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The Dynamic Mechanism of Music Intervention in Reshaping Depression-related Brain Networks: Key Targets, Specific Patterns, and Comparative Advantages over Medication

Jianing Yuan

Changsha Changjun High School, Changsha, Hunan, 410000, China

ABSTRACT
The essence of depression lies in the abnormality of brain networks such as the limbic system - prefrontal cortex brain network, the hippocampus - amygdala brain network and the reward brain network. Music therapy is another effective intervention for depression besides drug therapy, but the mechanism of music therapy on the brain network for depression is still unclear. What are the brain networks of music intervention? Which brain networks are involved in music intervention? What are the differences between the brain networks of music intervention and drug therapy? Based on the clinical and basic evidence in recent years, this paper presents several core viewpoints of music intervention, suggesting that the core brain networks of music intervention include the prefrontal cortex - amygdala emotional network, the hippocampus - prefrontal cortex memory - emotion integration network, and the nucleus accumbens - VTA reward network. Five-element music regulates the balance of the emotional network through serotonin, drum circle music regulates the balance of the reward network through dopamine, and individualized music regulates the emotional neural plasticity through BDNF and repairs the memory - emotion network. Compared with drug therapy, music therapy has unique advantages such as adjusting brain network connections, having no adverse reactions and preventing recurrence. This paper aims to construct a "target - pattern - advantage" model framework to provide an empirical basis for the standardized clinical development of music intervention.

KEYWORDS
Depression; Music intervention; Brain network; Neurotransmitter BDNF

1 Introduction

Depression, one of the most common diseases in the world, is characterized by core symptoms such as low mood, loss of pleasure, and cognitive impairment. The neural basis of depression involves abnormal structure and functional connectivity in multiple brain networks. Studies have shown that patients with depression have weakened functional connectivity between the frontal cortex (PFC) and the amygdala (mood disorder), impaired hippocampal neurogenesis (damaged memory-emotion connection), and activation of the ventral tegmental area-frontal (VTA) reward network (loss of pleasure) and other brain network changes [1-2].

At present, drug therapy is mainly used to treat SLLIs, such as depression. The disadvantages of drug treatment for depression are: it takes a long time for the drugs to take effect (about 4-6 weeks), 30% of patients are insensitive to the drugs, long-term use of drugs has side effects (such as dizziness, gastrointestinal reactions, etc.), and the recurrence rate after drug withdrawal is high (more than 50%). Therefore, exploring safe and efficient non-drug intervention methods has become an important direction for the prevention and treatment of depression.

As a non-invasive music therapy based on physiological and psychological regulation, music intervention has been proven effective for patients with depression due to its simplicity and multiple points of action. It can reduce the HAMD score by 20-30%, improve sleep quality and social function [3-4]. Neuroimaging studies suggest that music intervention can activate the connections of key brain regions such as the limbic system - prefrontal cortex and reward circuit, or exert its effects by regulating brain network relationships [5-6].

However, there are still several important scientific questions in the above research: First, among the numerous brain networks related to depression, which ones are the effective targets for music intervention? Second, what are the differences in the mechanisms of the five-element music, drum circle music, and individualized music? Third, what are the characteristics of the mechanism of music intervention on brain networks compared to drugs? And so on. This study focuses on the above questions and integrates from the perspectives of neural plasticity, neurotransmitter homeostasis, inflammatory response, and brain network remodeling, in an attempt to establish a relatively complete mechanism framework to support music intervention.

2 Key brain network targets for music intervention

There are many brain networks related to depression, but not all networks are sensitive to music intervention. Based on the accumulated neuroimaging and clinical evidence, the prefrontal-amygdala emotional regulation network, the

hippocampus-prefrontal memory-emotion integration network, and the nucleus accumbens-VTA reward network are the main targets for music intervention. Their functional disorders are significantly related to the severity of the disease and are the most sensitive to music stimulation.

2.1 Prefrontal-amygdala emotional regulation network

The prefrontal-amygdala circuit is the regulatory center of emotions. The prefrontal cortex exerts an inhibitory effect on the amygdala from top to bottom (inhibiting the amplification of excessive negative emotions), and the amygdala transmits emotional information to the prefrontal cortex for subsequent processing [7, 2]. In depression, the function of the above circuit is reduced, the inhibition of the amygdala by the prefrontal cortex is weakened, and negative emotions are difficult to suppress, which is significantly related to the elevated scores of depression and anxiety/somatization in the HAMD [1, 5].

Music intervention has the greatest impact on this network. Song Qi et al. (2025) found through fMRI technology that after three months of angular tone music intervention, the functional connectivity level of the prefrontal cortex - amygdala in patients with depression increased by 27.6% compared with the control group, and it was significantly negatively correlated with the reduction of HAMD scores ($r = -0.38$, $P < 0.05$) [7]. This is related to the level of neurotransmitters, specifically 5-HT. Angular tone music increases the level of 5-HT in patients' serum by 19.2% (118.4 ± 21.7 ng/mL vs 146.3 ± 25.9 ng/mL), which can increase the inhibitory projection of prefrontal cortex neurons to the amygdala [1, 8]. The molecular mechanism is that the vibration of music sound waves can increase the activity of tryptophan hydroxylase (TPH, serotonin homologous color homologous) and the synthesis of 5-HT, increase 5-HT1A receptors, and thereby improve the signal transmission efficiency of the emotional regulation network [7, 2].

2.2 Hippocampus - prefrontal cortex memory - emotion integration network

The hippocampus is responsible for encoding memory and experience. The area connected to the prefrontal cortex links the encoding of emotions and memory ("sad memory" encoding). In patients with depression, this network suffers from two types of damage simultaneously: smaller hippocampal volume (on average, smaller than that of normal people), lower neurogenesis rate, and weaker hippocampus - prefrontal cortex connection, resulting in "emotional memory bias" (preservation of negative events) [5].

Music intervention may influence this network through multiple pathways. In terms of structural changes, Wang Kaixin et al. (2025) reported that patients with mild PSD experienced a 2.3% increase in hippocampal volume and a 15.1% rise in serum BDNF levels (352.88 ± 66.46 pg/mL vs 408.76 ± 5.33 pg/mL) after a 4-week five-element music intervention. Moreover, there was a positive correlation between the increase in BDNF levels and the expansion of hippocampal volume ($r = 0.42$, $P < 0.01$) [1]. BDNF is a neuroplasticity factor that can promote the proliferation of neural stem cells in the hippocampal dentate gyrus, providing a structural basis for network repair [5].

In addition, targeted music intervention also has advantages in improving functional connectivity. Ning et al. (2022) found that after 8 weeks of familiar music exposure, the effective connection strength of adolescent depression patients increased by 19.4%, and the delayed recognition score increased by 17.6%, which was attributed to the improvement of emotional memory integration ability [5, 9]. Music intervention can achieve therapeutic effects by optimizing the network microenvironment through improving the inflammatory factor levels of depressed patients. Zhang et al. (2024) discovered that after one week of music intervention and one week of music training, the serum IL-6 level of PDS patients decreased by 31.7% (12.6 ± 3.2 pg/mL vs 8.6 ± 2.1 pg/mL), reducing the death of hippocampal neuron cell bodies and protecting connections [5].

2.3 Nucleus accumbens - VTA reward network

The reward circuit formed by the nucleus accumbens and VTA plays a crucial role in pleasure sensation and motivational behavior. The weakening of this circuit is the neural basis for anhedonia and motivational impairment in depression. In depressed patients, the activity of dopaminergic neurons in this circuit is reduced, and the connection strength between the nucleus accumbens and VTA is weakened by 23-30%, and this connection strength is negatively correlated with SHA scores.

Music intervention has specificity in activating this network. Drum circle music can activate mirror neurons and increase dopamine secretion in the form of group interaction: Wu Lianfeng et al. (2025) found that adolescents with depression and non-suicidal self-injury who received 4 weeks of drum circle therapy had a 21.4% increase in urine HVA concentration, a 23.5% increase in the connectivity of the nucleus accumbens-VTA, and a 24.8% increase in the score of the Social Skills Performance Inventory (SSPI). The release of dopamine, which is mainly characterized by social interaction, alleviated the withdrawn behavior.

Personalized music activates the reward circuit through emotional arousal: Ning et al. (2022) found through fMRI research that when subjects heard music they liked, the connection related to the VTA and nucleus accumbens in adolescents increased by 27.3%, and the percentage of dopamine transporters (Verrandinoxin, VTA) increased by 1.56% (r correlation = 0.41, P < . 05). Due to the "emotion-reward" mechanism, personalized music can better alleviate the symptoms of "anhedonia" compared to music without personalized intervention [8].

3 Specific mechanisms of different music intervention models

The specificity of brain network regulation by different forms of music intervention (Five-Element Music, Drum Circle Music, Personalized Music, etc.) stems from the differences in intervention forms (individual/group), intervention stimuli (rhythmic beats/ melodies), and theoretical bases (Traditional Chinese Medicine theory/psychological resonance), thus resulting in different mechanisms of action.

3.1 Five-element music: emotion network regulation based on the "five tones enter five organs" theory

Five-Element Music applies the Traditional Chinese Medicine theory of "Five Tones (Gong, Shang, Jue, Zhi, Yu) Enter Five Organs", matching specific tonal music stimuli to corresponding brain regions. Among them, the Jue and Gong modes are the most effective in stimulating the brain network of depression.

The "Liver-Invading" Effect of the Musical Piece "Eighteen Stanzas of a Reed Pipe" in the Horn Mode Mainly Engages the Prefrontal Cortex - Amygdala Emotional Network. It Primarily Activates the Left Prefrontal Cortex via the Fundamental Frequency Sound of 262Hz, which is Close to the Resonance Frequency of the Liver Belonging to Wood in the Left Side, Enhancing the Inhibitory Effect of the Cortical Layer on the Amygdala. Previous Studies Have Shown That Four Weeks of Horn Mode Music Therapy Reduced the HAMD Score of Patients with Liver Qi Stagnation Depression (Depressed Mood, Reduced Interest) by 28.7%. The Greater the Intensity of the Prefrontal Cortex - Amygdala, the Lower the Anxiety Score ($r = -0.38$, $P < 0.05$) [1-2]; Horn Mode Music Can Also Reduce IGFB-1, Cooperating with Cortisol to Protect Hippocampal Neurons and Indirectly Participate in the Emotional Network [1].

Palace mode music (such as "Spring River Moonlit Night"), "entering the spleen", regulates the synchrony of body movement and emotion integration through the insular prefrontal pathway. Combined with the horn mode, it is beneficial for improving the daily living ability of patients with post-stroke depression: Xia Wumei et al.'s (2024) research shows that the combination of the positive horn and positive palace modes can increase the BATel score of elderly PSD patients by 18.5 points and reduce IL-6 by 34.2% (better than the horn mode alone), with the advantage of multi-target intervention [2]. This is considered to be related to the reduction of sympathetic activity and the stability of autonomic nerve regulation at the slow tempo of palace mode music (60-70 beats per minute) [1].

3.2 Drum circle music: group interaction activates reward network dopamine

Drum circle music, in the form of group drumming, activates the reward network and social brain network through social contact and synchronous rhythm. Different from individual-level music intervention, it has a clear mechanism for correcting social function deficits.

One of the core processes is the activation of the mirror neuron network: during synchronous drumming, the superior temporal gyrus (a dense area of mirror neurons), the prefrontal cortex (with a 23.5% increase in functional connectivity), dopamine release (18.9%), and the activation of the nucleus accumbens and VTA [10, 8]; Wu Lianfeng et al. (2025) found that after 4 weeks of drum circle music intervention, there was a significant increase of 21.4% in HVA (a dopamine metabolite in urine) and 24.8% in the SSPI assessment scale, suggesting a high correlation between dopamine and the improvement of social functions.

Another very important mechanism is the "synchronous perception" in rhythm: the fixed (120 beats per minute) rhythm of drum circle music promotes increased activity in the nucleus accumbens and dorsal striatum, thereby alleviating motivational deficiency symptoms. When used in combination with drugs, the advantages of drum circle music can be more fully demonstrated: the HAMD score reduction rate (23.4%) in the drum circle combined with sertraline treatment was significantly higher than that of drug administration alone (16.8%). The neuroplasticity changes brought about by social interaction may enhance the drug's regulatory effect on the reward system.

3.3 Personalized music: repairing the plasticity of the emotional network

By using the music that patients enjoy (i.e., individualized music) to activate autobiographical memories and evoke emotional resonance, the hippocampus-prefrontal cortex memory-emotion integration network is restored and

reconstructed, with BDNF as the main mechanism for neuroplasticity and neuroemotional regulation.

On the one hand, familiar music activates the autobiographical memory encoding area of the hippocampus, thereby increasing the connection between the hippocampus and the medial prefrontal cortex. After 8 weeks of individualized music training, the delayed memory score of patients increased by 17.6%, which was closely related to a 2.1-fold increase in the mRNA content of BDNF in the hippocampus (neural regeneration). On the other hand, the selection of "emotion-matched" music (sad music) reduces the excessive activation of the amygdala (activity decreased by 21.3%), and after emotional adaptation, it promotes the management of emotions by the prefrontal cortex [8].

In addition, the rhythmicity in personalized brain music (such as a song that the patient likes) can enhance the topological optimization of brain networks: He Yujia et al. (2017) found that personalized music (in normal order) could increase the total clustering coefficient of brain networks by 12.7% and the average path length by 9.3%, and the small-world index by 18.5%, which was correlated with the improvement of structural music stimulation ($r = 0.62$, $P < 0.01$), suggesting that structural music stimulation has a certain promoting effect on the improvement of brain network efficiency [9].

4 The advantage mechanism of music intervention over drug treatment

Compared with therapeutic interventions such as SSSLI, music intervention has three major advantages in regulating brain networks: dynamic brain network connections rather than static connections, multiple target points in brain networks rather than regulating only one neurotransmitter, and low toxicity and side effects with good compliance, thereby exerting long-term protective effects on brain networks. Therefore, it has unique advantages in the treatment of depression.

4.1 Advantage one: regulation of dynamic brain network connections, not static balance of a single neurotransmitter

SSRI drugs mainly reduce 5-HT reuptake and increase neurotransmitter content, which is "static" (stabilizing neurotransmitter content) and cannot increase brain connections (such as task-rest connections between brain regions). Music intervention, on the other hand, can increase dynamic brain network connections, that is, rhythmic and rhythmic intervention promotes brain network connections, such as music with a tempo of 60-80 beats per minute.

He Yujia et al. (2017) found that compared with the drug group (7.2%), the small-world index of the depression brain network could increase by 18.5% after music intervention, and information transmission was more effective [9]. Cheng Yuhong et al. (2024) found that after 4 weeks of music therapy combined with SSLLIs treatment, the glucose metabolism rate of the DLPFC increased by 18.7% compared to the drug group, and was positively correlated with the reduction rate of HAMD ($r = 0.39$, $P < 0.05$), suggesting that the drugs can improve the metabolic activities of the brain network, and music intervention has a promoting effect. It is precisely due to these dynamic changes that music intervention is more likely to affect "emotional flexibility" (escaping from negative emotions).

4.2 Advantage two: multi-target regulation, avoiding the limitation of "single pathway dependence" of drug treatment

Drug treatment usually only targets a single neurotransmitter pathway (such as SSLLIs only using the 5-hydroxytryptamine system), and is prone to instability in efficacy due to receptor differences (such as differences in sensitivity of the receptor for the neurotransmitter), while music intervention acts on multiple neurotransmitter and inflammatory responses such as neural plasticity, neurotransmitters, inflammation, and network topology structure, forming a "multi-pathway synergy".

For instance, personal music intervention simultaneously increased 15.1% neuroplasticity (BDNF), 23.6% neurotransmitters (5-HT), 31.7% inflammation (IL-6), and 19.4% connectivity networks (hippocampus - prefrontal cortex). Therefore, the response rate of music intervention was approximately 70%, and the effective rate was 42% (compared to the 28% of ineffective drugs for depression), which is higher than that of 50% for discontinuation of medication for depression.

4.3 Advantage three: no side effects and high compliance

The side effects of drug treatment (such as nausea and insomnia caused by SSCLIs), the recurrence rate upon discontinuation (over 50%), etc., limit the continuity of drug treatment's protective effect on the continuous remodeling of brain networks. The music intervention treatment method is non-invasive and interesting, with better compliance (85%

and 62%), and it achieves the continuous remodeling of brain networks.

The follow-up study found that 6 months after the music intervention, the strength of the connection between the prefrontal cortex and the amygdala in the patients remained at 82% of the level after the intervention, and the recurrence rate was 21.3%, significantly lower than that of the drug group (48.5%). This is because under the music intervention, the plasticity of the nerves has undergone long-term changes. Fu et al. (2023) discovered in animal models that 4 weeks of music intervention increased the synaptic density of depressed mice by 38% compared to the control group after the intervention, and this increase was sustained for at least 8 weeks, while the drug group only had this effect for 4 weeks [5]. That is to say, the reconstruction of the brain network structure has greater long-term stability.

5 Mechanism integration and causal model

Music intervention reconstructs the depressive brain network: a collection of non-independent mechanisms, but a "hierarchical causal chain"! Based on the above evidence, the following causal model can be established.

Music (melody / rhythm / activity) → Activation of the central point (plasticity / neurotransmitters / inflammation) → Enhancement of important network connections (anterior cingulate cortex to / hippocampal cingulate cortex to / anterior hippocampus / frontal cingulate cortex) → Reduction of depression

Among them, neural plasticity is at the fundamental level: the activation of neurotrophic factors such as BDNF provides the material basis for synaptic remodeling and neuronal regeneration, and reconstructs important brain network structural connections; neurotransmitters and inflammatory regulation are at the intermediate level: the homeostasis of serotonin and dopamine, as well as the decrease of IL-6 and TNF-α, provide the "chemical microenvironment" for network functional connectivity; brain topological optimization is at the output level: the increase of small-world index and connection strength directly correspond to the enhancement of functions such as emotion regulation and reward processing.

This model emphasizes different intervention processes for each item. The five-element music focuses on the "neurotransmitter-balance-emotional network" process, the drum circle music on the "dopamine activation-reward-network" process, and the personalized music on the "neuroplasticity-memory-emotional network" process, providing guidance for the precise clinical "intervention targets".

6 Controversies and limitations

Although the research on the intervention mechanism of music intervention has made the above progress, it still has limitations: Although the research on the intervention mechanism of music intervention has made the above progress, it still has limitations: Most studies are single-center small samples ($n < 100$), mainly focusing on post-stroke depression and adolescent depression, and less involving subtypes such as elderly depression and bipolar depression, making it difficult to represent the entire population; Most studies are short-term studies (< 6 months), and it is unknown whether the long-term reshaping of the brain network (1 year) will be maintained, and most mechanism evidence comes from peripheral (serum) indicators (such as serum BDNF, IL-6) rather than brain internal (such as in vivo neurons) indicators; No "optimal music parameters" (i.e., 60 vs 120 beats/min rhythm, 60 dB vs 80 dB) have been found to correspond to the quantification of brain network, and no standardized scheme can be formulated [9]; Most studies use music combined with drugs as the control group, rather than directly comparing drugs, and it is impossible (i.e., the same treatment course of brain network changes) to quantify the benefits of intervention.

7 Conclusion and outlook

Music intervention can promote depression treatment by targeting the frontal-limbic emotional network, hippocampus-frontal lobe memory-emotional network, and nucleus accumbens-VTA reward network. The types of music intervention are different. The five-element music emphasizes regulating the emotional network, the drum circle music focuses on activating the reward network, and personalized music mainly aims to repair the damaged memory-emotional network; It is superior to drug treatment in regulating the dynamic changes of the brain network, multi-target combination, and maintaining stability time.

In future research, the following aspects need to be explored: (1) Conduct multi-center, large-sample studies to investigate the sensitivity of different depression subtypes to music intervention; (2) Utilize multimodal imaging systems such as fMRI/EEG to conduct long-term (more than one year) tracking scans of the chronic changes in the brain network; (3) Employ AI algorithms to conduct music intervention based on the attribute values of the brain network (such as the connectivity between the prefrontal cortex and the amygdala); (4) Conduct head-to-head comparative studies to quantify

the differences in brain regulation between music intervention and medication. These studies will facilitate the standardization and precision of music intervention in the prevention and treatment of depression.

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