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Monochord sounds and progressive muscle relaxation reduce anxiety and improve relaxation during chemotherapy: A pilot EEG study☆

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KEYWORDS
Monochord;
Progressive muscle relaxation;
State anxiety;
Chemotherapy;
EEG;
Music therapy

Summary
Background: Chemotherapy is the most distressing form of cancer treatment in oncology, but listening to music can be an adjuvant during chemotherapy. Monochord (MC) sounds are used in music therapy for the alleviation of pain, enhanced body perception, and relaxation. This study investigated the relaxation effect of MC sounds for patients during chemotherapy compared with progressive muscle relaxation (PMR), an established relaxation technique.
Methodology/principal findings: Two randomized groups of patients were observed during chemotherapy. One group listened to recorded MC sounds ($n = 20$) and the other group listened to recorded PMR ($n = 20$). Each session was investigated pre and post using Spielberger's State Anxiety Inventory (SAI) and a questionnaire about the patient's physical and psychological states. Further, for the first and the last session, multivariate electroencephalogram (EEG) signals were recorded.

Patients in both MC and PMR groups showed significant improvement in their physical and psychological states and in state anxiety. The EEG data showed that the MC and the PMR groups were associated with an increase of posterior theta (3.5—7.5 Hz) and a decrease of midfrontal beta-2 band (20—29.5 Hz) activity during the end phase of relaxation treatment. Further, the MC group was associated with decreased alpha band (8—12 Hz) activity in comparison with PMR group.
Conclusions: This study shows that both listening to recorded MC sounds and practising PMR have a useful and comparable effect on gynaecologic oncological patients during chemotherapy, with partially overlapping but also notably divergent neural correlates. Future research should establish the systematic use of MC in oncological contexts.

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Introduction

Several studies show that patients diagnosed with gynaecological carcinomas have a high level of distress,[1–3] both physical and psychological, with a multitude of side effects.[4,5] Further, a recent psycho-oncological study shows that the most distressing form of cancer treatment is chemotherapy.[2] For patients undergoing chemotherapy, psychological support is especially required to help patients overcome their illness status by reducing their anxiety, alleviating their pain, and strengthening them psychologically. The provision of such support can also minimize post-treatment psychological distress.[6]

Music is a powerful and effective medium which can assist in reducing anxiety, pain, and stress.[7–9] Listening to music can improve the psychological state of patients and promote their physical well-being in different oncological contexts, including palliative care[10] and radiotherapy.[11] Several studies demonstrate the positive effects of music in alleviating anxiety,[12] reducing nausea and emesis,[13,14] and inducing relaxation in patients undergoing chemotherapy.[15] However, an evidence-based concept for the use of music still needs to be established. In particular, the specific illness situation of patients should be considered when assessing how music is used in the clinical context. An adequate explanation of this music-psychological and music-physiological phenomenon needs to be elaborated to develop the clinical use of music. Moreover, none of these current studies[11–15] have analysed the subjective psychological feedback from patients in combination with neurophysiological data to gain deeper insights into the positive effects. Therefore, little information is available on the possible neural mechanisms underlying the therapeutic effects by music in the oncological context.

The current study attempted to address these limitations by recording large scale neural responses (producing an electroencephalogram (EEG)) from oncological patients undergoing chemotherapy with special emphasis on the general therapeutic effects of monochord (MC) sounds. The MC is an ancient instrument with approximately 30 strings that is tuned to one base tone while nevertheless producing many overtones. MC sounds merge into one continuous sound with varying overtones and do not have definite scale, harmony, or accords, unlike what we usually associate with music. MC sounds are generally perceived as calming or pleasant, and listeners express positive feelings of a physical and psychological nature.[16] Although MC sounds are often used in music therapy, especially in Germany, it has rarely been studied in the clinical context. One clinical study in the context of oncological rehabilitation was conducted regarding the effect of sound meditation, which is a relaxation method combining mainly the MC with a variety of other sounds such as a gong, sound bowls, and (overtone) singing. 75.6% of oncological patients ($n = 105$) reported positive body sensations from 'sound meditation'.[16]

Since research into the effects of music in the clinical context is still in its infancy, the actual effect of relaxation through music can only be shown reliably by comparing — as in previous studies[17,18] — against a proven psychological relaxation method.[19] Comparison with a non-treatment control group could lead to distorted results due to the placebo effect in the group receiving treatment. Furthermore, since the main purpose of this study is to find out the effect of relaxation during chemotherapy, this excludes comparison with a waiting list control group. Ethical considerations prohibited the use of a placebo control group. Jacobson's progressive muscle relaxation (PMR) exercise is a relaxation method that has been demonstrated to be effective among oncological patients.[20,21] In this study, we have therefore compared the relaxing effect of monochord sounds against that of PMR on gynaecological cancer patients undergoing chemotherapy.

The current study had two principal objectives: (i) to investigate — from both subjective and neurobiological perspectives — the extent of therapeutic effects of monochord sounds in gynaecologic oncological patients undergoing chemotherapy and (ii) to compare these effects against those achieved with PMR.

Methods

Participants

This study was conducted in the Oncological Outpatients Clinic of the University Women's Hospital of Heidelberg, Germany. For patient selection, we have sought the participation of patients who had been diagnosed with breast cancer or gynaecological cancer, such as ovarian carcinoma and cervical carcinoma, who were about to receive chemotherapy for the first time in their life. Further, chemotherapy needed to be conducted for a minimum of 6 times (at 3-week intervals) and a maximum of 9 times (at 2-week intervals). Exclusion criteria were: previous experience with chemotherapy, regular practice of relaxation techniques, exceeding the age of 65 years, brain tumour or other metastases, other neurological diagnosis or prior brain operation, and pregnancy. The patients were randomly assigned to the MC group or the PMR group by means of permuted-block randomization. The group allocation was not communicated to the patients until the first relaxation treatment (Fig. 1).

Procedure

From the second to the fifth sessions of chemotherapy, relaxation treatment for both groups was provided after their premedication and in sync with the start of chemotherapy. To ensure that the first chemotherapy session ran as smoothly as possible, the relaxation treatment was provided only from the second chemotherapy session. During relaxation treatment, patients were instructed to remain awake in supine position with eyes closed. They listened to professionally recorded MC sounds or instructions for PMR by in-ear-phones (Sennheiser CX300II) from an iPod for a period of 30 min. The PMR instructions and MC sounds both lasted for approximately 25 min. There was a verbal introduction (4 min) before and a silent period (5 min) after each treatment, producing a total listening time of 34 min.

In each session, both before and after the relaxation treatment, patients in MC and PMR groups completed the German version of the State Anxiety Inventory (Spielberger's STAI-G Form X-1[22]) and a questionnaire about their physical and psychological states and their perception of the relaxation treatments (FB).[16] The State Anxiety Inventory (SAI)

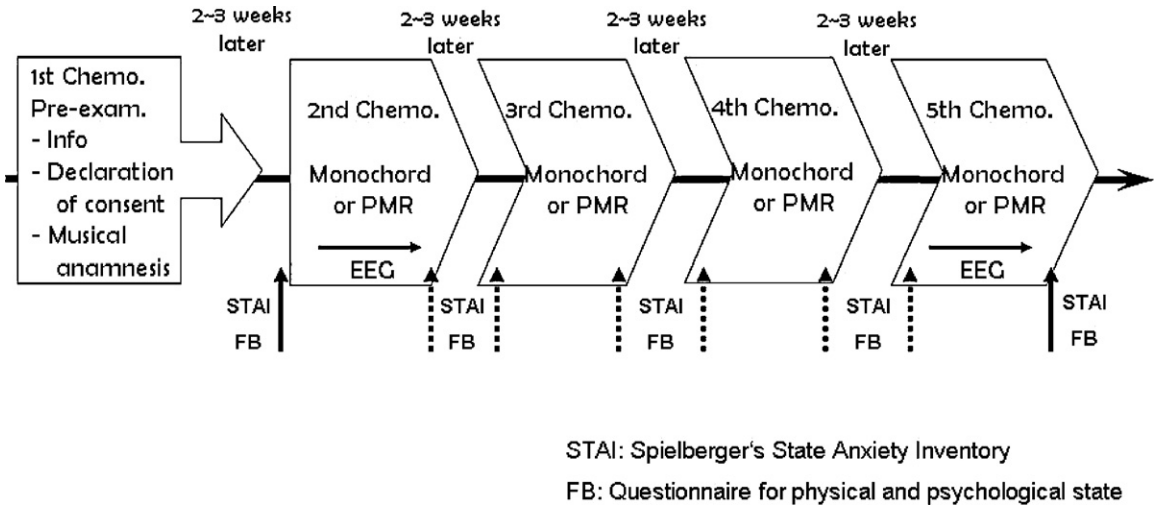

Figure 1 Monochord and PMR study design.

has 20 items with total score ranging from 20 (almost never) to 80 (almost always); higher score indicates greater anxiety. In the FB questionnaire, the analysis concentrated on the first four items with total score ranging from 5 to 20; higher scores suggest more positive state.

On the first and last sessions of both relaxation treatments, multivariate EEG signals were continuously recorded by placing 21 Ag/AgCl electrodes (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T1, T2, T3, T4, T5, T6, O1, O2) according to the extended International 10-20 electrode placement system.[23] The EEG signals were amplified using EEG amplifiers (SIGMA Medizin Technik, Neurowerk) and digitized at a sampling rate of 128 Hz. All electrode impedances were kept below 10 kΩ. The EEGs were re-referenced offline to the algebraic mean of the two earlobe electrodes.

Ethics

Each participant received information about this study in writing and a verbal explanation of this study individually by the researcher. Participation was entirely voluntary. Individual participants in this study gave written informed consent and a signed declaration of consent. This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Ethics Committee of the University Hospital of Heidelberg (S-365/2008).

Statistical methods

All data analyses were made by repeated-measures factorial analysis of variance (ANOVA). To analyse the behavioural data from both relaxation groups across treatment sessions, we used gain scores, i.e. the difference between pre- and post-treatment scores. For SAI scores, we analysed pre- minus post-treatment scores. For FB scores, post- minus pre-treatment scores were used. These orderings ensured that gain scores would be positive when the treatment has been effective. The difference scores of both measures were analysed by a 2$\times$4 mixed factorial ANOVA with *group* (2 levels: MC, PMR) as a between-subjects factor and *session* (4 levels) as a within-subjects factor.

The EEG data analysis concentrated on two 5-min periods within the 34-min EEG recording in each relaxation treatment session: *Begin* period (4th—9th min) and *End* period (25th—29th min). These periods were chosen so that the within-session effect of each relaxation treatment could be reliably assessed. The EEG recording started simultaneously with the relaxation treatment, thereby enabling accurate control of the timeline of events. Within each period, the data were divided into non-overlapping epochs of 10 s. Epochs containing amplitudes larger than $\pm$ 75 μV were considered artefactual and were therefore eliminated from subsequent analysis.[24,25] The power spectral density was estimated by the Welch periodogram algorithm[26] with a frequency resolution of 0.5 Hz. Mean spectral power was calculated for standard frequency bands: delta (under 3 Hz), theta (3.5—7.5 Hz), alpha (8—12 Hz), beta-1 (12.5—19.5 Hz), beta-2 (20—29.5 Hz), and gamma (30—45 Hz). Mean power values were log-transformed to reduce variance.

The EEG power values within each frequency band were analysed with a four-way repeated-measures mixed ANOVA with a between-subject factor *group* (2 levels: PMR, MC), and three within-subject factors *time* (2 levels: *Begin*, *End*), *session* (2 levels: first, last), and *hemisphere* (2 levels: left, right) at two different ROIs (regions of interest), anterior (Fp1, F3, F7 vs. Fp2, F4, F8) and posterior (P3, T5, O1 vs. P4, T6, O2). These ROIs were chosen in order to study the distribution of effects by including a broad spatial coverage of the recording electrode regions.

The statistical significance was set at $p < 0.05$ (corrected for sphericity, as appropriate). All statistical analyses were performed using SPSS (version 16.0).

Results

The data were obtained from 43 patients (aged 27—65 years, mean age: MC = 49.3 years, PMR = 51.3 years) between February and September 2009.

Before undergoing each chemotherapy session, patients received premedication to reduce the side effects and to

strengthen their tolerance of chemotherapy. A total of 41 patients received Fortecortin (MC = 21, PMR = 20), 39 patients Granisetron (MC = 21, PMR = 18), and 29 patients Aprepitant (MC = 16, PMR = 14). There were no statistically significant differences between groups. Of the various side effects of Aprepitant, fatigue can affect some patients, but this is just one of the diverse variables during chemotherapy that cause tiredness. Consequently, the possible side effect of fatigue caused by Aprepitant is not considered as a significant factor influencing the relaxation effect in our study.

During the main chemotherapy treatment, patients also received different combinations of medication. 16 patients received Cyclophospamid, Fluorouracil, and Epirubicin (MC = 7, PMR = 9), and seven patients Doxorubicin, Cyclophospamid, and Docetaxel (MC = 4, PMR = 3). No statistically significant difference was found between the two groups regarding either premedication or chemotherapy medication.

Behavioural responses

The behavioural responses of 40 patients (MC = 20, PMR = 20) were analysed. The data of three patients were excluded: one patient in the PMR group due to an insufficient command of the German language, and two patients in the MC group due to delayed completion (caused by the side effects of chemotherapy). Two patients in MC group were diagnosed with ovarian cancer and 38 patients in MC and PMR group were diagnosed with breast cancer.

Fig. 2(a) shows the difference in state anxiety level in four sessions for both groups. The degree of state anxiety was clearly reduced by MC and PMR. Mixed ANOVA indicated a significant main effect of *session* ($F(3,114) = 4.12$, $p = .008$). Post hoc contrasts revealed that, compared to the first session, the second ($F(1,38) = 5.95$, $p = .019$) and the fourth ($F(1,38) = 7.31$, $p = .010$) sessions produced a larger reduction in the degree of state anxiety level. The main effect of *group* was not significant ($F(1,38) = .83$, $p = .36$, n.s.), suggesting no overall differences between the MC and PMR groups in terms of reduction of state anxiety as a function of treatment. There was no significant interaction *session* × *group* effect.

Fig. 2(b) shows the difference in physical and psychological states for both groups. There was a substantial improvement of the overall state as a function of treatment in both groups in all four sessions. Mixed ANOVA indicated a significant main effect of *session* ($F(3,114) = 5.09$, $p = .002$). Post hoc contrasts revealed that, compared to the first session, all other sessions produced a greater state enhancement ($p < .05$). The main effect of *group* was not found to be significant ($F(1,38) = .195$, $p = .66$), suggesting no overall differences between MC and PMR groups in terms of state enhancement. However, there is a significant interaction *session* × *group* effect ($p < .05$), which was caused solely by the interaction between first and fourth sessions ($F(1,38) = 7.80$, $p < .05$).

EEG responses

For the EEG data, seven patients ($n = 2$ (MC), $n = 5$ (PMR)) were excluded from subsequent analysis due to excessive artefacts. There was one left-handed patient in each relaxation group. The power spectral densities at frontal brain region for the *Begin* (dashed line) and *End* (solid line) periods are displayed in Fig. 3(a) and (b) for PMR and MC groups respectively. Both groups showed a notable decrease of power in beta-2 band (20—29.5 Hz) during the *End* period in comparison to the *Begin* period, and the effect was statistically robust for the anterior ROI (main effect of *time*, $F(1,32) = 38.17$, $p < .001$). Further, this effect was significantly different between the two groups ($F(1,32) = 3.41$, $p = .07$). The mean (±SEM (standard error of mean)) power values indicate that the MC group (pre: -0.05 ± 0.05, post: -0.67 ± 0.03) has a greater decrease in beta-2 band activity than the PMR group (pre: 0.35 ± 0.05, post: -0.05 ± 0.03),

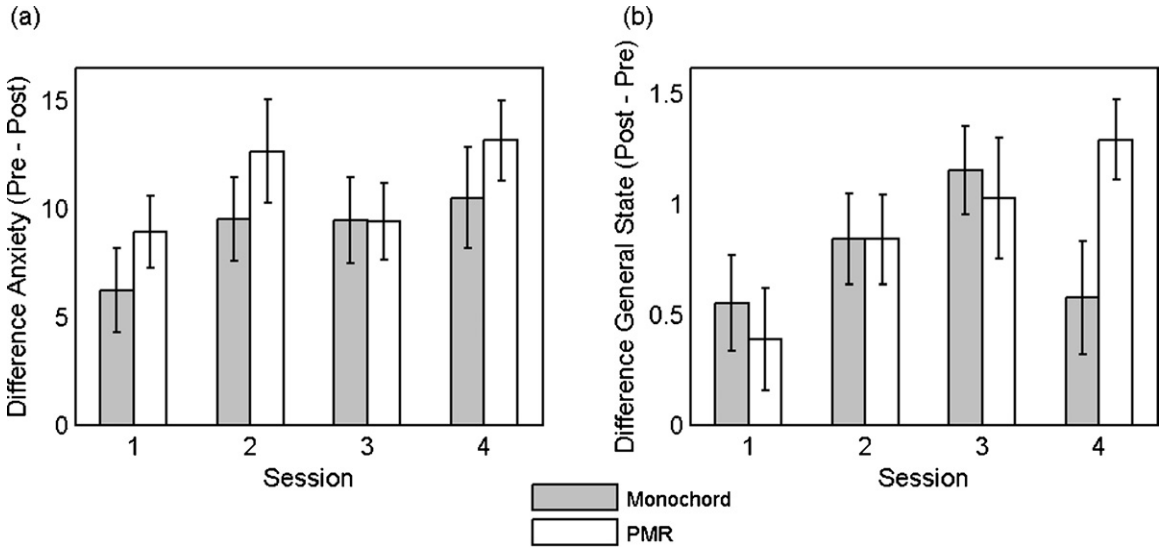

Figure 2 Change in behavioural data.

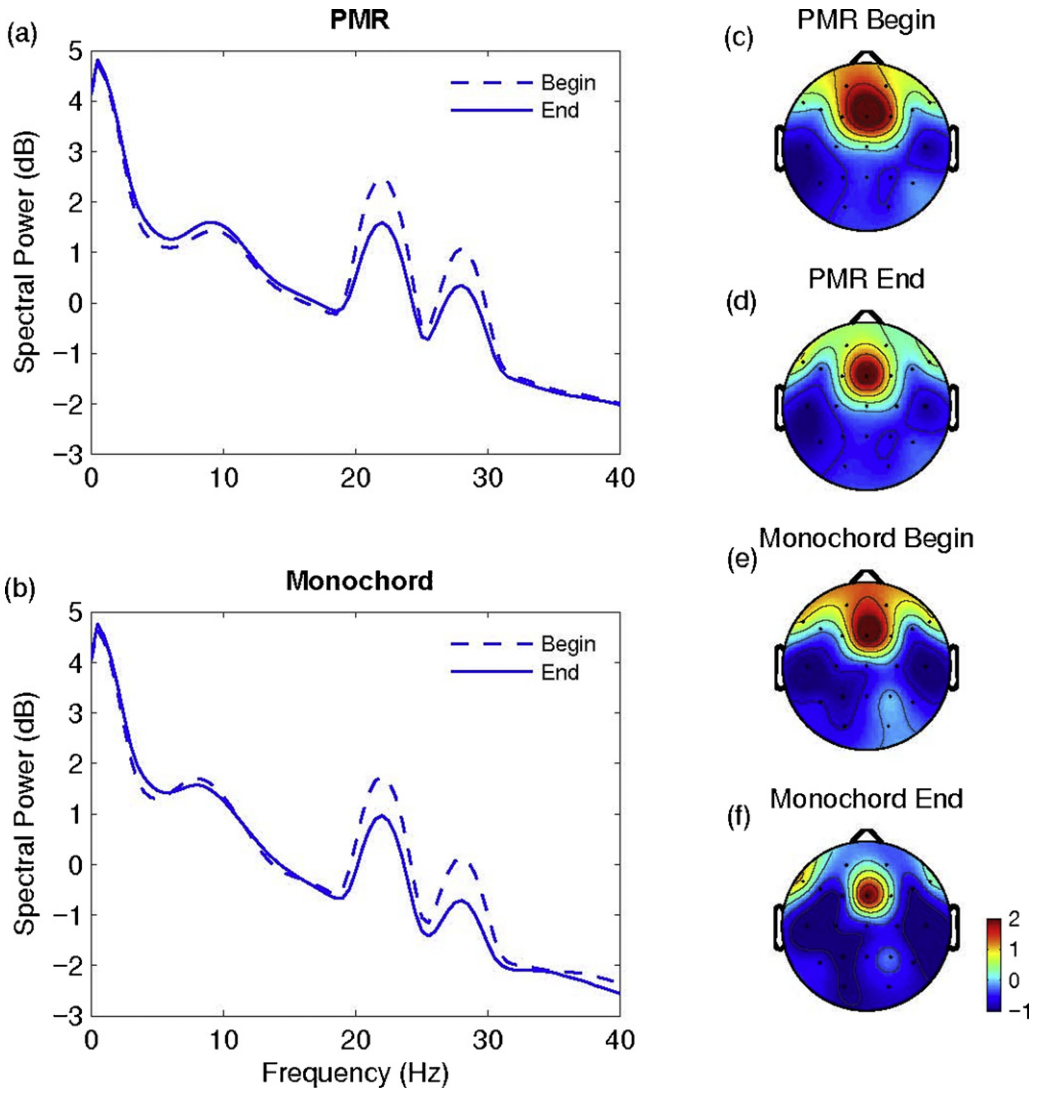

Figure 3 EEG activity in the frontal region and brain mapping for midfrontal beta-2 band activity.

and the overall trend of beta-2 activity is lower in the MC group than in the PMR group. The scalp maps of beta-2 power (Fig. 3(c)—(f)) showed the decrease in activity to be localized predominantly over the midfrontal brain region. Further, there is a remarkable consistency of the scalp maps during both *Begin* and *End* periods for the two groups, although the MC group showed more localized activity.

The power spectral densities at posterior brain region for *Begin* (dashed line) and *End* (solid line) periods are displayed in Fig. 4(a) and (b) for PMR and MC groups respectively. The power in the low frequency oscillations, 8 Hz and below, which includes theta band (3.5—7.5 Hz), increased substantially during the *End* period in comparison to the *Begin* period in both groups. Mixed ANOVA for theta band at posterior ROI revealed a main effect of *time* ($F(1,34) = 13.40$, $p = .001$). No group difference was observed between the theta power at posterior ROI of two groups ($p > .4$, n.s.). However, group difference was observed for alpha (8—12 Hz) band power as reflected by a *group* × *time* interaction effect ($F(1,34) = 7.34$, $p = .01$); compared to *Begin*, posterior alpha band power was reduced in the *End* period in the MC group but not in the PMR group. The same tendency was found in the beta-1 band (12.5—19.5 Hz) power over posterior ROI *group* × *time* interaction effect ($F(1,34) = 5.62$, $p = .02$). For gamma band (30—45 Hz) power at anterior ROI, a significant difference was obtained between the groups ($F(1,32) = 13.91$, $p = .001$), whereby MC group was associated with higher gamma power than PMR group. This similar effect was also observed at anterior ROI ($F(1,32) = 9.62$, $p = .004$). No significant differences were observed in the delta band (<3 Hz) power.

Discussion

The primary purpose of the present clinical study was to gain novel insights into the therapeutic effects of monochord sounds by comparing monochord sound-induced relaxation treatment against PMR-induced relaxation treatment. The behavioural data demonstrated that both MC and PMR relaxation treatments significantly reduced anxiety and improved physical and psychological states during chemotherapy. The

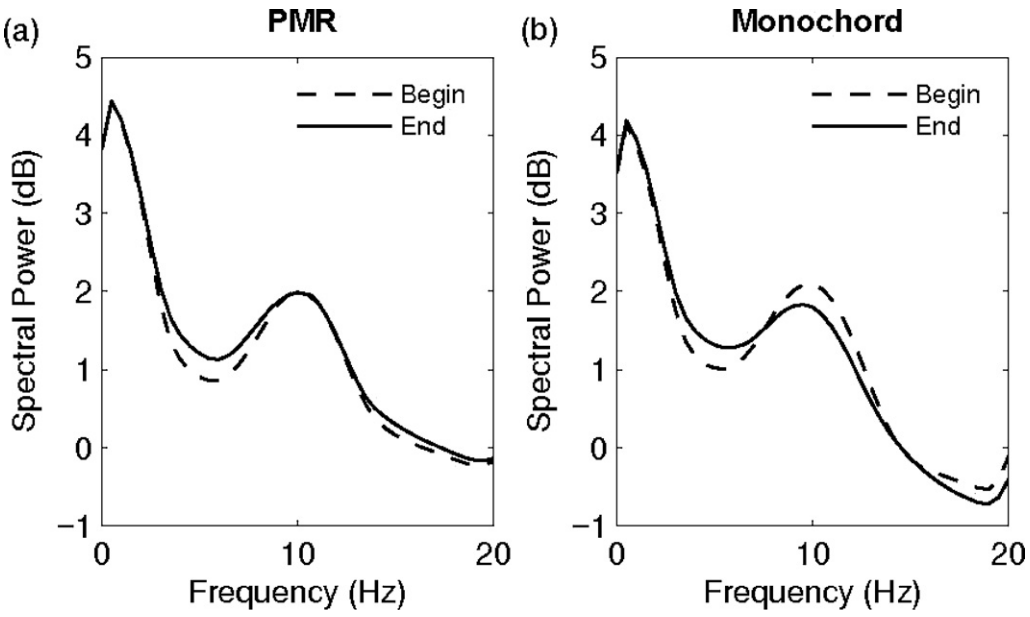

Figure 4 Theta band activity in the posterior region.

EEG data demonstrated that both MC and PMR treatments were associated with an increase of posterior theta band activity and a decrease of midfrontal beta band activity.

Both groups not only showed a reduction in the degree of state anxiety within treatment sessions, but they also produced an almost gradual reduction in anxiety as the treatment progressed across sessions. Further, no significant differences were found between the two types of relaxation treatment, suggesting both are effective to a similar extent in reducing anxiety. Both relaxation treatments were also similarly effective, to a large extent, in enhancing the overall physical and psychological states within and across sessions. However, Fig. 2(b) shows a different tendency between third and fourth sessions between groups. The general state in MC group was reduced in the fourth session compared with the third session, while the improvement in PMR group becomes greater with each subsequent session. This difference could stem from the different nature of the two exercises: PMR can become more effective after the patient has performed the exercise several times, whereas there is currently no evidence pointing to an increase in the effectiveness of listening to MC sounds the more often a patient practices it. Further, the results might also be influenced by the less optimistic prognosis for the two patients with ovarian cancer, both of whom were in MC group, given the small sample size.

Unlike previous studies investigating the effects of music during chemotherapy,[12,15] this study compared the behavioural results of the MC group primarily to those of the PMR group (see non-oncological studies[17,18] with a similar approach). Other oncological studies[12–15] about the clinical use of music compared their results only against a control group, whereas the inclusion of the PMR group — PMR being an established relaxation method — increases the validity of the MC treatment. Further, in contrast to other studies,[12–15] the distinguishing feature of our study is the use of monochord sounds, which offer the benefit of being unfamiliar to patients and yet they are widely used for relaxation and the alleviation of pain and anxiety in music therapy. Furthermore, this study conducted the relaxation treatments regularly from the second to the fifth sessions of chemotherapy, which enabled investigation of the specific effect of the relaxation treatments, whereas a previous study[15] only performed one music intervention during the whole course of chemotherapy, without any specification of the timing of the intervention or any control for the varying levels of physical and psychological distress during each chemotherapy session.

Our current study is the first that systematically studied and compared the EEG responses to MC relaxation treatment against those to PMR. In our study, similarities have been shown between MC and PMR groups in terms of enhanced posterior theta and reduced midfrontal beta-2 activity as the treatment progressed within individual sessions. Several EEG studies demonstrate spectral power changes in the theta and alpha bands during relaxation[27–29] or meditation.[30,31] For example, there is a significant increase of theta band activity and the total alpha band activity during meditation,[30] an increase of frontal theta band activity and deactivation in the parietal-occipital brain region during meditation in comparison with the state of relaxation,[31] higher alpha band activity during hypnosis, and a combination of greater theta brain band activity with lower alpha band activity during relaxation after hypnosis.[32] Therefore, the reported enhancement of posterior theta power is taken to reflect a higher degree of relaxation at the end of each treatment session. The reduction of midfrontal beta-2 band power as a function of treatment is a novel finding in the context of relaxation treatment. Given that other studies observed enhanced beta activity in the frontal regions during the stress caused by ongoing pain,[33] anxiety, and anxiety-related disorders[34,35] and, in this study, beta-2 band was reduced at the end of a treatment session from its onset, this possibly reflects a neural correlate of the

reduced anxiety. These results raise the possibility that posterior theta and anterior beta-2 band spectral power in combination could be an appropriate marker of the brain's response to relaxation technique, possibly serving as a complementary marker to the alpha band.[27,28,33–35]

Consequently, we can reasonably conclude that MC sounds, like PMR, are effective in inducing relaxation, reducing anxiety, and promoting physical and psychological states in gynaecologic oncological patients undergoing chemotherapy. The underlying neural correlates, although largely overlapping, are not necessarily identical. This is not entirely surprising as PMR and MC relaxation treatments have different intervention protocol: with PMR, patients are instructed to actively tense up and relax their muscles, whereas MC sounds are passively listened to. If both relaxation treatments have similar positive therapeutic effects, the question remains as to which method would be most efficient (and effective) for which kind of patient. PMR is a cognitive exercise that, by virtue of its neutrality, can reach many people generally. Nevertheless, patients need to concentrate while performing the PMR exercises, which could potentially counteract relaxation. By comparison, MC relaxation treatment is a passive method of listening to sounds that does not require any active response from patients. Therefore, it is generally quicker at achieving a deeper level of relaxation than PMR and does so while maintaining an alert state of consciousness, as demonstrated in other monochord studies.[36,37]

The current study nevertheless faces certain limitations. First, the MC sounds were not tailored to individual patient's preference and experience, which might compromise their optimal effectiveness as a musical stimulus in music therapy, whereas music therapy is usually most effective when the musical intervention has been adapted after taking the individuality of the patient into consideration.[38,39] Second, MC sound may be more efficient when played live due to the presence of the vibrations and overtones, whereas, in this study, monochord sounds were played via in-ear-phones, which did not allow any regulation of the volume of the base tone and the overtone (even though patients could regulate the overall volume by themselves). Third, the durations for which the relaxation effects of the MC and PMR relaxation treatments remained were not measured. An accurate assessment of how long the effect of relaxation lasts after treatment has been administered would definitely be useful in a therapeutic setting at hospital and for home care and in particular to study the effect of therapeutic support for psychological and physical enhancement. Fourth, for ethical reasons, no control group was conducted in this study. We sought to avoid causing additional stress with our research, given that cancer patients already have to endure a physically and psychologically demanding situation during chemotherapy. However, in a future study, setting up a control group would help to clarify the exact relaxation effect between pre and post measurement in each session.

Conclusion

This study has demonstrated that monochord relaxation treatment is as effective as PMR, an established relaxation treatment, for gynaecologic oncological patients during chemotherapy by reducing state anxiety and promoting psychological and social states. Further, both relaxation treatments are associated with partially overlapping but also notably divergent neural responses. This study could be considered a first step towards developing an evidence-based music therapeutic concept in gynaecologic oncology to improve the psychological and physical state of patients, not only in a clinical context but also as home care.

Conflict of interest statement

The authors declare that they have no competing financial interests.

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