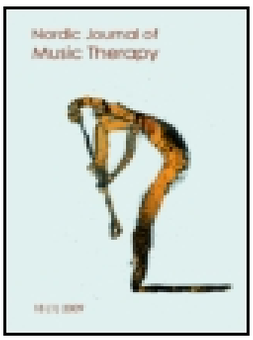

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ORIGINAL RESEARCH ARTICLE

Study protocol of the MUSED study: A randomized controlled trial to evaluate the psychobiological effects of group music therapy in women with depression

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ABSTRACT

Introduction: People suffering from depression commonly show impaired emotion regulation, accompanied by deficits in the regulation of psychobiological stress systems. Initial studies indicate that music therapy can impact depressive symptoms and psychobiological mechanisms, and may therefore contribute to effective treatment for depression.

We will investigate the effects of music therapy on depressive symptoms. Moreover, we will examine the impact of this therapy on circadian biological rhythms in daily life. In particular, we will monitor the circadian rhythm of vagal tone, indexed by heart rate variability (HRV), and of the hypothalamic-pituitary-adrenal (HPA) axis, indexed by the diurnal cortisol profile, within the framework of ecological momentary assessment (EMA).

Method: Seventy-four women aged 18–65 years with a diagnosis of depression or dysthymia will be eligible for participation. Participants will be randomly assigned to the intervention group (10 weeks music therapy + treatment as usual, TAU) or the control group (TAU only).

Self-report data will be collected before and after the intervention period, and 10 weeks after the post-assessment. Psychobiological data (48 hours HRV, salivary cortisol from six samples each of two consecutive days) and observer ratings will be gathered before and after the intervention period.

Discussion: The study aims to validate previous findings that music therapy is effective in the treatment of depression. The results will foster the understanding of how music therapy affects HPA axis and autonomic regulation processes. The EMA approach offers the potential to test for covariance between different psychobiological markers in daily life.

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KEYWORDS Music therapy; randomized controlled intervention study; depression; vagally mediated heart rate variability; cortisol; ecological momentary assessment

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Supplemental data for this article can be accessed here.

Introduction

Depressive disorders are among the most prevalent mental illnesses and a leading cause of the global burden of disease worldwide (Kessler & Bromet, 2013; Whiteford et al., 2013; World Health Organization, 2017). The World Health Organization (2017) estimates that the proportion of the world population suffering from depression lies at 4.4%, with women (5.1%) being more frequently affected than men (3.6%). Depressive disorders are associated with a number of symptoms, such as impaired mood leading to a loss of quality of life, alterations in emotion regulation, loss of interest and pleasure in activities, and feelings of worthlessness (e.g. Aldao et al., 2010; Berlim & Fleck, 2007). There are increasing calls to relate psychopathology to the associated alterations in neurobiological systems, e.g. circadian rhythms, in order to better understand mental disorders and improve treatment options (Leubner & Hinterberger, 2017). To this aim, the US National Institute of Mental Health (NIMH) has published the Research Domain Criteria Initiative (RDoC system), which integrates multiple levels of information, e.g. psychophysiological and behavioral information, to achieve a multi-perspective, comprehensive understanding of mental disorders (National Institute of Mental Health, 2019).

Dysregulation of stress perception and response in depressive disorders

The emergence and maintenance of depressive symptoms has been attributed to the interaction of biological and psychosocial dispositions with acute and lifetime stress (Hammen, 2005). The organism's physiological reaction to cope with these environmental circumstances is known as the human stress response (Cannon, 1935). In this regard, the individual appraisal (e.g. previous experiences and prognosis or expectations about the future) can lead to a stimulus being interpreted as a stressor (Folkman et al., 1986). The psychophysiological response to stimuli which represent uncertainty, novelty, and threat prepares the organism for action. However, in the daily life of modern society, the continuous threat perception appears to be maladaptive, and can be associated with dysregulation of hippocampal circuits and of endocrine and autonomic output, leading to a decline in cognitive and general health (Thayer et al., 2012). Particularly in individuals with depression, the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) show altered functioning (Bassett, 2016; H. M. Burke et al., 2005; M. N. Jarczok, Koenig, et al., 2018; Kemp & Quintana, 2013; Palazidou, 2012; Porges, 1997; Thayer & Lane, 2000). The current state of both the HPA axis and ANS are commonly indexed by noninvasive salivary cortisol and heart rate variability (HRV) measures.

Heart rate variability

The human heart rate (HR) is subject to multiple and dynamic influences, with the ANS contributing significantly to the variation of inter-beat intervals (normal-to-normal, NN). Whereas high HRV is associated with more parasympathetic activity and relaxation, lower HRV is associated with an increased risk of morbidity and mortality within various physical and mental diseases, including depression (Kemp & Quintana, 2013; Kemp et al., 2012, 2010; Koch et al., 2019; Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). Kidwell and Ellenbroek (2018) reported evidence of a bidirectional relationship between HRV

and depression, insofar as reduced HRV might on the one hand result from depression and on the other hand predict the occurrence of depression.

The circadian course of vagally mediated HRV depicts characteristic variations, with a peak between midnight and 4 a.m., and a trough in the afternoon (M. N. Jarczok et al., 2017). Moreover, during awakening, there is an increase in HR and some HRV parameters, indicative of cardiovascular activation (Trinder et al., 2003). The circadian variation pattern of vagally mediated HRV was found to be associated with depressive symptoms (M. N. Jarczok, Aguilar-Raab, et al., 2018; M. N. Jarczok, Koenig, et al., 2018; M. N. Jarczok et al., 2017). M. N. Jarczok, Koenig, et al. (2018) reported sex differences in employees reporting depressive symptoms. Here the circadian rhythm adjusted mean was found to be higher in women but lower in men when comparing individuals over vs. below the top 90th percentile on the depressive symptom scale.

Salivary cortisol

Cortisol is a glucocorticoid hormone that is released following activation of the HPA axis (Ulrich-Lai & Herman, 2009). Most of the variability in cortisol levels is determined by a distinct circadian rhythm, characterized by a strong rise in cortisol levels immediately after awakening and a decrease over the course of the day, reaching its minimum in the early morning of the next day (Miller et al., 2016). However, salivary cortisol levels rise within 10 to 20 minutes following exposure to a stressor (Schlotz, 2014; Ulrich-Lai & Herman, 2009). Alterations in the circadian rhythm of cortisol are indicative of adaptive changes in HPA axis functioning in the light of environmental challenges (McEwen, 2004; Pruessner et al., 1997). Consequently, the assessment of diurnal cortisol profiles can provide information about psychobiological stress reactivity and general HPA axis functioning in everyday life. Long-term disruptions of normal circadian patterns are associated with a broad range of physical and psychological illnesses, including major depressive disorder (Adam et al., 2017; Dedovic & Ngiam, 2015; DeMorrow, 2018; Veen et al., 2011). Despite a growing number of investigations regarding HPA axis functioning in individuals with depression, the research findings are inconsistent (Bhagwagar et al., 2005; Knorr et al., 2010; M. Pruessner et al., 2003; Stetler & Miller, 2011).

Music therapy to treat stress-related symptoms and depressive disorders

Depression is associated with elevated stress levels and altered emotion regulation (Hammen, 2015; Nolen-Hoeksema & Aldao, 2011). Therefore, the treatment of depressive disorders focuses on coping with stress and on the regulation of emotions and motivation. Despite substantial progress in the development of antidepressant medication and psychotherapy, non-responses in approximately one-third of all patients with depression underline the need for effective complementary treatment options (Himmerich & Wranik, 2012). As music directly addresses the emotions (Blood & Zatorre, 2001; Koelsch, 2014; Koelsch et al., 2006) as well as the psychobiological stress systems (Fancourt et al., 2014; Thoma et al., 2013), music therapy is potentially beneficial in the treatment of depression.

Music has been proposed as a therapeutic agent in the treatment of affective disorders since the emergence of modern psychiatry (Kümmel, 1977). Today, music therapy is defined as "the systematic use of music within a therapeutic relationship which aims at restoring, maintaining and furthering emotional, physical, and mental

health" (German Society of Music Therapy, para. 1). Active music therapy interventions involve participants playing or singing live music with or without the musical accompaniment of a therapist. Receptive music therapy techniques, by contrast, comprise active listening either to live music played by the therapist or pre-recorded music (Bruscia, 2014).

Recent studies on music therapy have revealed enhanced affective expression, social interaction, motivation and social participation in participants with depression (Aalbers et al., 2017; Leubner & Hinterberger, 2017; Zhao et al., 2016). Neuroimaging studies found that music processing activates neural circuits associated with emotion regulation and the reward system (Blood & Zatorre, 2001; Koelsch, 2014; Koelsch et al., 2006; Menon & Levitin, 2005). Moreover, music listening can affect the psychological and physiological stress response (Thoma et al., 2013). Fancourt et al. (2014) outlined four categories with regard to how music achieves stress-reducing effects: (a) the sound of the music (including tempo, tonality, instrumentation), (b) a person's physical involvement to produce music, (c) social aspects (making music together), and (d) individual aspects (musical preferences). The authors were able to show that all four of these categories interact with psychobiological systems, including the central nervous system, the ANS, the endocrine system, and the immune system. However, the underlying psychobiological mechanisms are still unexplained.

State of the art

An increasing number of reviews within the past few years on the effectiveness of music therapy in the treatment of depression underlines the high relevance of the issue. A common finding of these reviews is that music therapy showed the capacity to reduce depressive symptoms in both adults (Aalbers et al., 2017; Leubner & Hinterberger, 2017) and in elderly people (Li et al., 2019; Zhao et al., 2016).

The stress-reducing effects of music have been determined from various perspectives. One focus of this broad research area refers to the reduction in self-perceived stress (Bradt et al., 2013; Lee et al., 2012; Pelletier, 2004; Taets et al., 2013). While music-listening interventions have only shown small effects with regard to stress reduction, the majority of studies used music medicine or music-listening interventions without the presence of a music therapist (Gold et al., 2011). Other studies measured the outcomes regarding different psychobiological stress systems that can be affected by music (Chanda & Levitin, 2013; Ellis et al., 2012; Ribeiro et al., 2018). The authors of a Cochrane Review on music for stress and anxiety concluded that music has beneficial effects on psychobiological stress, as indexed by HR, blood pressure and respiratory rate (Bradt et al., 2013). Moreover, music listening and music therapy were found to promote a relaxation response, indexed by an increase in HRV parameters related to vagal activity (Bradt et al., 2013; Chiu et al., 2003; Gäbel et al., 2017; Iwanaga et al., 2005; Kim et al., 2018; Warth et al., 2015). Similarly, music interventions were found to reduce cortisol levels (Fancourt et al., 2014; Hou et al., 2017; Uedo et al., 2004), although the respective findings remain inconsistent (Cheung et al., 2018).

Despite the growing interest in the effects of music therapy on depression and other stress-related diseases, there is still a lack of research using complementary psychobiological assessments. The majority of trials faced methodological limitations, including small sample sizes, heterogeneity of the study population, poor reporting of the study procedure (e.g. randomization, allocation concealment, blinding) or of the music therapy

intervention itself (Aalbers et al., 2017; Leubner & Hinterberger, 2017), as well as the restriction to immediate effects. Medium- and long-term effects of music therapy in daily life, reflecting a sustainable therapeutic benefit, have rarely been investigated. The majority of previous studies used music-listening interventions only, although Bradt et al. (2015) emphasized the advantages of employing a professional music therapist to develop a therapeutic process encompassing situational reactions, appropriate selection of music interventions depending on the patient's current needs, and a parallel assessment of emotional processing. The above-mentioned literature provides first evidence for the effectiveness of music therapy in the treatment of depression and stress-related symptoms. However, to fully explore the potential, more studies which simultaneously assess the subjective and psychobiological effects, including measurements in daily life, are needed.

Objectives

We designed a randomized controlled trial entitled "*Music Therapy for Depression* (MUSED)" to evaluate the effectiveness of a group-based music therapy in women suffering from depression. Our music therapy approach aims to improve depressive symptoms and the functioning of the psychophysiological stress systems in daily life.

Methods and design

This study was designed as an individually randomized, parallel group treatment trial with clustering only in the experimental group receiving music therapy treatment over a period of 10 weeks. Patients in the control condition individually continued with their usual treatment plan.

Ethics, consent, and permissions

The MUSED study was registered with the German Clinical Trials Register (DRKS00016616) on the 21st February 2019 before the first patient was randomized. The study is being conducted at the outpatient clinic of the Institute of Medical Psychology, Center for Psychosocial Medicine, University Hospital Heidelberg, Germany. Participants will be informed according to the Declaration of Helsinki. Study participation is completely voluntary. Detailed written and verbal information on study aims, procedure, benefits and risks will be provided. After providing written informed consent, eligible participants will be enrolled. Reassignment will lead to full deletion of obtained study material and data. Ethical approval has been obtained from the ethics committee of the Medical School Heidelberg, Heidelberg University (S-545/2016). The study conduct will be performed according to the guidelines of the ethics committee of the Medical School Heidelberg, Heidelberg University. Above, the study conduct will be monitored by an independent researcher who is not otherwise involved in the study.

Participants, recruitment, and screening

Participants

Previous findings showed that prevalence rates for depression are higher in women than in men (Maske et al., 2016). It was also reported that women were more likely to participate in research on psychosocial interventions including music therapy studies. This effect was already observed in former music therapy studies (Erkkilä et al., 2011; Warth et al., 2015). Moreover, numerous studies identified sex differences in both levels and reactivity of both HRV and salivary cortisol (M. N. Jarczok, Koenig, et al., 2018; Stalder et al., 2016). Hence, in this study, we decided to focus on women only to facilitate the recruitment procedure, increase statistical power, and prevent methodological and analytic biases.

Participants will be included if they are (a) female, (b) between 18 and 65 years old, (c) meet the criteria for a primary current depression or persistent depressive disorder (dysthymia), excluding depression with psychotic symptoms and remitted depression, according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) and the *International Classification of Diseases* (ICD-10) codes: F32.0; F32.1; F32.3; F32.4; F32.8; F32.9; F33.0; F33.1; F33.2; F33.41; F33.8; F33.9; F34.1, respectively, (d) meet the criteria for at least mild depression as diagnosed with the observer-rated *Hamilton Depression Rating Scale* (HDRS) and according to the clinician-led Structured Clinical Interview for DSM-5 (SCID-5) (Beesdo-Baum et al., 2019a) and (e) meet the criteria for at least mild depression diagnosed with the self-rated *Beck Depression Inventory* (BDI-II, see paragraph *Screening* for cut-off points).

Participants will be excluded if they (a) meet the DSM-V criteria for primary severe mental disorders (schizophrenia, bipolar disorder, acute suicidal tendency, psychotic symptoms as primary diagnosis), (b) have a borderline personality disorder, (c) meet the criteria for substance abuse or acute addiction or (d) have participated in another music therapy within the last three months.

We will record the occurrence of diabetes, cardiovascular diseases, and altered physical conditions (pregnancy; current breastfeeding; chronic diseases, other endocrinological, neurological, nephrological or hepatic disorders), enabling us to create subsets of data for secondary biomarker analysis.

Recruitment

Participants will be recruited between summer 2019 and summer 2020 from different inpatient and outpatient clinics at the Center for Psychosocial Medicine at Heidelberg University Hospital (Germany). Additionally, psychotherapists and alternative practitioners in private practice, registered physicians, psychiatric and psychosomatic clinics as well as outpatient centers for counseling and psychotherapy in and around Heidelberg will be asked to refer patients on their waiting lists for individual therapy. Further recruitment will be conducted via university mailing lists, social media (Facebook, Twitter, Instagram), the internet (e-Bay) and print media. Based on the advertisement and referral from clinics and colleagues, interested patients will contact the study coordinator by e-mail or telephone. The eligibility screening will proceed in two steps (see below).

Screening

The first part of the screening procedure will consist of a short telephone interview in order to evaluate the fulfillment of the inclusion criteria (pre-screening). The second

part of the screening will be conducted at the Institute of Medical Psychology. First, each potential participant will be informed about the study goals and asked to sign the informed consent form. Afterwards, both self- and observer-rated diagnostics of psychopathology and depression will be performed. The following instruments will be used to determine the presence of a depressive disorder: the SCID-5 (Beesdo-Baum et al., 2019a, 2019b) according to criteria of the DSM-V, the observer-rated HDRS, 17-item version (Hamilton, 1960), and the self-rated BDI-II, 21-item version (Beck et al., 1996). According to the German Association for Psychiatry, Psychotherapy, and Psychosomatics (DGPPN), the cut-off scores of the German-language HDRS version are defined as follows: 0–8: no depression/remitted; 9–16: mild depression; 17–24: moderate depression; ≥ 25: severe depression (German Society for Psychiatry, 2017). Cut-off scores of the BDI-II are defined as follows: 0–13: no or minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression. The recruited women will be eligible for participation if they meet DSM-V criteria for major depressive disorder in combination with HDRS ≥ 9 and BDI-II ≥ 13.

Assessments

The MUSED study includes a comprehensive assessment plan to determine psychological and psychobiological effects of music therapy: pre-assessment prior to the intervention period, process measures during the intervention period, post-assessment after the intervention period, and follow-up assessment 10 weeks after the post-assessment. The study design is depicted in Figure 1, including the timing of interventions and all assessments.

Pre-assessment

The pre-assessment will span four days and will include psychometric and psychobiological assessments. On the first day (lab day 1), participants will take part in the screening procedure and the first part of the psychometric assessment. All psychological questionnaires in this study will be online-based. Please refer to the Appendix[1] for an overview of the timing and application of all questionnaires. At the end of lab day 1, each participant will receive the material for the psychobiological assessment of the two subsequent days: (a) a one-lead ambulatory ECG monitor (eMotion FAROS 180° Mega Electronics Ltd. Kuopio, Finland) on a chest belt with dry electrodes sampling at 1000 Hz and (b) 12 saliva collection tubes (RE69985 IBL International GmbH Hamburg, Germany). The participants will be given instructions on the correct handling of the material. The instructions for saliva sampling are based on the recommendations of Adam and Kumari (2009) and Stalder et al. (2016).

On days two and three (everyday life assessment days 1 and 2), the participants will be asked to wear the ECG monitor for a minimum of 48 hours, beginning in the evening before the first day of saliva sampling (typically in the evening of lab day 1) and ending in the evening of the second day of saliva sampling. During the two days of everyday life assessments, participating women will be asked to collect saliva samples at the following time points for the analysis of diurnal cortisol profiles: immediately after awakening, 30, 45, 150, and 480 minutes after awakening, and immediately before going to bed (Stalder et al., 2016). The everyday life assessments will be conducted on

[1]Add link to online supplemental.

	STUDY PERIOD								
	Enrolment			Allocation	Post-allocation			Close-out	
	Telephone interview	Lab day 1	Everyday life assessments (days 1 + 2)	Lab day 2	Intervention phase	Lab day 3	Everyday life assessments (days 3 + 4)	Follow-up assessment	Intervention phase
TIMEPOINT	$-t_3$	$-t_2$	$-t_1$	t_0	$t_{1\text{-}11}$	t_{12}	t_{13}	t_{14}	$t_{15\text{-}25}$
Duration	*30 min.*	*4 h*	*48 h*	*2 h*	*10 weeks*	*1,5 h*	*48 h*	*1 h*	*10 weeks*
ENROLMENT:									
Pre-screening	X								
Informed consent		X							
Eligibility screen		X							
Randomization				X					
INTERVENTIONS:									
Music therapy					X				X*
Treatment as usual					X				
ASSESSMENTS:									
Observer-ratings		X				X			
Self-ratings		X				X		X	
EMA			X				X		
ECG			X				X		
Saliva			X				X		
Process measures					X				

Figure 1. SPIRIT diagram for the MUSED study. *Participating in the music therapy during the second intervention phase is optionally and refers only to the waitlist control group. EMA = ecological momentary assessment; ECG = electrocardiogram

weekdays to ensure comparability of diurnal cortisol profiles (Kunz-Ebrecht et al., 2004; Stalder et al., 2016). The women will be instructed to store the saliva tubes in a refrigerator immediately after sampling until the return of all material to the Institute of Medical Psychology (Stalder et al., 2016).

Analogously to the psychobiological assessments, we will conduct an ecological momentary assessment (EMA) to assess participants' "current experiences, behaviors and moods as they occur in real time and in their natural environment" (L. E. Burke et al., 2017, p. e77). We will use an event-related fixed-occasion design, with the time of awakening acting as event (Kudielka et al., 2012). The women will receive six text messages daily, with a link to an online-based EMA inquiry. As saliva sampling will proceed analogously to the EMA, every text message will also serve as a reminder and provide instructions for saliva sampling.

Having completed all saliva samples during the two consecutive days, participants will be asked to return the samples and equipment to the Institute of Medical Psychology (lab day 2, typically the day after the second day of everyday life assessments). The samples will be stored at −80°C and analyzed using enzyme-linked immunosorbent assays (ELISA) inhouse at the Stress Biomarkers Laboratory at the Institute of Medical Psychology. Having returned the material to the study personnel, the participants will complete the second part of the psychometric assessment.

Process measures

All participants will complete a brief weekly online-based survey between the pre- and post-assessment in order to ascertain variations in the self-perceived stress levels as well as positive and negative affect in relation to the music therapy treatment. The link to the survey will be sent to the participants by text message.

Post-assessment

The post-assessment protocol includes all steps of the pre-assessment plan with the exception of the SCID interview, and will therefore take three days (instead of four days as at the beginning of study participation): lab day 3 plus everyday life assessment day 3 and 4.

Follow-up assessment

The follow-up assessment includes self-ratings only and can therefore be completed from home in order to minimize effort required from the participants and maximize compliance at the same time. Participants from both study conditions will receive a text message with a link to the online-based survey. This questionnaire will encompass the same self-ratings used during the pre- and the post-assessment.

Having completed all assessments, every participating woman will receive feedback on her individual stress profile, including information on cortisol profiles and self-perceived stress during the study period.

Randomization and blinding

Having completed the pre-assessment, 12–18 participants will be block-randomized at the individual patient level either to the intervention or the control group condition (block size = 6–9). This procedure will be repeated until the required sample size is achieved. Allocation concealment will occur through the use of sequentially numbered

sealed envelopes. Block randomization will be conducted with R Version 3.5.1 using the package *blockrand* (R Core Team, 2018). A researcher at the Institute of Medical Psychology who is not otherwise involved in the MUSED study will perform the randomization procedure.

The outcome assessors conducting the observer-rated assessments will be blinded with respect to participants' allocation to either the intervention group or the waitlist control group. The self-rating assessments will be completed pseudonymously, as they will be conducted via online surveys. Statistical analysis of all data will be blinded with regard to group allocation. Blinding of participants and therapists will not be possible due to the nature of the intervention. Therefore, all participants and therapists will be informed about the aims of the study.

Interventions

This RCT will have the following two parallel arms: the waitlist control group delivered with treatment as usual (TAU) until completion of all assessments, and the intervention group delivered with TAU plus music therapy. Afterwards, participants of the waitlist control group will be given the opportunity to take part in an equivalent music therapy program at the Institute of Medical Psychology.

Treatment as usual

All participating women will receive TAU irrespective of group assignment. TAU can include general practitioner care, psychotherapy treatment, contact with community mental health teams, and/or antidepressant pharmacological treatment. Participants will be requested to maintain their treatment plan during the study period (intervention phase + assessment phases before and after intervention). We will ask the participants to report changes of the TAU conditions during their study participation in order to take this statistically into account.

Music therapy intervention

Participants allocated to the intervention group will participate in the group music therapy program between pre- and post- assessment. The waitlist control group will receive an equal therapy program after having finished all assessments. Therapy sessions will be carried out by SR (qualified music therapist with approved academic training in music therapy) together with one co-music therapist at the Outpatient Treatment Unit at the Institute of Medical Psychology, Heidelberg University Hospital. The music therapists will conduct the therapy sessions either together or in close collaboration and consultation under joint supervision to ensure an equal clinical-practical orientation and adherence of both therapists to the protocol.

The therapy program includes an anamnestic preliminary interview and 10 group music therapy sessions (120 minutes each, once a week). The anamnestic interview will be conducted by one of the music therapists at the Institute of Medical Psychology and is conceptualized as a 60-minute single session with only verbal dialogue and without using music therapy interventions. It will serve to obtain information about the participants' biography, their relationship to music, individual therapy goals, and background regarding the emergence of the depressive symptoms. Additionally, participants will be invited to do some exercises at home (homework) on an optional basis between the therapy sessions, e.g. keeping a therapy diary. Therefore, each participant

will receive a therapy diary and will be provided sound recordings or written texts of selected therapy interventions in digital form. In the last therapy session, the participants will be given a collection of intervention instructions in written form for further practicing at home. Furthermore, the music therapists encourage the participants to continue spending (at least) one fixed evening per week (e.g. the same weekday on which the music therapy took place) with practising the given homework or with meeting the other group members constantly. The group size for the group music therapy sessions will amount to 6–9 patients. All therapy sessions will be videotaped and recorded in writing to ensure protocol adherence as well as comprehensibility and replicability of the therapy procedure. We will conduct an anonymous evaluation after the half of the ten therapy sessions and after the last therapy session in order to maintain and improve the quality of the music therapy. There will be an assortment of different kinds of musical instruments, including rhythm instruments (e.g. cajon, djembe, small percussion, frame drums, steelpans, slit drums, chimes etc.) and harmony and melody instruments (e.g. piano, guitar, monochords, vibraphone, string instruments etc.). Furthermore, the patient's body and voice will be included through the use of focused interventions for expression purposes (body percussion, singing, vocal improvisation, etc.).

As we are not aware of the existence of a manual on music therapy for depressive disorders at the moment, SR and CG drafted a group music therapy program based on our clinical experience. The therapy program is composed of three phases: The aim of the first phase is to enhance wellbeing and to develop a trustful, stable therapeutic relationship between patients and therapists. Phase two focuses on symptom- and problem-related work, whereas phase three targets the transfer of therapy contents to daily life as well as the disengagement from the therapeutic relationship (Howard et al., 1993). In particular, we will use a number of therapy modules comprising receptive and active music therapy interventions, whereby every therapy module will be deployed as either fixed or variable therapy module. Active music therapy techniques will include free improvisation (variable), theme-centered improvisation (variable and fixed), music-centered improvisation (variable), musical role-play (variable), and musical constellation work (variable). Receptive music therapy techniques will encompass imagery techniques (variable), mindfulness (variable and fixed), and relaxation exercises accompanied by music (variable). Beyond the aforementioned techniques, every therapy session will include verbal reflection on the music intervention and home-based practice. The selection and timing of modules will be process-driven and will occur flexibly according to the music therapists' perception of the groups' needs and dynamics; thus, it may vary between study groups. The potential procedure of a typical music therapy session with two phases of music therapy interventions is shown in Figure 2. The therapists will record in writing and document all therapy sessions to assess the comparability between the music therapy groups and to provide transparency for traceability and reproduction purposes.

The therapist adherence will be monitored via video ratings. With this aim, randomly chosen therapy videos will be rated by a blinded independent researcher at the Institute of Medical Psychology who is not otherwise involved in the study.

The main purpose of this experience-based therapy approach is to decrease depressive symptoms through a differentiation of emotion regulation techniques. The women should feel encouraged to deal with negative experiences in life and replace these negative experiences with new multi-sensory and emotional experiences during the

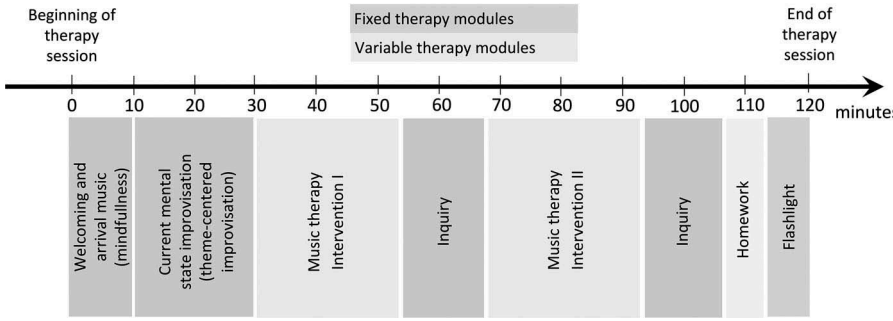

Figure 2. Schematic procedure of a music therapy session

music therapy treatment. Hence, stress experiences should be reduced as a beneficial effect. Ideally, after completion of the program, the participants will use music as a source to adaptively regulate emotions and stress in their daily life even beyond the scope of the therapy.

Erkkilä et al. (2011) reported adverse events in the form of a worsening of depressive symptoms and back pain in individual cases. Whereas, Aalbers et al. (2017) found the occurrence of adverse events in music therapy interventions and TAU equally. Possibly emerging negative emotional states will be discussed within the group sessions and addressed by the therapists leading the group sessions. We will document and report any possible adverse events which might occur during the study intervention phase. In the case of decompensation for any reasons, optional supplemental individual therapy sessions will be offered to the patient by the therapists or study supervisors (SR, CG, MW, BD). There are no risks or side effects known with regard to the psychological assessment or the psychobiological measurements.

Outcome measures

To examine the effectiveness of music therapy from a comprehensive, multidimensional perspective, we will investigate different psychological constructs as well as psychobiological biomarkers in daily life.

Primary and secondary outcome measures

The primary outcome measure for the proposed study is the decrease of depressive symptoms from pre- to post-intervention measured by the HDRS (Hamilton, 1960) as described in the paragraph *Screening*.

The secondary outcome measures comprise the reduction of self-rated depressive symptoms and changes in the psychobiological measurements (HRV and salivary cortisol). Self-rated depressive symptoms will be assessed using the BDI-II (Beck et al., 1996) as described in the paragraph *Screening*. The BDI-II will be applied at the pre-, post- and follow-up assessment. Psychobiological data collection (ECG and

saliva sampling) will proceed in parallel, within a timeframe of two consecutive days each in the pre- and the post-assessment.

Cortisol data will be analyzed using different approaches to determine HPA axis functioning as a stress-sensitive system:

1. Cortisol awakening response (Stalder et al., 2016)
2. Areas under the curve on average cortisol output (AUCg) and average down-regulation of cortisol (AUCi) within one day (Pruessner et al., 2003)
3. Diurnal cortisol slopes, which are indicative of the extent to which cortisol levels decrease from (a) morning to evening and (b) from after the awakening response to the evening (Adam & Kumari, 2009; Adam et al., 2017)

HRV data will be derived from electrocardiogram (ECG) measured on two consecutive days (48 hours, pre and post). The combined activity of the sympathetic and parasympathetic branch can be represented, for example, by calculating the standard deviation of normal-to-normal (NN) intervals (SDNN). By contrast, fast HR variations can be attributed to parasympathetic (vagal) activity (Benson, 1983; Warner & Cox, 1962). These rapid variations are represented, for example, by calculating the root mean square of successive difference (RMSSD) or the high-frequency (HF) component from spectral analysis. The aim of the ECG measurement in the proposed study is to determine pre- to post-intervention changes in the circadian variation pattern of vagally mediated HRV due to therapy effects. Therefore, the following three cosine function parameters will be calculated and analyzed:

1. Midline estimating statistic of rhythm (MESOR, M, rhythm-adjusted mean)
2. Amplitude (A, difference between MESOR and maximum of a cycle)
3. Acrophase (φ, time of overall high values recurring in each cycle, unit: [negative] degrees)

Other outcomes and controls

In addition to the primary and secondary outcome measures, an EMA and self-ratings will be assessed. The EMA will accompany all psychobiological assessments, including control questions on sleep quality and sleep duration as well as the time point of awakening, consumption behavior (food, beverages, alcohol, coffee, cigarettes), physical activity, and mental states (e.g. stress, anger, motivation, anxiety, happiness, nervousness) following the recommendations of Stalder et al. (2016) and Adam and Kumari (2009). The combination of EMA and the psychobiological assessments will allow for the detection of treatment effects in daily life. Furthermore, it may help to explicate potential relationships between daily life circumstances and circadian courses of these biomarkers. Moreover, we will monitor and statistically control for the menstrual cycle stage because previous research showed variations in HRV and cortisol according to the current cycle phase (Brar et al., 2015; Schmalenberger et al., 2019).

Furthermore, the following psychometric constructs will be examined with the help of self-rating questionnaires: stress perception, emotion regulation, musical preference, stress coping, quality of life, loneliness, social support, and quality of social relationships (see the Appendix for the full list of self- and observer-rated questionnaires). All self-ratings will be assessed at three time points (pre, post, and follow-up),

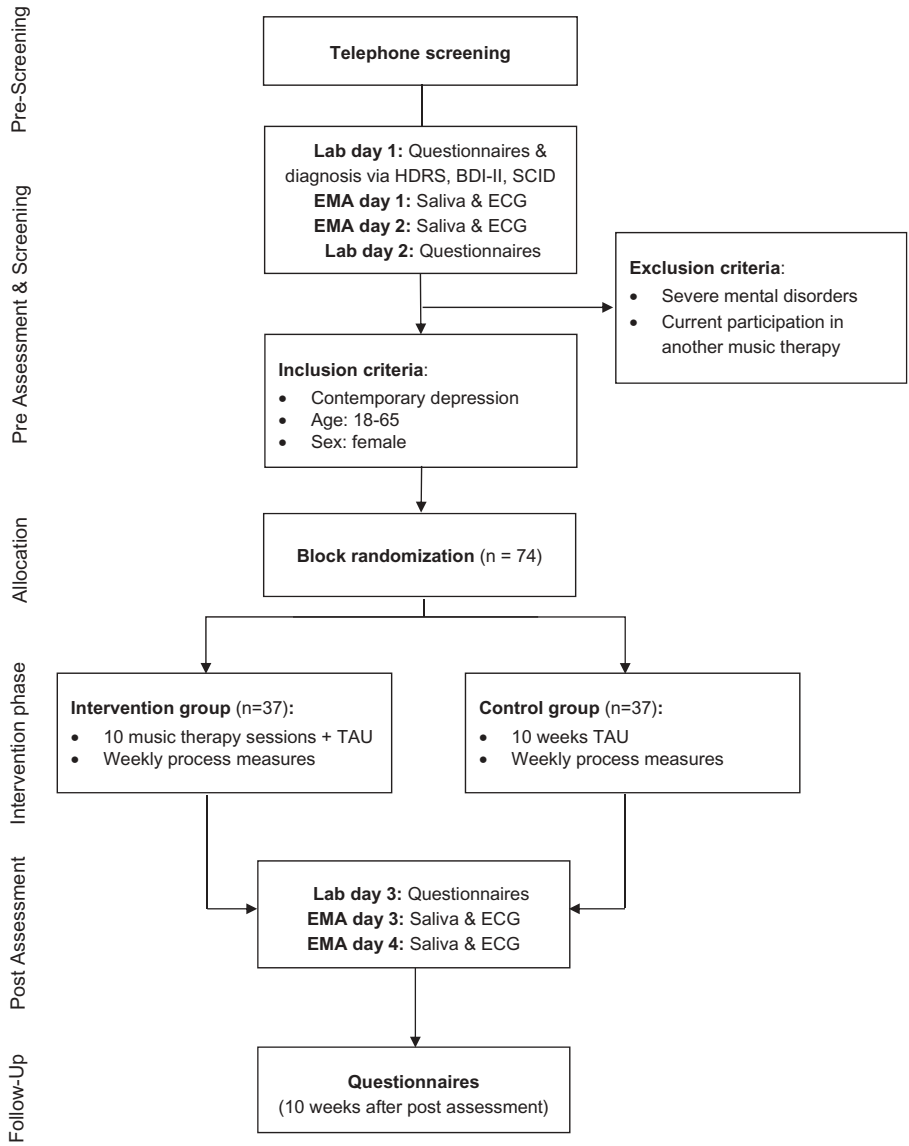

Figure 3. Study procedures. HDRS = Hamilton depression rating scale; BDI = Beck depression inventory; SCID = Structured clinical interview according to DSM-V; EMA = Ecological momentary assessment; ECG = Electrocardiogram; TAU = Treatment as usual

with the following exceptions: questions on sociodemographic factors and traumatic life events in childhood will only be applied once within the pre-assessment; self-perceived stress will additionally be assessed weekly during the intervention phase. Figure 3 provides an overview of all major study procedures.

Hypotheses

The MUSED study aims to evaluate the effectiveness of music therapy (plus TAU) in depressive women on both a psychological and psychobiological level. We hypothesize that music therapy will be superior to TAU with regard to

1. the decrease of observer-rated depressive symptoms as measured by the HDRS
2. the reduction of self-rated depressive symptoms as measured by the BDI-II
3. health-promoting effects in terms of the following psychological constructs: stress perception, emotion regulation through music, musical preference, stress coping, quality of life, loneliness, social support, and quality of social relationships, e.g. self-perceived stress reduction, quality of life.
4. an adaptive regulation of the HPA axis characterized by
   (a) a steeper diurnal cortisol slope and decrease in AUCi as well as
   (b) changes in the CAR and in AUCg dependent on the severity of depression (increased CAR in severe depression, decreased CAR in moderate depression)
5. an improved autonomic regulation indexed by higher circadian vagally mediated HRV parameters (increases in MESOR and Amplitude).

Comparing the intervention group and the waitlist control group, we expect significantly greater improvements for all of above-mentioned outcome measures within the intervention group.

Statistical data analysis

Hypotheses tests for the primary outcome and secondary self-rating outcomes will be conducted using multilevel modeling as observations (level 1) are nested in participants (level 2), and participants are nested in therapy groups (level 3). Given that variation in the outcomes of interest can be explained by cluster-assignment (as seen by calculation of the intra-class-correlations (ICC's)), we will account for the unbalanced, nested structure of the data by imposing random effects (i.e. random intercept and/or random slope) on the given level. We hypothesize a cross-level interaction between the outcomes' time course on level 1 and the group assignment as a level 2 factor. Type-I error probability will be set on $\alpha = 0.05$.

A two-stage modeling with the HRV parameters will be derived from 48 hours ambulatory ECG recordings. First, the 48 hours ECG will be segmented into intervals of 5 minutes (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, 1996). For each segment of the ECG, the following parameters will be derived (stage 1): NN, RMSSD, PNN50, and HF as well as SDNN or total power. Trigonometric regression will be performed to determine the circadian rhythm of vagal activity. Stage two of the analysis includes the estimation of the three cosine function parameters MESOR, A and φ. For further information, Refinetti et al. (2007) provide a detailed explanation of mathematical algorithms for the analysis of circadian rhythms. Cosine functions will be estimated for each individual to capture circadian variation patterns. Furthermore, the cosine function will be transferred as dependent variables to multivariate regression models for simultaneous effect estimation on the individual circadian vagal activity profile. Alpha error reduction will be

achieved by the use of a single regression model with simultaneous estimation of more than one outcome variable.

Statistical analysis of the cortisol data will be performed using multilevel analysis (Raudenbush & Bryk, 2010), which is recommended as a standard procedure for the modeling of cortisol in ambulatory assessments (Schlotz, 2014). Three-level models will be calculated in order to gain an understanding of associations between cortisol and psychological variables within each day (observations nested in days nested in individuals). Two-level models will analyze associations of psychological parameters with indicators of HPA axis functioning (e.g. AUCg or CAR) across days (observations nested in individuals). Standard centering approaches will be performed to disentangle within-person and between-person effects (Hoffman & Stawski, 2009). Cortisol levels in saliva can be confounded by a broad range of variables, such as sleep, caffeine consumption, smoking, sports etc. (Kudielka et al., 2012, 2009). Thus, we will control for these in statistical analyses as required. Moreover, as cortisol values within one day are non-normally distributed and heteroskedastic by nature, we will perform transformation techniques on criterion variables before fitting the models (Miller & Plessow, 2013). An iterative process will then be applied, in which model parameters, e.g. random slopes or autocorrelations, will be added or removed depending on their ability to improve the overall model fit. The model fit will be assessed using the Akaike Information Criterion (AIC); different models will be compared using likelihood ratio tests for nested models. Standard procedures for multiple testing will be applied if necessary. To test our hypothesis of changes in cortisol and its parameters as a result of our intervention, we will interpret group-by-time interactions. Exploratory analysis will be performed to identify possible cross-level interactions as well as mediating and moderating effects of covariates on intervention success.

Patients who discontinue participation will be asked to state the reasons for their early study termination, enabling us to modify aspects of the treatment or measurement procedure if necessary and to analyze and interpret missing data adequately. We will handle missing data and changes of the TAU condition in the course of sensitivity analyses. After diagnosis of the missing data mechanism (missing not at random, missing at random, missing completely at random), we will create an imputed dataset (for the primary intention-to-treat approach most likely by multiple imputation) and compare results for robustness with a per-protocol analysis.

We will run subgroup analyses exploratively e.g. with regard to age, severity of depression, body mass index, and music preference.

Sample size calculation

A recently published Cochrane Review provided pooled effect sizes for the effects of music therapy treatment in depressive disorders based on the available evidence (Aalbers et al., 2017). The authors found a pooled effect of $d = -0.98$ for clinician-rated depressive symptom severity comparing music therapy + TAU versus TAU alone for an effect duration of up to 3 months. Sample size calculations with the reported effect size were conducted using the *clsampsi* command in STATA, which accounts for unbalanced clustering of patients in groups between intervention and waitlist control group (Batistatou et al., 2014). Assuming statistical power of $(1\text{-}\beta) = 0.80$, type-I-error probability of $\alpha = 0.05$, an average expected cluster size of $k = 8$ in the intervention group, and an intra-class correlation of ICC = 0.1 (Creamer et al., 1999), analysis revealed an optimal

sample size of $N = 64$ for the primary outcome in this study. Expecting an attrition rate of 15% between pre- (before intervention period) and post- (after intervention period) assessment, we will aim at recruiting a total of at least $N = 74$ participants.

Data management and publication

Data will be collected and stored pseudonymously. Person-related data will be stored encoded and separated from the rest of the data. Only the study-related personnel but no third parties will have access to the person-related data. Having finished the data collection, all non-personally related data will be stored at the heiDATA Dataverse Network for an indefinite period. The biomaterials and the questionnaire data will become property of the Institute of Medical Psychology at Heidelberg University Hospital. The saliva samples will be analyzed, stored at the Institute of Medical Psychology for the duration of 10 years, and will be destroyed afterwards. The participants have the right at any time to demand the destruction of the original data or biomaterials.

Discussion

The MUSED study combines psychometric and psychophysiological approaches to examine the effects of music therapy on depression in women. To evaluate the music therapy approach, a number of psychological constructs, primarily depressive symptoms, and psychobiological markers (circadian HRV and diurnal salivary cortisol) will be assessed. The combination of psychological and psychobiological measurements will provide a multidimensional perspective on the underlying mechanisms of music therapy in the treatment of depression. As such, the study will build on previous findings on the effectiveness of music therapy in the treatment of depression, which were mainly based on psychometric outcomes (Aalbers et al., 2017; Erkkilä et al., 2011; Leubner & Hinterberger, 2017), and will provide the field with additional information about the chronobiological effects of music therapy in depression.

The utilization of a randomized controlled study design with high evidence strength will enable us to draw conclusions about the effectiveness of music therapy in the treatment of women with depression. The absence of an alternative intervention offer in the waitlist control group might entail difficulties in ascribing possibly disclosed effects to power factors of the music therapy intervention. Above, we will need to take into consideration the influence of different control conditions on the effect size (Furukawa et al., 2014). As we know that in clinical daily routine, music therapy is predominantly embedded in the treatment plan as an add-on therapy ancillary to TAU, we are convinced that the experimental design of the presented study conditions depicts clinical reality in the best possible way. On this basis, we aim to find out whether music therapy achieves additional health benefits for patients with depression compared to TAU only.

We are aware that the study participation contains a relatively high burden for the participants. We try to minimize the risk of attrition by making the study procedures transparent before the enrolment, by giving an incentive (individual stress profiles), and by restricting the duration of an individual study participation to a minimum (Zweben et al., 2009). Prior studies on the dose-response effect of music therapy in samples with depressive symptoms reported large effect sizes after 16 hours of music

therapy (Gold et al., 2009). Hence, we expect large effect sizes due to our therapy program containing 21 hours of music therapy in total.

As the EMA serves to obtain information within an ecological setting, this approach stands in contrast to laboratory settings. While it harbors the difficulty of possible measurement inaccuracy due to non-compliance, the advantage of EMA lies in the possibility to measure the treatment effects in the patient's daily life. Furthermore, EMA data will allow us to test for covariance between moods and behaviors in daily life and the psychobiological markers.

The involvement of psychobiological markers in therapy evaluations represents a step towards a better understanding of the underlying mechanisms between psychopathological factors and towards new treatment options. From the methodological perspective, the parallel assessment of ECG and salivary cortisol brings the advantage of an objective and reliable determination of awakening time, which is an important criterion for accurate saliva sampling (Adam & Kumari, 2009; Stalder et al., 2011, 2016; Trinder et al., 2003). Beyond this, the parallel elicitation of diurnal cortisol patterns and the circadian HRV offers the opportunity to investigate a possible interplay between HPA axis and ANS functioning.

According to the recommendations of Adam and Kumari (2009) and Stalder et al. (2016), we have chosen a design including a sufficient number of saliva samples to obtain adequate reliability and statistical power of results. Assuming equal distribution of severity levels of depression between the groups, we expect equal cortisol profiles in the two study groups within the pre-assessment. Subsequently, we anticipate an improvement of HPA axis functionality mainly within the intervention group, as indexed by changes in CAR and AUC as well as by an enhanced down-regulation of the cortisol slope after the peak within the CAR.

Analysis of diurnal variation of vagally mediated HRV is a relatively innovative approach. Data on altered circadian variation patterns of vagally mediated HRV will provide insight into parasympathetic activity reflecting the health-promoting relaxation response in daily life (Benson, 1983; Dusek & Benson, 2009; Segerstrom & Miller, 2004). Thus, we expect stronger parasympathetic outflow after the intervention period due to stress reduction, reflected in an increase in MESOR and Amplitude from pre- to post-assessment.

Conclusion

We aim to investigate whether music therapy can serve as an effective treatment for women suffering from depression. We assume that music therapy will reduce depressive symptoms and psychobiological stress responses. The proposed study offers the potential to extend the knowledge on the psychobiological mechanisms and improve treatment options in depressive disorders.

Author's contributions

CG, MW, MS, and MNJ prepared the manuscript. CG, CAR, MNJ, MS, and BD conceptualized the study. MW and SR contributed crucially to the design of the study. All authors critically revised the recent version of the manuscript equally and gave final approval of this version to be published.

Disclosure statement

No potential conflict of interest was reported by the authors.

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