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Effects of group singing versus group music listening on hospitalized children and adolescents with mental disorders: A pilot study

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Abstract

Background: There is an emerging view that music-related interventions (MuRI) may play an important role for youth with mental disorders. Here, we assessed the potential neuroendocrine (cortisol), immune (IgA) and psychological (mood state, health-related quality of life (HRQOL), well-being) efficacy of a brief program of MuRI (group singing versus group music listening) in children and adolescents with mental disorders in a clinical setting.
Methods: We performed this observational pilot study with 17 patients (aged 11–18; 11 female) admitted to the Department for Child and Adolescent Psychiatry/PMU Salzburg, Austria between March 2015 and April 2016. Patients participated in either a singing program or a music listening program, delivered through five daily, consecutive 45-minute sessions in one week.
Outcomes: Saliva samples for cortisol and IgA, and subjective measures of mood were taken daily, pre- and post-MuRI. HRQOL and well-being were measured pre- and post-5-day-program of MuRI. The program in singing led to a significantly

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larger mean drop in cortisol than in music listening (mean difference: −0·32; 95% CI −0·57 to −0·07), while listening led to a significantly higher mean positive change in the dimension calmness (mean difference: −2·66, 95%CI −4·99 to −0·33) than singing. Moreover, singing was associated with an improvement in HRQOL, and listening with an improvement in well-being.

Interpretation: Our preliminary findings suggest that MuRI may provide benefits for children and adolescents with mental disorders. The differences in psychobiological responses to singing and music listening invite further investigations. A larger, suitably powered study is now needed to provide a precise estimate of the effects of MuRI for mental health promotion, both on psychological and biological experiences. Funding: Salzburg Festival, Austria, and Focus Area 'Science and Art', Salzburg, Austria.

Keywords: Clinical psychology, Psychology, Psychiatry, Pediatrics

1. Introduction

Mental disorders constitute a major global disease burden among children and adolescents from low-, middle- and high-income countries alike [1]. It is estimated that 13.4% of children and adolescents worldwide suffer from mental illness; a recent nationwide study in Austria revealed an even higher prevalence of 23.9% among Austrian children and adolescents [2]. Mental disorders drastically impair children and adolescents' quality of life and psychological well-being; they induce disturbances in the emotion and stress domains, which are strongly associated with alterations in specific neural structures and abnormalities in neuro-endocrine and neuro-immune system processes [3]. In particular, stressful events and the corresponding bodily and neurohormonal reactions are central in the development of mental disorders [4]. Stressful events during pregnancy, early childhood and later on have an impact on brain functionality and structures involved in cognition and mental health [5]. Also, stress influences the immune system and interact with different types of behaviour, e.g. parenting behaviour [6], thus shaping mental symptomatology. However, the effects on brain function and subsequently on cognition, behaviour and the immune system develop as a function of the timing and the duration of the exposure and also depend on the interactions between genetic factors and environmental adversities. Stress causes activation of the pituitary-adrenocortical system, which remediates the physiological and psychological adaption to stress [6]. Cortisol is the central active agent in the stress response [7] and e.g. in adults after trauma this dysregulation was described as hypocortisolism [6]. In contrast, hypercortisolism was also described after trauma exposure. These reactions are associated with alterations in various parts of the immune system [8]. Immunoglobulin A (IgA) is a first line mucosal protector from pathogens [9] and production of IgA is modulated by

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physical and psychological effectors such as stress. These effectors cause reduced or increased production while social support can also increase IgA production [10].

Scholars have accepted the biopsychosocial model [11] and the corresponding dimensional conceptualization of child psychopathology [12], which suggests that human emotions and behaviours exist on a continuum, with environmental and personal factors interacting with the grade of an individual's pathological traits or vulnerabilities. Thus, the range and multifaceted nature of mental disorders have led to the emergence of multimodal treatment concepts and adjuvant therapeutic approaches [13] (see also AMWF-Guidelines [14]). We assumed that it is important to identify interventions that may increase an individual's motivation and behaviors to regulate the abnormal imbalance in stress and mood states (cortisol down/IgA up/mood state up), which in turn may beneficially impact pathological traits. In this context, music-related interventions (MuRI) can take on a crucial role within the entire indication spectrum and serve as a complement or alternative to pharmacological and other treatments [15].

1.1. Why music as an adjunct remedy in children and adolescent psychiatry?

MuRI beyond formal music therapy, such as listening to and actively engaging in music, promise a wealth of positive applications to health and well-being (cf. [16]), which are predicted to be potent modulators of mood [17] and stress [18]. Neuroimaging studies have revealed that music listening in healthy adults activates the cortical and subcortical limbic neural structures that process emotions and reward [19, 20, 21], some of which are known to help regulate mood, endocrine (including hypothalamic-pituitary-adrenal (HPA) axis) and corresponding immune systems [19, 22]. In particular, Blood and Zatorre [23] revealed that instrumental music familiar to subject and selected as highly pleasurable caused activation in brain structures know to be involved in endocrine and immune functions, particularly the hippocampus, amygdala, medial/orbitofrontal prefrontal cortex, and ventral striatum (probably the nucleus accumbens; NAc). It is noteworthy, however, that unfamiliar music selected as pleasurable elicited activation in similar neural structures [24, 25]. Recent data provide evidence that musical pleasure is associated with mesolimbic dopaminergic reward processing [26]. Thus, there is intristic evidence that music-evoked emotions in the central nervous system (CNS) can initiate not only psychological mood changes but also neuro-chemical modulations underlying stress and immunity [27, 28]. Koelsch et al. [19, 29] proposed that the effect of music-elicited emotions on the alterations of endocrine and immune effectors (cortisol down and IgA up) are thought to act via: (a) the activation and inhibition of limbic and paralimbic structures (particularly the amygdala, hippocampus, medial/orbitofrontal prefrontal cortex, insula), which influence the hypothalamus and endocrine stress responses in the HPA-axis, and (b) the activation of

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the dopaminergic reward system (especially through heightened activity in NAc), which inhibits the work of the HPA axis (in this respect, see also [30]). The downregulation of HPA activity is a possible biological mechanism to strengthen the immune status and mitigate associated psychiatric illnesses [28]. The pleasurable factor of music appears to be important in mediating these effects.

Moreover, some scholars have suggested that the neural processes involved in active MuRI such as singing or playing an instrument are related to those involved in listening, due to the fact that participants listen to themselves [31]. For example, music making in healthy children and adolescents led to more rapid cortical maturation within various brain regions including the orbitofrontal and ventromedial prefrontal cortices, which are the areas responsible for impulse and emotion regulation [32]. Overt singing in particular may influence the emotional tone by activating the anterior cingulate cortex and the insula [33] that is, areas implicated in evoking emotions.

Likewise, it has been argued that MuRI promote social bonding and attachment [19, 21, 34], which in turn are associated with subjective feelings of joy, pleasure and happiness [19, 21]. There is emerging evidence that coordinated and synchronous group musical activities (e.g. group singing) promote social bonding [35]. For example, active group singing induces feelings of closeness [36], connectivity and inclusion [37, 38]; it seems to affect positive feelings and mood more than passive music listening or speaking in dialogue [39, 40], while also relating to the release of oxytocin [40] and possibly β-endorphin [35, 41, 42]. These two neurohormones are related to social behaviour [41, 43, 44] and have been involved in mood and stress regulation [35, 45, 46]. Moreover, it has been speculated that attachment-related emotions generate hippocampal activity, suggesting possible oxytocin release and involvement of the stress-related HPA mechanism [21]. It is therefore plausible to posit that MuRI can cause positive mood, stress and immune regulation through probable social functions [17, 19, 21] and their neurochemical underpinnings [35].

Beyond such social functions, it can be hypothesized that musical activities like singing can lead to stress reduction and immune system strengthening because they are related to physical movement [39]; this is known to protect and stimulate the endocrine and immune system [39, 47].

The interaction of music with the neurochemical processes regulating stress and immunity prompted new studies over the last few years (see, e.g. Refs. [45, 48, 49, 50]). Several studies in adults have shown evidence that the stress-reducing and emotion-regulating effects of MuRI (receptive and active) can be objectively quantified by a reduction of the stress hormone cortisol and an increase of the immune antibody IgA in saliva (for review see Refs. [28, 39, 49]). In general, cortisol levels appear more likely to decrease while IgA increases significantly in response to tranquil and slow instrumental music pieces (see e.g. Refs [28, 45, 50]). In contrast, increases in cortisol levels were recorded after listening to techno music or faster pop and rock

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music [47]. A comparison of different modes of music delivery found greater immune responses with active participation rather than more passive listening [39, 51, 52]. Active group singing in particular seems to be associated with positive neuroendocrine and immune responses [39, 40, 53, 54, 55]. We hypothesized that the effects of music in the central domains of psychoneuroendocrinology may have essential implications for the treatment of a variety of psychiatric disorders as well.

Previous systematic review [56] has suggested that music therapy is effective in addressing a range of symptoms in adult psychiatric in-patients. In children and adolescents with psychopathology, a meta- analysis of eleven experimental studies on the use of music therapy identified a medium effect on clinically relevant outcomes [57]. However, these authors suggested the need for more studies in clinical settings. Two subsequent trials with control designs (waitlist control and treatment as usual control) [58, 59] and one uncontrolled retrospective trial [60] that investigated the effects of music-based therapy (eclectic approaches) in children and adolescents with a variety of psychiatric conditions in a clinical setting were conflicting. One trial showed no effect [59], but two trials reported effectiveness in reducing depression and improving communication skills, self- esteem [58] and acute mood [60]. However, it has not yet been determined in what ways active and receptive MuRI compare with each other. Yinger and Gooding [61] in their overview have suggested that active participation in music has a greater effect on clinical outcomes in children and adolescents with psychopathology than a receptive approach. Some researcher also recommended the use of a more intensive approach (e.g., with several sessions per week) [59]. Additionally, meta-analyses showed that MuRI have effectiveness in addressing symptoms of depression and anxiety [62], and of autism [63]. Very few of these studies explored the use of informal music-related interventions in place of a formal music therapy model; for example, an RCT by Chen et al. [64] showed that music listening (Chinese five-tone music) had a significant positive effect on depressive outcomes in adolescents with depressed mood. There have only been two studies outside of a clinical setting that assessed the impact of a receptive MuRI on biochemical measures in adolescents suffering from depression [64, 65], with one study showing a significant immediate decrease in salivary cortisol levels [65]. There are no studies related to neuroendocrine and immune responses to MuRI in children and adolescents with psychiatric disorders within a hospital setting. Moreover, it is not yet clear whether these effects are due solely to receptive MuRI or whether they might also be achieved through engaging in active MuRI such as group singing as well. As indicated above, informal group singing may influence significant subjective mood, endocrine functions and immune effects in adults. Furthermore, music therapy approaches emphasizing singing interventions in various pediatric populations were associated with promising effect on mental health (overview in [66]). Qualitative data suggested that active group singing may have benefits for psychological wellbeing in healthy children and adolescents [67].

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Therefore, we performed a pilot observational study aiming to assess the feasibility and potential psychobiological effectiveness of two brief five-day music-related interventions, active group singing versus a receptive group music experience (music listening) in a "real life" clinical setting for children and adolescents with various mental disorders. The study was part of our two-year research and art project 'Art as a doctor', that ran from August 2014 to April 2016. Our intention was to offer creative-artistic tools such as singing, music listening, textile design, drama, or clownery incorporated into traditional treatment routines to support creative expression and increase awareness of subconscious emotions. We assessed the consequent impact of each art intervention program in this population. This paper only draws on data from the interventions directly involving music; the data from the other creative-artistic interventions will be described elsewhere. We hypothesized that compared with the music listening condition, the short-term five-day program of group singing would lead to more positive changes in psychological outcomes such as improvement of self-reported mood state, patient wellbeing and quality of life, and would induce positive changes in hormone and immune responses, such as an increase in salivary IgA levels (immune response) and a reduction of salivary cortisol (stress response).

2. Methods

2.1. Study design and participants

We conducted this prospective, pilot observational, parallel cohort study of group singing (experimental) versus group music listening (control) between March 2015 and April 2016 at the University Department for Child and Adolescent Psychiatry/Paracelsus Medical University (PMU) in Salzburg, Austria. Recruitment at the clinic lasted from 14 days until three days before each music intervention was scheduled to begin. The study protocol was approved by the Salzburg State Ethics Committee (reference number 415-E/1787/4-2014).

Patients who were admitted for inpatient or day-clinical treatment were assessed for the study. Patients were eligible if they were 10−18 years old and had a current clinical diagnosis of mental disorder, defined according to Chapter V (F00−99) of ICD-10. They were included regardless of their medication status and any concurrent therapies and were allowed to continue their usual care during the intervention time.

Patients were ineligible if they were diagnosed with any significant hearing impairments (according to a self-report and the patient's file); if they exhibited a state of confusion, an aversion to music (according to a patient-reported assessment and the patient's file), an inability to verbalize, suicidal tendencies, or alcohol/substance dependency; if they posed a danger to others or themselves; or if they had participated previously in the same intervention. Musical skills or a specific musical background was not required. Patient enrolment was done by one medical specialist.

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Potential participants were informed that they might be assigned to the workshop and their participation in the study was voluntary. Written informed consent from each patient, parent, or legal guardian was obtained prior to the study.

2.2. Procedure

We conducted two music listening intervention programmes from March 23–27 and April 20–24, 2015, and two singing intervention programmes from Feb 15–19 and April 20–24, 2016. Randomisation occurred by the fact that patients participated in whichever intervention programme happened to be running when they were admitted to the clinic. Both the singing and music listening programmes were provided in strict daily sessions from 2 to 2·45 p.m. to take into consideration circadian variations in salivary cortisol levels. Participants were instructed not to ingest any meals, alcoholic drinks or drugs, and to refrain from smoking for one hour before the measurement of each session.

The singing sessions were led by a professional choirmaster without a therapeutic background. Each session initially focused on an approximately ten-minute-long breathing and vocalisation phase. During the rest of the session, songs from various styles chosen by the choirmaster as well as songs known by the participants were rehearsed. The following pieces were rehearsed: ‘Take me home, Country Roads’ written by John Denver, Bill Danoff and Taffy Nivert Danoff and performed by Denver in 1971; ‘Lemon Tree’ written by Peter Freudenthaler and Volker Hinkelin in 1995; ‘Get up, stand up!’ composed by Bob Marley and Peter Tosh published in 1973; ‘Supergirl’ written by German band Reamonn and released in 2000; ‘Someone like you’ written by Dan Wilson and Adele and released in 2011; and ‘It’s the hard knock life’ from the Musical “Annie”, composed by Charles Strouse with lyrics by Martin Charnin and premiered in 1977.

The music listening sessions were provided by a trained music therapist, but there was no therapeutic relationship existing between the patients and therapist, unlike in formal music therapy. Soothing and calming instrumental pieces of contemporary classical music (John Cage: ‘Dream’, ’In a landscape’ for solo piano composed in 1948 and performed by Stephen Drury in 1995; Arvo Pärt: ‘Spiegel im Spiegel’ for piano and violoncello, composed in 1978 and performed by Alexander Malter and Dietmar Schwalke in 1999) and calming music without voice (pieces from CD ’Feelings’, Volume 2, published by Grüne Erde) were compiled by the musicologist (KGH) and the music therapist. Music was selected by the researchers rather than the participants themselves, according to evidence that this approach positively affects stress reduction [18]. We did not include pieces with lyrics because of the previously reported positive influence of listening to instrumental tunes on neural and psychobiological competence and to ensure that any effects were related to the receptive music itself rather than any verbal cues. Each session began with about ten minutes of muscle relaxation instruction

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provided by the music therapist. The music listening phase lasted about 32 minutes. Afterwards, the patients were gently retrieved from the music listening phase. We combined the music with verbal relaxation techniques because this approach seemed to be most effective in stress reduction [18]. In each session, music was played in a group setting using a stereo system while participants were in the prone position. During these sessions, children were accompanied by appropriate healthcare professionals.

2.3. Data

At baseline, medical professionals recorded data regarding the psychiatric condition, medication, and therapies of each patient. Patients also filled out a questionnaire on socio-demographic data and musical background.

Our prespecified psychological outcomes were positive changes in self-reported mood state, psychological wellbeing and health-related quality of life (HRQOL). We assessed the mood state using the Multidimensional Mood Questionnaire (MDBF [68]), which used three mood dimensions: good-bad mood (GM), feeling awake-tired (AT), and calm-nervous (CN). The questionnaire was given daily immediately before and after each 45-minute musical intervention. We assessed psychological wellbeing using the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS [69, 70]) and HRQOL using the Pediatric Quality of Life Inventory 4.0 Generic Core Scale Child Self-Report Version (PedsQL; [71] 4 domains summarized to an overall scale of HRQOL). Data were obtained at two time points: at baseline (3 days before the MuRI) and postline (after the last session). Higher scores in all these measures reflect a better condition in the patient.

Biological outcomes were assessed by salivary cortisol and salivary IgA. Sample collection was made daily by taking two samples immediately before and after each 45-minute MuRI using Salivette® from Sarstedt as a tube. For sample collection, the children and adolescents were asked to chew a cotton suction roll for 1 minute. After each sampling, this swab was placed back into the tube and cooled in the refrigerator at 4 °C for about 1.5 hours before being stored at −20 °C until assayed. Saliva analyses were conducted at the central laboratory of the Christian-Doppler-Klinic/PMU, Salzburg using a nephelometric measuring method for IgA and electrochemiluminescent-immunoassay (Cobas®-6000) for cortisol. Cortisol is reported in ng/ml and IgA in mg/dl.

The patient self-report question on MuRI valence was used to assess the subjective perception of either the music listening or singing session. Patients were required to rate how much they liked the intervention on a 5-point Likert scale every day immediately after the intervention. High values are indicative for increased liking.

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2.4. Statistical analysis

No formal sample size calculation was done for this preliminary study. However, following the orientation of other studies (e.g. [40, 72]), the target sample size of 20 patients per intervention (i.e. 40 patients) was considered adequate to obtain reliable sample size estimates. Standard descriptive statistic measures were calculated for all variables. Differences in baseline demographics, musical background and health-relevant characteristics between the singing and music listening groups were compared using the two-sample *t*-test and Fischer's exact test. We measured the daily changes (post-pre) in MDBF as well as in cortisol and IgA levels in each patient. The mean values of these differences for the singing group and the music listening group were compared taking repeated measurements into account. We used Repeated Measures Analysis, which in the SPSS is named Mixed Models procedure. The analysis of the repeated measurements (post-pre differences) showed that the correlation structure of cortisol and IgA could be represented by one-stage heterogeneous autoregression. The repeated differences in MDBF, however, turned out to be almost uncorrelated; this means that for these variables, the mean change in the two groups can be compared using the two-sample *t*-test. We measured a daily score for subjective perception of the MuRI. This score was highly correlated from day to day. Applying the Mixed Models procedure in SPSS again to compare the two groups using the respective means of their question scores, it was found that the best model for the repeated data was Compound Symmetry (the variances of the scores on all five days are the same and correlation of the scores for all pairs of days is the same). For PedsQL and WEWBS, we used the paired *t*-test to test for pre-post changes over time within each group. The two-sample *t*-test was used to compare the two groups with respect to the mean values of the pre-post change. In cases of missing pre- or post-measurements, the difference was unknown and not included in the analysis. Statistical analysis was conducted using IBM® SPSS® Statistics, Version 18.0. Statistical significance was set at $p \leq 0.05$.

3. Results

3.1. Population

49 patients were screened for eligibility in a singing intervention, of whom 12 (24%) were enrolled, and 36 for a music listening intervention, of whom 11 (31%) were enrolled (Fig. 1). The sample size was smaller than expected because the dropout rate was higher than initially anticipated and because the inclusion criteria were too limiting. All 23 enrolled patients entered an intervention. Patients who attended fewer than four sessions or withdrew from the programme were excluded from the analysis (Fig. 1). Patients were not excluded from the analysis if single measurements were missing, e.g. due to a patient not answering a question or a lack of saliva

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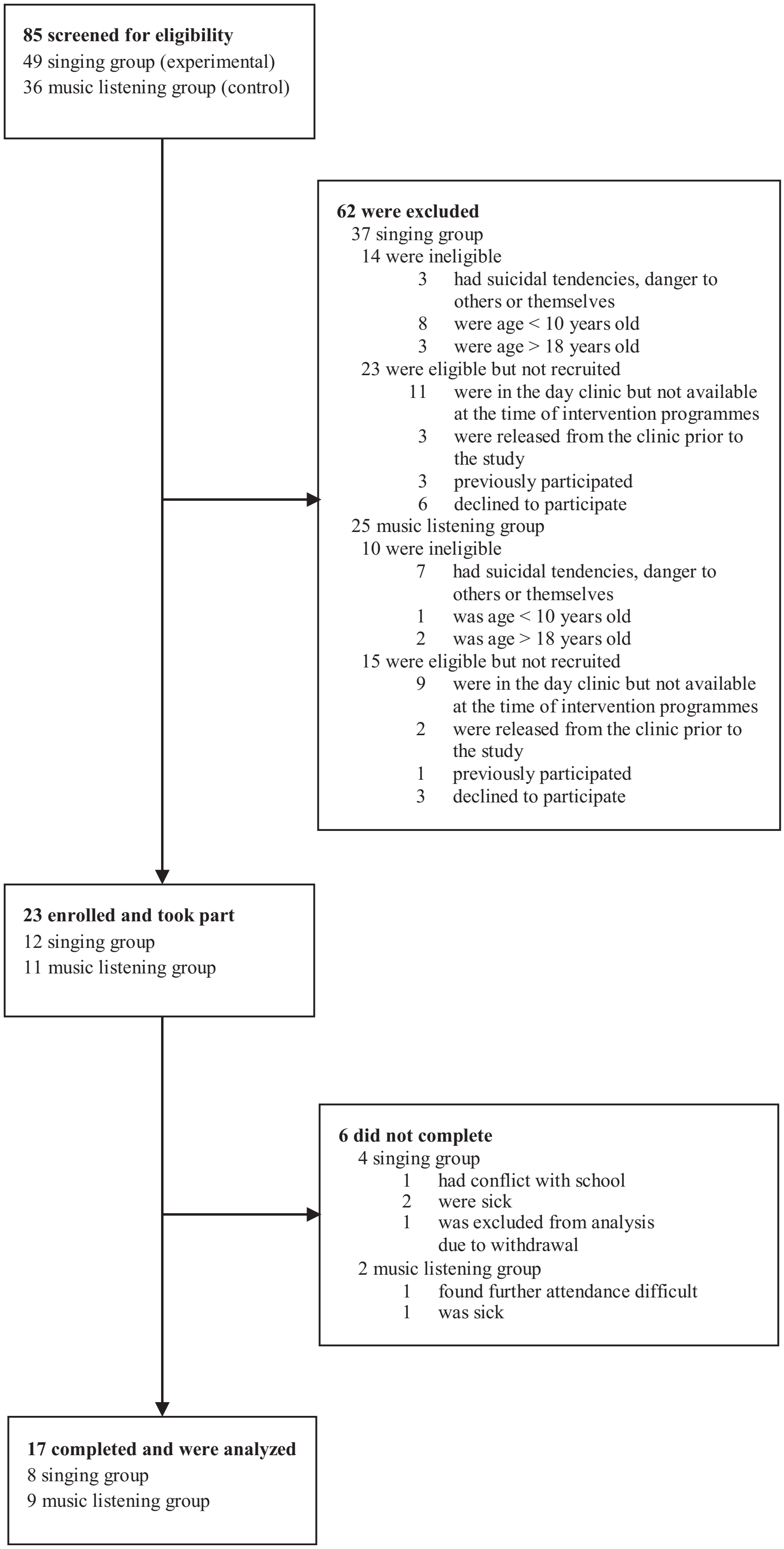

Fig. 1. Study profile.

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in the collected sample. Overall, 17 patients (20%; singing group n = 8; music listening group n = 9) completed the study and were analysed (Fig. 1).

There were no differences in demographic, health-related, musical background, and psychological data between patients who completed the study and patients who did not complete the study (see Table 1).

Demographic and health-related characteristics were similar between the singing and music listening groups (Table 2). The noticeable difference was that formal musical education in the singing group was significantly higher than in the music listening group. Moreover, the number of patients taking medication was significantly higher in the music listening group than in the singing group. At baseline, the WEMWBS score for psychological well-being was significantly higher in the singing group than in the music listening group (see Table 2).

3.2. Characteristics of music-related interventions

Participants liked both music-related interventions (music listening: mean = 4.3; 95% CI 3.75, 4.81; singing: mean = 3.7; 95% CI 3.12, 4.25; see Table 3 for means and SDs by day and activity). The groups do not differ significantly with respect to mean subjective perception of MuRI characteristics ($p = 0.123$). One participant in the music listening group and none in the singing group expressed negative comments about the interventions (music pieces or singing repertoire).

3.3. Psychological measurements of mood state

Fig. 2 shows the changes (post-pre) in MDBF measurements over five consecutive days according to type of musical activity and day of the week (for means and SDs of all variables by day and activity (pre, post and differences), see Table 4).

A comparison of the two groups of MDBF scales showed that there was a significant difference in current mood state in the dimension calmness: the mean difference (post-pre) was significantly higher in the music listening group than in the singing group (mean difference −2.66; 95% CI −4.99, −0.33; $p = 0.026$). There were no significant differences in the dimensions mood and alertness (more precise details, including limits of the 95% confidence interval for mean differences between mean (post-pre)/singing and mean (post-pre)/music listening, are summarized in Table 5). Furthermore, over five days, the music listening group experienced significant improvement in current mood state in the dimensions mood (mean 1.86; 95% CI 0.13, 3.58; $p = 0.036$) and calmness (mean 2.71, 95% CI 1.07, 4.36; $p = 0.002$), but not in the dimension alertness (Table 5). No significant changes were found on any of the three scales in the singing group (Table 5).

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Table 1. Baseline characteristic of patients who did not complete the study and patients who completed the study.

	Patients who did not complete the study (n = 6)	Patients who completed the study (n = 17)	p-value (t-test or Fisher's exact test)
Age (years): mean (±SD)	14·8 (±1·7)	15·7 (±2·0)	p = 0·380
Sex			p = 0·621
Female	5	11	
Male	1	6	
Education			
Lower secondary education	3	3	Not applicable*
Trade school	0	2	
Gymnasium (secondary school)	2	7	
Vocational education	1	2	
University/Academy/College	0	1	
Information not provided	0	2	
Musical experience			
Formal music education	0	4	p = 0·539
Currently or previously play an instrument	2	8	p = 0·660
Currently or previously singing in the choir	1	1	p = 0·500
Diagnosis			
Affective disorders	1	5	Not applicable*
Neurotic and posttraumatic disorders	3	6	
Eating disorders	1	2	
Personality disorders	0	1	
Autism	0	1	
Attention deficit disorders	0	1	
Mix of disorders	1	1	
Medication			
Neuroleptics	1	4	Not applicable*
Stimulants	0	1	
Antidepressants	0	3	
Vitamin/supplementation	0	3	
No medication	5	6	p = 0·069
Other therapies (e.g. yoga, psychotherapy, physiotherapy, ergotherapy, light therapy)	4	15	p = 0·270
Hospital admittance			p = 0·739
Day clinic patients	0	1	
Inpatients	6	16	

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Table 1. (*Continued*)

	Patients who did not complete the study (n = 6)	Patients who completed the study (n = 17)	p-value (t-test or Fisher's exact test)
Psychological scale			
PedsQL: mean (±SD)	60·3 (±15·1)	70·2 (±12·7)	p = 0·137
WEMWBS: mean (±SD)	37·3 (±8·2)	39·0 (±8·8)	p = 0·696

Data are mean (±SD) or n.
PedsQL = Pediatric Quality of Life Inventory TM.
WEMWBS = Warwick Edinburgh Mental Wellbeing Scale.
* Sample size too small for meaningful test.

Table 2. Baseline characteristic of the analysed population.

	Singing (n = 8)	Music listening (n = 9)	p-value (t-test or Fisher's exact test)
Age (years): mean (±SD)	15·8 (±1·4)	15·6 (±2·5)	0·846
Sex			
Female	5	6	1·000
Male	3	3	
Education			
Lower secondary education	1	2	Not applicable*
Trade school	1	1	
Gymnasium (secondary school)	3	4	
Vocational school	1	1	
University/Academy/College	1	0	
Information not provided	1	1	
Musical experience			
Currently or previously play an instrument	4	4	1·000
Formal music education	4	0	**0·029**
Currently or previously singing in the choir	1	0	0·400
Diagnosis			
Affective disorders	2	3	Not applicable*
Neurotic and posttraumatic disorders	2	4	
Eating disorders	2	0	
Personality disorders	1	0	
Autism	0	1	
Attention deficit disorders	0	1	
Mix of disorders	1	0	
Medication			
Neuroleptics	2	2	Not applicable*
Stimulants	0	1	
Antidepressants	1	2	

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Table 2. (*Continued*)

	Singing (n = 8)	Music listening (n = 9)	p-value (t-test or Fisher's exact test)
Vitamine supplement	0	3	
No medication	5	1	**0·050**
Other therapies (e.g. yoga, psychotherapy, physiotherapy, ergotherapy, light therapy)	6	9	0·206
Hospital admittance			
Day clinic patients	1	0	0·471
Inpatients	7	9	
Psychological scale			
PedsQL: (mean (±SD))	71·9 (±10·7)	68·9 (±14·6)	0·655
WEMWBS: mean (±SD)	44·1 (±4·5)	35·0 (±9·7)	**0·038**

Data are mean (±SD) or n.
PedsQL = Pediatric Quality of Life Inventory TM.
WEMWBS = Warwick Edinburgh Mental Wellbeing Scale.
Bold means p<= 0.05 = significant.
* Sample size too small for meaningful test.

Table 3. Means and SDs for Music Related Interventions perception by day and activity.

Day	Singing			Music listening		
	N	mean	SD	N	mean	SD
1	8	3.9	0.99	7	4.1	0.69
2	8	3.5	0.93	8	4.0	**1.41**
3	6	3.2	0.98	9	4.4	0.73
4	8	3.9	0.99	9	4.4	0.73
5	7	3.9	0.90	9	4.3	0.87

Note: The music listening group displayed a noticeable high level of SD on the second day. We can explain this through the rating "1" in this group on this day. Except on this day, the participants in the music listening group showed more homogeneity in their evaluations of the music (they displayed lower levels of SD) than participants in the singing group. We can see from the average evaluations that the music listening group rated the intervention slightly higher than the singing group did.
Bold means p<= 0.05=significant.

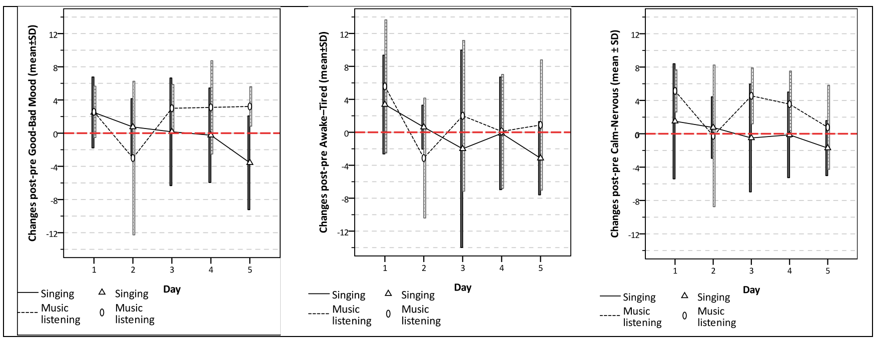

Fig. 2. Changes in the Multidimensional Mood Questionnaire subscales (mean differences ±SDs) by workshop day: singing vs. music listening.

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Table 4. Means and SDs for all variables (pre, post and differences) by day and activity.

	Day 1				Day 2				Day 3				Day 4				Day 5			
	Singing		Music listening		Singing		Music listening		Singing		Music listening		Singing		Music listening		Singing		Music listening	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MDBF_GM (pre)	25.9	7.4	24.3	8.7	24.0	9.1	29.8	6.3	28.5	8.0	28.2	8.7	25.4	11.2	26.6	11.1	27.5	5.7	27.4	10.7
MDBF_GM (post)	28.4	7.7	26.9	8.2	24.8	10.6	26.8	9.8	25.7	11.9	31.2	8.8	25.1	9.4	29.7	10.1	25.0	9.7	30.7	10.5
MDBF_AT (pre)	26.8	3.6	17.1	7.4	25.6	8.1	26.6	8.1	29.3	4.5	22.3	10.2	24.1	7.9	24.2	9.2	27.0	6.7	26.8	8.4
MDBF_AT (post)	30.1	5.9	22.7	9.1	26.3	9.2	23.5	9.4	27.7	11.7	24.3	8.0	24.0	9.6	24.3	9.4	24.9	8.6	27.7	6.9
MDBF_CN (pre)	27.9	7.2	23.4	6.5	28.3	7.2	27.5	7.0	31.3	6.5	27.1	5.0	27.4	5.2	27.6	8.4	27.3	7.2	29.2	7.3
MDBF_CN (post)	29.4	8.1	28.6	5.9	29.0	7.7	27.3	7.2	29.3	5.9	31.7	5.3	27.3	8.3	31.1	7.7	26.3	6.6	30.0	8.4
Cortisol ng/ml (pre)	1.3	0.5	3.0	1.1	1.2	0.5	2.5	0.5	1.5	0.7	2.2	0.6	1.7	1.0	2.2	0.3	1.9	1.1	2.5	0.6
Cortisol ng/ml (post)	1.1	0.3	2.3	1.0	0.9	0.5	2.3	0.5	1.1	0.5	2.1	0.4	1.1	0.5	2.2	0.4	0.9	0.6	2.3	0.5
IgA mg/dl (pre)	2.89	1.66	3.37	2.36	4.06	3.60	3.09	1.06	3.93	4.45	2.49	1.18	2.55	1.16	3.40	1.67	4.14	3.21	3.03	1.18
IgA mg/dl (post)	3.16	2.66	3.06	.95	3.45	2.71	3.77	1.37	5.01	3.05	4.05	2.42	3.51	2.64	3.43	1.90	2.86	1.02	4.15	2.31
Changes post-pre MDBF_GM	2.5	4.3	2.6	3.1	0.8	3.4	−3.0	9.3	0.2	6.5	3.0	2.9	−0.3	5.7	3.1	5.6	−3.6	5.7	3.2	2.4
Changes post-pre MDBF_AT	3.4	6.0	5.6	8.1	0.6	2.7	−3.1	7.3	−2.0	12.0	2.0	9.2	−0.1	6.8	0.1	6.9	−3.1	4.5	0.9	7.9
Changes post-pre MDBF_CN	1.5	6.9	5.1	2.5	0.8	3.7	−0.3	8.5	−0.5	6.5	4.6	3.4	−0.1	5.1	3.6	4.0	−1.7	3.3	0.8	5.0
Changes post-pre Cortisol ng/ml	−0.3	0.6	−0.5	0.6	−0.3	0.5	−0.1	0.2	−0.4	0.2	−0.1	0.3	−0.5	0.7	0.0	0.5	−1.1	0.4	−0.2	0.4
Changes post-pre IgA mg/dl	0.27	2.60	−0.66	3.21	−.61	4.98	0.67	1.47	1.27	5.77	1.56	1.63	0.12	0.86	0.03	1.97	−0.50	2.20	1.12	2.35

MDBF_GM = Multidimensional mood questionnaire_ good-bad mood.
MDBF_AT = Multidimensional mood questionnaire_feeling awake-tired.
MDBF_CN = Multidimensional mood questionnaire_feeling calm-nervous.

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Table 5. Estimated means and standard errors (SEs) of the differences (post-pre), p-values and 95% CIs for singing and music listening as well as mean differences between mean (post-pre)/singing and mean (post-pre)/music listening, p-values and 95% CIs.

	Change/Singing (post-pre)				**Change/Music listening (post-pre)**				**Difference: $Change_{Singing} - Change_{Music\ listening}$**			
	D_S		**95%CI**		**D_{ML}**	**95%CI**			**Δ**		**95%CI**	
	Mean Diff.(±SE)	**p-value***	**lo**	**hi**	**Mean Diff.(±SE)**	**p-value†**	**lo**	**hi**	**D_S- D_{ML}(±SE)**	**p-value‡**	**lo**	**hi**
MDBF_GM	0 (±0.860)	1.000	−1.74	1.74	1.86 (±0.854)	**0.036**	0.13	3.58	−1.86 (±1.22)	0.131	−4.28	0.57
MDBF_AT	−0.08 (±1.113)	0.942	−2.34	2.18	0.98 (±1.232)	0.433	−1.51	3.46	−1.06 (±1.68)	0.531	−4.40	2.29
MDBF_CN	0.05 (±0.837)	0.949	−1.64	1.75	2.71 (±0.816)	**0.002**	1.07	4.36	−2.66 (±1.17)	**0.026**	−4.99	−0.33
Cortisol (ng/ml)	−0.46 (±0.09)	<**0.0005**	−0.65	−0.26	−0.14 (±0.07)	0.075	−0.29	0.02	−0.32 (±0.12)	**0.014**	−0.57	−0.07
IgA (mg/dl)	0.037 (±0.471)	0.937	−0.935	1.010	0.193 (±0.437)	0.664	−0.713	1.098	−0.155 (±0.642)	0.811	−1.484	1.173
PedsQL	6.28 (±2.35)	**0.037**	0.533	12.02	7.49 (±4.87)	0.163	−3.74	18.72	−1.21 (±5.41)	0.827	−13.07	10.64
WEMWBS	2.14 (±3.25)	0.534	−5.80	10.09	5.78 (±2.43)	**0.045**	0.172	11.38	−3.63 (±3.97)	0.375	−12.15	4.88

p-value* - for testing $D_{Singing} = 0$ vs. $D_{Singing} \neq 0$.
p-value† - for testing $D_{Music\ listening} = 0$ vs. $D_{Music\ listening} \neq 0$.
p-value‡ - for testing $\Delta = 0$ vs. $\Delta \neq 0$.
MDBF_GM = Multidimensional mood questionnaire_good-bad mood.
MDBF_AT = Multidimensional mood questionnaire_feeling awake-tired.
MDBF_CN = Multidimensional mood questionnaire_feeling calm-nervous.
PedsQL = Pediatric Quality of Life Inventory.
WEMWBS = Warwick-Edinburgh Mental Well-Being Scale.
Bold means p<= 0.05=significant.

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3.4. Biological measurements on cortisol and IgA

Fig. 3 shows the changes (post-pre) in cortisol and IgA levels over five consecutive days according to the type of musical activity and day of the week.

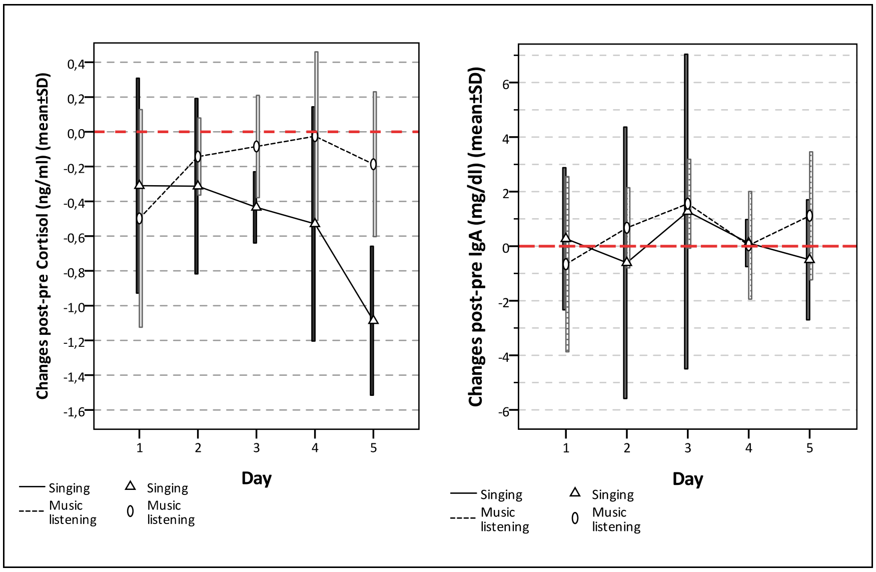

Fig. 3. Changes in Cortisol and IgA (mean differences ±SDs) by workshop day: singing vs. music listening.

The mean drop in cortisol in the singing group was significantly larger than in the music listening group (mean difference −0.32; 95% CI −0.57, −0.07; $p = 0.014$). Moreover, the singing group demonstrated significantly declining cortisol values over 5 consecutive days (mean −0.46; 95% CI −0.65, −0.26; $p < 0.0005$). In the music listening group, the same trend could be observed but was not significant at the 5% level (Table 5). No differences in the level of IgA were observed within or between the groups (Table 5).

3.5. Psychological measurement of well-being and quality of life

Patients in the singing group displayed a significant improvement in quality of life between the two time points (mean 6.28; 95% CI 0.533, 12.02; $p = 0.037$) but not in psychological wellbeing (Table 5). In contrast, the music listening group showed significant improvement in psychological well-being between the two time points (mean 5.78; 95% CI 0.17, 11.38; $p = 0.045$) but no difference in quality of life (Table 5).

No differences in well-being or quality of life were observed between the two groups (Table 5).

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4. Discussion

The aim of this observational pilot study was to compare the potential effects of two different intensive 5-day music intervention programmes added to standard care in hospitalized children and adolescents with mental disorders. Specifically, we examined the effects of an active group singing intervention versus a receptive music-listening intervention on psychological, and in parallel, neuroendocrine and immune outcomes. Our results show that intense MuRI programmes are likely to have potential psychobiological benefits, but the data are heterogenic. We found that patients who participated in a singing intervention had a larger significant decrease in cortisol levels over the five consecutive days compared with those participating in a music listening intervention. In contrast, patients who participated in the music listening intervention had a larger significant increase in the psychological measures of mood state, in the dimension *calmness*, over the five consecutive days than patients who participated in the singing intervention. We did not find significant group differences with regard to the mood-scales *alertness* and *good mood*, but we found a significant increase in the subjectively perceived *good mood* in the listening group over five days.

Previous studies that investigated the therapeutic efficacy of MuRI in children and adolescents with mental disorders in a clinical setting were conflicting, showing effects on different clinically important outcomes in this population; however, these studies all used formal music therapy. None of these studies evaluated neuroendocrine and immune system markers in the same population or considered MuRI as an additive recreational remedy. To our knowledge, our study is the first to show that the concentration in cortisol levels decreased during a brief active group singing programme intervention in this population. The present finding extends those from previous studies in clinical [54] and healthy adults [53, 55], in which group singing was associated with lower salivary cortisol levels. Notably, our study shows for the first time that a positive neuroendocrine response is more noticeable after active group singing than after group music listening. That preliminary finding thus corroborates the view that active group singing might have calming and stress-reducing effects. When considering the potential clinical effects of MuRI, it is important to note that the cortisol levels in this study decreased within the reference value for mid-afternoon salivary cortisol concentrations in youth; thus, the clinical significance of these changes is not clear. The lack of pronounced clinical changes may have been due to a diurnal effect. The highest cortisol value is reached in the morning shortly after waking up, while the lowest value occurs towards midnight; in the afternoon, there is a relatively stable plateau phase where cortisol changes occur less frequently. Since the interventions took place between 2 and 2.45 p.m., the secretion dynamic of cortisol may have been limited at this time of day, a suggestion that has already been made in preclinical studies by Kreutz et al. [39] and Bullack et al. [38] However, in that plateau phase, changes are also more diagnostically conclusive

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[73]. Therefore, it is plausible that the modest decrease in cortisol levels reflects the impact of the active musical intervention despite the diurnal effect. This preliminary finding that cortisol levels show effects allows a preliminary speculation that group singing might have a clinically important effect in promoting mental health in youth with mental disorders. However, the causal relationship and underlying mechanism remain to be proved.

Unexpectedly, our study did not find any improvement in the psychological measures of mood state in the singing group. This is contrary to evidence from previous research in other populations, which assessed an improvement in mood in parallel to a decrease in cortisol values in response to group singing [53, 54]. Notably, a previous study outside a clinical setting involving adolescent women with depression disorders [65] similarly showed significantly decreased cortisol levels after a single session of listening to music without any psychological effects, which suggest that music interventions may elicit inconsistent responses in psychological and biological measures. The authors observed that this dissociation may have resulted because the biological changes are more quickly observable than subjective mood changes; they suggested that behavior should be observed *second-by-second* and mood state assessed using additional measures [65].

Interestingly, our study found significant mood changes in response to receptive music, with no significant changes found in endocrine responses. Studies in other populations previously reported a decrease in cortisol levels and an increase in good mood in response to receptive music (cf. [28, 49]). Nevertheless, the changes displayed in our study did not conform to this tendency. Listening to music improved *calmness* and partially *good mood*, which is consistent with evidence of the emotionally-evoked effect of receptive music in healthy individuals [19, 20]. These types of findings may indicate that music developed to elicit heightened emotional and mood reactions among a larger group of individuals. As a therapeutic intervention, the ability to alter emotional states quickly seems beneficial, as it assists patients in identifying emotions and moving away from problematic mood stated, as suggested by Shuman and colleagues [60].

No differences between groups were observed with regard to the HRQOL and well-being across time, but a significant increase in HRQOL in the singing group, and a significant increase in well-being in the music listening group were observed. Future studies could test whether these findings can be replicated. Finally, in our study, no significant changes in IgA levels were observed among both the singing and music listening groups. Previous studies showed similarly conflicting results in response to MuRI: some studies suggest a parallel decrease in cortisol and increase in immune activities [54, 55], but the same negative cortisol-immunoglobulin A relationship has also been found [39]. So far, the immune activities during pleasure stimuli such as

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MuRI are not well understood. Since this is a preliminary study, we also cannot yet offer a definite conclusion based on our findings.

4.1. Strengths and limitations

A strength of this study is that it was added to standard care in a routine clinical setting, which might provide benefits for children and adolescents with mental disorders. MuRI are non-invasive, safe and inexpensive and the young subjects in our study appreciated it.

Our study has a number of limitations. The randomisation of enrolled patients was not a regular randomisation procedure; however, this was attributed to the particular clinical and "real-life" circumstances in which the study took place. Since this was a small-scale observational pilot study with a limited sample of 17 subjects who self-identified willingness to participate in the intervention, interpretations on direct causality and effect are necessarily limited. We did not achieve the target sample size of 40 patients; however, the data we collected during our recruitment process may help to inform the recruitment strategy for a further larger study. Also, the group sizes were very heterogeneous with regard to gender, medication, and psychiatric diagnosis. Compared with the music listening group, the singing group had significantly higher formal music experience. Furthermore, the significant variety of un-medicated and medicated patients among the singing and listening conditions with more medication users in the group listening condition were observed; however, a closer observation showed that the group differences were mainly due to the use of vitamin and other supplements, whereas group differences in the psychotropic medication which may influence neurometabolic processes seemed to be negligible. Nevertheless, medication, diagnosis, or gender might have affected the biological end-points. Significantly, our study did not include any covariates in the analyses. However, due to the insufficient number of participating patients, this would not result in statistically meaningful outcomes. Clearly, covariates should be incorporated and examined as possible confounders in the analysis of a larger study.

Moreover, the specificity of music stimuli should be emphasized. The most critical point is probably that the music genres differed between the singing and music listening conditions. Instrumental melodies might have different effects than songs with lyrics [74]. In our study, however, we compared active and receptive music interventions which had already been evaluated as emotion and stress modulators in studies of healthy adults. Previous studies indicated the activation of specific limbic and reward-processing brain areas that modulates endocrine responses in preferred, i.e. self-chosen [23, 26], and pleasurable music stimuli [24]. The fact that patients in our study expressed an affinity to music (patients were not included in the study if they had any aversion to music) and positively assessed both the singing and music

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listening interventions may have contributed to the positive psychobiological effects. For the listening group, we chose to use only music selected by researcher. However, due to the practical considerations in a rehearsal choir situation, the singing repertoire was decided by the choral conductor. Moreover, the singing group included the possibility to choose self-selected/familiar songs, which may influence the biochemical end-point. Further trials should take this confounder into consideration. Future investigations could also achieve enhanced results by using different musical selections based on individual patient preferences, which were previously reported as meaningful and rewarding in other groups of patients [30]. Several studies on active group singing have speculated on its social functions (e.g. [34, 40]) and their benefit for stress modulation [46]. Notably, our study did not include oxytocin measurements as an indicator for social bonding on the recommendation of the laboratory, because oxytocin in saliva is unspecific with low validity. Future research should investigate whether the capacity of singing to reduce stress could be explained by social activation. Moreover, we cannot rule out the possibility that cortisol is influenced by the physical activity of singing, which is known to affect endocrine system responses [47]. Since singing is physically more demanding than listening [39], future research might investigate whether different physical exertion (e.g. dance activity, sports) could explain the observed effect of singing on cortisol in this group of patients. Furthermore, it remains unclear whether the positive psychobiological effects are specific to pleasurable music stimuli per se or whether other pleasurable non-musical artistic-creative activities (such as drama, textile design, etc.) may have similar effects. Finally, the incorporation of brief relaxation exercises prior to singing and listening could lessen the effects of music on mood and stress.

Beyond these limitations, there were major methodological challenges to realizing a long-term, controlled, randomised, comparative study with correspondingly large patient numbers in a clinical setting. These challenges were due to the nature of the symptoms and to daily fluctuations in sensitivities among the participants. Further longitudinal research with larger patient numbers and additional measurements is needed to clarify the heterogeneity of the data and to determine whether the effects remain over a long term, whether they have an impact on the recovery process, and whether they depend on the clinical picture.

Declarations

Author contribution statement

Katarzyna Grebosz-Haring: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Leonhard Thun-Hohenstein: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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