance, prolonged stress states disrupt the rhythmicity of the hypothalamic-pituitary-adrenal axis (HPA axis), thereby upsetting homeostatic balance and leading to persistently elevated hormone levels. This prolonged hormonal burden not only diminishes neural plasticity but may also precipitate metabolic disorders and immune dysfunction. A growing body of research indicates that the interaction between stress responses and the immune system is a pivotal link in understanding the stress-disease chain. Through pathways such as inflammatory responses and cytokine release, this interaction further exacerbates brain damage and functional impairment.

Concurrently, the impact of chronic stress is not uniform, exhibiting significant variations across gender, age, and individual genetic backgrounds. For instance, some studies indicate women are more prone to emotional disorders under prolonged stress, while the elderly are more susceptible to cognitive decline. Such individual differences suggest that the mechanisms underlying stress-related brain damage may not follow a single model but rather result from the combined effects of multiple factors. Furthermore, environmental and social factors cannot be overlooked. The fast pace of urban living, workplace competition, familial pressures, and feelings of social isolation can all serve as significant triggers or perpetuators of chronic stress. While modernisation and the development of the information society have enhanced convenience, they have also substantially increased the risk of prolonged psychological tension among populations.

At the neural circuit level, chronic stress exerts particularly pronounced effects on the limbic system and prefrontal cortex. The limbic system constitutes the core region for emotional processing, while the prefrontal cortex governs higher-order cognition and emotional regulation. When the equilibrium between these two systems is disrupted by prolonged stress, individuals often exhibit excessive emotional reactivity, attention deficits, diminished decision-making capacity, and impaired impulse control. This imbalance is particularly prevalent in patients with depression and anxiety disorders, often correlating positively with symptom severity. Recent combined applications of functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have provided more intuitive evidence for these neural mechanisms.

More significantly, chronic stress is not merely a risk factor for a single disorder; it is recognised as a common pathological foundation for multiple neuropsychiatric conditions. For instance, depression, anxiety disorders, post-traumatic stress disorder, and Alzheimer's disease are all closely associated with chronic stress to varying degrees. This 'cross-disease' pathological mechanism suggests that researchers must move beyond traditional diagnostic classifications and adopt a transdiagnostic perspective to understand stress-related brain dysfunction. This approach not only deepens our understanding of the nature of these conditions but also provides new entry points for precision interventions and personalised treatment. Looking ahead, the application of multi-omics technologies (genomics, proteomics, metabolomics, etc.) and artificial intelligence methodologies holds promise for systematically unravelling the multidimensional impact of chronic stress on brain function. For instance, large-scale population cohorts and longitudinal follow-up studies may identify key biomarkers predicting individual vulnerability, while computational modelling could chart the dynamic trajectories of brain network changes under stress. Such advances will lay a robust foundation for developing novel therapeutics, optimising psychological interventions, and establishing early warning systems.

In summary, chronic stress represents not only a pervasive socio-psychological phenomenon but also a central, indispensable topic within neuroscience and psychiatric research. From molecular to systems levels, and from individual variation to population health, the deepening

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exploration of chronic stress research will offer novel perspectives on understanding the brain's complex functions. It will also play a vital role in the prevention and treatment of mental disorders, as well as in the formulation of public health strategies.

2. Clinical Implications and Future Research Directions

The effects of chronic stress on brain structure and function have far-reaching clinical implications. For example, chronic stress can lead to long-term changes in brain structure and function, increasing the risk of depression, anxiety, and cognitive impairment [5]. Therefore, understanding the mechanisms of chronic stress on the brain can help develop effective intervention strategies such as stress management, physical exercise, mindfulness meditation, and medication to improve brain health and mental health [5].

The impact of chronic stress on brain structure and function is multifaceted, involving multiple levels such as neural structure, neurotransmitters, neuroplasticity, and neurotransmitter systems [4]. These changes not only affect individual cognition, emotions and behavior, but are also closely related to the occurrence of a variety of mental illnesses [4]. Therefore, delving into the mechanisms of chronic stress on the brain is of great significance for the prevention and treatment of related diseases [5].

In addition to direct neural damage and functional impairment, chronic stress can also indirectly alter brain function by affecting the hypothalamic-pituitary-adrenal axis (HPA axis) and the autonomic nervous system [3]. Prolonged stress stimulation leads to sustained elevations in cortisol levels, and this hormonal imbalance can have significant effects on regions such as the hippocampus, amygdala, and prefrontal cortex [2]. Research indicates that elevated cortisol levels suppress neurogenesis and reduce synaptic plasticity, thereby impairing learning and memory functions [2]. Meanwhile, the amygdala exhibits hyperactivity under chronic stress, leading individuals to experience heightened anxiety, fear, and hypervigilance in emotional regulation. Weakened inhibitory function in the prefrontal cortex can result in difficulties with executive function, decision-making, and impulse control [6]. More complexly, chronic stress also alters the balance of neurotransmitters such as dopamine, serotonin, and glutamate [7]. At the molecular level, chronic stress-induced oxidative stress, inflammatory responses, and mitochondrial dysfunction are also considered important mechanisms of brain damage [8]. These changes can be partially identified through biomarkers, providing potential directions for early intervention [5].

2.1 Core Area of Impaired Memory and Mood Regulation

Chronic stress can lead to a decrease in hippocampal volume, which is due to long-term exposure to high levels of cortisol [2]. The hippocampus, a key brain region responsible for memory and emotional regulation, is reduced in size and can lead to memory dysfunction and decreased emotion regulation [2]. Chronic stress inhibits neurogenesis, the production of new neurons, in the hippocampus [2]. Neurogenesis is an important mechanism by which the hippocampus maintains learning and memory functions. Inhibition of neurogenesis can lead to a decline in hippocampal function, further affecting memory and emotion regulation [2].

2.2 The Structural Basis for Decline in Decision-Making and Executive Function

Chronic stress causes changes in synaptic density and functional connectivity in the prefrontal cortex [6]. The prefrontal cortex is responsible for executive function, decision-making, and emotional regulation, and its impaired function can lead to decreased decision-making ability and weakened emotional regulation ability [6]. Impaired function of the prefrontal cortex can lead to decreased cognitive flexibility and working memory function [6]. The prefrontal cortex, which is responsible for higher cognitive functions such as decision-making, planning, and emotional control, is impaired and can lead to cognitive decline [6].

2.3 Emotional Overactivation Is Associated With Anxiety Mechanisms

Chronic stress can lead to increased amygdala volume and activity. The amygdala, a central area of emotional processing, has increased activity that can lead to decreased emotion regulation, leading to emotional overactivation and anxiety [9]. Increased activity in the amygdala can lead to an increased stress response and reduced emotional regulation. The amygdala is responsible for emotional responses, and its increased activity can lead to emotional overactivation, leading to anxiety and emotional instability [10].

2.4 Mechanisms of Chronic Stress Influence on Brain Function

Chronic stress may lead to persistent activation of the hypothalamic-pituitary-adrenal axis (HPA axis), resulting in chronically elevated cortisol levels in the body [3]. Specifically, excess cortisol can damage neuronal structures,

leading to dendritic atrophy, reduced number of synapses, and even induced apoptosis of nerve cells [2].

Chronic stress is widely recognized as an important factor affecting the homeostasis of the neurotransmitter system. The dopamine system is downregulated, leading to anhedonia and impaired executive function [8]. Serotonin dysfunction leads to emotional instability and higher risk of impulsivity [8]. Norepinephrine and glutamate imbalances further aggravate excitatory neurotoxicity [7].

Chronic stress not only causes disturbances in the neurotransmitter system, but also profoundly alters synaptic plasticity [4]. It suppresses long-term potentiation (LTP) and enhances long-term depression (LTD), impairing learning and memory abilities [4]. At the same time, remodeling of connectivity between the DMN, limbic system, and prefrontal-amygdala pathway increases vulnerability to depression and PTSD [9].

3. Summary

To sum up, chronic stress has a profound impact on brain structure and function through multiple levels and pathways. Long-term overactivation of the HPA axis can lead to a sustained increase in cortisol levels, disrupt the negative feedback regulatory mechanism, and trigger neurotoxic effects in key brain regions such as the hippocampus and prefrontal cortex. Disorders in the neurotransmitter system, especially dopamine and serotonin imbalance, weaken emotional regulation and cognitive processing]; At the same time, chronic stress can also lead to synaptic plasticity imbalance and neural network function remodeling. These mechanisms interact to form a vicious circle that ultimately increases the risk of mental illnesses such as depression, anxiety disorders, and post-traumatic stress disorder.

In summary, chronic stress exerts comprehensive and multi-layered effects on both the structure and function of the brain. From neurobiological mechanisms to psychosocial manifestations, and extending to the public health sphere, chronic stress demonstrates profound and enduring influence. It not only directly damages neurons through prolonged activation of the HPA axis and elevated cortisol levels, but also indirectly impairs learning, memory, and emotional regulation by disrupting neurotransmitter systems and altering synaptic plasticity. This prolonged imbalance within neural circuits renders individuals more susceptible to high-risk states for mental disorders such as depression, anxiety, and PTSD. However, understanding chronic stress solely at the neural level is insufficient. A growing body of research indicates that chronic stress also generates cascading effects through the immune and metabolic systems. For instance, persistent chronic inflammation and the continuous release of pro-inflammatory cytokines not only exacerbate neural damage but also interact with chronic somatic conditions like cardiovascular disease and diabetes. Thus, chronic stress serves as a pivotal hub for ‘mind-body co-morbidity,’ with its mechanisms extending far beyond the traditional scope of mental illness. Clinically, the long-term impact of stress necessitates establishing a comprehensive health management system spanning prevention, intervention, and rehabilitation. Psychological interventions such as mindfulness meditation, cognitive behavioural therapy (CBT), and building social support networks can effectively mitigate the adverse effects of chronic stress. Concurrently, lifestyle modifications including physical exercise, balanced nutrition, and regular sleep patterns have been demonstrated to improve HPA axis function and reduce cortisol levels, thereby enhancing physiological resilience to stress. Regarding pharmacological interventions, antidepressants and anxiolytics targeting neurotransmitter function, alongside emerging therapies targeting inflammatory pathways, have shown efficacy. However, further validation is required regarding their long-term safety and individualised therapeutic responses.

It is worth emphasising that future research should place greater emphasis on integrating interdisciplinary perspectives and multimodal technologies. Observations at a single level are insufficient to reveal the complex full picture of chronic stress. Combining neuroimaging, molecular biology, multi-omics data, and artificial intelligence computational modelling will help construct multidimensional dynamic maps of brain function under stress. This will not only aid in discovering more precise biomarkers but may also advance the development of personalised diagnosis and treatment. For instance, longitudinal large-scale cohort studies could identify sub-groups within populations exhibiting heightened sensitivity to chronic stress, thereby enabling more targeted prevention and intervention strategies.

Finally, from a public health and social policy perspective, the burden of chronic stress should not be borne solely by individuals. Social structures and environmental factors—such as urbanisation, workplace pressures, and social isolation—play pivotal roles in its onset and maintenance. Consequently, formulating sound social policies, optimising working practices, and strengthening community support systems are equally crucial for reducing chronic stress-related disorders. Deepening research into chronic stress not only expands our understanding of neuroscience but also provides robust scientific foundations for societal mental health and sustainable development.

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References

[1] Lupien S J, McEwen B S, Gunnar M R, et al. Effects of stress throughout the lifespan on the brain, behaviour and cognition [J]. Nature Reviews Neuroscience, 2009, 10(6): 434-445. https://doi.org/10.1038/nrn2639

[2] McEwen B S, Morrison J H. The brain on stress: Vulnerability and plasticity of the prefrontal cortex, hippocampus and amygdala [J]. Cerebral Cortex, 2013, 23(9): 2253-2261. https://doi.org/10.1093/cercor/bhs333

[3] De Kloet E R, Joëls M, Holsboer F. Stress and the brain: From adaptation to disease [J]. Nature Reviews Neuroscience, 2005, 6(6): 463-475. https://doi.org/10.1038/nrn1683

[4] Popoli M, Yan Z, McEwen B S, et al. The stressed synapse: The impact of stress and glucocorticoids on glutamate transmission, synaptic plasticity and neurotoxicity [J]. Nature Reviews Neuroscience, 2012, 13(1): 22-37. https://doi.org/10.1038/nrn3138

[5] Slavich G M, Irwin M R. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression [J]. Psychological Bulletin, 2014, 140(3): 774-815. https://doi.org/10.1037/a0035302

[6] Arnsten A F T. Stress signalling pathways that impair prefrontal cortex structure and function [J]. Nature Reviews Neuroscience, 2009, 10(6): 410-422. https://doi.org/10.1038/nrn2648

[7] Duman R S, Sanacora G, Krystal J H. Altered connectivity in depression: GABA and glutamate neurotransmitter systems [J]. Nature Reviews Neuroscience, 2019, 20(10): 593-603. https://doi.org/10.1038/s41583-019-0213-7

[8] Felger J C, Treadway M T. Inflammation effects on motivation and motor activity: Role of dopamine [J]. Neuropsychopharmacology, 2017, 42(1): 216-241. https://doi.org/10.1038/npp.2016.143

[9] Vyas A, Mitra R, Shankaranarayana Rao B S, et al. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons [J]. Journal of Neuroscience, 2002, 22(15): 6810-6818. https://doi.org/10.1523/JNEUROSCI.22-15-06810.2002

[10] Rauch S L, Shin L M, Phelps E A. Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research—past, present, and future [J]. Biological Psychiatry, 2006, 60(4): 376-382. https://doi.org/10.1016/j.biopsych.2006.06.004