



Emotional Inhibitory Effect of Music Therapy on Anxiety Neurosis Based on Neural Content Analysis in Hippocampus

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ABSTRACT

With the development of society, the incidence of Anxiety Neurosis has increased year by year, which has aroused widespread concern in the medical community. The current therapeutic treatment mainly relies on anti-anxiety drugs, but drug resistance, addiction and adverse reactions engendered have caused many problems and inconveniences to patients, thus music therapy is gradually recognized as a safe and economical non-drug treatment that can assist in the treatment of Anxiety Neurosis. With the rat models of chronic anxiety as the research object, this study focuses on the anti-anxiety effect of music therapy with 40 rats divided into groups, extracts two important neurotransmitters, Glu(glutamic acid) and GABA(aminobutyric acid), from the rat hippocampus to go deeply into the changes in their contents, and further explores the physiological mechanism of emotional inhibition of music therapy on Anxiety Neurosis, laying a foundation for the application of music therapy in the treatment of Anxiety Neurosis. The results show that music therapy can alleviate the anxiety-induced inhibition of weight increase in rats, anxiety symptoms can be improved to some degree by adjusting the ratio of Glu/GABA, and thus the emotions of Anxiety Neurosis can be inhibited to a certain extent.

Key Words: Music therapy; Anxiety Neurosis; Hippocampal neurons; Neurotransmitters

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53

Introduction

Anxiety Neurosis is a neurological disorder accompanied by dizziness, nausea, and heart palpitations (Beiske *et al.*, 2008), which is mainly divided into generalized anxiety disorder and panic disorder (Mayanagi *et al.*, 1996). Studies have shown that the incidence of Anxiety Neurosis in certain populations (Kendler *et al.*, 1992) is as high as 10%, which has a serious impact on the normal living, working and learning of patients (Spitzer *et al.*, 2006). However, it has not received much attention in China (Martin *et al.*, 1995), which is due in a large part the fact that the disease is mainly shown in emotional experiences, thus many patients do not

realize that they are sick (Amir *et al.*, 2009). The treatment of Anxiety Neurosis mainly relies on medications, such as benzodiazepines and clonazepam, which can relieve symptoms and have a sedative effect, as well as traditional Chinese therapies (Chen *et al.*, 2014) such as acupuncture, psychotherapy, and other methods. A large number of studies are currently focused on the evaluation of efficacy and therapeutic effects of anti-anxiety drugs, but they ignore the fact that some patients may produce adverse reactions to medications (Parker *et al.*, 1999), and are prone to dependence, and that some patients are not suitable for medications, so

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a safe and effective non-drug therapy has important significance for some special patients with Anxiety Neurosis.

Music therapy (Gutiérrez and Camarena, 2015), an integration of music, medicine and psychology, is increasingly used as a non-drug therapy for the alleviation and treatment of diseases in the nervous system (Goldbeck and Ellerkamp, 2012). Music can not only improve people's moods (Mckinney *et al.*, 1997), but also activate and improve certain brain functions by stimulating the brain (Nayak *et al.*, 2000). Music therapy plays a notable role in the treatment of Anxiety Neurosis (Wang *et al.*, 2011). Going from passive music therapy to active music therapy, patients gradually develop interest in music (Raglio *et al.*, 2015), and they can relax both psychologically and physically when interacting with music, thus physiological indicators such as respiration and blood pressure will change towards the opposite direction of anxiety, achieving good therapeutic effects.

This study detects the content of hippocampal neurons in the brain tissue by stimulating the rats with music, then discusses the role of music therapy in the nervous system and emotional inhibition of Anxiety Neurosis patients from the aspects of nerve cells, and explores the effect of different types of music on Anxiety Neurosis, which lays a foundation for the wider application of music therapy on Anxiety Neurosis.

Anxiety neurosis and music therapy Pathogenesis of Anxiety Neurosis

Anxiety Neurosis, also known as anxiety disorder, is a group of mental disorders characterized by significant feelings of anxiety and fear. Anxiety is a worry about future events and fear is a reaction to current events, which often cause dizziness, heart palpitations, shortness of breath and other physical tension in patients.

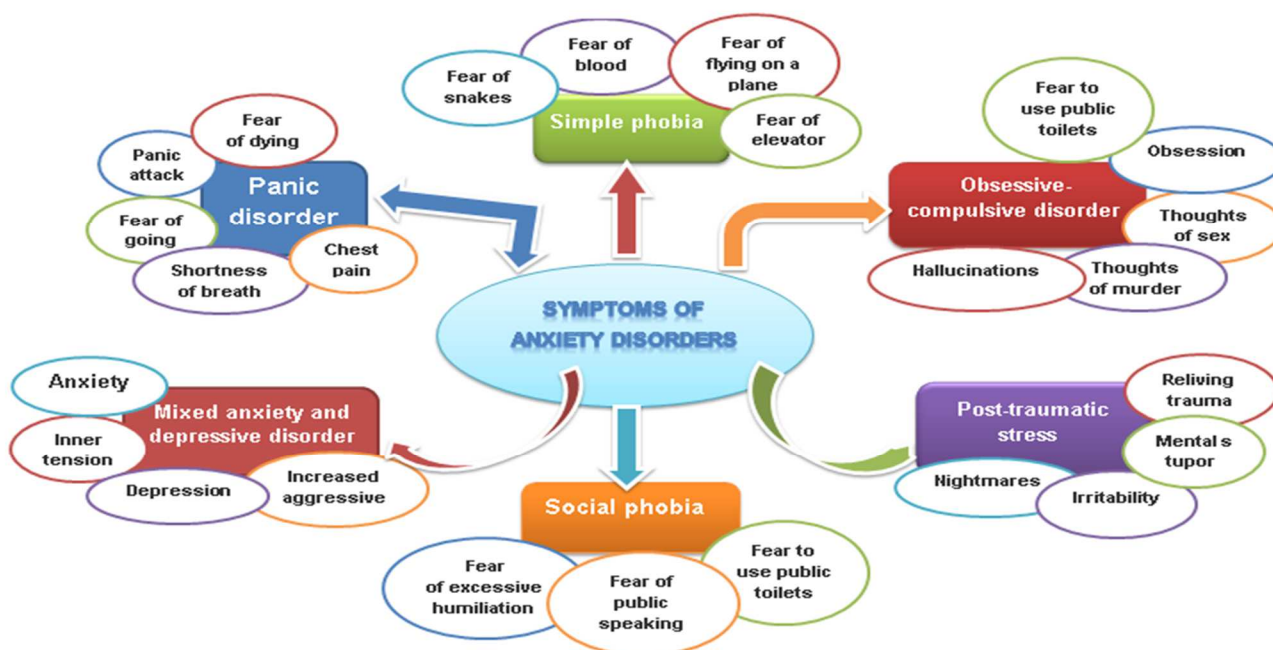


Figure 1. Ymptoms of anxiety neurosis

At present, the pathogenesis of Anxiety Neurosis is not very clear, but people often have more than one type of anxiety disorder, which may be caused by genetic and environmental factors, or may also occur with other diseases. The following figure lists several major mechanisms that can induce Anxiety Neurosis, divided into physiological and psychological mechanisms.

Anxiety Neurosis detection techniques

Anxiety Neurosis is more of a mental illness, but there is no instrument that can directly detect what has happened in people's inner world, so we can only judge the severity of Anxiety Neurosis by some external indicators that can be evaluated, including sleep status, appetite, thinking, self-assessment of interpersonal relationships, etc. At



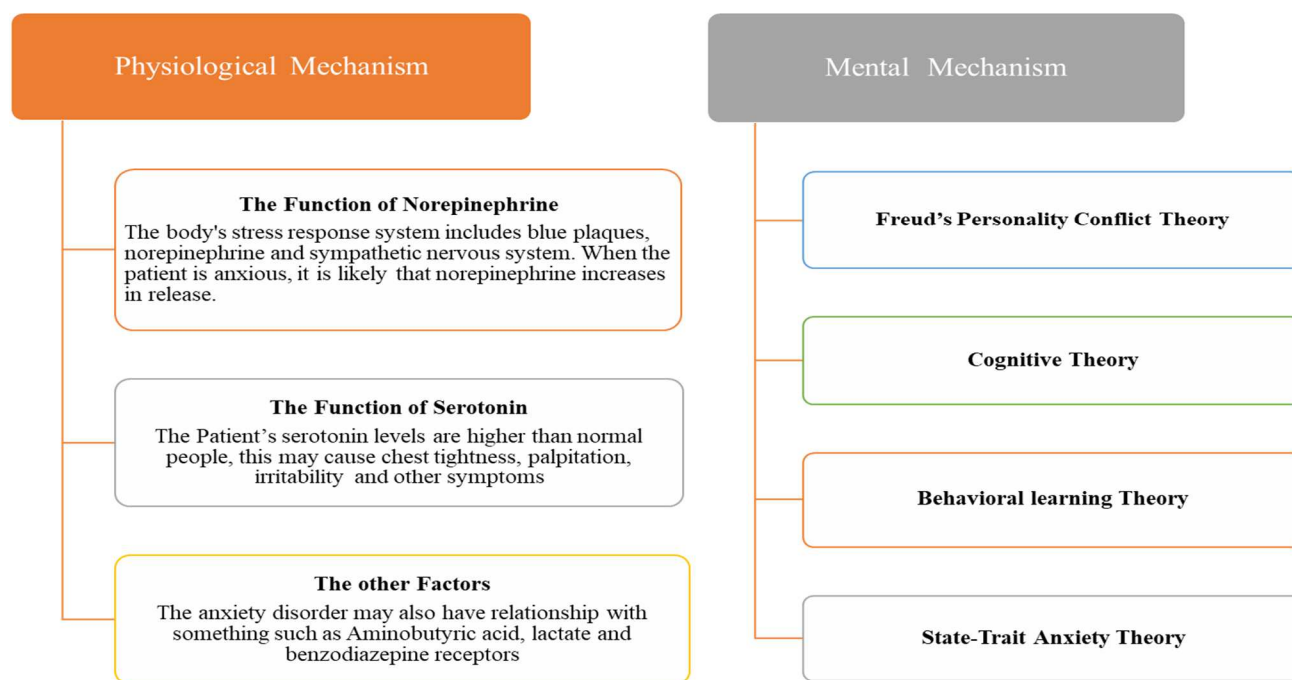


Figure 2. Echanism of anxiety neurosis

present, the main basis for the diagnosis of Anxiety Neurosis is the several major standards commonly used in the medical field. The more people meet these criteria, the more likely that they are ill. The three indicators, including Symptom Checklist (SCL-90), self- rating Anxiety Scale (SAS) and Heart Rate Variability (HRV) are commonly used.

SCL-90 is one of the most widely used measurement tools for mental illness and mental disorders, which can only be used to assess the severity of anxiety in patients and cannot be used for diagnosis. SAS is mostly used in the assessment of Anxiety Neurosis in adults. These two scales enable the patient to evaluate and get to know his own psychological and mental state, and at the same time, they also signify the patient's subjective evaluation of himself. Therefore, a physiological index that combines heart rate variability, which reflect the information of sympathetic nerves in nervous system can make a more accurate and objective assessment of the patient's condition.

Music therapy

There have been attempts since ancient times to use music to assist in the treatment of certain diseases of human beings and to improve their mental state, such as recorded in *Yue Ji*, the earliest monograph of music aesthetics and

literature theory in ancient China, "This kind of music can make people interested, intelligent, and peaceful in mind." There are also stories about the use of hymns to treat diseases in the west. In the middle of the 19th century, music therapy was applied to the treatment of patients with mental illness and the effect was significant. Then in the middle of the 20th century, there already appeared scientific research institutions specializing in research and promotion of music therapy the United States. In recent years, music therapy has been introduced into the treatment of some diseases as an auxiliary means in China. Studies have shown that music can reduce heart rate and increase blood pressure by controlling the secretion of hypothalamic norepinephrine, thus to relieve tension and anxiety. Music therapy is a safe and non-invasive non-drug treatment that is very helpful for clinical treatment.

The methods of music therapy are basically divided into receiving, recreation and the impromptu, as shown in the picture below. Receiving music therapy mainly induces physiological or psychological experience of the patients by playing suitable music for them, consisting of song discussion, music memory, music imagination, etc., which allows the patients to understand and relax themselves through music, thus to achieve therapeutic effects. The recreation music therapy is mainly to let the patient participate in the music creation process,



in which he can personally compile the music or plays the musical instrument to allow himself to be integrated into the music. The impromptu music therapy is to allow the patients to release tension and depression as they wish through the musical instruments. Without any music background required, they can play the simple musical instruments at their wishes, such as various drums, percussion instruments and so on.

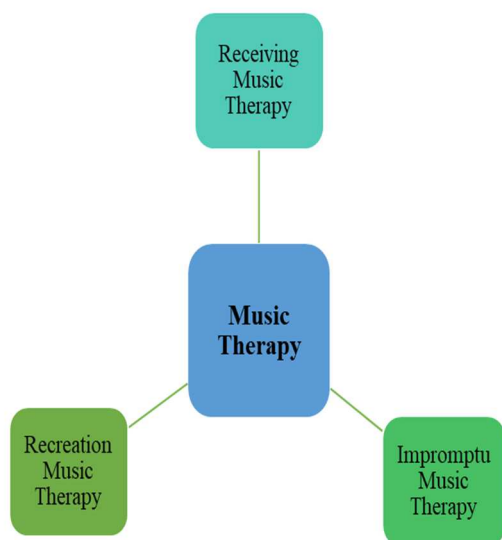


Figure 3. Methods of music therapy

Materials and Methods

Experimental objects and instruments

A total of 40 healthy male rats weighing between 320g and 360g are used in this experiment, which are randomly divided into four groups, including blank control group, anxiety group, Mozart music group and rock music group. The rats are domesticated in the laboratory for one week, given 12 hours of lightness and 12 hours of darkness.

The instruments needed for the experiment include: vortex meter (QL-901), fast-speed freezing centrifuge (H1650R), high performance liquid chromatography (LC-20A) and so on.

The reagents used in the experiment include aminobutyric acid (GABA), glutamic acid (Glu), sodium acetate, acetonitrile, etc.

Experimental methods

(1) Establishment of anxiety models

The method used in this study for establishing anxiety models is unpredictable chronic emotional stress stimulation. After the rats are adapted to the environment, those of the anxiety

group, the Mozart music group and the rock music group are subjected to continuous stimulation for a period of 21 days. The stimulation items include water and food deprivation, long-term light exposure, long-term darkness, tilting and shaking of the rat cage, one of which is performed per day at random.

(2) Music therapy experiment

No treatment is done with the mice in the blank control group, which can eat and drink as normal. Rats in the anxiety group are given unpredictable stimulation for 21 days. For the Mozart music group and the rock music group, music is provided for about one hour each day when they are in a dark environment, and one hour later the anxiety modeling experiment is performed.

Evaluation index and detection method

(1) General conditions

During the experiment, the body weight changes of each group of rats are recorded on the 1st day, the 7th day, the 14th day and the 21st day, and the basic conditions of the rats are known based on the general condition of the body.

(2) Anxiety degree evaluation

In this study, the anxiety degree of rats is evaluated through the elevated cross maze test. As shown in Figure (4), the experimental device is cross-shaped, consisting of two open arms and two closed arms, and the device is 0.5 meters above the ground. Rats are placed in the center of the cross, and the times of their entering into open arms or closed arms and the time of stay respectively are recorded within five minutes.

(3) Collection of tissue specimens

At the end of the 21-day experiment, the experimental rats of each group are prepared for the collection of hippocampus so as to determine the contents of neurotransmitters, GABA and GLU. First, anesthetize the rats, cut off their heads, take out their whole brain, and separate and weigh the hippocampus; and then add with saline and acetonitrile, take out 1 ml supernatant after centrifugation, naturally volatilize it in the centrifuge tube and filter it for the test.

The standards for GABA and GLU at concentrations of 0.2 mm, 1 mm, 2 mm, 5 mm, and 10 mm, respectively, are prepared for chromatographic measurements. The GABA and GLU contents are calculated by the formula as follows:

Content=sample peak area/control peak area* control concentration * sample volume



Figure 4. Device of elevated cross maze

Statistical analysis

SPSS17.0 software is used for statistical analysis, P<0.05 means that it is statistically significant, and all data are expressed in mean±S.E.M. One-way variance analysis is used for comparisons between different groups.

Results and Discussions

Comparison of general conditions

The weight of different groups during the experiment is shown in Table 1.

Table 1. Body Weight of Different Group

Group	1 st Day Weight(g)	7 th Day Weight(g)	14 th Day Weight(g)	21 st Day Weight(g)
Control Group	334±11.2	354±20.2	368±16.6	376±18.4
Anxiety Group	336±13.5	338±18.8	339±19.8	345±15.5
Mozart Music Group	332±18.2	348±16.2	357±17.2	368±19.2
Rock Music Group	335±10.8	340±20.0	343±16.2	348±16.6

Before the experiment, the weight of the four groups of rats is measured and there is no significant difference between the four groups, as shown in 1 of Figure (5). Seven days after the start of the experiment, the weight of rats in each group is measured again. It is found that the weight of the rats in the control group increases significantly, while the weight of the rats in the anxiety group does not change significantly compared to seven days ago, the body weight of rats in the Mozart group increases, but it is less than that of the control group, and the weight increase in the rock music group is slight, only a

little higher than that of the anxiety group. Fourteen days later, the weight of the control group shows the highest increase, followed by the Mozart music group, while the body weight of the rock music shows a slight higher increase than that of the anxiety group, but there is no significant difference found, and the weight of the anxiety group shows almost no change.

The experimental results show that the weight of the rats in the anxiety group slowly increases during the entire experiment, with almost no significant change, while the weight of the other groups of rats increases steadily, varying in growth rates, suggesting that anxiety modeling has a significant effect on the body weight of rats..

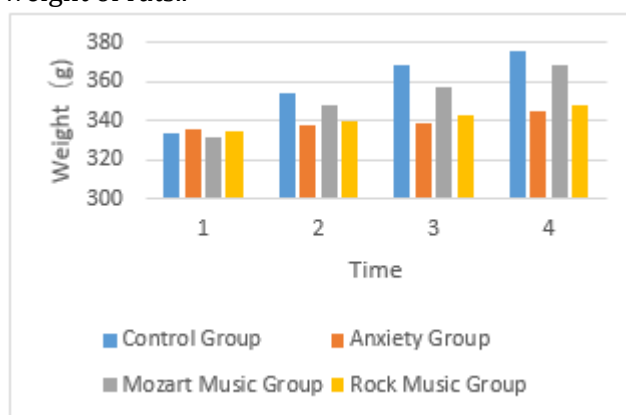


Figure 5. Weight comparison of different group

Analysis of anxiety degree assessment results

In this study, the changes of anxiety in rats are evaluated by the elevated cross maze, which has a pair of open arms and a pair of closed arms. Rodents are active in closed arms because they like dark environments. However, because of curiosity and inquiry psychology, they will go into the open arms, which will cause psychological contradictions in rats, thus producing anxiety. Anxiety has a negative correlation with the times of rats entering the open arms(Open-arms Entries, OE) and the time of stay in the open arms (Open-arms time, OT), i.e., the higher the OE, and the longer the OT, the lighter the anxiety of the rat will be; otherwise, the anxiety is getting more serious. In this experiment, the statistics of the proportion of OE to the total entries into both kinds of arms (TE) and the proportion of OT to Total Time (TT) are calculated. Tables (7) and (8) show the percentage of OE and OT of each group of rats at different time periods, respectively.

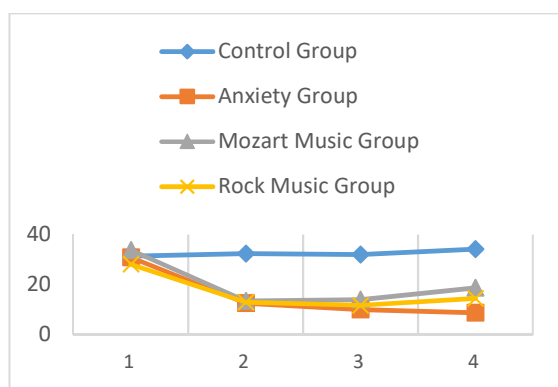


Figure 6. Comparison of open-arms entries times of different group

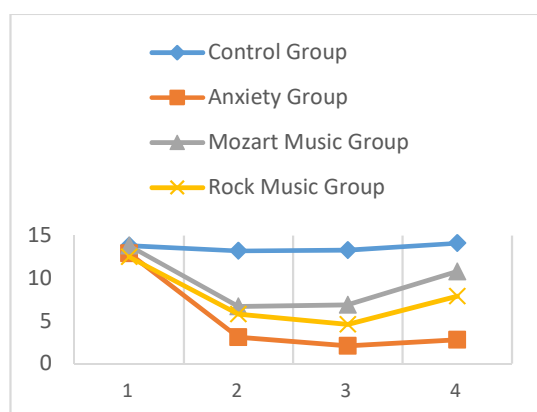


Figure 7. Comparison of open-arms time percentage of different group

As can be seen from the above two figures, there is no significant difference in the behavior of the rats before the start of the experiment, thus the experiment is comparable. In the control group, the percentages of OE and OT remain almost unchanged during the entire experiment period, thus there is no statistical significance. However, the percentages of OE and OT of the anxiety group rats decrease significantly on the seventh day of the experiment, and continue to decrease, which is statistically significant. The percentages of OE and OT of the Mozart and rock music groups are significantly smaller than those before the experiment, which is statistically different. However, during the experiment, such data of both music groups show a rising trend, especially in the Mozart music group, which indicates that Mozart music has a certain degree of improving and alleviating effects on anxiety, and the effect is better than that of rock music.

Analysis of GABA and GLU in Hippocampus

Glu is an important excitatory neurotransmitter in the central nervous system, and its content in the

body should be maintained within a range. If the content is too low, it will affect the normal physiological activity of cells, if the content is high beyond the range, it will produce excitatory neurotoxicity, causing damage to neurons. GABA is a neurotransmitter that has inhibitory effect on neurons, and plays an important role in regulating the mood of human body. Studies have shown that the occurrence of Anxiety Neurosis has an important link with the imbalance of these neurotransmitters in vivo. Therefore, studies on the changes in the content of Glu and GABA in vivo can help to understand the physiological mechanism of Anxiety Neurosis, and provide clinical reference for its treatment. The maintenance of a balanced Glu/GABA ratio has important significance for the equilibrium of excitation and inhibition of nerve cells in the brain, and plays a crucial role in maintaining normal emotions of humans.

No significant difference is found in the hippocampal weight of the rats in each group, indicating that the changes in the contents of GLU and GABA in the hippocampus specimens are comparable. The following Figure (8) shows the comparison of Glu and GABA content of each group of rats after sampling analysis.

The Glu content in the anxiety group rats increases significantly compared with that of the control group, while the Glu content of other two music groups shows only a small increase, which is far smaller than that of the anxiety group. The results show that Mozart music can significantly reduce the content of Glu in the hippocampus of the anxiety model rats, and has an important regulatory effect on the excitatory neurotransmitters.

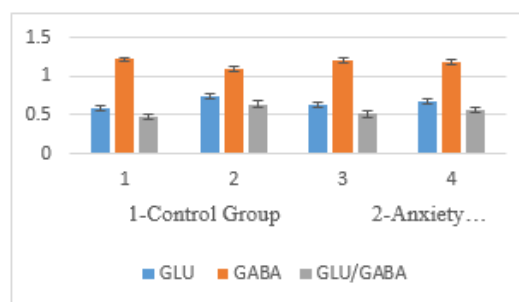


Figure 8. Comparison of glu and gaba of different group

The GABA content has an opposite regulatory effect. Except for the anxiety group, there is no significant difference in GABA content of the other two music groups and the control group, but the GABA content in the anxiety group shows a decreasing trend. Through the



comparison of the Glu/GABA ratio, it is found that music has a regulatory effect on it, and the Mozart music shows a more significant regulatory effect, which could achieve anti-anxiety effect, while the rock music has no obvious regulatory effect.

Conclusions

With the rat models of chronic anxiety as the research object, this study focuses on the anti-anxiety effect of music therapy, extracts two important neurotransmitters, Glu(glutamic acid) and GABA(aminobutyric acid), from the rat hippocampus to study the changes in their contents, and further explores the physiological mechanism of emotional inhibition of music therapy on Anxiety Neurosis. The conclusions are drawn as follows.

(1) Music therapy can relieve the inhibitory effect of Anxiety Neurosis on body weight increase in rats to a certain extent. In particular, a better effect is shown in Mozart music group than in rock music group and the weight of rats in Mozart music group increases significantly.

(2) Music therapy can improve anxiety behavior of rats. In the elevated cross maze experiment, OE and OT percentages of the Mozart music group increase significantly compared to those of the anxiety group, suggesting that Mozart music has a certain improving and easing effect on anxiety, and it has a better effect than rock music.

(3) Music has a regulatory effect on the contents of Glu and GABA in the hippocampus of the brain. Through inhibition of the Glu content and enhancement of the GABA content, it can regulate the ratio of Glu / GABA so as to adjust the balance of excitatory and inhibitory function of brain hippocampus, thus inhibiting the emotions of Anxiety Neurosis.

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