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Review Article

Mechanisms of exercise against anxiety disorder: A review of the research progress

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ABSTRACT

Objective: This review aims to explore the efficacy of exercise in the treatment of anxiety disorders and its underlying mechanisms, summarizing recent research advances and focusing on the potential biological and psychological pathways through which exercise exerts its anxiolytic effects.
Methods: To ensure comprehensive coverage of relevant studies, we conducted a systematic search in databases such as PubMed, Web of Science, and Embase, combining MeSH terms with free-text terms. Keywords included "exercise," "physical activity," and "anxiety disorder."
Results and conclusions: Current research widely supports exercise as a safe and effective intervention for anxiety. Both aerobic exercise and resistance training have shown significant anxiety-reducing effects across various populations. The mechanisms of action can be categorized into three main types: cellular and molecular mechanisms, systemic immune effects, and behavioral and cognitive pathways. Different forms of exercise have distinct advantages: aerobic exercise is suitable for the general population, resistance training is beneficial for individuals with coexisting physical conditions, and low-intensity exercises such as yoga and Tai Chi are suitable for pregnant women, the elderly, or postoperative recovery patients. Given its good safety profile and broad applicability, moderate exercise should be considered a first-line treatment for mild anxiety and an adjunctive intervention for moderate to severe anxiety. Future research should further clarify the mechanistic differences between various exercise modalities and promote the development of individualized exercise prescriptions.

1. Introduction

Anxiety disorders are typically characterized by persistent feelings of anxiety or fear, irritability, difficulty concentrating, and sleep disturbances. As the most prevalent mental health condition, the World Health Organization reported anxiety disorder affected approximately 301 million people globally in 2019, however, only 27.6% of individuals with anxiety disorder receive treatment,[1] and some patients remain undertreated due to insufficient empirical support for certain treatments, resistance to psychotherapy and psychotropic medications, and adverse medication side effects,[2] resulting in varying levels of impairment. Among U.S. adults with anxiety disorders, an estimated 22.8% experience severe impairment, 33.7% moderate impairment, and the majority have a mild impairment (43.5%) according to a survey done by Havard Medical College.[3]

The treatment of anxiety disorders includes pharmacological therapy,

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Abbreviations

m6A	N6-methyladenosine
mPFC	medial prefrontal cortex
BDNF	brain-derived neurotrophic factor
SIRT1	silent information regulator 1
IGF-1	insulin-like growth factor 1
DLPFC	dorsolateral prefrontal cortex
WHO	The World Health Organization
PrL	prefrontal cortex
FMRP	Fragile X mental retardation protein
NE	norepinephrine
HPA	hypothalamic-pituitary-adrenal
RCT	randomized controlled trial

psychological interventions, and exercise-based approaches. Currently used anti-anxiety medications are often associated with varying degrees of side effects, including the risk of dependence, increased risk of dementia, higher suicide risk, as well as gastrointestinal disturbances, headaches, and drowsiness.[4–7] As a result, growing attention has been directed toward non-pharmacological interventions. Among these, exercise has emerged as a promising and effective rehabilitation strategy for anxiety disorders due to its safety profile and broad health benefits.

A growing body of evidence highlights the therapeutic benefits of exercise in anxiety recovery. Exercise can improve mood regulation and alleviate anxiety symptoms through multiple mechanisms, such as modulating neurotransmitters, enhancing neural plasticity, improving immune function, and promoting psychological adaptation. A randomized controlled trial (RCT) showed that a 12-week exercise intervention significantly reduced anxiety levels in patients with chronic anxiety, with an odds ratio (*OR*) of 4.88 (95% *CI*: 1.66–14.39).[8] Compared to pharmacological treatments, exercise interventions offer excellent safety, compliance, and applicability, and have been shown to produce positive anti-anxiety effects in various populations.[9–12] Furthermore, exercise can enhance cardiovascular function, improve quality of life, and help reduce anxiety and accelerate recovery in postoperative patients.[13–15] Various forms of exercise, including aerobic exercise, resistance training, yoga, and Tai Chi, have all been shown to have varying degrees of anti-anxiety effects.[16,17] In summary, exercise, as a multidimensional and low-side-effect non-pharmacological intervention, holds great potential for application in anxiety disorder treatment. However, significant differences exist between populations in terms of physiological conditions, psychological stressors, and exercise tolerance, which can influence their response to exercise interventions. Therefore, conducting tailored exercise intervention studies for different populations is crucial for enhancing anti-anxiety efficacy and clinical feasibility.

The World Health Organization (WHO) Guidelines recommend that all adults engage in at least 150–300 minutes (min) of moderate to vigorous physical activity per week for health benefits.[18] This review aims to explore recent advancements in the mechanisms by which exercise mitigates anxiety, summarize recent research trends and accomplishments, identify existing gaps, outline future research directions, and offer practical exercise recommendations for the prevention and treatment of anxiety disorders.

2. Method

To ensure comprehensive coverage of relevant research, we combined MeSH terms with free-text terms and conducted a search in databases such as PubMed, Web of Science, and Embase, using keywords such as “exercise,” “physical activity,” and “anxiety disorder.” Inclusion criteria were: experimental or review studies focusing on exercise interventions and their effects on anxiety. Exclusion criteria were: studies for which abstracts or full texts were unavailable, interventions unrelated to exercise, or studies with unclear subject populations. A total of approximately 70 studies meeting these criteria were included to support the content and discussion of this review.

3. Results

3.1. Evidence for exercise as an anxiolytic

3.1.1. Dose-response relationship between exercise and anxiety

Research indicates a significant link between sedentary behavior and increased mental illness, such as anxiety, along with decreased psychological well-being, including satisfaction with life and happiness.[19] Several studies have established a notable dose-response relationship between exercise and anxiety reduction. As exercise intensity increases, the degree of anxiety relief also tends to increase progressively. Regular moderate-to high-intensity exercise has demonstrated more substantial improvements in mood compared to low-intensity exercise,[20] with supervised and consistent exercise programs proving particularly effective in anxiety management. Notably, more significant mood improvements were observed with exercise sessions exceeding 3 times per week, lasting 20–60 min each.[21,22] Together, these findings suggest that gradually increasing exercise duration and intensity, according to individual tolerance levels, can be beneficial for both preventing and recovering from anxiety.

While exercise is generally recognized as effective for alleviating anxiety, individual responses to exercise interventions can vary, influenced by factors such as age, health status, and exercise baseline. For example, elderly individuals, whose physical condition may not tolerate high-intensity exercise, may benefit more from gentler activities, such as walking or Tai Chi. One study found that engaging in moderate-intensity activities, such as brisk walking for 10 min per day, 5 days a week, can reduce the risk of generalized anxiety disorder in older adults.[23] In adolescents, moderate-intensity aerobic exercise has been shown to improve emotional stability.[24]

Additionally, exercise is beneficial for certain special populations who may not be suitable for medication use. For instance, pregnant women can effectively alleviate pregnancy-related anxiety and reduce complications through low-to-moderate intensity exercise, improving labor expectations.[7,25] For lung cancer patients, moderate exercise can also improve anxiety and depression levels during treatment.[26]

Therefore, when designing exercise intervention programs, it is essential to consider individual differences and tailor strategies to achieve optimal anti-anxiety effects.

3.1.2. Comparison of the effects of different exercise modes on anxiety

The comparison of various exercise modes and their effects on anxiety has been a topic of interest. Studies have shown that both aerobic and resistance training offer therapeutic benefits for anxiety, with aerobic exercise showing greater efficacy for general anxiety, while resistance training appears more effective for anxiety related to specific medical conditions.[17,27,28] Individuals engaged in both aerobic and resistance training reported lower levels of anxiety and higher cognitive functioning compared to those who exclusively performed either aerobic or resistance training.[29] In addition, activities such as yoga, Tai Chi, and meditation have also been found to be beneficial for anxiety treatment.[30,31] For individuals who are physically unable to engage in aerobic or resistance exercises (such as postoperative or cancer patients), these activities can serve as supplementary forms of exercise to enhance the effectiveness of anxiety treatment. See Figure 1.

3.2. Mechanisms of exercise anti-anxiety

Exercise can regulate neural function, synaptic plasticity, and emotional states through various cellular and molecular mechanisms, thereby exerting anti-anxiety effects. Among these, m6A modification, the mTOR pathway, brain-derived neurotrophic factor (BDNF), lactate metabolism, and changes in neurotransmitters are considered key

biological pathways. These mechanisms primarily involve the regulation of intracellular signaling and gene expression in neurons, playing a central role in the onset and alleviation of anxiety.

3.2.1. Cellular and molecular mechanisms

3.2.1.1. The medial prefrontal Cortex (mPFC). Chronic stress can induce anxiety, and one of its key mechanisms involves methylation regulation in the brain. Studies have shown that chronic stress leads to a decrease in RNA N6-methyladenosine (m6A) levels in the medial prefrontal cortex (mPFC), which is associated with the upregulation of the demethylase Alkbh5 expression. This, in turn, triggers metabolic disorders and functional impairments, contributing to the onset and development of anxiety.[32] Additionally, it has been found that the activity of the mTOR signaling pathway in the brain significantly decreases under anxiety conditions, which is closely related to impaired synaptic plasticity and emotional regulation dysfunction.[33]

Exercise can reverse these changes through multiple mechanisms. On the one hand, it enhances the liver's synthesis of methyl donors, inhibiting the expression of ALKBH5 in the prefrontal cortex, thereby promoting the recovery of m6A levels.[34] On the other hand, m6A can inhibit the expression of Fragile X mental retardation protein (FMRP) in the brain, relieving its suppression on the mTOR pathway, ultimately promoting neural network remodeling, synaptic transmission, and myelination, which helps alleviate anxiety-like behaviors.[33,35]

Moreover, exercise can directly activate the mTOR pathway through other pathways. Studies have found that exercise-induced BDNF secretion can upregulate mTOR downstream signaling, thereby promoting cognitive and emotional regulation.[36] Therefore, m6A modification and the mTOR signaling pathway may together form an important molecular mechanism network through which exercise improves anxiety.

3.2.1.2. Neuroplasticity. Neuroplasticity refers to the central nervous system's ability to adapt to internal and external stimuli.[37] Exercise can positively impact the nervous system in several ways, enhancing mood and reducing anxiety levels. The hippocampus, critical for mood regulation, benefits significantly from improved neural function, aiding in anxiety control.

Studies have shown that lactate produced during exercise can cross the blood-brain barrier via monocarboxylate transporters (MCTs), accumulating in the brain, with this process significantly enhanced during exercise.[38,39] Research by Van Hall and colleagues further confirmed that lactate becomes an important energy source for the brain during exercise, supporting the maintenance of brain tissue function.[40] Notably, lactate crossing the blood-brain barrier has been shown to activate silent information regulator 1 (SIRT1) in the hippocampus,[41] initiating the PGC-1α/FNDC5 pathway, which promotes the expression of BDNF, thereby improving hippocampal structure and function.[41–44]

In addition, exercise can induce the secretion of the myokine cathepsin B from skeletal muscles. This molecule can also enter the hippocampus and activate the aforementioned BDNF signaling pathway.[42] Exercise also promotes the expression of RGS6 in neural cells, reducing the sensitivity of GABAB receptors in neurons, which positively impacts emotional regulation and cognitive function.[45] The increase in irisin concentration induced by exercise can also promote synapse formation and neuroplasticity.[46–49] These mechanisms work together to alleviate anxiety symptoms.

However, there are still some discrepancies regarding the effects of different exercise modalities on BDNF expression. Some studies suggest that short-term aerobic exercise is more likely to induce an increase in BDNF, while in individuals who engage in long-term regular exercise, serum BDNF levels tend to decrease compared to sedentary individuals.[50,51] This phenomenon may reflect the complex dynamic relationship between central and peripheral BDNF distribution. In contrast, the effects of resistance training vary widely across different studies, potentially influenced by factors such as exercise intensity, duration, and individual characteristics.[52,53] While preliminary evidence suggests some heterogeneity in BDNF responses, there is a lack of systematic subgroup comparisons or meta-analyses to quantify these differences. This highlights the need for further research to explore the effects of various exercise parameters on neuroplasticity markers.

Additionally, some studies have shown that exercise can upregulate insulin-like growth factor-1 (IGF-1) in hippocampal cells, thereby promoting the expression of synapsin-1 and synaptophysin, which may also be an important mechanism underlying its anti-anxiety effects.[54]

3.2.1.3. The change of neurotransmitters. Research indicates that the levels of neurotransmitters in the brain change after exercise, leading to physiological alterations. Long-term exercise reduces the number of 5-HT receptors in brain neurons and decreases receptor sensitivity, thereby alleviating anxiety-like symptoms. The mechanism may involve increased 5-HT concentrations post-exercise, where repeated stimulation of 5-HT receptors through prolonged exercise results in receptor desensitization and downregulation.[2,55] Additionally, elevated 5-HT levels can activate 5-HT_{1A} receptors, exerting inhibitory effects that reduce neuronal excitability.[56] During exercise, increased blood lactate levels can cross the blood-brain barrier and enter brain tissue, leading to elevated GABA concentrations in the dorsolateral prefrontal cortex (DLPFC). As an inhibitory neurotransmitter, GABA decreases neuronal excitability, thereby reducing anxiety.[57–59] Furthermore, exercise-mediated elevation of norepinephrine (NE) levels can activate the GPCR-MAPK-PI-3K pathway, promoting the release of more BDNF by neurons and improving neuronal function.[60]

3.2.2. Systemic immune effects

Anxiety is often accompanied by immune system dysregulation and dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. Exercise interventions can alleviate inflammatory states and stress responses at the systemic level by influencing the expression of immune factors, modulating microglial activity, and regulating HPA axis-related proteins such as FKBP5 and Crabp1. These mechanisms highlight the systemic regulatory effects of exercise on the immune network.

Anxiety has detrimental effects on the immune system, as chronic stress activates the immune system and disrupts the hypothalamic-pituitary-adrenal (HPA) axis, leading to an imbalance between pro- and anti-inflammatory responses.[61] This disruption is characterized by increased microglia activation within the brain, elevated levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α), and altered expression of synaptophysin, impacting normal neuronal function through a pathological process similar to that of autoimmune diseases.[62]

10.1016/j.eqrea.2025.100392Research has identified high expression of Crabp1 in the hypothalamus and pituitary, with FKBP5—a key regulatory protein in the HPA axis—potentially being a target of Crabp1.[63] Studies have shown that individuals who engage in regular exercise exhibit significantly reduced levels of FKBP5 compared to sedentary individuals, suggesting an influence on HPA axis function.[64] Based on this, we hypothesize that exercise may promote methylation of the Crabp1 gene promoter, leading to decreased Crabp1 expression, which in turn reduces FKBP5 expression and cortisol secretion, thereby alleviating anxiety-like symptoms. However, there is currently a lack of direct evidence supporting the hypothesis that “exercise induces Crabp1 methylation,” and future research is needed to verify this through systematic epigenetic studies at the population level.

Besides, studies have also shown that after prolonged exercise, cortisol peaks more rapidly and its concentration returns to baseline more quickly, indicating improved stress resilience.[65] Concurrently, exercise leads to a decrease in hippocampal microglia, an increase in anti-inflammatory cytokines (e.g., IL-10, TNF-β), and a reduction in peripheral neutrophils,[66–68] collectively contributing to the attenuation of low-grade chronic inflammation both centrally and peripherally and protecting nervous system function.

3.2.3. Behavioral and cognitive pathways

In addition to its direct effects on the nervous and immune systems, exercise also alleviates anxiety through psychological and behavioral mechanisms. For example, the bodily sensations induced by exercise can serve as a form of interoceptive exposure, helping individuals build tolerance to anxiety-related physiological responses and enhancing psychological resilience. Moreover, exercise can divert attention, interrupt anxiety-driven avoidance behaviors, and exert positive effects on cognition and emotion. These pathways form a critical psychological basis for the anxiolytic effects of exercise.

Anxiety sensitivity refers to an individual's heightened perception of anxiety-related sensations, encompassing alertness to stimuli that may induce anxiety, concern about potential anxiety experiences, and the motivation to avoid anxiety-provoking situations.[69] This concept can be further categorized into three dimensions: fear of physical, cognitive, and social aspects.[70]

Studies have demonstrated that brief bouts of aerobic exercise effectively reduce anxiety sensitivity.[71] Exercise elicits physiological responses—such as increased heart rate, cardiac output, sweating, and respiratory rate—similar to those experienced during anxiety episodes, offering a form of interoceptive exposure. Research suggests that repeated exposure to fearful stimuli in the absence of negative outcomes can diminish fear responses. Similarly, exercise helps individuals recognize that these sensations are normal physiological responses and that enduring discomfort during exercise can build tolerance, promoting exercise adherence in the long term.[72–74] Moreover, contrary to avoidance behaviors associated with anxiety, exercising necessitates tolerating uncomfortable physical sensations, which can enhance psychological resilience. Additionally, exercise serves as a distraction from daily worries, leading to transient reductions in anxiety immediately post-exercise.[2] See Figure 2.

4. Discussion

This paper examines the mechanisms and effects of exercise as a treatment for anxiety and provides a summary of recent research advances and key findings. A growing body of research indicates that regular exercise—particularly moderate-intensity aerobic activity—has a beneficial effect on alleviating anxiety, demonstrating a potential dose–response relationship. Different types of exercise offer distinct advantages in anxiety intervention: aerobic exercise is suitable for individuals with generalized anxiety; resistance training may be more targeted for patients with comorbid physical illnesses; and mind–body exercises such as yoga and tai chi provide feasible options for those with physical limitations. These interventions not only improve emotional symptoms but have also attracted widespread attention due to their safety and scalability.

Although increasing research shows that regular exercise helps alleviate anxiety, there is significant variability in individual responses to exercise interventions, especially in terms of exercise intensity. Some studies suggest that moderate to high-intensity exercise is generally beneficial for anxiety, but there is also evidence indicating that excessive high-intensity exercise may trigger or exacerbate anxiety symptoms in certain populations.[75–77] Therefore, it is currently difficult to establish a universal dosage recommendation. At present, we recommend tailoring exercise plans based on an individual's physical condition, past exercise experience, and psychological responses. In general, moderate-intensity aerobic exercises (such as brisk walking, jogging, cycling, etc.) for at least 150 min per week are considered a safe and effective option for most anxiety patients. For frail populations (such as those in the postoperative recovery period, pregnant women, and elderly individuals), low-intensity exercises like Tai Chi or yoga may be substituted.[9,78] After implementing exercise interventions, it is important to assess the body's response to exercise and adjust the exercise plan accordingly to maximize therapeutic effects while minimizing side effects. Future research requires more randomized controlled trials and meta-analyses to identify the most effective exercise intensity and type for improving anxiety.

At the mechanistic level, exercise promotes neuroplasticity, improves the function of key brain regions such as the prefrontal cortex and hippocampus, and thereby regulates emotional states. The mTOR signaling pathway is one of the core pathways mediating this process, although further research is needed to clarify how it regulates the function of mPFC neural circuits. At the same time, BDNF is a key factor in exercise-induced neuroplasticity, and its signaling mechanisms (such as the involvement of second messengers) and optimal induction methods remain unclear. Immune regulation is also an important mechanism underlying exercise's anti-anxiety effects. Exercise can lower cortisol levels by modulating the Crabp1/FKBP5 axis, alleviating the stress response, with related mechanisms such as promoter methylation changes warranting attention. In addition, exercise reduces microglial activation and downregulates peripheral neutrophils, improving both central and peripheral inflammation, thus supporting neural system homeostasis.

Future research should prioritize epigenomics, particularly changes in m6A methylation, to further explore the molecular mechanisms through which exercise impacts anxiety. Existing studies have demonstrated that RNA modifications, such as m6A, play crucial roles in neuroplasticity and emotional regulation. Exercise can influence the mTOR pathway by modulating m6A-related enzymes (such as ALKBH5), thereby exerting anti-anxiety effects. Therefore, integrating m6A sequencing, chromatin accessibility analysis, and other epigenomic technologies can systematically explore how exercise affects transcriptional regulatory networks in key brain regions (such as the mPFC and hippocampus), providing new insights into the role of exercise in neural circuits and emotional regulation.

Further research should also focus on biomarkers that can guide personalized exercise prescriptions. For example, BDNF levels can reflect neuroplasticity responses, cortisol rhythms indicate stress states, lactate can mediate VEGF expression and BDNF activation through HCAR1, and IGF-1 has been confirmed to play an important role in neurogenesis and synaptic plasticity. These biomarkers can help more precisely evaluate exercise effects and intervention responses. Additionally, the role of epigenetic mechanisms in neural regulation and emotional management is gradually emerging, and future studies could use m6A sequencing and other omics technologies to explore the molecular basis of exercise's regulation of anxiety.

In conclusion, exercise is a safe, effective, and widely applicable intervention for anxiety. Future research should integrate physiological mechanisms, biomarkers, and differences in behavioral responses, conducting high-quality randomized controlled trials and multi-center longitudinal follow-ups, to advance exercise interventions towards a more personalized and precise approach. See Figure 3.

CRediT authorship contribution statement

Zhengyuan Fang: Writing – review & editing, Data curation, Writing – original draft, Conceptualization. **Yuan Qian:** Project administration, Writing – original draft, Methodology. **Shuya Sun:** Conceptualization, Writing – review & editing. **Haochen Qin:** Writing – review & editing. **Yulian Zhu:** Visualization, Resources. **Jiayin Tang:** Visualization, Conceptualization, Project administration. **Shuo Chen:** Supervision, Project administration. **Zhiwen Luo:** Project administration, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendices.

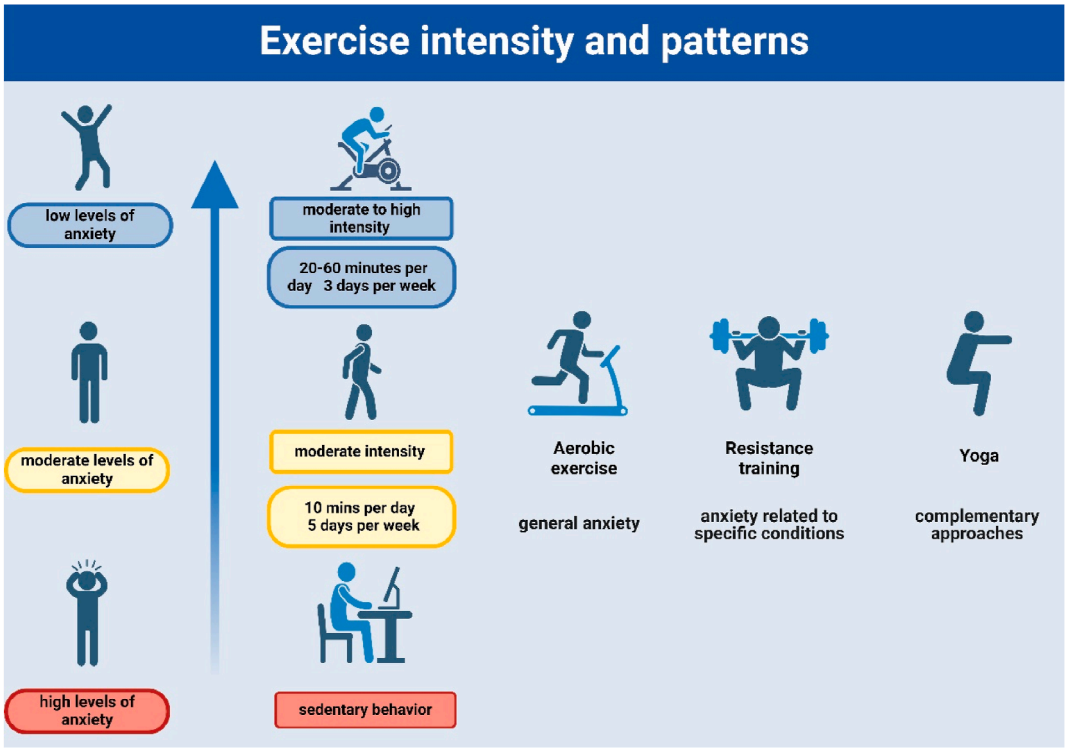

Fig. 1. Dose-response relationship between exercise and anxiety; the effects of different exercise patterns.

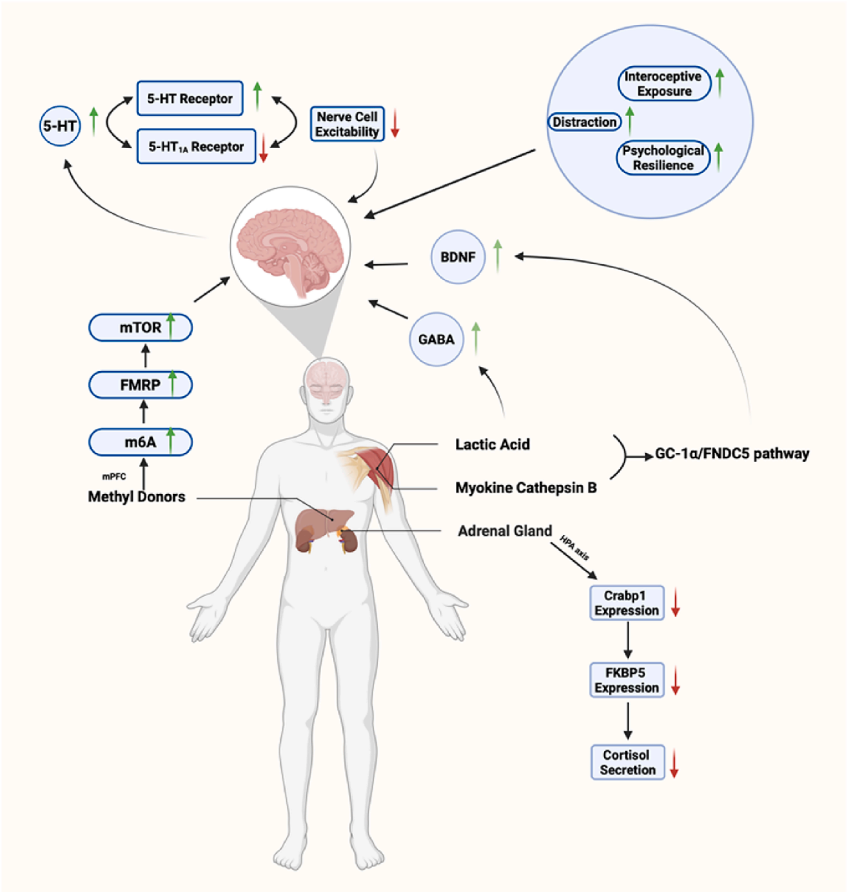

Fig. 2. Mechanisms of exercise anti-anxiety m6A: N6-methyladenosine; mTOR: mammalian target of rapamycin; BDNF:brain-derived neurotrophic factor; mPFC: medial prefrontal cortex; GABA: γ-Aminobutyric Acid; BDNF: brain-derived neurotrophic factor

Fig. 3. Possible future research directions

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