Effects of music therapy on major depressive disorder: A study of prefrontal hemodynamic functions using fNIRS[☆]

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ABSTRACT

Major depressive disorder (MDD) is a recurrent, chronic mental illness. While music therapy has been established as an effective treatment for MDD patients, the effects of this therapy on brain function remain unclear. This research employed near-infrared spectroscopy (NIRS) to explore the effects of music therapy on brain activity in mild or moderate MDD patients and to illustrate the potential mechanism of music therapy. Methods: Fifteen MDD patients and fifteen healthy controls (HC) underwent neuropsychological evaluations and NIRS measurements. All participants were treated with continuous music therapy for 10 days. Subsequently, all individuals were evaluated with neuropsychological assessments and NIRS measurements again. Results: The verbal fluency task (VFT) performances of the participants yielded significantly higher scores after music therapy in terms of vegetables, four-footed animals and fruit blocks. After the music treatment, the NIRS data showed that the mean active oxy-Hb values of channels 21, 23, 19, and 41 were significantly increased in both the MDD and HC groups. The MDD group showed significant activation in the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC) after music therapy. The results indicate that music therapy could improve the brain function of MDD patients.

1. Introduction

Major depressive disorder (MDD) is a common, chronic and recurrent psychiatric disease: 6% of adults worldwide suffer from MDD annually (Browne et al., 2011). MDD is characterized by depressed mood, decreased interest, anhedonia, and diminished social function (Association, 2013) . The main impairments of MDD are in cognitive and social function(Boschloo et al., 2014; der Wee et al., 2011; Hardeveld et al., 2013), which is more severe than that in other chronic diseases (Kessler et al., 2003). The more severe the depressive symptoms, the worse the psychosocial function (Judd et al., 2000). Due to the high prevalence and recurrence rate of this disorder, MDD is becoming a major contributor to the global disease burden.

Therefore, it is essential to improve the effectiveness of treatment for MDD. ("Depression in adults: recognition and management," 2016; Gartlehner et al., 2008; McAllister-Williams et al., 2015). There are two types of therapeutic options for MDD: psychopharmacology and psychotherapy (Gelenberg, 2010). Although drug therapy is the most commonly prescribed primary treatment for MDD, fewer than 50% of patients respond to antidepressant treatment (ADT) (Rush et al., 2014); moreover, approximately 20% of patients are unable to adhere to ADT due to the severe adverse drug reactions (Xing et al., 2011). More than 60% of patients have at least one adverse event during ADT that often leads to withdrawal (Gartlehner et al., 2016). One meta-analysis illustrated that the effect of ADT in mild or moderate depression is comparable to that of a placebo (Fawcett et al., 2010). Therefore, psychotherapy is an alternative choice for MDD patients who are noncompliant with antidepressants.
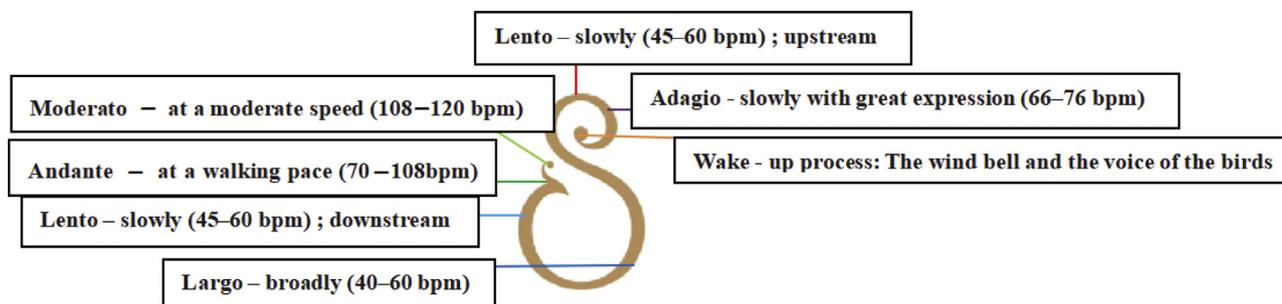
Fig. 1. New music therapy technique: the 'S' sequence. This sequence begins with a moderate speed and then consists of reductions in musical tempo, musical instrument size, frequencies and volume to achieve a state of relaxation. After achieving relaxation, the patients reach the phase of vitality.

Many caregivers provide nonverbal expressive therapies, such as music therapy, dancemovement therapy, art therapy and drama therapy, which may serve as effective means of communication for patients (Castillo-Pérez et al., 2010; Fachner et al., 2011). In recent clinical studies, researchers suggested that music therapy could alleviate the symptoms of depression and increase positive emotional experiences (Gold et al., 2009). Another prospective controlled clinical trial also supported this finding. Brandes (Brandes et al., 2010) found that music therapy could reduce the symptoms of depression and enhance treatment compliance. Another meta-analysis revealed that music therapy helped to relieve symptoms and improve quality of life (Van Assche et al., 2015). Thus, music therapy has been demonstrated as a new option for MDD patients.

Music is an effective emotion inducer that is often used as a coping strategy to adjust one's emotional state in depression (Aalbers et al., 2017; Zatorre and McGill, 2005). Music therapy is a noninvasive intervention with the advantages of good tolerance, high feasibility, and low drop-out rates for MDD patients (Van Assche et al., 2015). A survey demonstrated that 82% of depressive patients agreed that listening to music is an effective treatment measure (Holzinger et al., 2012).

No obvious side effects have been found to be associated with music therapy to date. A neuroimaging study investigated the effects of music therapy on the normal brain (Raglio et al., 2016) and suggested that many brain areas involved in memory and autobiographical processes are activated during music therapy.

NIRS is a noninvasive, real-time neuroimaging technique because of its high-frequency time resolution compared with other neuroimaging tools, such as MRI, that can detect changes in oxygenated and deoxygenated hemoglobin (oxy-Hb and deoxy-Hb, respectively) concentrations triggered by nervous activity (Ferrari and Quaresima, 2012). According to the mechanism of neurovascular coupling, regional cerebral blood flow (rCBF) increases with neuronal activity in areas of cortical activation. The ultimate consequence is the activation of brain areas, accompanied by functional hyperemia, which ensures an adequate energy supply (Boas et al., 2004). Therefore, NIRS is a promising technique for evaluating cortical functional changes in real time.

The aim of this study was to compare the NIRS differences before and after music therapy. This research provides a foundation for music therapy and will improve the usage of music therapy in clinical practice.

2. Materials and methods

2.1. Subjects

This study was a nonrandomized clinical controlled trial (CCT) that was approved by the Ethics Committee of Yuquan Hospital. The recruitment and experimental procedures were conducted from March 2017 to February 2019. Fifteen patients with moderate MDD were recruited from the Psychiatry Department of Yuquan Hospital as subjects, all of whom were untreated at the first onset of depression and met the diagnostic criteria for MDD based on the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V). Fifteen healthy controls (HC) were recruited from the local community and matched to the MDD patients in terms of age, gender, level of education and right-handedness.

Notably, patients with the following psychiatric disorders were excluded: mental retardation, dementia, autism spectrum disorders, schizophrenia and bipolar disorders. Participants with chronic substance abuse and neurological diseases related to cognitive function were also excluded.

2.2. Design

The thirty subjects were all right-handed, and all attended the entire 10-day therapy session, with zero dropouts. The depressed patients and HC group all underwent the neuropsychological evaluations and NIRS measurements before and after 10 days of continuous music therapy intervention.

2.3. Music therapy

There are two fundamental methods of music therapy: (1) 'creative', wherein subjects compose music or songs with their voices or musical instruments; and (2) 'receptive', wherein subjects listen to music. Receptive relaxation music therapy is often used to treat anxiety, depression and cognitive impairment (Guétin et al., 2005). Our clinical practice has shown that S-sequence can relieve symptoms in patients with mild to moderate depression. A meta-analysis of relaxation inducing music shows that music-induced emotions affect one's cognitive ability (Westermann et al., 1996).

In this study, the second method was used for all subjects. Only original music was used for the treatment, and the music design originated from the original 'S' sequence (Fig. 1) designed by Bruce Copen Laboratories (SINCE 1947). Every session included 60 min of music listening, which was divided into several stages and gradually progressed. According to the 'S' sequence, each patient felt relaxed and peaceful.

The following steps were included in the 'S' sequence: in step 1, the music was synchronized with the emotional state; in steps 2–3, the melodies occurred gradually and the tempo slowed down, both of which helped the patient's body become progressively relaxed; in step 4, the patient's body became deeply relaxed; in step 5, the melodic lines gradually increased upward; in step 6, the musical elements increased, synchronizing the body and emotion with the music once again; and in step 7, positive emotions were stimulated, effectively improving the psychological state of emotion. The entirety of the musical 'S' sequence was designed by Bruce Copen Laboratories (SINCE 1947).

During each of the ten treatment sessions, the participants laid down in the music therapy room with patches over their eyes so that they felt relaxed. They listened to music through earphones.

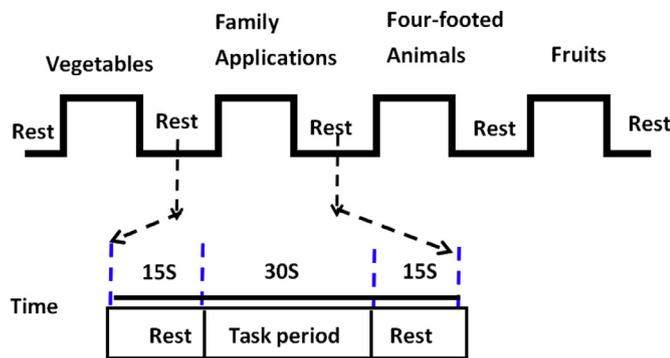Before the 1st therapy session, the selection process involved

Fig. 2. VFT task design
Note: Four-block (vegetables, family applications, four-footed animals, and fruits) semantic category versions of the VFT included a 15 s pre-task baseline, a 30 s VFT, and a 15 s post-task baseline.
Abbreviation: VFT, verbal fluency task.

identifying the instruments and types of music that each patient liked. A questionnaire was administered before the music therapy to understand the music preferences of each patient to make the appropriate choices for treatment. Each session lasted 60 min, at a rate of one session per day. The entire process lasted 10 days.

2.4. Activation task

A semantic category version of the verbal fluency task (VFT) was utilized as the activation task. The VFT task contains four blocks, namely, vegetables, domestic applications, four-legged animals, and fruits. Each block was composed of 3 periods, namely, a 15-s pre-task baseline, a 30-s task, and a 15-s post-task baseline (Fig. 2). The participants were asked to verbally describe as many words as possible pertaining to a certain semantic category, with all categories believed to be equivalent in stimulating the prefrontal cortex. The number of correct words generated during the task was evaluated as cognitive performance.

2.5. Assessments

All subjects were interviewed by two experienced psychiatrists according to the Structured Clinical Interview for DSM Disorders. The Hamilton Depression Rating Scale (HDRS, 24 items; Hamilton, 1960) and the Hamilton Anxiety Rating Scale (HAMA, 17 items; Hamilton, 1956) were completed by the participants to determine the severity of depression and anxiety, respectively. Questionnaires developed by our group were used to collect demographic information.

2.6. NIRS measurements

Hemodynamic responses in the prefrontal cortex (PFC) were measured using a 45-channel near-infrared spectroscopy system (FOIRE-3000, Shimadzu, Kyoto, Japan), with a sampling frequency of 5 Hz. Based on the modified Beer-Lambert Law, relative concentrations of oxy-hemoglobin (oxy-Hb), deoxy-Hb and total-Hb were recorded during the task, which consisted of a 15-s pre-task baseline, a 30-s VFT, and a 15-s post-task baseline. Forty-five logic channels were established by 14 emission probes and 14 detector probes (Fig. 3), with one emission probe and detector probe consisting of a logic channel. In accordance with the International 10–20 System of electroencephalogram electrode placement, the lowest probes were positioned along the Fp1–Fp2 line (Fig. 4) (Hori et al., 2008).

2.7. Statistical analysis

The demographic and clinical data were compared by t-tests or chi-

Fig. 3. Fourteen pairs of probes comprised 45 channels. Red and blue numbers represent emission and detector probes, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
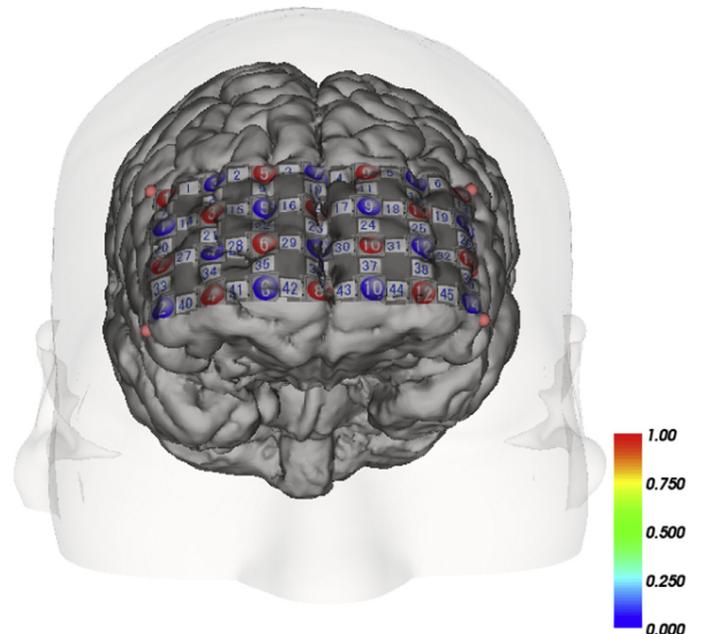

Fig. 4. Channel layout of the NIRS cap over the prefrontal cortex. Relative position of the near-infrared spectroscopy (NIRS) channels and the PFC.

square tests. Student's t-test was used to analyze differences in age and education level between the HC group and the MDD group at baseline.

Regarding the NIRS data, the mean oxy-Hb increase was calculated as the difference between the mean oxy-Hb during the task and that during the pretask period. The mean oxy-Hb changes were calculated by subtracting the mean relative concentration of oxy-Hb in the pretask period from the mean oxy-Hb in the task period.

We used a two-way mixed ANOVA with different groups (MDD group vs. HC group) as the between-subject factor and time (pre vs. post) as the within-subject factor to analyze the effect of the music therapy intervention on the oxy-Hb values. The two-way mixed ANOVA included a 2 (time point: pre- and post-music therapy) × 2 (group: MDD group and HC group) design. Oxy-Hb was selected as the analysis index because of its reliability in demonstrating changes in rCBF (Kono et al., 2007; Singh and Dan, 2006). The Statistical Package for Social Sciences version 22.0 for Windows (SPSS, IBM Corporation, Armonk, NY, USA) was used for the analyses.

3. Results

3.1. Demographic and clinical data

The demographic data and clinical characteristics of the participants are presented in Table 1. There were no significant differences in

Table 1
Demographic data of MDD patients and controls (mean ± SD).

Demographics	Patients MDD (n-15)	Healthy controls HC (n = 15)	MDD vs. HC t/χ²	p
Gender (female/male)	8/7	9/6	0.136	0.713[a]
Age (years)	30.93 ± 13.47	30.87 ± 10.11	0.154	0.879[b]
Education (years)	13.8 ± 1.821	14.80 ± 1.014	−1.858	0.077[b]
Marital status (married/ unmarried)	6/9	8/7	0.536	0.464[a]

MDD: major depressive disorder group; HC: healthy controls.
[a] chi-square test;.
[b] t-test (p value).

gender, age, marital status, or education level between the MDD and HC groups (all p-values > 0.05).

3.2. Clinical data and VFT task performance of participants before and after therapy

3.2.1. Clinical data

The HDRS was employed to assess the severity of depression in the MDD patients and HC group. A 2 (group: MDD group, HC group) * 2 (time point: pretherapy, posttherapy) two-way mixed ANOVA was conducted to examine the effect of music therapy on participants. The results showed that the main effect of Group was significant [$F_{(1,28)} = 151.782$, $p < 0.001$, $\eta_p^2 = 0.844$], meaning that HDRS scores in the MDD group were higher than those in the HC group. The main effect of Time point was significant [$F_{(1,28)} = 218.273$, $p = 0.002$, $\eta_p^2 = 0.886$], meaning that HDRS scores decreased after music therapy in all participants (see Table 2). The interaction between Group and Time point was significant [$F_{(1,28)} = 153.719$, $p < 0.001$, $\eta_p^2 = 0.846$]. Simple effect analyses revealed that HDRS scores in the MDD group were significantly reduced at the post-therapy assessment compared with the pre-therapy time point ($p < 0.001$), while the HC group did not show significant differences between the two time points ($p = 0.104$); according to the simple effect analysis of treatment time, the results showed that the HDRS scores in the MDD group were significantly higher than those in the HC group not only at the pre-therapy time point but also at the post-therapy time point ($p < 0.001$).

3.2.2. VFT task performance

During the VFT task, the numbers of words generated by the MDD and HC groups are summarized in Table 2. A 2 (Group: MDD group, HC group) * 2 (Time point: pre-therapy, post-therapy) two-way mixed ANOVA was conducted to examine the performance of subjects on the VFT task.

Task 1 (vegetables block): The results showed that the main effect of Group was significant [$F_{(1,28)} = 13.769$, $p = 0.001$, $\eta_p^2 = 0.330$] in terms of the vegetables block, meaning the performances on the VFT task (vegetables block) in the MDD group were lower than those in the HC group. The main effect of Time point was also significant [$F_{(1,28)} = 12.620$, $p = 0.001$, $\eta_p^2 = 0.311$] in terms of the vegetables

block, meaning that the vegetables block performances were improved after music therapy in all participants (Table 2). The interaction between Group and Time point was not significant [$F_{(1,28)} = 0.789$, $p = 0.382$, $\eta_p^2 = 0.027$].

Task 2 (family applications block): The results revealed no significant difference in the main effect of Group, main effect of Time point, or the interaction between Group and Time point between the normal control group and MDD group.

Task 3 (four-footed animals block): The results showed no significant difference in the main effect of Group and the interaction between Group and Time point in the normal control group and MDD group. The main effect of Time point was significant [$F_{(1,28)} = 21.831$, $p < 0.001$, $\eta_p^2 = 0.438$] in terms of the four-footed animals block, meaning that the performances on this task were improved after music therapy in all participants (Table 2).

Task 4 (fruits block): The results were similar to those for Task 1. The main effect of Group was significant [$F_{(1,28)} = 12.328$, $p = 0.002$, $\eta_p^2 = 0.306$] in terms of the fruits block, meaning that the performances on the VFT task (fruits block) in the MDD group were lower than those in the HC group. The main effect of Time point was also significant [$F_{(1,28)} = 8.599$, $p = 0.007$, $\eta_p^2 = 0.235$], meaning that the performances in the fruits block were improved after music therapy in all participants (Table 2). The interaction between Group and Time point was not significant [$F_{(1,28)} = 1.777$, $p = 0.193$, $\eta_p^2 = 0.060$].

3.3. NIRS data analysis

A 2 (Group: MDD group, HC group) * 2 (Time point: pretherapy, posttherapy) two-way mixed ANOVA was applied to examine the mean [oxy-Hb] changes in participants.

3.3.1. The main effect of time point

The results showed that the main effect of Time point was significant in channel 21 [$F_{(1,28)} = 7.254$, $p = 0.012$, $\eta_p^2 = 0.206$], channel 23 [$F_{(1,28)} = 7.633$, $p = 0.010$, $\eta_p^2 = 0.214$], channel 41 [$F_{(1,28)} = 7.464$, $p = 0.011$, $\eta_p^2 = 0.210$], channel 44 [$F_{(1,28)} = 4.318$, $p = 0.047$, $\eta_p^2 = 0.134$], and channel 19 [$F_{(1,28)} = 5.054$, $p = 0.033$, $\eta_p^2 = 0.153$] (Fig. 5), indicating that the mean active oxy-Hb values in the above channels were increased after music therapy in the participants.

3.3.2. The main effect of group

The results showed that the main effect of Group was significant in channel 20 [$F_{(1,28)} = 5.996$, $p = 0.021$, $\eta_p^2 = 0.176$], channel 35 [$F_{(1,28)} = 4.260$, $p = 0.048$, $\eta_p2 = 0.132$], channel 36 [$F_{(1,28)} = 5.693$, $p = 0.024$, $\eta_p^2 = 0.169$], and channel 41 [$F_{(1,28)} = 7.104$, $p = 0.013$, $\eta_p^2 = 0.202$] (Fig. 6), indicating that the mean active oxy-Hb values in the MDD group were lower than those in the HC group. Channel 23 showed a marginal significant change [$F_{(1,28)} = 3.948$, $p = 0.057$, $\eta_p^2 = 0.124$], which also indicated that the mean active oxy-Hb value in the MDD group was lower than that in the HC group.

Table 2
Clinical data and VFT task performance of MDD patients and controls (mean ± SD).

Condition	MDD-pre music therapy	MDD-post music therapy	HC-pre music therapy	HC-post music therapy
HDRS	24.73 ± 4.862[a]	12.53 ± 5.097[a]	4.07 ± 0.884[a]	3.00 ± 0.845[a]
HAMA	17.13 ± 2.774[a]	6.60 ± 4.239[a]	3.67 ± 1.676[a]	2.73 ± 1.223[a]
VFT-Vegetables	8.33 ± 2.024[a]	9.67 ± 2.350[a]	11.73 ± 2.187[a]	12.53 ± 3.114[a]
VFT-Family applications	8.87 ± 1.922[a]	9.60 ± 1.639[a]	10.33 ± 2.526[a]	10.53 ± 2.666[a]
VFT-Four-footed animals	9.13 ± 1.995[a]	11.67 ± 2.944[a]	11.47 ± 3.044[a]	12.53 ± 2.900[a]
VFT-Fruit	9.0 ± 1.309[a]	10.07 ± 1.907[a]	12.00 ± 2.699[a]	12.40 ± 2.558[a]

MDD: major depressive disorder; HC: healthy controls; NIRS: near-infrared spectroscopy; VFT: verbal fluency task; HDRS: 24-item Hamilton Depression Rating Scale; HAMA: Hamilton Anxiety Rating Scale.
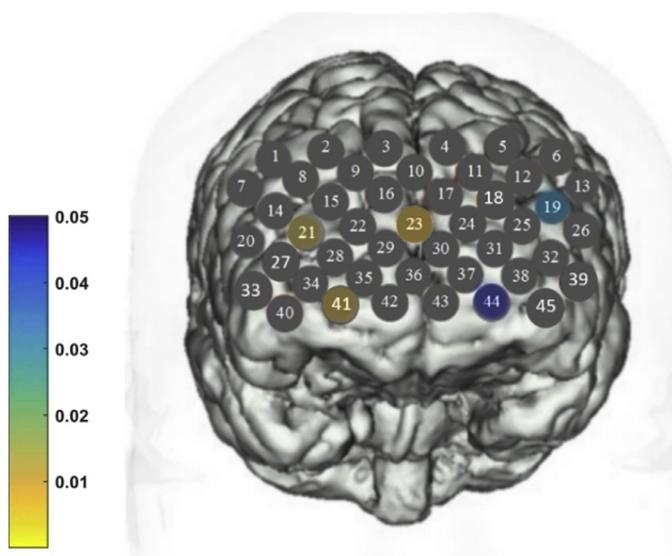[a]: Two-way mixed ANOVA.

Fig. 5. The main effect of time: The figure shows that the mean oxy-Hb value in the pre-group was significantly lower than that in the post-group during the VFT. Channels in dark colors show significantly lower oxy-Hb changes during the VFT in the pre-therapy group compared with the post-therapy group during the VFT ($P < 0.05$). The gray channel represents $P > 0.05$.
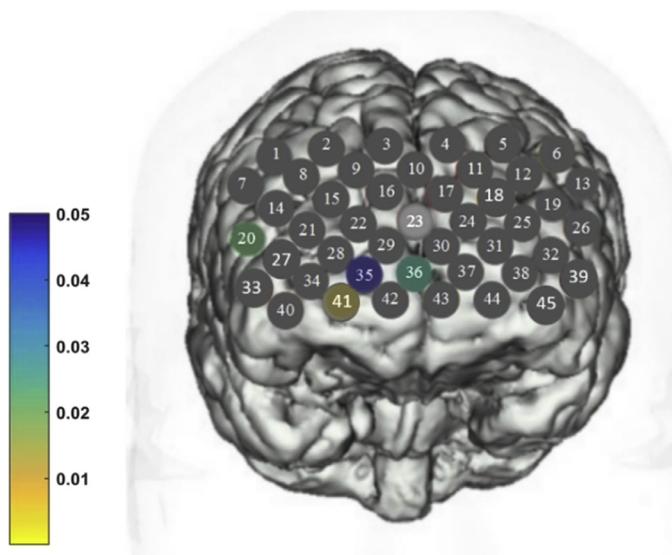

Fig. 6. The main effect of group: The figure shows that the mean oxy-Hb value in the HC group was significantly higher than that in the MDD group during the VFT. Channels in dark color show significantly lower oxy-Hb changes during the VFT in the MDD group compared with the HC group during the VFT ($P < 0.05$). The gray channel represents $P > 0.05$. A marginal significant change was found in Channel 23.

3.3.3. The interaction between group and time point

The interaction between Group and Time point was significant in channel 41 [$F(1,28) = 6.428$, $p = 0.017$, $\eta_p^2 = 0.187$]. Channel 23 showed a marginal significant change [$F(1,28) = 4.040$, $p = 0.054$, $\eta_p^2 = 0.126$]. The mean active oxy-Hb values in participants are shown in Fig. 7.

Simple effect analyses revealed that the mean active oxy-Hb value in channel 41 was significantly increased at the post-therapy assessment compared with the pre-therapy time point ($p = 0.001$), while the significant differences between the two time points were not found in the HC group ($p = 0.890$); according to the simple effect analysis of treatment time, the results demonstrated that the mean active oxy-Hb value

in the MDD group was significantly lower than that in the HC group at the pre-therapy time point ($p = 0.007$), but no significant change was found at the post-therapy time point between the MDD and HC groups ($p = 0.390$).

Simple effect analyses revealed that the mean active oxy-Hb value in channel 23 was significantly increased at the post-therapy assessment compared with the pre-therapy time point ($p = 0.002$), while the HC group did not show any significant difference between the two time points ($p = 0.599$). According to the simple effect analysis of treatment time, the results demonstrated that the mean active oxy-Hb value in the MDD group was significantly lower than that in the HC group at the pretherapy time point ($p = 0.024$), but no significant change was found at the posttherapy time point between the MDD group and the HC group ($p = 0.680$).

4. Discussion

To the best of our knowledge, this study is the first to use NIRS to investigate the effects of music therapy on oxy-Hb changes in the PFC of MDD patients. It is also the first study to use the 'S' sequence technique as the music therapy intervention for MDD patients.

Our results showed that the mean active oxy-Hb values of channels 21, 23, 19, and 41 were significantly increased in the two groups after music therapy. These results indicate that music therapy is effective in improving brain function in both MDD patients and HC participants. The most relevant cortexes include the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (VMPFC). Altogether, these results indicate that music therapy could change the hemodynamics of the left DLPFC, VMPFC and OFC.

The mean active oxy-Hb values of channel 23 and channel 41 in the MDD group post-therapy were significantly increased compared with the values in the MDD group pre-therapy, whereas there was no significant difference between the HC-pre and HC-post groups. The interaction effect showed no significant difference between MDD-post and HC-post in channel 23 and channel 41. The results revealed that the hypofunction of channel 23 and channel 41 in MDD patients was significantly recovered in the VMPFC and right DLPFC.

4.1. Hypofunction in the MDD group pre-therapy during the VFT

Previous neuroimaging studies have consistently reported hypofunction in the DLPFC and the frontopolar cortex in MDD patients during the VFT (Akashi et al., 2015; Murray et al., 2011; Golkar et al., 2012). These studies helped researchers localize the dysfunction in MDD to the orbital and frontal cortices. Some researchers found that depressed individuals had decreased activity in the DLPFC, which made it difficult for the patients to make plans and decisions and to mediate social behavior (Ohtani et al., 2015; Hirano et al., 2017). Other studies found that deactivation in the OFC of MDD patients was related to emotion regulation, decision making and sensory integration (Noda et al., 2012; Rolls and Grabenhorst, 2008). In addition, this deactivation of the OFC impaired the related learning, emotional behaviors and subjective experiences (Rolls, 2017) . Current imaging studies have shown that the DLPFC and the lateral OFC are activated to contribute to emotion regulation through reappraisal (Ochsner and Gross, 2005). The VMPFC is associated with emotional and autonomic processing (Zald et al., 2002); for example, patients with brain lesions in this area have difficulty reacting to emotional stimuli (Damasio et al., 1990). The VMPFC is also related to social cognition, involving facial emotion recognition and internal reflection (Wolf et al., 2016). For MDD patients, deactivation in the regions mentioned above would make it difficult for these patients to estimate context-related emotion in response to stimuli and to choose appropriate behaviors on the basis of those evaluations. In the experiment involving the MDD group, our finding of hypofunction in the DLPFC, VMPFC and OFC was in accordance with those of previous studies. In our research, we sought to investigate whether
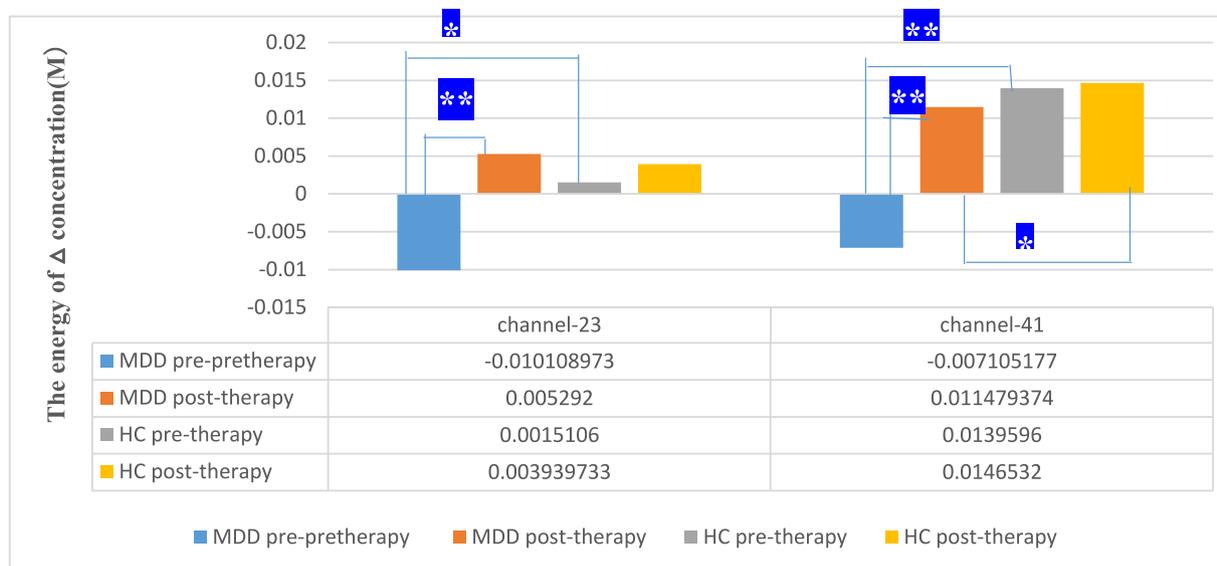
Fig. 7. The mean oxy-hemoglobin (oxy-Hb) changes in the two channels across the groups. $* p < 0.05, ** p < 0.01$.

music therapy is involved in the process of emotion regulation.

4.2. Effects of music therapy on MDD patients revealed by NIRS: activation in the OFC, VMPFC and DLPFC

The findings showed that the DLPFC, VMPFC and OFC of MDD participants were significantly activated after music therapy. This result indicated that music therapy could change the hemodynamics of the left DLPFC, VMPFC and OFC. In accordance with the neurovascular coupling mechanism (Phillips et al., 2015; Leithner and Royl, 2014), the increase in the mean oxy-Hb value after music therapy implied that the compensatory mechanisms in response to oxygen consumption were significantly recovered in the OFC, VMPFC and right DLPFC.

Neuroimaging studies have shown that DLPFC is related to executive function and cognitive function (Miller and Cohen, 2002), and the imbalance of cortical activity in the DLPFC is related to cognitive impairment and affective disorder of depression. Researchers used transcranial direct current stimulation (tDCS) to study the effects of DLPFC stimulation on cognitive function in MDD patients. The results showed that DLPFC stimulation could improve executive dysfunction in MDD patients (Salehinejad et al., 2017). Mohammad reported that emotion regulation was associated with cognitive control in MDD, which was related to hypofunction in the DLPFC. Some researchers found that emotion regulation and cognitive control were improved by activating the left DLPFC in MDD patients. Similar results were found in other studies (Brunoni and Vanderhasselt, 2014).

The orbitofrontal cortex (OFC) is related to reward and emotional value, which represents the value of target action. Subjective experience of emotional stimulation can activate the orbital frontal lobe. Consistent with this theory, low activation in the medial orbitofrontal cortex and high activation in the lateral orbitofrontal cortex have been shown to be related to depression (Rolls, 2017). An fMRI study reported that music could enhance the feeling of affective images and showed that many regions (VMPFC, OFC and other regions) in the brain activated by music therapy are involved in the emotion process (Baumgartner et al., 2006). Some similar studies also demonstrated the power of music in emotion regulation. These studies showed that music listening elicited emotional experiences that are involved in reward, motivation and arousal, involving the OFC and prefrontal regions (Blood and Zatorre, 2002). In addition, an fMRI study indicated that music listening was involved in the reward process through cognitive and emotion regulation and involved the OFC and temporoparietal junction (Li et al., 2015).

The VMPFC is related to emotional control (Plewnia et al., 2015). Another fMRI study showed that music therapy is effective in normal brains and that the VMPFC was activated after music therapy (Raglio et al., 2016).

In this study, activation of the right DLPFC, VMPFC and OFC of MDD patients was detected after music therapy. Our results implied that music therapy could improve the ability of MDD patients to regulate emotions and make decisions through activation of the VMPFC, OFC and DLPFC. These findings may indicate that music therapy could enhance emotion regulation by helping patients become sensitive to and recognize their emotions. When treatment strategies reduced negative emotions, activation of the DLPFC, vmPFC and OFC increased (Ochsner and Gross, 2005). Regarding the OFC, this region is related to the reward mechanism. Music therapy, as a pleasurable stimulus, could become involved in the reward system by activating the dopaminergic system, including the OFC (Lepping et al., 2016).

This research demonstrated that music therapy could activate the DLPFC and VMPFC to enhance positive emotions and cognitive function. It was also shown that music therapy could activate the OFC to improve the reward mechanism.

4.3. Other results

Although the depressive symptoms of MDD patients were significantly improved after music therapy, their HDRS scores were still significantly higher than those in the HC group. In the HC group, no significant difference was found between pre-therapy and post-therapy. These results indicate that 10 consecutive receptive listening music treatments can significantly improve the symptoms of patients with mild to moderate depression but cannot completely eliminate the depressive symptoms. A recent meta-analysis showed that music therapy could relieve symptoms of depression and provide short-term beneficial effects in patients (Aalbers et al., 2017).

4.4. VFT performance

The VFT has been confirmed as a standard procedure that can be applied to study cognitive performance and language retrieval abilities (Herrmann et al., 2003). This performance task has been widely used to study executive capability in depression, which has been purported to be associated with cognitive impairment (Wolfe et al., 1987).

The number of words generated by the HC group was significantly greater than that generated by the MDD group within the categories of

vegetables and fruits. A major discrepancy was shown between the post-therapy and pre-therapy groups in three categories, with the exception of Task 2 – family application. Although no significant increase was illustrated by Task 2, the average number of words collected post-therapy was greater than that pre-therapy. Thus, these findings suggested that a performance improvement in cognitive capacity accompanied music therapy.

The underlying mechanism of this finding has not been clearly demonstrated. Music therapy has been confirmed to be beneficial for emotion regulation, including depression, in which cognitive impairment is a prominent symptom. Along with remission of depressive mood, cognitive performance also exhibited improvement.

Picazio's research suggested music listening in combination with transcranial cerebellar Direct Current Stimulation (tcDCS) can improve cognitive functions (Petrosini et al., 2015). Furthermore, based on the study of Fiveash, language and music may share common syntactic processing resources, which can give an explanation of this result (Fiveash et al., 2018). However, one study illustrated that music listening(without cerebellar continuous theta burst stimulation) did not influence cognitive performance (Oliveri et al., 2013).

4.5. Limitations

This study has some limitations. First, NIRS can only detect relative concentrations of oxyhemoglobin and cannot provide absolute quantitative results. Second, the S-curve technology used in this study was developed by the German music therapy system. Since the tracks are protected by copyright, other researchers need to obtain copyright approval if they want to repeat our experiments. Finally, the sample size of this study was not sufficient; therefore, additional large-scale cohort studies are necessary for further validation of the results.

Author contributions

Conceived and designed the experiments: K.F., C.Y.S., P.Z.L., and Y.J. Performed the experiments: K.F., X.Y.M., M.L.Z., and B.X.. Analyzed the data: K.F. and G.F.C. Contributed reagents/materials/analysis tools: X.M.L., X.Q.Z., and B.X. Wrote the manuscript: K.F. and C.Y.S. Operated the equipment: J.J.S. and X.J.R. Collected the data: B.X.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.03.015.

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