

Study on the progress of three pathways in anxiety disorders

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Abstract. An overview is presented in this review, which delves into the neural pathways associated with anxiety disorders. The emphasis is placed on the amygdala and prefrontal cortex circuit, the GABAergic pathway, and the serotonin pathway. The amygdala-prefrontal cortex circuit is essential to processing fear and making decisions; anxiety disorders have been linked to disruption in this circuit. The GABAergic pathway, characterized by the release of GABA and inhibition of neuronal activity, is implicated in anxiety through its role in regulating neuronal excitability. Altered GABAergic function is associated with various anxiety disorders. The serotonin pathway, involving the release of serotonin and modulation of mood and stress responses, is also involved in anxiety disorders. Medications targeting these pathways can help modulate the circuits and alleviate anxiety symptoms. Awareness of these pathways is still limited, though, because anxiety is a complicated illness influenced by a number of factors. The main goals of future research should be the development of individualized treatment plans for anxiety disorders and better clarifying the processes of dysregulation.

Keywords: anxiety disorders; the amygdala-prefrontal cortex circuit; the GABAergic pathway; the serotonin pathway.

1. Introduction

Anxiety is a prevalent mental health issue globally, with approximately 301 million individuals diagnosed in 2019 [1]. In the US, around 40 million adults are affected annually, making it the most common mental illness. Symptoms vary, but common manifestations include rapid breathing, sweating, increased heart rate, and trembling. Individuals with previous episodes of mental illness are more prone to developing anxiety-related conditions due to the complex interaction of different factors that result in anxiety disorders [2, 3].

According to recent research, dysfunctions in various brain regions and neurotransmitters have been found to be linked with anxiety disorders. Emotion recognition and memory are attributed to the amygdala, whereas emotion regulation and decision-making are functions associated with the prefrontal cortex. The hippocampus is associated with memory and fear conditioning. Neurotransmitters such as GABA and serotonin are believed to be involved in anxiety, with GABA having calming effects and serotonin regulating mood.

There are currently several problems and bottlenecks in the treatment of anxiety disorders. The general population's lack of awareness and understanding of anxiety disorders results in delays or misdiagnoses, impeding early intervention and appropriate treatment. Furthermore, there is a shortage of mental health professionals, particularly those with expertise in anxiety disorders. The limited number of experts in this field makes it challenging for individuals with anxiety disorders to access timely and appropriate treatment. Additionally, there is a lack of standardized treatment protocols for anxiety disorders, resulting in inconsistent care and varying treatment outcomes. Moreover, the available treatment options for anxiety disorders, such as medication and therapy, do not work effectively for all individuals. Some patients may not respond well to medication or may experience undesirable side effects. Similarly, certain therapy approaches may not be suitable for everyone, underscoring the need for personalized treatment plans.

In this paper, the amygdaloprefrontal cortex circuit, GABAergic pathway and serotonin pathway are reviewed. In addition, the existing treatment methods for anxiety are introduced, and the limitations of the three approaches and the future development of anxiety are discussed.

2. Three pathways in anxiety disorders

2.1. Amygdala-Prefrontal Cortex Circuit

The amygdala-prefrontal cortex circuit, discovered by Joseph LeDoux and colleagues in the 1990s, has gained significant attention in the study of anxiety disorders. This circuit comprises the amygdala, particularly the basolateral amygdala (BLA) and the prefrontal cortex. Understanding the communication between these two structures is essential for unraveling the processes involved in fear processing, threat assessment, and decision-making related to anxiety.

Playing a crucial role in emotional processing and fear responses, the amygdala stands as a significant brain structure. It consists of several subregions, with the basolateral amygdala being particularly relevant to anxiety. Conversely, the prefrontal cortex assumes the role of facilitating advanced cognitive abilities, including decision-making, regulating emotions, and assessing potential risks [4]. The amygdala and prefrontal cortex are connected through direct and indirect pathways, allowing for bidirectional communication between the two.

2.1.1. Main Mechanism

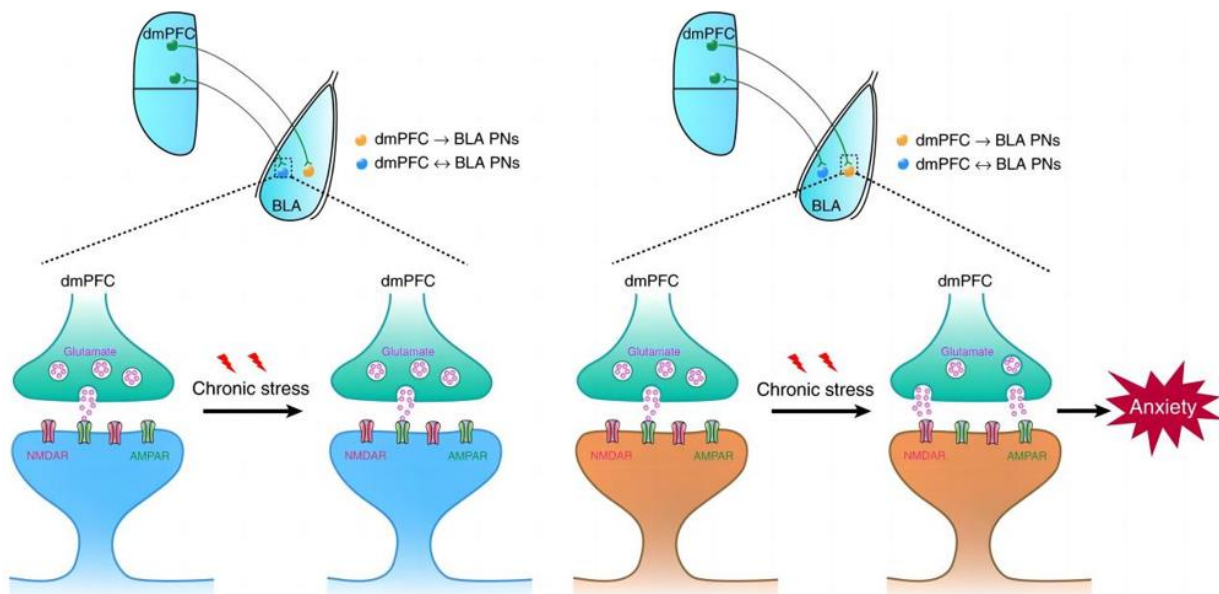


Figure 1. A functional framework illustrates the dysregulation of dmPFC-to-BLA transmission in target cells, linked to anxiety caused by chronic stress [5].

The amygdala-prefrontal cortex circuit is heavily influenced by chronic stress, which can have distinct effects on the release of neurotransmitters within this circuit. Studies have specifically demonstrated that the release of glutamate from the prefrontal cortex onto basolateral amygdala principal neurons (BLA PNs) that have reciprocal connections with the dorsal medial prefrontal cortex (dmPFC) remains unaffected by chronic stress. Nonetheless, chronic stress does enhance the release of prefrontal glutamate onto BLA PNs that receive inputs solely from the dmPFC. Stress-induced anxiety-like behavior in mice has been linked to an increase in prefrontal glutamate release.

Animal studies have also been instrumental in understanding the mechanisms of the amygdala-prefrontal cortex circuit. Lesion studies, involving the selective removal or inactivation of specific brain regions, have demonstrated that disruptions in this circuit can lead to anxiety-like behaviors in animals. Manipulations of the amygdala or prefrontal cortex in animal models have been shown to

modulate anxiety-like behaviors, further supporting the involvement of this circuit in anxiety-related processes.

Additionally, pharmacological interventions targeting neurotransmission within the amygdala-prefrontal cortex circuit have shown promise in reducing anxiety symptoms. For example, drugs that act on serotonin and gamma-aminobutyric acid (GABA) neurotransmitter systems within this circuit have demonstrated efficacy in alleviating anxiety symptoms in both animals and humans.

2.1.2. Reflection

Although the amygdaloid-prefrontal cortical circuit's involvement in anxiety disorders is widely acknowledged, further research is necessary to completely comprehend the intricate mechanisms underlying its dysregulation. Understanding how chronic stress affects the release of glutamate onto various types of basolateral amygdala main neurons can help explain why anxiety-like behavior increases in response to stress.

The strengths of the amygdala-prefrontal cortex circuit's role in anxiety disorders lie in its well-established involvement in fear processing and emotion regulation. The consistent findings from neuroimaging studies, along with evidence from various research methods, provide robust support for its significance in anxiety disorders. Nevertheless, there are still obstacles in comprehensively grasping the precise mechanisms and establishing a direct cause-and-effect relationship between circuit dysfunction and the emergence of anxiety disorders.

Anxiety disorders are complex and multifaceted, involving interactions between multiple brain regions and neurotransmitter systems. While the amygdala-prefrontal cortex circuit is a crucial component, it is just one piece of the puzzle. Future research should aim to integrate findings from various brain regions and systems to provide a comprehensive understanding of anxiety disorders.

In conclusion, the amygdala-prefrontal cortex circuit plays a central role in anxiety disorders. Chronic stress affects the release of glutamate onto distinct types of basolateral amygdala principal neurons. Ongoing research efforts, including neuroimaging studies, animal models, and pharmacological interventions, continue to enhance our understanding of this circuit and its dysregulation in anxiety disorders. By unraveling the precise mechanisms, researchers can develop more effective therapeutic strategies for individuals with anxiety disorders resulting from chronic stress.

2.2. GABAergic Pathway

The GABAergic pathway is a basic mechanism that regulates neuronal excitability and promotes brain relaxation by releasing GABA and inhibiting neuronal activity. GABA, which was first identified in the middle of the 20th century, serves as the brain's main inhibitory neurotransmitter. The work of many scholars has contributed to our understanding of GABA and its inhibitory properties.

2.2.1. Main Mechanism

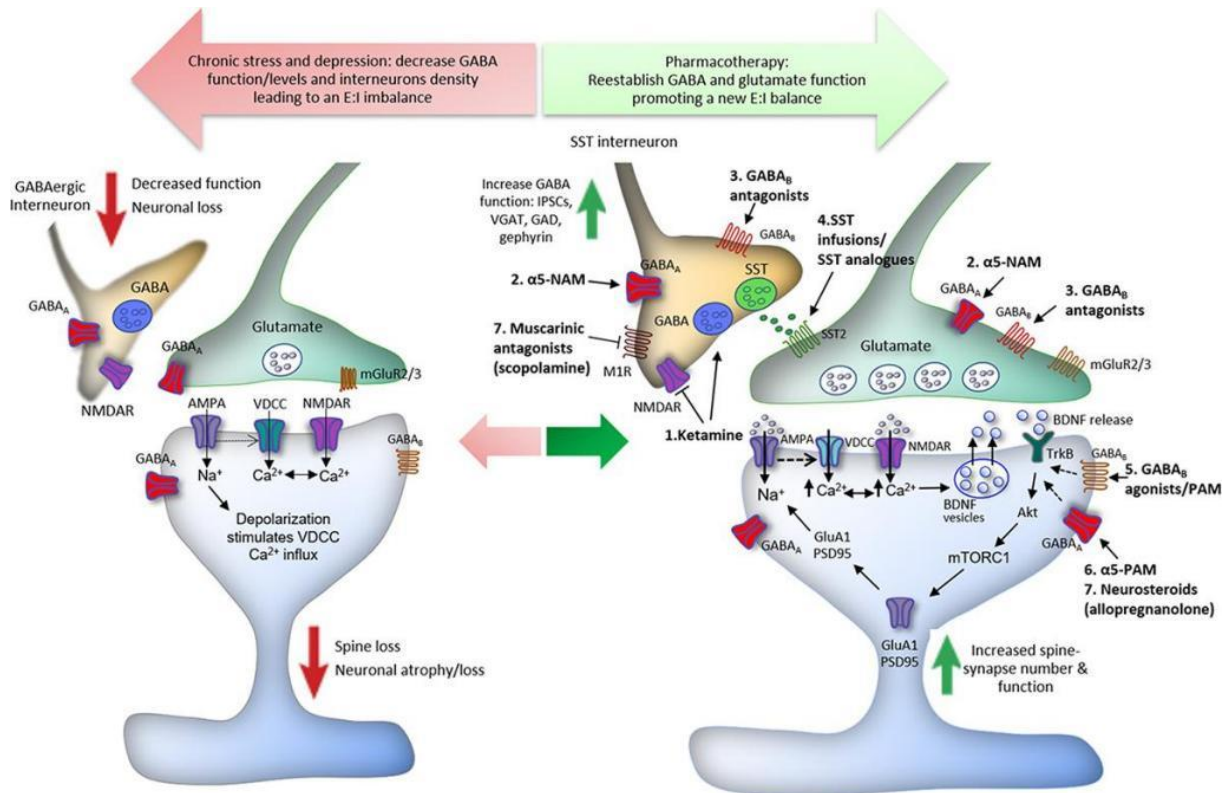


Figure 2. The hypothesized mechanisms that explain how ketamine and GABA-related drugs affect brain excitatory and inhibitory processes to restore equilibrium [1].

GABAergic interneurons, which are found all across the brain, are the main actors in the GABAergic circuit. These interneurons are essential for controlling neuronal excitability and preserving a balance between inputs that are excitatory and inhibitory. Activation of the GABAergic pathway occurs through the release of GABA, which can be triggered by neuronal stimulation.

GABAergic interneurons inhibit the activity of excitatory neurons through the binding of GABA to GABA receptors located on postsynaptic neurons. When GABA binds to these receptors, it reduces the firing rate and overall neuronal activity of excitatory neurons, promoting relaxation and inhibiting excessive neuronal firing. The GABAergic system creates inhibitory circuits that help to control processes connected to anxiety. Dysfunction in the GABAergic system has been consistently observed in individuals with anxiety disorders. To better understand how the GABAergic system contributes to anxiety, researchers have carried out experiments like "Deficits in GABA(A) receptor function and working memory in non-human primates subjected to early life stress." The GABAergic system's dysfunction is associated to a variety of anxiety disorders. Altered GABAergic function in these disorders can manifest as reduced GABA levels and impaired GABA receptor functioning. The disruption of GABAergic signaling can be influenced by multiple factors, including genetic predisposition, environmental factors, and abnormalities in GABA synthesis or release.

Valuable animal research have provided insights into the function of the system here. For example, research on mice with a GABA receptor mutation has demonstrated an increased susceptibility to anxiety-like behaviors. Additionally, experiments involving the modulation of the receptors in animal models have shown the ability to alter anxiety-related behaviors.

2.2.2. Reflection

Medications that enhance GABAergic transmission, such as benzodiazepines [6], have been used to modulate the GABAergic circuit and reduce anxiety symptoms. These medications increase the inhibitory effects of GABA by enhancing its binding to GABA receptors, leading to a decrease in neuronal excitability. However, because to their possible adverse reactions and dependence risk,

GABAergic drugs need to be used with caution. While the involvement of the GABAergic pathway in anxiety disorders is well-supported, there may still be ongoing debates regarding specific aspects of GABAergic signaling. The exact mechanisms underlying GABA dysfunction in anxiety disorders are not fully understood and may involve complex interactions with other neurotransmitter systems.

The gaba pathway does, however, play a demonstrable function in anxiety disorders. A number of studies have consistently reported changes in gaba function in anxiety patients, providing strong evidence for its role. In addition, the efficacy of GABAergic drugs in reducing anxiety symptoms further supports the involvement of GABAergic pathways. It's critical to recognize the GABAergic pathway's limits in the treatment. Altered GABAergic function is inclusive to anxiety disorders and can be present in other psychiatric conditions as well. Additionally, the use of GABAergic medications has limitations, including potential side effects and the risk of dependence, which may limit their long-term effectiveness and applicability for all individuals with anxiety.

Future studies could explore the specific genes associated with GABAergic dysfunction in anxiety disorders and investigate potential therapeutic interventions targeting these genes. Additionally, advancements in imaging techniques can provide a better understanding of GABAergic system activity in individuals with anxiety disorders, allowing for more targeted treatment approaches. Moreover, the role of GABAergic dysfunction in other psychiatric conditions should be further explored. Developing more personalized and effective treatment strategies can be facilitated by comprehending the variations and resemblances in GABAergic alterations across various disorders [7].

The development of novel medications that target specific components of the GABAergic pathway could also enhance treatment options for anxiety disorders. For example, researchers are exploring the potential of developing GABA receptor subtype-selective drugs that can provide more precise modulation of GABA activity. Ulk4 suggests great potential for the development of innovative anti-anxiety therapies [8]. Non-pharmacological strategies like cognitive-behavioral therapy (CBT) can be helpful in controlling anxiety disorders in addition to pharmaceutical therapies. CBT has been successful in easing anxiety symptoms because it tries to recognize and change unhelpful thoughts and actions that cause anxiety. Additionally, incorporating lifestyle factors such as exercise, stress management techniques, and sufficient sleep can significantly support GABAergic function and overall mental well-being.

2.3. Serotonin Pathway

The discovery of serotonin's functions involved the contributions of various researchers. Since its initial discovery in the 1940s, scientists have dedicated significant efforts to understanding the role of serotonin in mood regulation and anxiety. The collective body of work has consistently reported alterations in serotonin function in individuals with anxiety disorders, which has sparked interest in investigating its involvement in anxiety regulation.

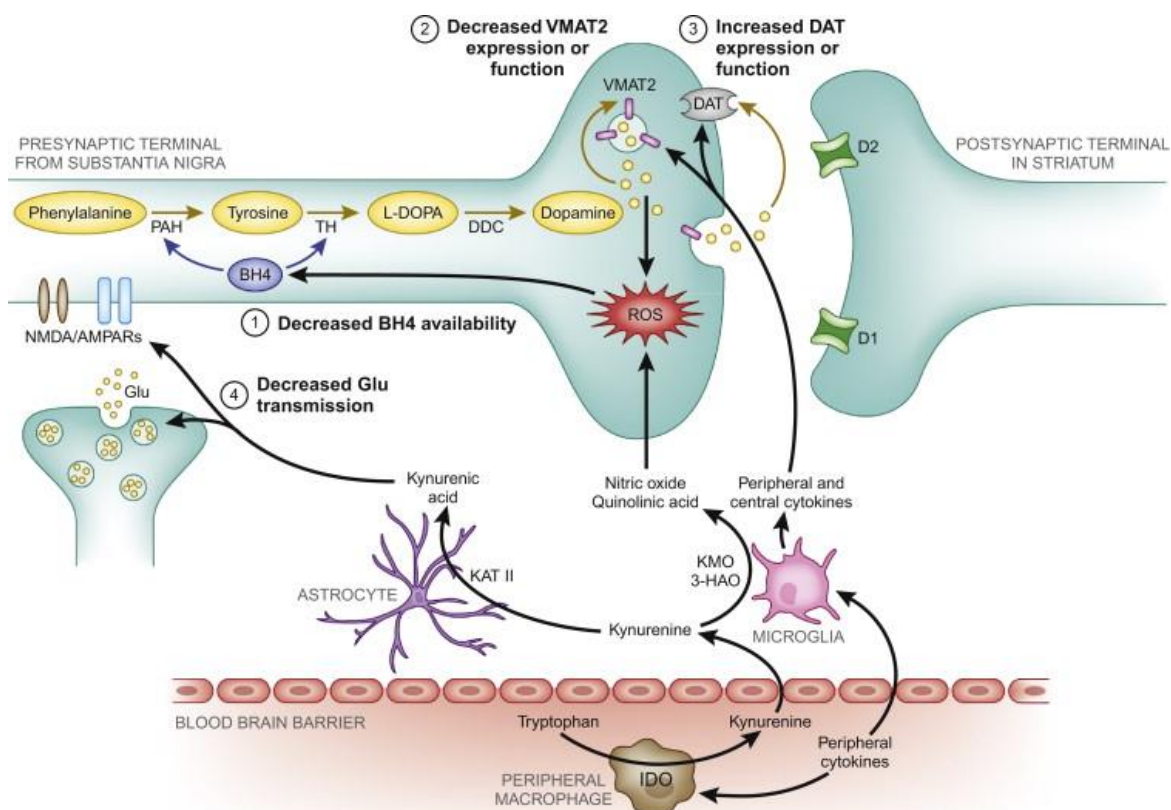


Figure 3. Possible mechanisms by which inflammatory cytokines affect the synthesis and release of dopamine in the basal ganglia [9].

2.3.1. Main Mechanism:

In order to control anxiety, the serotonin pathway, which is generated in the brainstem's raphe nuclei, is extremely important. The amygdala, prefrontal cortex, and hippocampus are just a few of the brain areas that the route connects to. The activation of this pathway is triggered by the release of serotonin, a neurotransmitter that plays a role in regulating mood.

The circuitry involving the serotonin pathway interacts with various brain regions, contributing to anxiety regulation. The amygdala is one such area that is crucial in the responses to fear and anxiety. Serotonin projections to the amygdala influence its functioning and help modulate emotional processing. Additionally, the pathway also impacts the prefrontal cortex, responsible for cognitive control and emotion regulation. Serotonin's influence on the prefrontal cortex further contributes to anxiety regulation.

Moreover, the hippocampus, a region associated with memory and learning, is influenced by serotonin [10,11]. By modulating the functioning of the hippocampus, serotonin affects stress responses and contributes to anxiety regulation. The serotonin pathway's modulation of these brain regions helps regulate emotions, mood, and stress, all of which play significant roles in anxiety disorders.

Research exploring the serotonin pathway's role in anxiety disorders has significantly advanced our understanding of these conditions. Specific anxiety disorders have been linked to altered serotonin function. Neurochemical, genetic, and pharmacological studies have provided robust evidence supporting this association. Reduced serotonin levels or impaired receptor functioning have been consistently observed in individuals with anxiety disorders. Furthermore, genetic variations in serotonin-related genes have shown associations with an increased susceptibility to anxiety disorders.

2.3.2. Reflection

Medications that target the serotonin pathway offer potential therapeutic options for individuals with anxiety disorders. By modulating the serotonin circuit, these medications can reduce anxiety symptoms. Despite ongoing debates regarding specific aspects or mechanisms of serotonin's involvement in anxiety, its overall significance in anxiety regulation is widely recognized.

Numerous studies indicate the function of serotonin in anxiety disorders. Serotonin, an extensively researched neurotransmitter, has a recognized function in regulating both mood and anxiety. Abnormalities in serotonin function, such as reduced levels or impaired receptor functioning, have been consistently observed in individuals with anxiety disorders. This suggests that serotonin deficiency contributes to the development and maintenance of many illnesses.

Additionally, SSRIs, which raise serotonin levels, are frequently recommended as initial therapies for anxiety disorders. These drugs are frequently utilized in therapeutic settings because they have shown promise in lowering anxiety symptoms. The effectiveness of SSRIs emphasizes the significance of serotonin in controlling anxiety and offers verifiable proof of its significance. However, it is essential to acknowledge the complexity of the relationship between serotonin and anxiety. Serotonin dysfunction is not the sole cause of anxiety disorders and may interact with other neurotransmitter systems and environmental factors. Not all individuals with anxiety disorders exhibit abnormalities in serotonin function, indicating the involvement of other pathways and mechanisms. Consequently, further research is needed to unravel the intricate mechanisms.

3. The Current Treatment of Anxiety Disorders

There has been a remarkable progress in the field of anxiety disorder treatment, as professionals have increasingly emphasized the integration of psychotherapy and medication. Depending on the type and severity of the anxiety disorder, the approach to treatment can differ, as well as the individual's preferences and requirements.

Psychotherapy, especially cognitive-behavioral therapy (CBT) is the main method used to treat anxiety problems [12]. It enables sufferers to identify and change the negative patterns and actions that intensify their anxiety. This therapy incorporates various techniques, including exposure therapy and cognitive restructuring. For example, exposure therapy gradually and safely exposes individuals to their dreaded situations or objects, demonstrating that their anxiety diminishes with time. This process helps desensitize the individual to their fears and reduces avoidance behaviors. Cognitive restructuring is another essential component of CBT, which aims to challenge and reframe irrational or negative thoughts associated with anxiety. By identifying and modifying these thoughts, individuals can develop healthier and more balanced thinking patterns, leading to reduced anxiety symptoms [13,14].

Medication can be a valuable resource in managing anxiety disorders too. Serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are antidepressant drugs shown to be useful in treating anxiety disorders [15]. These drugs work by making more of certain neurotransmitters available in the brain, such as serotonin, which helps control mood and anxiety. Alprazolam and lorazepam are two examples of benzodiazepines that may be administered to treat acute anxiety symptoms. However, due to the possibility of reliance and other negative effects, benzodiazepines are normally used with caution and for a brief period of time.

Although drugs can lessen symptoms, they do not treat anxiety disorders. Therefore, for the best results, a mix of medication and psychotherapy is frequently advised. Additionally, it is crucial to follow up with medical specialists on a frequent basis in order to monitor progress, modify the treatment plan as needed, and handle any issues or adverse effects that could appear.

4. Limitations and Future Developments

Despite the progress made in the treatment of anxiety disorders, there are still limitations and areas for future development. One limitation is the variability in treatment response among individuals. Not everyone responds equally to the same treatment approach, and some may require a trial-and-error process to find the most effective treatment. Personalized medicine approaches, such as genetic testing and neuroimaging, may hold promise in identifying the most suitable treatment options for each individual. By understanding an individual's genetic makeup or brain functioning, treatment plans can be tailored to maximize effectiveness. Furthermore, there is a need to develop more targeted and precise interventions that directly modulate the amygdala-prefrontal cortex circuit. The amygdala and prefrontal cortex play significant roles in anxiety regulation. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been developed as a result of advancements in neuroscience and technology [16]. These cutting-edge techniques present possible substitute therapies for a range of illnesses. These techniques involve applying a mild electrical current or magnetic field to specific brain regions to modulate their activity, potentially reducing anxiety symptoms. Furthermore, there is an increasing acknowledgment of the significance of integrating lifestyle factors into the management of anxiety disorders, alongside these personalized approaches. Research has shown that regular exercise, healthy sleep patterns, and stress management techniques can have a positive impact on anxiety symptoms. Integrating these lifestyle interventions into the treatment approach may enhance overall outcomes and provide individuals with additional tools for managing their anxiety.

Another area for future development is the exploration of novel treatment modalities [17,18]. For example, virtual reality exposure therapy has gained attention as a potentially effective method for treating anxiety disorders. This innovative approach allows individuals to face their fears in a virtual environment, providing a safe and controlled setting for exposure. Additionally, mindfulness-based therapies have demonstrated efficacy in lowering signs of anxiety, placing a high priority on developing mindfulness, which emphasizes being fully present in the moment and accepting feelings and thoughts without bias. Through practice, individuals can establish a healthier relationship with their anxiety, leading to a decrease in its impact on their daily functioning.

In conclusion, the current treatment approaches for anxiety disorders involve a combination of psychotherapy and medication. However, there are limitations to the existing approaches, including variability in treatment response and the need for more targeted interventions. Future developments may involve personalized medicine approaches, non-invasive brain stimulation techniques, lifestyle interventions, and the exploration of novel treatment modalities. By continually advancing our understanding and treatment options, we can strive to provide more effective and individualized care for individuals with anxiety disorders.

5. Summary

In conclusion, this study highlights the importance of different brain regions in the development and progression of anxiety disorders. Although more study with bigger samples and longterm studies is required to evaluate and advance these findings, these results have significantly implied the development of precise therapies and interventions.

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