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Research on the neural circuits and treatment of anxiety

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Abstract. Anxiety disorders are widely recognized as one of the most widespread mental health conditions worldwide, which can have detrimental impacts on individuals, their families, and the broader communities they belong to. A clearer knowledge of the brain neural circuits linked to anxiety will be beneficial for early detection of at-risk individuals and the ability to take preventative interventions. Today, more specialized and individualized therapies for anxiety disorders have been developed as a result of neuroscientific research. The neural circuitry involves key brain regions like the amygdala, prefrontal cortex (PFC), anterior cingulate cortex (ACC), bed nucleus of the stria terminalis (BNST), and hippocampus, unraveling complex interactions contributing to anxiety pathogenesis. Treatment modalities are categorized as medicine and non-medicine approaches. This paper emphasizes the necessity for ongoing research to optimize therapeutic approaches and advocates combining pharmacological and non-medicine interventions for comprehensive anxiety disorder management, ultimately improving the well-being of affected individuals worldwide.

Keywords: Anxiety, neural circuits, non-medicine therapy, medicine therapy

1. Introduction

Anxiety disorders have been a serious mental disease which has attracted the attention of researchers. According to World Health Organization statistics, the pandemic has led to a massive increase of 26% in anxiety disorders globally [1]. Anxiety disorders cause excessive and persistent worry, fear, and anxiety response to real or perceived threat stimulus. Many patients suffer from the occurrence of symptoms such as lack of concentration, which results in great inconvenience in living and social life. How to control symptoms and improve the mental health of the masses is currently the most urgent problem. If left untreated, it can lead to other mental health problems, such as depression.

Anxiety disorders are a multifaceted phenotype that includes variations in behavior, peripheral physiology, cognition, and emotions [2]. The main symptoms of anxiety disorders include fight or flight responses, such as escape, avoidance, some psychophysiological responses, and some physical symptoms such as increasing heart rate. With the development of life science, it's widely believed that anxiety disorders are regulated by neural circuits. According to previous study, neural circuits for anxiety involve some brain regions including the amygdala, bed nucleus of the stria terminalis (BNST), anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), and hippocampus [3, 4]. A key element of the anxiety circuit is the amygdala, which integrates information from sensory inputs from the cortex and thalamus to generate behavioral output related to fear and anxiety [5]. Basolateral amygdala (BLA) and central amygdala (CeA) are two relatively important subsections in amygdala for anxiety response. In

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addition, a study conducted by Katherine and Michelle also demonstrated changes in connectivity between the amygdala and prefrontal cortical regions, highlighting the role of altered function of neural circuits related to anxiety regulation from amygdala to medial prefrontal cortex (mPFC) [6]. Recent study further indicates the role of BNST in anxiety-related behavior. For example, BNST lesions caused the reduction in anxiety response to strong light and infusion of corticotropin-releasing hormone [7]. The study conducted by Rytova et al. demonstrated that the activation of the relaxin-3 receptor on gamma-aminobutyric acid (GABA) neurons in the rat ventral hippocampus resulted in the manifestation of anxiety and social avoidance [4].

With the efforts of researchers, great research progress has been made in the treatment of anxiety. For example, Benzodiazepines are used to address generalized anxiety disorders [8], which can slow down the activity in the nervous system. In addition, D-cycloserine and short-term usage of Cortisol are effective in the maintenance of extinction learning processes [9]. Cognitive behavioral therapy (CBT) has been shown to be effective for anxiety and has also been linked to improved quality of life for people with anxiety disorders [10]. CBT is often conceptualized as a short-term, skills-focused therapy. This therapy can adverse emotional responses by changing the patient's thoughts, behavior, or both. The most commonly used methods in CBT are exposure therapy and cognitive therapy. Cognitive therapy is to reconstruct maladaptive thought patterns, making patients question their negative cognitive ability to build a healthy negative emotion. Exposure therapy, on the other hand, is a systematic desensitization, which contains dear hierarchy and relaxation training. Different exposure techniques are used in the contexts of patients, such as in vivo, imaginal, and/or interoceptive. In addition, psychotherapy treatment of disorders is used as novel treatment. The Pavlovian fear-conditioning paradigm is a tool to reconstruct fear learning in order to address anxiety behavior [11]. Some physical treatments show effective outcomes when treating anxiety disorders.

In this paper, the studies are summarized based on different brain regions. Different neural circuits, therapies, and medication prevention are discussed to foster the further studies of anxiety in the future.

2. Neural circuits of anxiety

2.1. Amygdala

The amygdala, which receives projections mostly from the sensory regions of the thalamus (Figure 2), is thought to play a crucial role in the development and expression of anxiety, according to a substantial body of data from research on rodents.

2.1.1. Amygdala in anxiety related research. For example, since the most significant tactile organ in newborn mice is their whiskers, bilateral whisker clipping is employed as a model of early tactile deprivation because anomalies in tactile perception are frequently seen in the processing of fear- and anxiety-related reactions [12]. In an experiment conducted by Soumiya et al., the amygdala circuits that manage reactions associated with fear and anxiety were found to be hyperactive in rats whose whicker had been shortened [13]. The results of this study indicate that the growth of emotional regulation, which relies on the amygdala, is impeded by the removal of whiskers in newborns. The neuropeptide Y2 gene, which is strongly expressed in the amygdala, was specifically deleted at one place, and Tasan et al. investigated the results. The CEA and BLA were subsequently discovered to be key locations for the neuropeptide Y2 receptor-mediated anxiety-related behavior in mice [14]. Evidence from structural magnetic resonance imaging (MRI) also suggests that the amygdala plays a part in CBT treatment [15]. At a one-year follow-up, one research team found that treatment response was associated with decreased amygdala gray matter volume in the treated individuals (Figure 1). These results suggest possible links between functional activation and amygdala structural volume during CBT.

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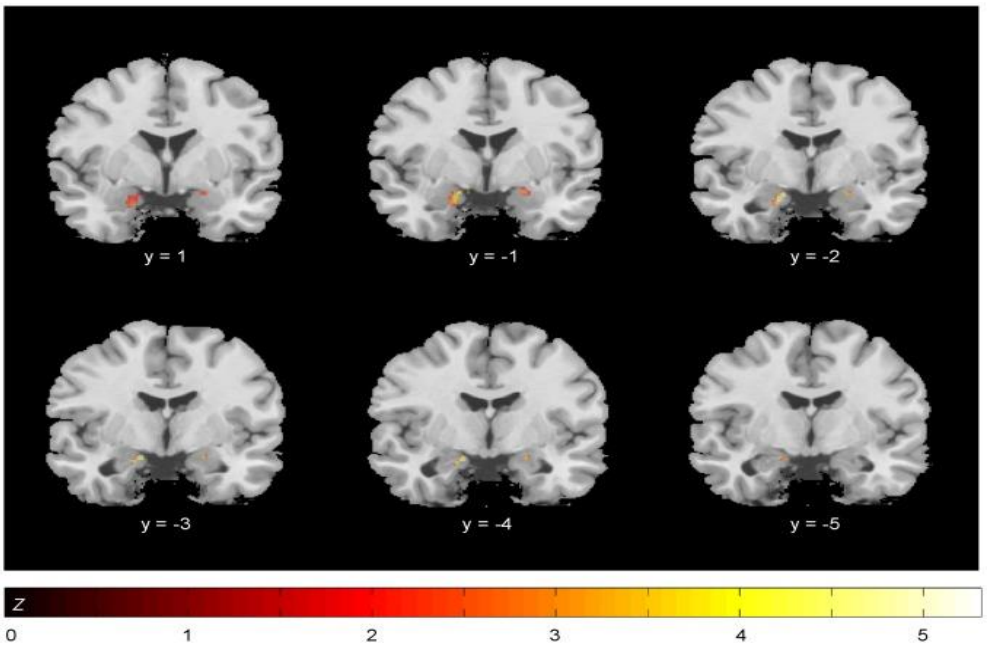

Figure 1. Gray matter volume Time × Group interaction effect in the left amygdala is displayed on multiple slices showing reduced volume in long-term responders [15].

The presence of anxiety disorder has been found to be linked with alterations in the activation patterns of the amygdala. Studies using neuroimaging have shown that anxiety and depression alter brain responsiveness to emotional signals. There has been evidence that the amygdala of anxiety disorders exhibits heightened responsiveness to unfavorable or dangerous signals [6] The central nucleus (CeA), a component of the centromedial amygdala (CMA), and the basolateral complex (BLA) are of special importance for anxiety [16]. Sébastien et al. examined how intercalated neurons alter impulse flow between the basolateral complex and CeA nucleus using whole-cell recordings, microstimulation of the lateral and basal amygdaloid nuclei, and local administration of glutamate receptor antagonists [17]. A nonstandard amino acid called gamma-aminobutyric acid (GABA) serves as the primary inhibitory neurotransmitter in the central nervous system [18]. Numerous neurophysiological processes, crucially including anxiety, involve GABA systems. By employing gold-conjugated WGA-apoHRP as a retrograde tracer and in situ hybridization to find the mRNA for the enzyme glutamic acid decarboxylase (GAD67) as a marker for GABAergic cells, Jongen-Rêlo and Amaral evaluated the GABAergic neurons in the amygdala [19]. This study gives proof that the brainstem of macaque monkeys receives lengthy, GABAergic axons from the central nucleus of the amygdala. The circuitry by which the amygdala participates in the modulation of the autonomic and visceral aspects of emotional behavior will be more clearly defined once it is known which neurons in the brainstem are innervated by these GABAergic efferents.

These findings indicate that the amygdala changes right away following successful psychological treatments for social anxiety disorder.

2.1.2. The circuits of BLA-CeA in anxiety. The intercalated neurons, which are located between the BLA and the CeA and operate as a relay of inhibitory GABAergic interneurons, are activated by the BLA and directly stimulate the CeA through an excitatory glutamatergic route (Figure 2) [20]. The primary amygdala output route is the CeA. Anxiety's bodily symptoms are caused by the activation of inhibitory GABAergic neurons, which project from the CeA to the brainstem and hypothalamus (Figure 2) [19].

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2.2. Prefrontal Cortex

The PFC has significantly more association area than some other regions of the human brain [21]. It is believed that this expansion is what gives humans' subjective experiences of anxiety its richness and complexity, as well as their ability to employ sophisticated methods to control anxiety-related reactions [22].

2.2.1. Prefrontal Cortex in anxiety related research. In a study included data from 4507 patients and 4755 control individuals [23], mood disorders, anxiety disorders, and posttraumatic stress disorder (PTSD) all exhibit similar neurobiologic traits in task-related fMRI. The inferior prefrontal cortex had significantly reduced activity in patients with mood and anxiety disorders. According to a study conducted by Janiri et al., a meta-analysis of 226 task-related fMRI studies in mood disorders, posttraumatic stress disorder, and anxiety disorders revealed statistically significant transdiagnostic clusters of hypoactivation in the putamen, inferior parietal lobule, and inferior prefrontal cortex [24]. These regions are integral to a brain system that is predominantly associated with the right hemisphere, which enables the ability to flexibly adjust and temporarily halt cognitive processes and behavioral responses in accordance with situational demands. Particularly, the right inferior prefrontal cortex plays a crucial role in the regulation of cognitive, emotional, and motor responses that are inappropriate for the setting. In mPFC, astrocytes play a crucial role in synaptic transmission, and in an experiment conducted by Xin et al., mouse malfunction results in neuropsychiatric diseases including anxiety [25]. The findings of the experiment showed that selective deletion of LXR in astrocytes in the medial prefrontal cortex (mPFC) perfectly recreated the behavioral phenotype of anxiety.

The lateral prefrontal cortex's inferior frontal gyrus (IFG), a subregion, is crucial in the connection of amygdala-PFC circuitry [26]. Cha et al. conducted an experiment wherein they employed entropic measures to assess circuit-wide regulation and feedback. They also utilized structural and functional measures to examine prefrontal-limbic connection within the circuit. The researchers collected fMRI time-series data from 57 human subjects who were engaged in a fear generalization task [27]. The findings imply that compared to healthy controls, autocorrelation lifespan of IFG activity was considerably shorter in those with GAD. The IFG's connection with the vmPFC, amygdala, and other areas of the prefrontal-limbic network may have an anatomical underpinning, according to their multimodal MRI method. This implies that the presence of either heightened excitatory inputs or diminished inhibitory feedback mechanisms may contribute to the manifestation of anxiety in individuals [28].

2.2.2. BLA-PFC circuits. The medial prefrontal cortex (PFC), among other forebrain regions, appears to have a significant part in the regulation of anxiety in addition to the amygdala's role [16]. These cortical regions are simultaneously engaged with the amygdala when emotional stimuli are presented, receiving and sending excitatory glutamatergic projections to and from the BLA [29]. It has been proposed that the medial PFC regulates the experience or expression of anxiety through modulation of neuronal activity in the BLA (Figure 2) [30]. The amygdala's output would be inhibited by this "top-down" regulation.

According to translational research, reactions following learnt extinction are mediated by amygdala-PFC circuitry. During extinction recall tasks, this circuit's functional connectivity may experience anxiety-related disturbances. The previous study's data are used in the current article to explore the relationship between anxiety and development and task-dependent amygdala-PFC connection [31]. Their whole-brain studies revealed substantial interactions between anxiety, age, and attention tasks on the functional connectivity between the left amygdala and the ventral anterior cingulate cortex and vmPFC. It is worth mentioning that children with anxiety had heightened negative coupling between the amygdala and prefrontal cortex (PFC) during the evaluation of threatening stimuli and conscious recall of threats. Conversely, adults with anxiety demonstrated increased positive coupling between these brain regions.

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2.3. Hippocampus

The dorsal hippocampus is primarily involved in specific types of learning and memory, particularly spatial learning. On the other hand, the ventral hippocampus may have a more prominent role in the neural mechanisms connected with anxiety-related behaviours [32].

2.3.1. Hippocampus in anxiety related research. In an experiment conducted by Bannerman et.al, a group of animals with hippocampal lesions are tested to determine how hippocampus contribute differentially to fear and anxiety [32]. Ventral hippocampal lesions had behavioral effects resembling those induced by benzodiazepines on these tasks, consistent with a reduction of anxiety [33]. In agreement with previous studies [34, 35], rats with selective ventral hippocampal lesions showed reduced hyponeophagia, displayed increased social interaction, were quicker to cross compartment box tests, and spent an increased proportion of time in a more anxiogenic section of the successive alleys apparatus. The ventral hippocampal lesions had effects that are consistent with an anxiolytic effect.

The ventral hippocampus, known for its crucial involvement in emotional and cognitive functions, exhibits a significant concentration of neuronal fibres that express relaxin-3 and binding sites for RXFP3. The signalling pathway of RXFP3 has been found to be associated with alterations in anxiety. Rytova et al. conducted a study on adult male rats to investigate the effects of chronic RXFP3 activation in the ventral hippocampus (vHip) on anxiety-like behaviour and social behaviour. This was done by expressing an RXFP3-selective agonist peptide, R3/I5, using a viral vector [4]. According to the research, there are various potential pathways for changing hippocampus output and producing anxiety-like behavior. These include the likely persistent suppression of several populations of hippocampal GABAergic neurons.

2.3.2. Amygdala-vHip and mPFC-vHip circuits. More ventral cortical areas of the hippocampus are thought to be in charge of implicit, subconscious control, while more dorsal areas are thought to be in charge of conscious, voluntary control of anxiety. The vHip receives/sends information from/to many emotional centers, such as the amygdala (Figure 2) [36], hypothalamus [37, 38], and medial prefrontal cortex [39].

A further line of evidence that also indicates separate roles for the hippocampus and amygdala in fear or anxiety-related behaviors derives from studies of potentiated startle. The acoustic startle reflex is a rapid contraction of the skeletal muscles elicited by a sudden auditory stimulus and is assumed to be an unconditioned protective reaction. The startle reflex is mediated by a brain-stem circuit [32], but modulated by forebrain sites [40].

The mPFC processes contextual information in order to modulate the manifestation of anxiety-related behaviours, which gets input from the vHPC (Figure 2). Additionally, it receives projections from many cortices, as noted by Vertes, Hoover, Szigeti-Buck, and Leranth, enabling it to acquire extensively processed environmental information [41]. The mPFC subsequently establishes direct connections with neural regions, including the amygdala and the periaqueductal grey (Figure 2) [42]. These connections facilitate the generation of suitable protective behaviours. The research conducted by Vidal-Gonzalez, Vidal-Gonzalez, Rauch, and Quirk suggests that the activation of the prelimbic cortex leads to a reduction in the ability to recall fear extinction [43]. This finding supports the notion that the medial prefrontal cortex subregion known as the prelimbic cortex plays a role in promoting anxiety-related behaviours.

2.4. Bed Nucleus of the stria terminalis

BNST, a brain area associated with anxiety-related behaviour. Through its close connections to the hypothalamic paraventricular nucleus (PVN), the hub of the hypothalamic-pituitary-adrenal (HPA) axis triggers cortisol responses, and BNST is in a prime position to trigger allostatic alterations in the brain. Indeed, BNST lesions affect the release of cortisol in response to stress [44], indicating that the BNST may be crucial in illnesses brought on by the stress response, such as addiction and anxiety.

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The research undertaken by Sajdyk et al. hypothesised that persistent reduction of inhibitory GABAergic activity in BNST would lead to the manifestation of generalized anxiety disorder-like behaviours [45]. In order to examine this idea, male rats were continuously fed L-allylglycine (L-AG) or its isomer D-AG directly into the BNST. The findings demonstrate that the suppression of GABA in the bed nucleus of the stria terminalis (BNST) elicits anxiety-like conduct. This suggests that the observed behavioural pattern aligns closely with generalized anxiety-like behaviour.

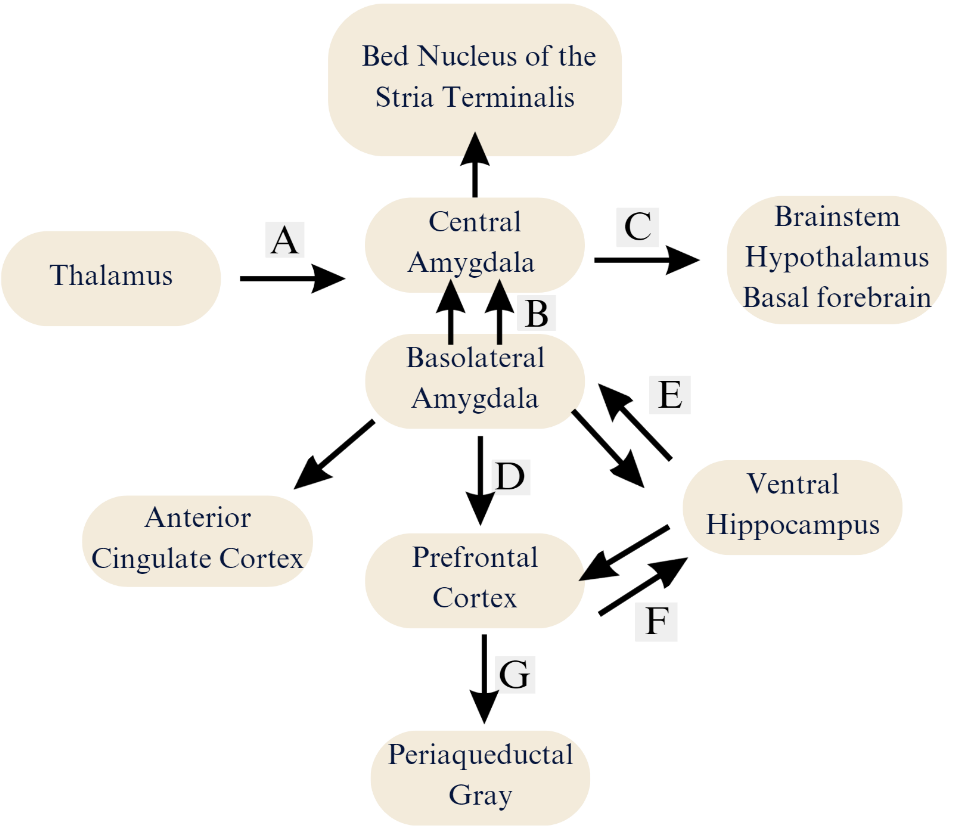

Figure 2. Neural circuits implicated in anxiety disorders. A: Amygdala receives projections from the sensory regions of the thalamus. B: Intercalated neurons are activated by the basolateral amygdala and directly stimulate the central amygdala. C: The neural circuits from central amygdala to the brainstem and hypothalamus cause anxiety's bodily symptoms. D: Medial prefrontal cortex regulates anxiety through modulation of neuronal activity in the basolateral amygdala. E: Ventral hippocampus receives/sends information from/to amygdala. F: Ventral hippocampus receives/sends information from/to medial prefrontal cortex [12, 19, 20, 30, 36, 39, 41, 42].

3. The treatment for anxiety

3.1. Non-medicine therapy

3.1.1. Cognitive behavior therapy. One of the most popular behavior treatments for anxiety problems is exposure-based therapy. Emotional processing theory provides one theoretical framework for comprehending the justification for exposure-based therapy. According to the idea of emotional processing [46], fear is represented by associative networks that store data on the feared stimulus, the fearful reaction, and the significance of the stimulus and reaction. Accordingly, the anxiety disorder's exposure therapy depends heavily on this fear emotional processing, with changes most frequently showing up in the focus placed on the exposure's content, which is unique to the patient's presenting

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problems (Figure 3). In order to treat anxious behavior, the Pavlovian fear-conditioning paradigm provides a method to reconstruct fear learning [11]. In a study conducted by Foa et al., a randomized assignment was made to two groups of female attack survivors who were diagnosed with PTSD. The first group received extended exposure (PE) therapy alone, while the second group received a combination of PE therapy and cognitive restructuring [47]. PE therapy alone reduced PTSD and depression, and improved social functioning. However, with cognitive restructuring, the outcome of treatment was not enhanced.

Another popular technique for treating anxiety problems is cognitive therapy. Beck's tri-part model of emotion, which postulates that thoughts, feelings, and behaviors are interconnected, forms the basis of cognitive therapy. The findings of a study indicate that compared to a previous cohort treated with TAU trauma-focused group therapy, veterans treated in the cognitive processing therapy (CPT) cohort during residential treatment for PTSD showed noticeably more improvement and more clinically significant improvement [48].

3.1.2. Physical treatment. An ancient Chinese therapy is acupuncture treatment [49]. The idea of holism, Zang-Fu viscera, meridians, and collaterals are the key sources of inspiration for acupuncture theory [50]. In an experiment conducted by Qing et al., they assigned one group of patients with generalized anxiety disorder being treated with western medicine, while another group being treated by Jin-3-needling therapy [51]. The needling group demonstrated the greatest effectiveness index, showing the ability of this therapy to change the activity of PFC, and the ability to regulate plasma corticosteroid, adrenocorticotropic hormone, and platelet 5-HT levels, etc. to relieve anxiety.

Although it has a long history, electroconvulsive therapy (ECT) remains a controversial treatment option for severe anxiety disorders [52]. According to Fox, ECT results in a form of unconscious aversive conditioning, which suggests that most patients, if not all of them, have intense dread that gets worse during the procedure [53]. Even though traditionally ECT was accepted as a treatment that helped patients overcome their severe concerns associated with pharmacy convulsive therapy [54]. Sadowsky makes a strong case that people's dread of ECT is rooted in social memory of ominous usage rather than just prejudice.

3.2. Medicine treatment for anxiety

3.2.1. Neuroenhancement of exposure therapy. Despite the substantial amount of research supporting CBT as the gold standard solution for anxiety disorders, some combinations of methods may increase effectiveness [55]. In some CBT treatments for anxiety, fear extinction learning processes are used by confronting the feared stimulus [10]. Neuroenhancers, also known as cognitive enhancers, may be useful in enhancing adaptive learning that takes place during therapy, according to recent studies. Extinction memories exhibit lability and fragility, employing a terminology derived from the field of learning theory. Therefore, an important target for pharmacotherapy is to identify pharmaceutical agents that aid in the formation, maintenance, and potentially context-independent nature of extinction memories [56]. One strategy for reaching this objective is to add medications as cognitive enhancers to exposure treatment in order to speed up the extinction learning process. For example, successful fear extinction is linked to increased extracellular noradrenaline levels in the mPFC [57], and noradrenaline can increase neuronal excitability in extinction-relevant brain areas such as IL [58]. Cain et al. conducted a study which revealed that the administration of yohimbine promoted the process of extinction for both cue and context fear [58]. The administration of propranolol, a β-receptor antagonist, resulted in the continued incubation of cue fear (Figure 3). Conversely, the administration of yohimbine, an α2-receptor antagonist, resulted in the sustained extinction of cue fear. The findings of this study suggest that Norepinephrine has a beneficial effect on the development of fear extinction memories in mice. According to research by Powers et al. mainly using young adults as samples, yohimbine combined with CBT can help individuals with social anxiety disorder and claustrophobia phobia feel less anxious [59].

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However, yohimbine does not support and facilitate virtual exposure therapy for patients who fear flying in a study [60].

3.2.2. GABAergic medications. One of the most important examples of GABAergic medications is benzodiazepines. The GABA-A-benzodiazepine receptor complex, which is coupled to the chloride channel, includes the benzodiazepine receptors, which are where benzodiazepines bind [61]. Benzodiazepines have been widely employed for the treatment of anxiety and continue to be extensively prescribed within the field of psychiatry globally, despite the emergence of negative perceptions surrounding its utilization in professional contexts [62].

A wide variety of conditions can be treated with benzodiazepines, which act as GABA-A agonists. The aforementioned problems include alcohol withdrawal, agitation or hostility, anesthesia, catatonia, mania, sleeplessness, muscular spasms, epilepsy or seizures, and movement abnormalities [63]. When used in the short term, benzodiazepines are recommended as the risk/benefit ratio is positive (Figure 3) [64].

3.2.3. Selective reuptake inhibitor. SSRIs include fluvoxamine, fluoxetine, sertraline and paroxetine. Despite their difference in pharmacological properties, the common effect of them is serotonin transporter inhibition [65]. In an experiment by Hjorth et al., two groups of patients with anxiety disorders were created [66]. The covert group was given escitalopram, which was falsely claimed to be an active placebo in a cover narrative, while the overt group got accurate treatment information. The current research provides evidence supporting the crucial involvement of dopamine neurotransmission in the therapeutic mechanisms of SSRIs and psychological factors contribute significantly to anxiolytic effects of SSRIs. The binding of dopamine transporters in the putamen, pallidum, and thalamus exhibited an increase with covert SSRI therapy, but it shown a reduction in the overt treatment group [66]. It may be deduced that elevated expectations have a positive correlation with enhanced levels of progress.

Selective noradrenaline reuptake inhibitor (SNRI) is also a medicine for chronic treatment of anxiety. Results from Iris et al. showed the value of SSRIs and SNRIs in the treatment of anxiety disorders in children and adolescents [67]. Ipser et al. found that twice as many patients reacted to the drugs as to the placebo, showing that SSRI and SNRI therapy is helpful for treating pediatric anxiety disorders and that the therapeutic benefits exceed the therapeutic drawbacks [68].

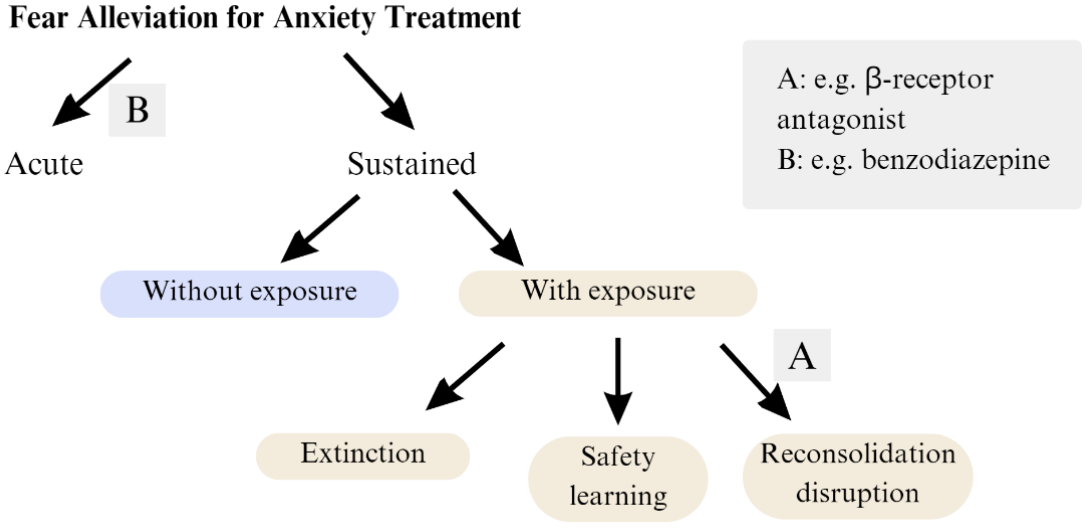

Figure 3. Various methods of anxiety reduction and potential pharmacological intervention locations. A: Propranolol led to persistent incubation of cue fear. B: Benzodiazepines are recommended as the risk/benefit ratio is positive when used in short term [55, 58, 64].

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4. Conclusion

This paper delves into the intricate neural circuits associated with anxiety disorders and explores the various treatment modalities available for managing this complex mental health condition. There exist many neural circuits, such as amygdala, PFC, BNST, and hippocampus, play crucial roles in the regulation of anxiety. The interactions between these brain regions, such as the CeA-BLA circuits and BLA-PFC circuits, provide valuable insights into the underlying mechanisms of anxiety disorders. Besides, this article focuses on the treatment options available for anxiety disorders, which are broadly categorized into medicine and non-medicine approaches. Non-medicine treatments like cognitive therapy and behavior therapy, with a particular emphasis on exposure therapy, offer promising avenues for managing anxiety disorders. Alternative treatments like acupuncture and ECT are explored, contributing to the growing understanding of non-pharmacological interventions for anxiety disorders. Additionally, medications targeting neural enhancement, such as noradrenaline agonists, GABAergic medications, SSRIs, SNRIs and so on, play important roles in promoting relaxation and reducing anxiety.

Anxiety disorders are a complex and delicate group of mental health disorders that need careful consideration and treatment. However, the mechanism of neural circuits for anxiety disorder remains unclear. For instance, the long-term efficacy of BZD anxiolytics is yet unknown, hence their long-term usage is not advised for the treatment of anxiety disorders. In addition, long-term BZD usage has been linked to adverse effects, including cognitive decline [69], fractures from falls [70], and impaired driving [71]. A thorough knowledge of the dynamic interactions taking place within the dispersed networks underpinning anxiety is required before the brain circuits for anxiety disease can be fully appreciated. The function of specific system components can be understood by optogenetic investigations of the individual pathways within circuits that are involved in the interpretation and assessment of external inputs. Examining the comorbidity of psychiatric diseases may provide an essential hint as to how these intricate networks could interact and affect one another's activity.

From medication, cognitive behavioral therapy, to psychotherapy, people with anxiety disorders have a variety of treatment options. Understanding the neural circuits involved in anxiety can help guide treatment decisions and ultimately improve patient outcomes.

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