THE SOUND OF MEDICINE

Evidence-based music interventions in healthcare practice

Rosalie Kühlmann

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GELUID IN GENEESKUNDE

Wetenschappelijk-onderbouwde muziekinterventies
in de gezondheidszorg

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Chapter 1

General Introduction

For centuries, music has been integrated in society, often in the context of social events, relaxation or entertainment. The past two decades have seen a rising interest in giving a role to music in healthcare. This is not a new development, however; the ancient Greeks also already used music to improve well-being and healing.[1] Music has been defined as vocal or instrumental sounds (or both) combined in such a way as to produce beauty of form, harmony, and expression of emotion.[2] To some, the feature of beauty is not crucial, and the broad definition explains the many different forms that music can take.

In today's medicine, an action that produces an effect or is intended to alter the course of a (pathologic) process – such as a new drug tested or a new type of surgery performed– is known as an intervention.[3] The studies presented in this thesis addressed the use of music to alter a specific condition such as anxiety and pain, and this specific use of music is referred to as a music intervention.

Music interventions have been studied in relation to sleep disorders, depression, cardiovascular disorders, and autism spectrum disorders in children.[4-10] Furthermore, guidelines have been issued that describe the use of music in palliative care.[11,12] Reductions in patients' anxiety and pain are important outcomes in studies of music interventions, both around various hospital procedures [13,14] and perioperatively.[15] Despite the broad ranges of settings and patients in which music interventions are tested, music interventions have not yet been broadly adopted in clinical practice. New treatments in medicine are usually introduced via the evidence-based-medicine principle, which implies collecting evidence supporting the usefulness of a therapy. Levels of evidence are scaled via the pyramid of evidence (Figure 1), in which the lower levels involve little evidence, such as expert opinion or case reports, and upper levels represent higher quality of the evidence, produced by randomized controlled trials (in which an intervention is tested in a population and compared against a control population), systematic reviews (in which qualitative findings of multiple randomized controlled trials are summarized) and ultimately meta-analyses (in which quantitative findings of multiple randomized controlled trials are summarized). In these days of high-quality healthcare, multiple randomized controlled trials with large sample sizes should be the backbone of a meta-analysis to create the highest level of evidence for a new treatment. Based on this evidence, guidelines can be written and the treatment can safely be implemented in practice. This path must be followed for music interventions as well.

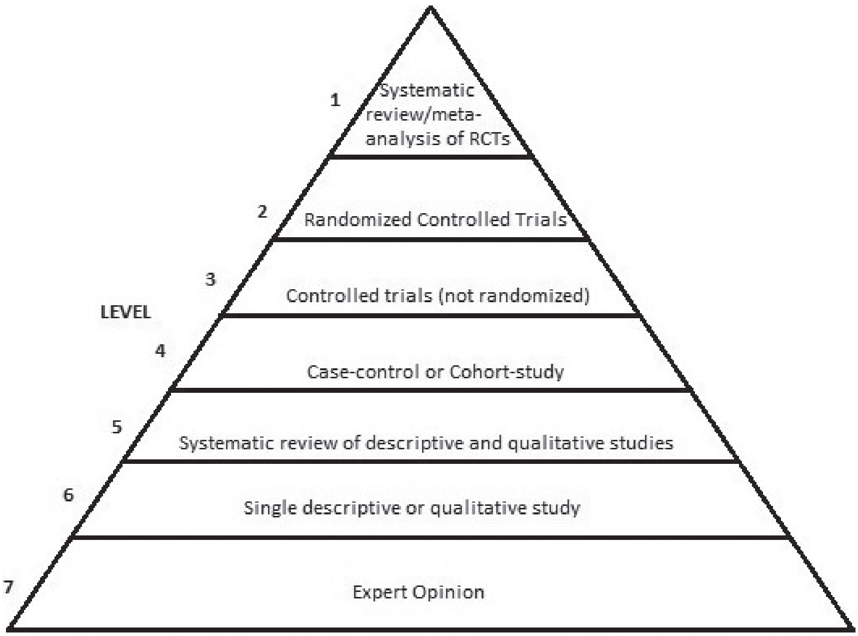

Figure 1. Pyramid of Evidence

Music interventions and music therapy

Basically, a music intervention can be administered to a patient in two ways; via exposure to previously recorded music, or via offering music therapy. Music therapy can be described as the use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed music therapist. The therapeutic relationship with a professional is an important aspect in the definition of music therapy. Research of music in medicine often refers to recorded music provided by medical researchers or healthcare practitioners.

This research performed in this thesis was supported by the Music as Medicine Foundation. Established in 2012 in Rotterdam, the Netherlands, this foundation aspires to investigate, and where possible to implement, the use of music interventions in healthcare. Thus, studies have been undertaken to investigate both music interventions and music therapy.[16-21] This thesis, however, focuses on the sole use of music interventions (thus without a therapeutic relationship between patient and music therapist) to improve health care outcomes.

1

Working mechanism of music

Acoustic oscillations enter the brain via the ear, from which nerve impulses are transferred via the nervus vestibulocochlearis (N VIII) to the medulla in the lower brain stem, the cochlear nucleus and the superior olivary nucleus. The impulses are then forwarded via the lateral lemniscus to the inferior colliculus, projecting to the medial geniculate body in the posterior thalamus. After that impulses enter the core auditory cortex and secondary regions (Figure 2).[22] Many parts of the brain are activated when hearing music, such as the nucleus accumbens and amygdala in the limbic system as described above, the basal ganglia (learning of melodies), and the motor cortex (beat induction, rhythm and moving of arms and legs).[23] Looking more deeply into the physiologic reactions created by sound and music, we can better understand the anxiety- and pain reducing capacities of music, reflected in the different effects on physiology and neuronal circuits.

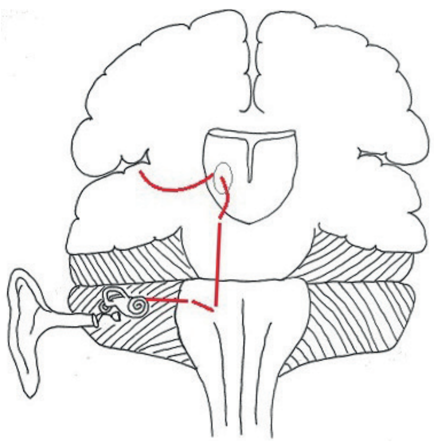

Figure 2. Acoustic oscillations enter the brain via the ear, from which nerve impulses are transferred via the nervus vestibulocochlearis (N VIII) to the medulla in the lower brain stem, the cochlear nucleus (1) and the superior olivary nucleus (2). The impulses are then forwarded via the lateral lemniscus to the inferior colliculus (3), projecting to the medial geniculate body in the posterior thalamus (4). After that impulses enter the core auditory cortex (5).

The thalamus is in part component of the limbic system. Music exposure can influence a person's emotions or moods[24,25] and decrease anxiety by the activation of specific areas in the limbic system: the nucleus accumbens, amygdala and hippocampus.[24,26-28] Listening to music creates expectation which in turn activates the reward system that is localized in the nucleus accumbens. Activation of the reward system gives rise to a release of neuropeptides, such as dopamine, and endogenous opioids.[24,27] Dopamine projects, among other things, to the prefrontal cortex (PFC), to the vm-PFC and also the anterior cingulate cortex (ACC). The prefrontal cortex in turn has an inhibiting function on the amygdala, which is sensitive to anxiety. Via glutamatergic projection neurons in the amygdala there is inhibition versus activation of neurons – resulting in less or more anxious behavior.[29] Activation of the reward system by music can thus result in lessening of anxiety.

The projection of dopamine to the PFC and ACC is also important in the reduction of pain. When experiencing pain, beta-endorphins (neuro-peptides) are released from the anterior pituitary gland that produces analgesia via a descending pathway from the brain through the periaqueductal grey and the dorsal horn of the spinal cord (dorsolateral funiculus),[30] by binding to opioid receptors in the peripheral nervous system, where they inhibit the release of substance P, which is important in the transmission of pain signals. The neuro-peptides also produce analgesia in the central nervous system by inhibition of the release of GABA, an inhibitory neurotransmitter, resulting in excess production of dopamine.[31] Dopamine in turn releases more beta-endorphins. Also via this pathway pain reduction may be achieved, and this mechanism is likely to be affected when hearing music.

This pathway has also been implicated in attention shifts. Music may shift one's attention from things anxious or painful to something pleasant instead, providing distraction.[32-34] Whether music is better suited to offer distraction than a book, a movie or something else, has not yet been decided. While some studies suggest that music works better than other distractions such as video (submitted work by M.J.E. van der Heijden et al, 2019), other studies report equal distraction or advice to combine both music and video.[35]

The limbic system in the brain is furthermore related to the autonomic nervous system via the thalamus and hypothalamus. Music induces effects based on autonomic responses, i.e. the shift in equilibrium from a more sympathetic state to a more parasympathetic state. For example, music interventions can slow down the breathing frequency and modulate autonomous cardiovascular regulation.[36-41] This leads to reduced levels of cortisol[42,43] and lowering of heart rate and blood pressure.[15,44-46]
Animal studies allow us to gain more knowledge on specific physiological and pathophysiological working mechanisms of therapies in the brain and the body. Several experimental studies on the effects of music in healthy rodents[47-49] and disease-induced rodents have been reported[50-52]. An overview of findings from animal studies could provide even more insight in specific working mechanisms of music. As this overview was still lacking, we set out to review the available studies.

Clinical application of music interventions in surgery: reduction of anxiety and pain

Anxiety and pain are important issues around surgical procedures. Both adults and children undergoing surgery may experience preoperative anxiety.[53-55] Preoperative anxiety affects patients immediately prior to the surgical procedure by increasing psychological and physiological distress, but it can have important implications after the procedure as well,[56] such as negative awakening from surgery (emergence delirium) and nightmares.[57] In children, negative behavioral responses even up to six months after the surgery have been reported.[58] Moreover, preoperative anxiety is associated with higher levels of postoperative pain.[54,59] This is important as more than 80% of surgical patients suffer from postoperative pain [60], which is even moderate to severe in 40 to 65% of patients – despite pharmacological pain-reducing interventions.[61,62]

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[63] As part of the reaction to pain, the body stress response increases, resulting in vasoconstriction in the little vessels and decreasing tissue perfusion, which could impair wound healing.[64,65] Preventing under treatment of postoperative pain, both in adults and children, remains a major challenge worldwide.[66,67] Pharmacological interventions play a major role in the treatment of perioperative anxiety and postoperative pain. Nevertheless, other treatment modalities gain terrain, the more so because the use of analgesics is associated with inherent side-effects.[62] Music interventions have been suggested as a way to reduce perioperative anxiety [68,69] and postoperative pain,[14,15,62] and side effects of music have thus far not been reported.[70]

As written previously, music interventions in healthcare practice are not used regularly. This could be due to unawareness of the existence of music interventions, or the lack of scientific evidence for music in specific situations such as surgery. Also, it is a complex matter to successfully implement a new guideline in daily practice, as this requires changes in processes which have been well established over time.[71] This process must be preceded by consideration of barriers and facilitators [72] and is important to address when implementing new research findings, especially with respect to healthcare processes.

Importance of valid measurement tools in scientific research

The effect of any intervention should be assessed with a valid and reliable measurement instrument. Validated instruments simplify measuring the effect of interventions and the interpretation thereof, especially in subjective or behavioral outcomes. An adult's pain, for example, can be described by the following definition: "Pain is whatever the experiencing person says it is, existing whenever and wherever the person says it does".[73] This broad definition as well as the specific subjective format of pain makes quantification of pain difficult. Therefore, validated global measures have been introduced to connect the pain intensity to a specific quantitative measurement, of which the visual analogue scale (VAS) was one of the first.[74] These measures, however, require obtaining a verbal response from the subject. Because infants and young children cannot express themselves verbally, various observational measurement instruments have been validated with which nurses or others can assess a child's behaviors related with pain or distress. For example, behaviors such as crying or muscle tension are assessed with the COMFORT-behavioral scale [75]; and behaviors such as activity and vocalization with the Yale Preoperative Anxiety Scale.[76]

Preoperative anxiety: mutuality between child and parents

It is not uncommon for parents to be anxious, too, when their child has to undergo a medical procedure in the hospital.[77] Several intrinsic psychological factors – such as coping style and locus of control [78,79] – as well as extrinsic factors – such as younger children's age [77,80,81] or more extensive surgery [77] – can affect parental anxiety. Mutual influences between a child's and the parents' preoperative anxiety have been reported, for instance resulting in a higher heart rate in both mother and child.[82,83] Although it is wide believed that children benefit from parental presence during induction of anesthesia, and this is a common procedure, studies have shown that this presence generally does not decrease the children's preoperative anxiety, [84,85] perhaps due to this previously mentioned mutual anxiety.

Outline of this thesis

This thesis aims to evaluate the evidence supporting the use of music interventions in healthcare, to more extensively deepen the biological and psychological pathways underlying music's effect, and to investigate whether music interventions can alleviate patients' anxiety, pain and other outcomes. The focus lies on the working mechanisms of music, and the effects of perioperative music interventions in both adults and children.

Part I includes a systematic review and two meta-analyses on the effects of music exposure in rodents and in adult patients (chapters 2, 3, 4). *Chapter 2* describes results from basic experimental studies in rodent models on the impact of music exposure on brain structure and neuro-endocrine responses, behavioral outcomes, immunological parameters and physiological variables. *Chapter 3* reports on a systematic review and meta-analysis we performed on 92 studies evaluating effects on adult patients' anxiety and pain of music interventions offered perioperatively. A Dutch translation can be found in *Appendix 1*. *Chapter 4* provides our systematic review and meta-analysis on the effects of music interventions on blood pressure in patients with hypertension.

Part II describes prospective studies performed in the Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands (chapters 5, 6, 7).

Chapter 5 describes the results of the randomized controlled trial investigating effects of music interventions on anxiety, distress and pain in 195 young children undergoing surgery for three common elective procedures. In *Chapter 6*, the validity and reliability were assessed of the modified Yale Preoperative Anxiety Scale-short form (mYPAS-SF) to measure preoperative anxiety in children less than 2 years of age. *Chapter 7* highlights parental preoperative anxiety, the mutuality that could affect both parent and child, and other factors that might play a role in the level of parental anxiety.

The general discussion in *Chapter 8* puts the results and new insights into perspective and provides directions for further research. The results of all studies are summarized in English and in Dutch.

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PART I

The working mechanisms and applications of music interventions

Chapter 2

Music affects rodents: A systematic review of experimental research

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Abstract

Background: There is rapidly emerging interest in music interventions in healthcare. Music interventions are widely applicable, inexpensive, without side effects and easy to use. It is not precisely known how they exert positive effects on health outcomes. Experimental studies in animal models might reveal more about the pathophysiological mechanisms of music interventions.

Methods: We performed a systematic review of experimental research in rodents. The electronic databases EMBASE, Medline(ovidSP), Web-Of-Science, PsycINFO, Cinahl, PubMed publisher, Cochrane and Google scholar were searched for publications between January 1st 1960 and April 22nd 2017. Eligible were English–written, full-text publications on experimental research in rodents comparing music versus a control situation. Outcomes were categorized in four domains: brain structure and neuro-chemistry; behavior; immunology; and physiology. Additionally, an overview was generated representing the effects of various types of music on outcomes. Bias in studies was assessed with the SYRCLE Risk of Bias tool. A meta-analysis was not feasible due to heterogeneous outcomes and lack of original outcome data.

Results: 42 studies were included. Music-exposed rodents showed statistically significant increases in neuro-chemistry, such as higher BDNF levels, as well as an enhanced propensity for neurogenesis and neuroplasticity. Furthermore, music exposure was linked with statistically significantly improved spatial and auditory learning, reduced anxiety-related behaviour, and increased immune responses. Various statistically significant changes occurred in physiological parameters such as blood pressure and (para)sympathetic nerve activity following music interventions. The majority of studies investigated classical music interventions, but other types of music exerted positive effects on outcomes as well. The SYRCLE risk of bias assessment revealed unclear risk of bias in all studies.

Conclusions: Music interventions seem to improve brain structure and neuro-chemistry; behavior; immunology; and physiology in rodents. Further research is necessary to explore and optimize the effect of music interventions, and to evaluate its effects in humans.

Introduction

There is growing interest in music interventions and music therapy in healthcare. Music interventions have a wide applicability, and the low cost, lack of side effects and ease of use make it an interesting intervention. Music interventions involve application of music in order to improve a clinical outcome, and can be administered recorded or live. They have been widely investigated in humans and can be linked to reduced depression levels in older people,[1] to reduced disruptive behaviors and anxiety, and improved cognitive functioning in patients with dementia.[2] A large number of studies have shown that music interventions alleviate anxiety and pain around medical procedures[3,4] and surgical procedures.[5] Music may have a beneficial effect on anxiety, systolic blood pressure, heart-rate, respiratory rate, quality of sleep and pain in patients with coronary heart disease,[6] and might reduce blood-pressure in chronic hypertension.[7] Lastly, music interventions appear to enhance immune function and to affect neuro-endocrine responses, such as a decrease in cortisol.[8]

Music interventions are thought to not only exert their effects in humans by improving relaxation or providing distraction for a specific situation, but also to achieve specific physiological changes in the human body. The exact mechanism of action remains unknown. Music listening can influence a person's emotions and moods[9,10] by activating specific pleasure areas in the limbic system, such as the nucleus accumbens, amygdala and hippocampus[9,11-13]. These activations in turn may release neuropeptides, such as dopamine, and endogenous opioids.[9,12] It cannot be excluded that such effects also occur in animals. Some studies in rodents indeed have shown that music exposure enhanced the expression of neuropeptides in the limbic system, which are known to be involved in pleasure and reward control.[14-16]

Moreover, several experimental studies in healthy rodents and in rodent disease models found similar effects as reported in humans, such as enhanced spatial ability,[17] improved neuroplasticity,[18] anxiety reduction,[19] blood pressure lowering,[15] and increasing immune function.[20,21]

The outcomes of systematic experimental studies in animal models could be of value in understanding the working mechanisms of music interventions and extending clinical applicability of therapies. To answer the question whether music interventions exert effects on brain structure, neurochemistry, behavior, immunology and physiology in rodents, we performed a systematic review of randomized experimental studies investigating music interventions in rodents compared to control situations.

Methods

Study design

We performed a systematic review of the literature, and reported this following the PRISMA statement for transparent reporting of systematic reviews.[22]

Search strategy and data sources

On April 22nd, 2017, a systematic literature search was performed in the electronical databases EMBASE, Medline(ovidSP), Web-Of-Science, PsycINFO, Cinahl, PubMed publisher, Cochrane and Google scholar for publications that would be relevant to answer the research question (see Supplementary Material I Search Strategy). Titles and abstracts of citations were screened for relevance, and full texts of relevant citations were screened for relevance by two investigators (AK and AR) independently. In case of disagreement a third researcher (JJ) was consulted and consensus was negotiated.

Participants, interventions, comparators

Studies meeting the following criteria were considered for inclusion: 1) experimental study performed in rats or mice; 2) investigating the effect of music interventions on neuronal processes, behavioral effects, endocrine and/or inflammatory responses or physiological conditions; 3) comparing the effect of a music intervention with a comparator situation without music, referred to as 'control'; 4) available full-text article; 5) written in English; 6) published after 1/1/1960. There were neither limitations to the type of music administered, the music had to contain melody, harmony, and rhythm (in case the intervention solely consisted of an auditory enrichment, such as white noise, the study was excluded); nor to the type of control condition. If study populations overlapped between studies, only the most extensively described study was included.

Data extraction and data analysis

The following study characteristics were collected in an Excel spreadsheet (Google Sheets, 2015): authors, year of publication, animal model characteristics (species, sex, age, number of animals, disease induced characteristics), music intervention (type, timing, duration, loudness), specific description of the music and genre, control condition (type, timing, duration, loudness), and performed tests. Study quality was assessed by two researchers (RK and AR) using the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) Risk of Bias tool, which is the adapted version for animal studies of the Cochrane Risk of Bias tool [23]. Outcome measures were extracted by two persons separately and categorized into four areas: 1. brain structure and neuro-chemistry; 2. behavior; 3. immunology; and 4. physiology. Additionally, an overview was generated representing the effects of various types of music on outcomes. A meta-analysis was not performed due to the heterogeneity in outcomes and the lack of reporting original outcome data in reviewed studies.

Results

Study selection and characteristics

The literature search resulted in 2784 citations after removal of duplicates. Following eligibility assessment, 42 full-text articles were eligible for inclusion (see Figure 1). Detailed study characteristics are presented in Table 1. Figure 2 represents an overview of domains in rodents that seem affected by music. Thirty studies (71.4%) were in rats; twelve in mice. All studies investigated recorded music interventions played by loudspeaker. Control conditions were described as no music (17 studies, 40%); ambient noise (14 studies, 33%); white noise (5 studies, 13%); undisturbed situation (5 studies, 12%); and no stress (1 study, 2%). Twenty-eight studies (67%) involved several interventions/comparators (see Table 1).

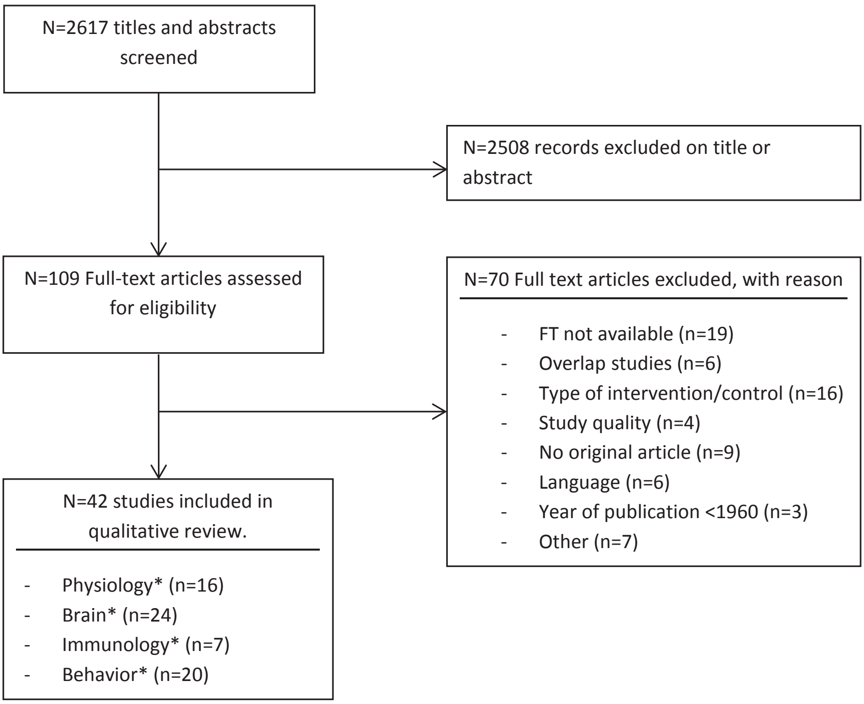

Figure 1. Flowchart. *Some studies investigated outcomes on several areas.

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Table 1. Study characteristics. Wk=weeks, mn=months, SD rat= Sprague Dawley rat, PND=post-natal day, NM= No Music, WN= White Noise; AS= Ambient Sound, MWM= Morris Water Maze, SDAT= Step Down Avoidance Task, EPM=elevated plus maze, MB=marble burying, LDT= light-dark transition test, OPF open field, PA task = passive avoidance task, ASDT: auditory signal-detection task, SDDT= sound duration discrimination task, CPP= center place preference SE= status epilepticus, TLE=temporal lobe epilepsy, SHR=spontaneously hypertensive rat, CPP= conditioned place preference, DA=dopamine, 5-HT= serotonin, TPH=tryptophan hydroxylase, HIF-1= hypoxia inducible factor-1, VEGF= vascular endothelial growth factor, METH= Methamphetamine, PP=place preference, NR= normotensive rat, (S)BP= (systolic) blood pressure, GVNA=gastric vagal nerve activity, RSNA= renal sympathetic nerve activity, LBD= Light-Dark Box transition test, LSSD= liver stagnation and spleen deficiency, FC= forebrain cortex, MC= motor cortex, SC= somatosensory cortex, HC= hippocampus, PFC= prefrontal cortex, FrC= frontal cortex, S=striatum, SN= striatal nucleus, MS= mesencephalon, CC= corpus callosum, AudC= auditory cortex, HT=hypothalamus, ACC=anterior cingulate cortex, DRN= dorsal raphe nuclei, MRN= median raphe nuclei, OVX= ovariectomized, Sham= sham operated, SHR= spontaneous hypertensive rat, temp=temperature *studies in which music intervention was used as stressor.

Author	Year	Animal	Age	N/ group	Disease/ Condition	Music Intervention
Gao	2016	Male Wistar rats	5-8 wk	10	Colorectal cancer bone cancer pain	Mozart K.448
Jiang	2016	SAMP8 mice	7.5 mn	10	Alzheimer's disease	Musico-electro-acupuncture
Lee	2016	Male SD rats	2 wk	8	Autism, valproic acid-induced	Comfortable classical music
Xing (1)	2016	SD rats	PND 1-98	5	-	Mozart K.448
Xing (2)	2016	Male SD rats	PND 1-98	15	-	Mozart K.448
Xing (3)	2016	Male SD rats	adult	10	SE in TLE rats	Mozart K.448
Cruz	2015	Albino Wistar rats	3-5 mn	10	Photoperiod (CD/SD/LD)	Mozart KV361
Kim	2015	Male ICR mice	4 wk	5	Anaphylaxis induction	Korean Buk Music
Kirste	2015	Female C57BL/6J mice	6-8 wk	10	-	Mozart K.448 (Transposed to 5-20 kHz)
Sheikhi	2015	Wistar rat	prenatal day 2-20	6	-	Classical Music
Escribano	2014	Female Wistar rat	3 mn	6	1. Normal 2. OVX/sham	Mozart K.448
de Camargo	2013	Albino Wistar rats	3-5 mn	10	1. Simvastatin 2. Silence	Mozart KV361
Kim	2013	SD Rats	new born	5	-	Comfortable music

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dB	Comparator	dB	Duration/frequency	Tests
60	No music	-	1h/day for 2 weeks	Weight, tumor volume, pain, p38α, p38β
-	**1. Electro acupuncture** 2. Alzheimer's control	-	20 minutes/day for 15 days	MWM test, brain glucose, amyloid-β frontal lobe
65	Undisturbed		1h/day from PND 15 to PND 28	SDAT; BDNF, TrkB, BrdU+ (HC)
70	**1. Ambient sound** 2. K.448 retrograde	65	12h 8pm-8am	MWM test
70	Ambient noise	65	12h/day from 8am-8pm	MWM test BDNF, TrkB
70	**1. Ambient noise** 2. Control with saline (no SE)	75	2h/day 8-10pm day 1-34 after SE	MWM test Swimming speed and distance
70	1. Ambient noise	50	24h prior to and during tests	EPM test OPF test
70	**1. No music** 2. White noise	70	5 minutes	mortality, HIF-1α, VEGF, histamine, TNF-α, IL-1β
70	**1. Ambient noise** 2. Silence 3. White noise 4. Pup calls	70	2h/day in dark cycle, 3-7 days	BrdU+ cells, BrdU+/Sox2+ cells, cell differentiation
60	No music	32	90 minutes 2/day	Corticosterone mother, neuroplasticity fetus
65	**1. Ambient Noise** 2. White Noise	55	45 min before and during tests	EPM test LDT test
70	1. Ambient noise	50	1 month music 5h/day, then 24h prior to/during tests	EPM test, OPF test, object recognition test
65	**1. Control** 2. Noise	1.- 2.95	1h/day from day 15 pregnancy till delivery	neurogenesis: BrdU MC, SC Thickness MC, SC

Author	Year	Animal	Age	N/ group	Disease/ Condition	Music Intervention
Zhang	2013	Male Wistar Rat	-	5	LSSD (stress by bondage, diet irregularity)	Gong Tone
Marzban	2012	Male Wistar rat	new born	15	-	Mozart K.448
Tasset	2012	Male Wistar rat	20 mn	5-6	1. normal 2. haloperidol blocking DA-system	Mozart K.448
Uchiyama	2012	C57BL/6, CBA, BALB/c mice	8-12 wk			Opera
Akiyama	2011	Male SHR	12 wk	10	SHR	Mozart K.205
da Cruz	2011	Albino Wistar rats	3-5 mn	10	1. Saline 2. Simvastatin	Mozart KV361
Amagdei	2010	female Wistar rat	new-born	10-16	1. PND1 sham surgery 2. PND1 callosotomy	Sham + 42 Mozart piano sonatas
Li	2010	C57BL/6 wild type, $BDNF^{Met/Met}$ and $BDNF^{+/-}$ mice	adult, 2-3 mn	6-9	Anxiety by $BDNF^{Met/Met}$ and $BDNF^{+/-}$	Diverse Chinese Classical, Western Classical pieces
Lu	2010	male Wistar rat	21 days	8	sensitized asthma, restraint stress (tube)	Asthma + Mozart K.448
Meng	2009	male C57BL/ 6J(B6) mice	28 days	20	-	Mozart K.448
Nakamura	2009	male Wistar rats	-	5	-	Schumann Traumerei Op.15-7
Xu	2009	male SD rats	new-born	4	-	Mozart K.448
Erken	2008	female Wistar Albino rats	adult	7	-	Mozart pieces
Feduccia	2008	Male SD rats	adult	11/10	MDMA	Euphoric House
Lemmer	2008	Wistar-Kyoto rat (NR) and SHR	adult	5	Hypertension	Mozart No. 40

dB	Comparator	dB	Duration/frequency	Tests
-	**1. No music** 2. Xiaoyoa Powder 3. Combined 4. No LSSD control	-	45 min	Gastrin, IgG, T-cell proliferation, macrophages
90	No music	-	6h/night for 60 days	BDNF (HC)
65	No music	-	2*2h/day over 4 days	brain dopamine (PFC, SN, MS) prolactin corticosterone
60	1. Mozart classical **2. No music** 3. New Age 4. Different frequencies 5. Eardrum perforation	40	24 h/day 6 days after Tx	heart Tx: survival, IL-4, IL-10, IL-3, TNF-γ adoptive Tx: splenocytes, CD4+, Foxp3, CD4+CD25+
70	**1. No music** 2. 4kHz-16kHz 3. 250Hz-2kHz 4. 32-125Hz	35	10h (12-22h)	BP tail-cuff method
70	1. Ambient noise	50	24h prior to and during tests	EPM test OPF test
70	**1. Sham + No music** 2. Callosotomy + music 3. Callosotomy + NM	-	12 h/night from PND2-PND32	T-maze Marble burying
55	1. Ambient Noise **2. White Noise**	1. 40 2. 55	6h/day (18-24h) for 3 wk	BDNF/TrkB mRNA and quantity (PFC, HC, amygdala), OPF , EPM test
55	1. Ambient Noise **2. Asthma** 3. Early asthma 4. Late asthma	50	6h/day 18-24h for 14 days from week 11	leukocytes, eosinophils, IL-4, IL-1β brain, corticosterone
55	Ambient noise	50	8h/day 22-6h 30 days	DNA microarray: gene expression changes FC/HC OPF test, MWM test, PA task
50	**1. No stimulation** 2. White Noise	50	60 minutes by earphones	GVNA, c-Fos expression in AudC
70	No music	55	12h/d for 42 days starting PND 14	ASDT, SDDT, NR2B protein expression AudC
70	**1. Control** 2. Rock Music 3. Noise	1. 42 2. 70 3. 95	1h/day for 14 days	RBC deformability RBC aggregation
70	**1. White noise** 2. No added sound	70	During tests	CPP, NAcc DA, 5-HT
75	**1. Same but no music** 2. Ligeti rock music 3. White Noise	75	2h	abdominal aorta sensor for SBP, DBP, HR

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Author	Year	Animal	Age	N/ group	Disease/ Condition	Music Intervention
Angelucci (1)	2007	Male BALB/c mice	adult (40 days)	10		New Age Music (slow rhythm)
Angelucci (2)	2007	Male BALB/c mice	adult (40 days)			New Age Music (slow rhythm)
Chikahisa	2007	Female Slc:ddy mice	8 wk	13	1. OVX 2. Sham 3. Progesterone inhibitor	Mozart K.448
Nakamura	2007	Male Wistar rats	-	5	-	Schumann Traumerei
Xu	2007	SD rats	-	5	-	**1. IC(Nightwish)** 2. IC (Nostalgy)
Chikahisa	2006	Female Std:ddY mice	Prenatal 7 days, PND 1-68	7	-	Mozart K.448
Kim	2006	Offspring SD rats	Prenatal	5	-	Music-applied
Kim	2004	Offspring SD rats	12 wk	5	-	Music-applied
Sutoo	2004	Male SHR	12 wk	10	Hypertension	Mozart K. 205
Morton	2001	C57/BL6 mice	adult	9/ 10	METH	Bach BWV1041
Nunez	2001	male BALB/c mice male SD rats	7-12 wk 2 mn	20 10	- W 256 carcinosarcoma	Herbert von Karajan Adagio
Rauscher	1998	rats	prenatal, PND 0-60	30		Mozart K.448
McCarthy*	1992	male SD rats	-	6	-	Rock music (noise stress)
Bueno*	1988	male NMRI mice	-	6	Fasting	Acoustic stress (by music)

dB	Comparator	dB	Duration/frequency	Tests
55	Ambient noise	50	6h/day for 21 days 6-12 pm	HT BDNF, HT NGF, weight
55	Ambient noise	50	6h/day for 21 days 6-12 pm	BDNF, NGF, PA task, weight
70	**1. Ambient Noise** 2. White noise	1. 55 2. 70	30-45 min before and during test	OPF test, EPM test, LDT test, MB test
50	**1. White Noise** 2. Chopin Etude	50	60 minutes by earphone	arterial BP,RSNA, H3 receptor
70	Control	<45	12h/day from PND 14	GluR2 protein in AudC and ACC
70	1. Ambient Noise **2. White noise**	1. 55 2. 70	Continuously played through dark period	Cross-maze test, BDNF, body weight, corticosterone
65	**1. Control** 2. Noise-applied	1. – 2. 95	1 h/day from preND 15 until delivery	Radial-arm maze test PND21, BrdU cells (HC)
65	**1. Control** 2. Noise-applied	1. – 2. 95	1 h/day from preND 15 until delivery	TPH, 5-HT (DRN/MRN)
70	Ambient noise	35	18-20h daily	tail-cuff SBP, serum calcium, brain DA
95	1. The Prodigy 2. Loud WN **3. Ambient Noise**	1. 95 2. 95 3. 65	3h	seizures, locomotion, CPP, reactive gliosis
<40	**1. Unstimulated controls** 2. auditory stressor 3. auditory stressor and music	100	9am-2pm/ 8 days	Lymphocytes, T-cell proliferation, NK-cell activity, ACTH N tumor nodules, %metastasis
65	**1. White Noise** 2. Philip Glass	65	12h nocturnal until PND 65	T-maze (working time, N errors)
70	Usual environment	45	24 hours	lymphocytes,IL1, superoxide anion, temp, activity counts
≤ 90	**1. No stress** 2. Cold stress	-	20 minutes	Gastric emptying

Risk of Bias

All studies were assessed as unclear risk of bias according to the SYRCLE risk of bias tool (see Supplementary Material II SYRCLE Risk of Bias tool). Most studies did describe animal and housing characteristics, and reported some attrition bias. Information on sequence generation, allocation concealment, blinding of caregivers/investigators and random outcome assessment was barely reported.

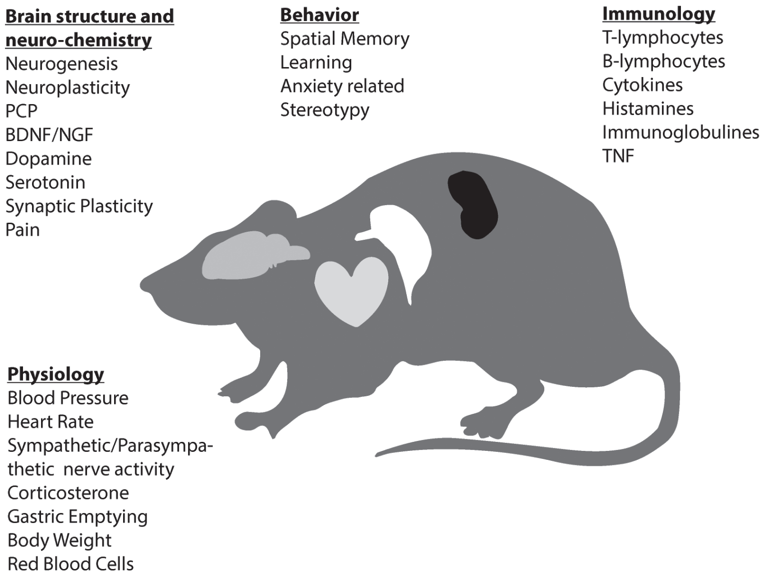

Figure 2. Music affects different domains in rodents. PCP=precursor cell proliferation, BDNF= brain derived neurotrophic factor, NGF= nerve growth factor, TNF= tumor necrosis factor.

Findings: music and brain structure and neuro-chemistry

Twenty-three studies investigated the effects of music on the neuro-anatomy of the brain (see Table 2),[14-18,21,24-40] such as neurogenesis and neuroplasticity as measured by precursor cell proliferation by bromodeoxyuridine (BrdU) labeled cells, levels of brain derived neurotrophic factor (BDNF) expression, and nerve growth factor (NGF); levels of dopamine and serotonine; seizures; expression of amyloid-β; and effects on neuronal pain pathways.

All four studies that investigated effects of music on levels of BrdU-cells found increased levels compared to a control condition.[18,27,29,30] Prenatal music increased the number of cells in the motor cortex and somatosensory cortex[27] as well as in the hippocampal CA1, CA2 and CA3 regions, but not in the dental gyrus.[29] Moreover, the brain cells of rat fetuses exposed to music were morphologically more complex than those of rat fetuses not exposed to music.[36] Music statistically significantly increased levels of BDNF compared to comparator situations in seven out of eight studies[17,24,25,30-32,37] – specifically in cells of the dorsal CA3 region of the hippocampus (HC), the dentate gyrus,[37] the prefrontal cortex, amygdala and hypothalamus+[24,25,31] whereas the NGF level was not altered in cells of the CA1 region.[37] One study found a decrease of BDNF in the cortex and no change in the HC and the cerebellum compared to comparator conditions.[26] One study found that music decreased nerve growth factor in the hypothalamus,[25] while it had no impact on the HC, frontal cortex or striatum. [24] In the same two studies, BDNF levels were elevated in both the HC and the hypothalamus.

Table 2. Brain outcomes. The signs '↑/↓/=' mean higher/ lower/ equal compared to control when no specific original data were presented. NM=no music, NS=no stimulation, WN=white noise, AN=ambient noise, UC=unstimulated control, (M)EA=(musico) elektro acupuncture, METH= Methamphetamine, 5-HT= serotonin, TPH=tryptophan hydroxylase, DA=dopamine, DRN= dorsal raphe nuclei, MRN= median raphe nuclei, FI= fluorescence intensity, MC= motor cortex, SC= somatosensory cortex, HC= hippocampus, N Acc=nucleus accumbens, dCA1/3/DG=hippocampal region CA1/3/dental gyrus, PC=parietal cortex, PFC= prefrontal cortex, FrC= frontal cortex, S=striatum, SN= striatal nucleus, MS= mesencephalon, CC= corpus callosum, HT=hypothalamus, AudC= auditory cortex, ACC=anterior cingulate cortex.*studies in which music intervention was used as stressor.

Author	Year	Outcome	Result Music	Result Comparator	P-value	Music; Comparator
Xing	2016	BNDF/TrkB	↑		<0.05	Mozart K.448; AS
Xing	2016	BDNF/ TrkB				Mozart K448; AN
		dCA3&dDG	↑		<0.05	
		dCA1	=		n.s.	
Lee	2016	BDNF/TrkB	↑		<0.05	Classical music;
		BrdU + cells	↑		<0.05	NM
Marzban	2012	BDNF	94.60 ± 6.22	86.30 ± 2.26	<0.01	Mozart K.448; NM
Li	2010	BDNF				Chinese/Western
		PFC/ HC/ Amygdala	↑/↑/↑		<0.05	Classical; WN
		BDNF/TrkB-mRNA				
		PFC	↑		<0.05	
		HC/ Amygdala	↑/↑		<0.01	
Angelucci	2007-1	BDNF				New Age Music;
		HC/FrC/S	↑/=/=		<0.05/ns/ns	NM
		NGF				
		HC/ FrC/S	=/=/=		ns/ns/ns	
Angelucci	2007-2	BDNF *HT*	↑		<0.01	New Age Music;
		NGF *HT*	↓		<0.05	NM
Chikahisa	2006	BDNF				Mozart K.448;
		Cortex	↓		<0.05	WN
		HC/cerebellum	=		n.s.	
		TrkB				
		Cortex	↑		<0.05	
		HC	=		n.s.	
Sheikhi	2015	Density PC	7.17 ± 0.6	5.5 ± 0.43	<0.05	Classical music; NM

Author	Year	Outcome	Result Music	Result Comparator	P-value	Music; Comparator
Kirste	2015	BrdU+ cells *N*	↑		<0.01	Mozart K.448; AN
		BrdU+/Sox2+ *N*	↑		<0.01	
		Diff cells	=		n.s.	
Kim	2013	BrdU MC *N cells*	486.79 ± 47.21	371.56 ± 29.29	<0.05	Comfortable music; Control
		BrdU SC *N cells*	926.26 ± 93.44	660.72 ± 58.90	<0.05	
		Thickness MC (mm)	1.204 ± 0.034	1.277 ± 0.034	n.s.	
		Thickness SC (mm)	1.241 ± 0.035	1.305 ± 0.023	n.s.	
Kim	2006	BrdU cells (HC) *N cells*				Music; Control
		CA1	3229.59 ± 119.04	2352.00 ± 111.40	<0.05	
		CA2/CA3	1393.70 ± 57.66	868.00 ± 40.50	<0.05	
		Dentate gyrus	2055.72 ± 124.39	2367.28 ± 138.25	n.s.	
Tasset	2011	Dopamine (ng/g)				Mozart K.448; NM
		PFC	96.00 ± 3.75	73.01 ± 2.02	<0.01	
		SN	69.70 ± 2.08	60.15 ± 2.84	<0.05	
		MS	71.60 ± 1.75	58.59 ± 2.20	<0.001	
Sutoo	2004	Dopamine (FI)				Mozart K.205; NM
		lateral neostriatum	5.31 ± 0.16	4.51 ± 0.21	<0.01	
		MC, SC, N Acc	=		n.s.	
Feduccia	2008	Dopamine N.acc.	↑		<0.05	House Music; WN
		5-HT	↑		<0.05	
Kim	2004	5-HT				Music; Control
		DRN	109.09 ± 10.77	159.15 ± 5.47	<0.05	
		MRN	37.93 ± 3.23	53.16 ± 2.18	<0.05	
		TPH				
		DRN	153.94 ± 7.81	184.32 ± 9.92	<0.05	
		MRN	42.50 ± 2.57	65.58 ± 3.10	<0.05	
Meng	2009	Gene expression				Mozart K.448; AN
		FrC *(N genes)*	454	-		
		HC *(N genes)*	437	-		
Xu	2009	NR2B protein expression AudC	163.00±18.9	88.65±22.7	0.046	Mozart K448; NM
Nakamura	2009	c-Fos expression AudC	↑		<0.05	Traumerei; NS
Xu	2007	GluR2 expression				Nightwish; Control
		AudC (nmol/mg)	1499.47 ± 114.55	860.31 ± 64.31	<0.05	
		ACC (nmol/mg)	2809.37 ± 191.83	1490.00 ± 90.63	<0.01	
Morton	2001	Seizures (% mice)	75.0%	38.7%	<0.01	Bach + METH; Silence + METH
		Reactive gliosis	↑		<0.05	
Nunez	2001	ACTH	=		n.s.	Adagio; UC
Jiang	2016	Brain glucose metabolism	↑		<0.05	MEA; EA
		Amyloid- β accumulation	↓		<0.05	
Gao	2016	p38α expression	35.4 ± 3.7	71.2 ±3.9	0.014	Mozart K.448; NM
		p38β expression	40.2±3.5	68.5±3.3	0.018	
		foot withdrawal (*time s*)	10.4±3.2	28.7± 6.2	0.011	
		heat pain threshold *(time s)*	49.3±5.7	27.8±4.3	0.031	
		free walking pain *(time s)*	2.5±0.3	3.6±0.6	0.033	

The three studies investigating effects of music on dopamine levels in the brain[14-16] found either an increase of dopamine in the nucleus accumbens;[14] in the prefrontal cortex, mesencephalon and the striatum;[16] or no differences in dopamine in the motor cortex, somatosensory cortex or nucleus accumbens.[15] Music prevented the decrease of dopamine after administration of a D2-receptor antagonist in rats.[16] In another study, music up-regulated the expression of dopamine-related genes in mice.[33] Effects of music on serotonin levels were investigated in two studies:[14,28] prenatal music decreased serotonin synthesis in the dorsal and median raphe nuclei in the offsprings;[28] but it increased serotonin in the nucleus accumbens after administration of methamphetamine.[14]

When methamphetamine was injected in mice, exposure to either rave or classical music increased the numbers of seizures and deaths, suggesting increased methamphetamine toxicity.[34] Rats exposed to music showed a significant increase in the expression of the NMDA receptor NR2B protein in their auditory cortex.[38] Similarly, the expression of another glutamate receptor subunit which can be involved in synaptic plasticity, GluR2, was also significantly increased in the auditory cortex following music exposure, suggesting induced plasticity in the auditory system. [39]

In a mouse model of Alzheimer's disease, addition of music to electro-acupuncture treatment statistically significantly improved the glucose metabolism level in the mice's brains, while the expression of amyloid-β, which is normally accumulated in Alzheimer's disease, was decreased.[40] Lastly, the one study examining effects of music on cancer bone pain found less pain intensity as well as decreased expression of p38α and p38β in the dorsal ganglia, which are involved in processing chronic neuropathic, inflammatory and cancer pains. [21]

Findings: music and behavior

Twenty-one studies investigated the effects of music on behavioral outcomes (see Table 3) [14,17,19,24,26,29-31,33,34,37,38,40-48] – specifically learning abilities, anxiety-related behavior and stereotypic behavior as investigated by behavioral tests explained in Supplementary Material III.

Music interventions enhanced learning abilities of rodents, specifically those involved with spatial learning.[17,26,29,30,37,38,40,41,44-46] Moreover, music statistically significantly decreased anxiety-related behavior in seven out of nine studies;[19,24,31,33,42,43,48] the remaining two studies found no differences between music and comparator groups. [41,47] The anxiety-decreasing effect of music diminished after ovariectomy and was restored by progesterone.[19,42] Music seemed to enhance anxiolytic effects of simvastatin.[47,48] Influence of music on stereotypic behavior was investigated in two studies; music enhanced stereotypic behavior after administration of methamphetamine, but not of saline.[14,34]

2

Table 3. Behavior outcomes. The signs '↑/↓/=' mean higher/ lower/ equal compared to control. NM=no music, WN=white noise, AN=ambient noise, AS=ambient sound, (M)EA=(musico) elektro acupuncture, MWM=Morris Water Maze, TET=Total Escape Time, TTQ= Time in Target Quadrant, SDAT=Step-down avoidance task, MB=marble burying, EPM=elevated-plus-maze, TTS= total time spent in open arms, EOA= entries in open arms, DOA= distance in open arms, LBT= Light-Dark Transition, TSLS= time spent light side, LBLS=latency before entering light side, OPF=open field, TDO= total distance in OPF test, TTC= total time center, TTI= total time immobile, ORT=object recognition test, PA-task=passive avoidance task, ASDT auditory signal detection test, SDDT= sound duration discrimination task, CPP=center place preference, X-maze=cross-maze.

Author	Year	Outcome	Result Music	Result Comparator	P-value	Music; Comparator
Xing	2016	MWM-test				Mozart K.448; AS
		TET	↓		<0.05	
		TTQ	↑		<0.01	
Xing	2016	MWM-test				Mozart K.448; AN
		TET	↓		<0.05	
		TTQ	↑		<0.05	
		Swimming speed	=		n.s.	
		Swimming distance	=		n.s.	
		Learning rate	↑		<0.05	
Xing	2016	MWM-test				Mozart K.448; AN
		TET	↓		<0.01	
		TTQ	↑		<0.05	
Jiang	2016	MWM-test				MEA; EA
		TET	↓		<0.05	
		TTQ	↑		<0.05	
		swimming speed	↑		<0.05	
Lee	2016	SDAT	↑		<0.05	Classical music; Undisturbed
Amagdei	2010	T-maze				Mozart; NM
		alteration performance	↑		<0.01	
		response latency	=		n.s.	
		MB test	=		n.s.	
Cruz	2015	EPM-test				Mozart KV361; AN
		TTS	↑		<0.01	
		EOA	↑		n.s.	
		Grooming time	↑		<0.01	
		Rearing time	↑		<0.01	
Escribano	2014	EPM-test				Mozart K.448; AN
		TTS	↑		<0.01	
		EOA	↑		<0.01	
		LBD-test				
		TSLS	↑		<0.01	
		LBLS	↓		<0.01	
de Camargo	2013	EPM test				Mozart KV361; AN
		TTS	↑		<0.05	
		EOA	↑		<0.01	
		OPF test				
		locomotion	↑		<0.01	
		TTI	↓		<0.05	
		ORT	=		n.s.	

Author	Year	Outcome	Result Music	Result Comparator	P-value	Music; Comparator
da Cruz	2011	EPM test				Mozart KV361; AN
		TTS	↑		<0.05	
		EOA	=		n.s.	
		OPF test				
		locomotion	=		n.s.	
		TTI	=		n.s.	
Li	2010	OPF-test				Chinese & Western Classical;
		locomotion	=		n.s.	WN
		TTC	↑		<0.01	
		EPM-test				
		TTS	↑		<0.05	
		EOA	↑		<0.01	
Meng	2009	OPF test	=		n.s.	Mozart K.448; AN
		Escape latency	↓		<0.05	
		TTQ	↑		<0.05	
		PA-task				
		Escape latency	↑		<0.01	
Xu	2009	ASDT				Mozart K.448; NM
		correct licking rate	=		0.097	
		performance index	↑		0.005	
		SDDT	↑		<0.01	
Feduccia	2008	CPP	=		n.s.	House Music; WN
Chikahisa	2007	EPM test				Mozart K.448; AN
		TTS	↑		<0.01	
		EOA	↑		<0.01	
		DOA	↑		<0.01	
		OPF test				
		TDO	=		n.s.	
		TTC	↑		<0.05	
		LDT test				
		TSLS	↑		<0.05	
		LBLS	↓		<0.05	
		MB-test	↓		<0.05	
Angelucci	2007	PA task				New Age music; AN
		LBLS	↑		<0.05	
		N trials to learn	↓		<0.05	
Chikahisa	2006	X-maze test				Mozart K.448; WN
		Running time	=		n.s.	
		Errors (N)	↓		<0.01	
Kim	2006	Radial-arm maze test				Music; Control
		Total time to complete	63.00 ±7.73	110.88 ± 14.42	<0.05	
		N correct choice	6.90 ± 0.23	6.44 ± 0.29	n.s.	
		N errors	3.20 ± 0.85	5.55 ±1.00	n.s.	
Morton	2001	CPP	↑		<0.01	Bach + METH; Silence + METH
		stereotypy	↑		-	
Rauscher	1998	Working time	34.72	44.29	<0.05	Mozart K.448; WN
		N errors	2.0	3.35	<0.01	

2

Findings: music and immunology

Seven studies investigated the effects of music on immunological outcomes (see Table 4),[20,21,35,49-52] such as specific and non-specific immunity; cytokines and histamines; anaphylaxis; tumor growth; and post-transplantation immunity.

Table 4. Immunologic outcomes. The signs '↑/↓/=' mean higher/ lower/ equal compared to control when no specific original data were presented. NM=no music, UE=usual environment, UC=unstimulated control, MST=median survival time, SI=stimulation index, OD=optical density. *studies in which music intervention was used as stressor.

Author	Year	Outcome	Result Music	Result Comparator	P-value	Music; Comparator
Gao	2016	Tumor volume	32.6 ± 12.2	114.3 ± 24.7	0.008	Mozart K.448; NM
Kim	2015	Mortality *(%)*	44.33 ± 14.01	77.77 ± 9.62	<0.05	Korean Buk; NM
		TNF-α	0.60 ± 0.15	1.44 ± 0.17	<0.05	
		Histamine	41.53 ± 1.53	52.72 ± 2.93	<0.05	
		IL-1β	1.41 ± 0.43	1.37 ± 0.12	n.s.	
		HIF-1	1.07 ± 0.33	1.80 ± 0.39	<0.05	
		VEGF	0.116 ± 0.009	0.172 ± 0.008	<0.05	
Zhang	2013	Gastrin	=		n.s.	Gong Tone; NM
		IgG (μg/ml)	64.18 ± 1.89	42.80 ± 8.98	<0.01	
		T cell (*SI*)	2.30 ± 0.19	2.03 ± 0.06	<0.01	
		Phagocytosis (*OD*)	0.36 ± 0.08	0.18 ± 0.07	<0.01	
Uchiyama	2012	heart Tx:				Opera; NM
		MST *(days)*	26.5	7	<0.001	
		Foxp3CD4+CD25+	↑		<0.001	
		IL-4	↑		<0.01	
		IL-10	↑		<0.05	
		IL-3	↓		<0.05	
		IFN-γ	↓		<0.05	
		adoptive Tx:				
		splenocytes MST *(days)*	36	10	<0.01	
		CD4+ MST *(days)*	68	8	<0.001	
		CD4+CD25+ MST *(days)*	>100	8	<0.005	
Lu	2010	IL-4 *(ng/ml)*	1.10 ± 0.17	0.73 ± 0.12	-	Asthma + Mozart K.448; Asthma
		IL-1β brain *(ng/ml)*	0.082 ± 0.003	0.080 ± 0.004	n.s.	
		leukocytes lung	↓		<0.05	
		eosinophils	↓		<0.05	
Nunez	2001	Lymphocytes	↑		<0.05	Adagio; UC
		T-cell proliferation	↑		<0.01	
		NK-cell activity	↑		<0.01	
		Tumor nodules *(N)*	=		n.s.	
		Area of metastasis *(%)*	↓		<0.05	
McCarthy*	1992	Lymphocytes *(N cells)*	4413 ± 766	4392 ± 1046	<0.0001	Rock music; UE
		Superoxide anion	2.0 ± 1.5	4.9 ± 9	<0.01	
		IL-1	↓		<0.05	

Music exposure enhanced the numbers of lymphocytes and natural killer cells as well as the levels of T-cell proliferation and phagocytosis.[35,51,52] Noise stress induced by loud rock music resulted in statistically significantly decreased production of superoxide anion and IL-1, suggestive of deprived leucocyte function.[51] Gong tone music up-regulated plasma-cells and proliferation of T-cells in rats with deprived spleen function,[52] and music exposure significantly decreased the number of eosinophils and increased cytokine levels in asthmatic rats compared to controls.[50] Mice exposed to Korean Buk music showed a statistically significantly decreased production of cytokines and histamines as well as statistically significantly lower mortality from anaphylactic shock.[49] Decreased tumor volume and decreased area of metastasis was found in the presence of music.[21,35] Rodents exposed to opera or classical music had statistically significantly prolonged survival after heart transplantation. Moreover, adoptive transfer of splenocytes and T-cells from music-exposed rodents into naïve recipients was associated with prolonged survival of these recipients.[20]

Findings: music and physiology

Sixteen studies investigated effects of music on physiological outcomes in rodents (see Table 5),[15,16,21,24-26,29,36,50,51,53-58] including blood pressure and heart rate; sympathetic and parasympathetic nerve activity; corticosterone levels; body weight and digestion; and red blood cell activity.

Table 5. Physiologic outcomes. The signs'↑/↓/=' mean higher/ lower/ equal compared to control when no specific original data were presented. NM=no music, NS= no stimulation, WN=white noise, AN=ambient noise, BP= blood pressure, HR= heart rate, GVNA= gastric vagal nerve activity, RSNA=renal sympathetic nerve activity, RBCD= red blood cell deformity, RBCA= red blood cell aggregation, GE=Gastric Emptying. *studies in which music intervention was used as stressor.

Author	Year	Outcome	Result Music	Result Comparator	P-value	Music; Comparator
Akiyama	2011	BP (mmHg)	↓ 16-28		<0.01	Mozart K.205; NM
Sutoo	2004	BP (mmHg)	↓ 13-24		<0.05	Mozart K.205; NM
		Serum calcium	↑ 5-6%		<0.05	
Lemmer	2008	NR				Mozart No.40; own
		SBP *(mmHg)*	=		n.s.	control (cross-over!)
		DBP *(mmHg)*	=		n.s.	
		HR *(b/min)*	=		n.s.	
		SHR				
		SBP *(mmHg)*	=		n.s.	
		DBP *(mmHg)*	=		n.s.	
		HR *(b/min)*	↓		<0.035	
Nakamura	2009	GVNA (% baseline)	↑ 154.9 ± 18.5		<0.05	Traumerei; NS
Nakamura	2007	MAP (% baseline)	↓ 87.9 ±6.1		<0.05	Traumerei; WN
		RSNA (% baseline)	↓ 32.8 ±10.6		<0.05	

Author	Year	Outcome	Result Music	Result Comparator	P-value	Music; Comparator
Erken	2008	RBCD	↑		< 0.05	Classical; Control
		RBCA	↓		<0.01	
Lu	2010	Corticosterone	6.47 ± 0.10	7.11±0.16	<0.05	Asthma + Mozart K.448; Asthma
Tasset	2012	Corticosterone	15.18 ± 0.62	19.27 ± 2.14	<0.01	Mozart K.448; NM
		Prolactin	19.90 ± 0.76	28.48 ± 1.75	<0.01	
Sheikhi	2015	Corticosterone	29.53 ± 1.43	37.01 ± 2.58	0.02	Classical music; NM
		Body weight	=		n.s.	
Chikahisa	2006	Corticosterone	=		n.s.	Mozart K.448; WN; NM
		Body weight	=		n.s.	
Angelucci	2007-1	Body weight	=		n.s.	New age music; AN
Angelucci	2007-2	Body weight	=		n.s.	New age music; AN
Kim	2006	Body weight	=			
McCarthy*	1992	Temperature	↑		-	Rock music; NM
		Activity counts	10.3 ± 3.2	8.1 ± 5.1	<0.001	
Bueno*	1988	GE (% total meal)	62.8±15.5	42.5±6.5	≤0.05	Acoustic stress; Control
Gao	2016	Weight (gram)	-4.9 ±1.2	-10.5±1.3	0.012	Mozart K.448; NM
		Feed efficiency ratio	62.3±5.8	35.4 ±6.2	0.026	

Four studies investigated effects of classical string music on blood pressure;[15,53,56,57] of which one also investigated effects on heart rate.[56] A statistically significantly decrease in blood pressure was noted in three out of four studies. High-frequency music was more effective in decreasing blood pressure than was low-frequency music, with an absent effect at the lowest frequencies.[53] Sympathetic nerve activity and blood pressure decreased after music exposure[57] while parasympathetic nerve activity increased.[58] Three out of four studies found significantly decreased corticosterone levels after music interventions.[16,36,50] While exposure to music was followed by a statistically significantly decrease of blood corticosterone in pregnant rats,[36] this phenomenon was not seen in the offspring upon pre- and postnatal daily exposure to music.[26] Classical music exposure decreased red blood cell functioning.[55] Acoustic stress by rock music increased gastric emptying, however administration of anti-corticotropic releasing factor prevented this.[54] Of six studies that evaluated the effect of music on body weight,[21,24-26,29,36] only one found statistically significantly weight reduction.[21]

Types of music

Overall, studies used a wide range of music interventions. Classical music was the most investigated intervention (29 studies, 70.7%; of which 14 studies used Mozart's sonata for two pianos, K.448). Table 6 represents an overview of the genres of music interventions and their effects on outcomes. Most studies investigating classical music found positive effects on outcomes regarding brain structure and neurochemistry, and on outcomes regarding behavior such as spatial memory or anxiety. Positive effects on physiological outcomes were also seen and suggested decreased sympathetic activity. Majority of these classical music studies investigated Mozart music, specifically Mozart K.448. Retrograde versions of this music piece had negative effects on spatial memory, this effect was also present when rodents heard the music for the first time. Furthermore, blood pressure decreasing effects were seen in high frequency music, while these effects were not present in low frequency music.

Table 6. Music genres and their effect on outcomes. The signs '+/=/-' mean 'positive/ equal/ negative' effect on outcome compared to control. Some studies investigated several types of music and several outcomes.

Type music	Specification	N	+/=/-	Outcome (specification)
Classical	Mozart *K.448*	14	+	↓ anxiety [19,42] ↑ spatial memory/learning [17,26,33,37,38,44,45] ↓ tumor gene expression; ↑ pain threshold [21] ↑ neuroplasticity [32,45], in hippocampus [37], in cortex [26], in auditory cortex [38] ↑ neurogenesis [18], in motor cortex/somatosensory cortex/hippocampus [27,29] ↑ dopamine prefrontal cortex/striatal nucleus/ mesencephalon [16] ↑ immune function, decreased innate immunity [50] ↓ tumor volume; ↓ weight loss [21] ↓ corticosterone [50] ↓ corticosterone; ↓ prolactin [16]
			=	equal neuroplasticity hippocampus [26] equal neurogenesis dental gyrus [29] equal corticosterone; equal body weight [26] equal physical performance [45] [26] gene expression result not specified [33]
	Mozart *K.448 (retrograde)*	1	-	↓ spatial memory [17]
	Mozart *KV361*	3	+	↓ anxiety 43,48
			=	equal anxiety [47] equal learning [48]
	Mozart *n.40*	1	+	↓ heart rate [56]
			=	equal blood pressure [56]
	Mozart *K.205*	1	+	↑ dopamine striatum, ↓ blood pressure [15]
			=	equal dopamine motor cortex/somatosensory cortex/nucleus accumbens [15]
	Mozart *K.205 high freq*	1	+	↓ blood pressure [53]
	Mozart *K.205 low freq*	1	=	equal blood pressure [53]
	Mozart	3	+	↑ immune function and prolonged graft survival [20] ↓ heart rate and erythrocyte functioning [55] ↑ learning [41]
			=	equal blood pressure [55] equal anxiety [41]

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Type music	Specification	N	+/=/-	Outcome (specification)
	Schumann *Traumerei*	2	+	↓ blood pressure, ↓ sympathetic activity [57] ↑ parasympathetic activity, ↑ neuroplasticity [58]
	Bach *BWV1041*	1	=	equal anxiety [34]
			-	↑ percentage seizures and ↑ reactive gliosis [34]
	Herbert von Karajan *Adagio*	1	+	↑ immunity and ↓ tumor area [35]
			=	equal number tumor nodules [35]
	Chopin *Etude*	1	=	equal blood pressure, equal sympathetic activity [58]
	Philip Glass (minimalistic)	1	=	equal spatial memory [44]
	Classical (Chinese/Western)	1	+	↓ anxiety; ↑ neuroplasticity hippocampus, prefrontal cortex, amygdala [31]
	Classical (not specified)	3	+	↑ learning, neuroplasticity, neurogenesis [30] ↓ corticosterone; ↑density parietal cortex [36]
			=	equal body weight [36]
Opera	Opera	1	+	↑ immune function and graft survival [20]
New Age	New Age	3	+	↑ learning, ↓ anxiety [24,25] ↑ neuroplasticity hippocampus [24], hypothalamus [25]
			=	equal immune function and graft survival [20] equal bodyweight [24,25] equal neuroplasticity frontal cortex/striatum; equal neurogenesis [24] ↓ nerve growth factor [25]
Cultural	Korean Buk	1	+	↓ mortality and ↓ activity cytokines and histamines [49]
	Gong tone	1	+	↑ cellular immunity [52]
			=	equal production gastrin [52]
Up beat	Euphoric house	1	+	↑ dopamine nucleus accumbens; ↑ serotonin [14]
			=	equal anxiety [14]
	Prodigy *Electronic*	1	+	↓ anxiety [34]
			=	equal *n* of seizures and reactive gliosis, equal stereotypic behavior [34]
	Ligeti *Rock music*	2	+	↓ blood pressure [55]
			=	equal heart rate, equal erythrocyte functioning [55]
			-	↑ immunology response, ↑ activity immune system [51]
Music (not specified)	Music	3	+	↑ learning [29] ↓ serotonin (5-HT) Raphe nuclei prenatally [28] ↑ spatial memory; ↑ physical performance; ↑ brain glucose metabolism [40]
			=	equal learning; equal body weight [29]
	Comfortable	1	+	↑ neurogenesis motor cortex/somatosensory cortex/ mesencephalon [27]
	Nightwish	1	+	↑ synaptic plasticity [39]
	Nostalgy	1	=	equal synaptic plasticity [39]
	Acoustic stress	1	-	↑ gastric emptying [54]

Other types of music showed variable effects. New age music increased neuroplasticity in one study compared to the control group, but did not affect neurogenesis or immunologic outcomes. Anxiety and learning were however improved.

Cultural music was investigated in two studies that both found positive results on immunologic functioning. Up-beat music also showed variable results. Rock music did not positively affect any outcomes, whereas electronic house music did decrease anxiety, and euphoric house music did increase dopamine and serotonin levels.

Studies that used non-specified music interventions found positive results as well, such as increased spatial memory, increased learning and increased physical performance. Studies that used music as acoustic stressor did not find positive results on outcomes.

Seven of 42 studies compared several types of music interventions[20,34,39,44,55,56,58] and allowed direct comparison of music on the outcomes due to the equality of the study conditions. A statistically significant increase in functional brain activity and plasticity was found after exposure to Nightwish music, this effect was not present after exposure to Nostalgy music,[39] however absence of specific description of these two music pieces inhibited a formal comparison between the types of music. Electronic music temporarily decreased anxiety after supplementation of methamphetamine whereas classical Bach music did not,[34] and classical Mozart music statistically significantly increased spatial memory compared to minimalistic classical music by Philip Glass.[44] There was no difference in neurologic outcomes after exposure to loud classical music by Bach, or to loud modern electronic music by The Prodigy.[34] Both classical and opera music significantly improved immune function and graft survival, whereas New Age music did not have any significant effect on these parameters.[20] Ligeti rock music, but not Mozart music, resulted in a long-lasting blood pressure decreasing effect, Mozart music on the other hand was significantly effective in reducing heart rate.[55] Both classical and rock music affected the erythrocyte response to stress with higher degree of significance in the classical music group.[55] Exposure to Schumann's Traumerei resulted in decreased sympathetic activity, but exposure to an Etude by Chopin did not.[58]

Discussion

Summary of findings

The results of this systematic review indicate that music exposure can exert positive effects on rodents' neurological, behavioral, immunological and physiological outcomes. These results are broadly consistent with studies in humans that found that music exposure can positively affect brain structure and chemistry,[59,60] behavioral read-outs,[1,3,4,61,62] immunological responses,[8,63] and physiological parameters.[3,64]

Music exposure increased rodents' spatial memory and learning in all studies that examined it. Music seems to specifically affect spatial memory, the one study examining non-spatial memory did not find any differences between the music and control situations.[48] Exposure to music decreased anxiety in all included studies. Both spatial memory and anxiety might be affected by the level of BDNF. Low levels of BDNF have been associated with anxiety and aggressive behavior in mice[31,65] and with anxiety and depression in humans.[66,67] This protein is involved in synaptic plasticity, learning and memory areas of the brain, such as the hypothalamus and hippocampus, and regulates neuronal structure and function.[25,26,32,68] In most studies examining, BDNF were elevated following exposure to music, and this might explain the reduced anxiety. The improved behavioral performance on spatial memory tasks and anxiety tests after music interventions is likely to be, at least in part, the effect of increased levels of BDNF. This finding suggests that music exposure has the potential to improve neuroplasticity and neurogenesis in the brain. This could be of value in the treatment of psychological disorders or acquired brain injuries and should be further explored.[18,29,37]

Furthermore, music exposure possibly counteracts the adverse effects of stress and thereby enhances the immune function. Music interventions were associated with increased functions of cellular and humoral immunity, increased phagocytosis and increased production of lymphocytes and immunoglobulins.[52] In rodent cancer models, music exposure was associated with lower tumor volume and smaller area of metastasis.[21,35] Regarding allergic reactions such as anaphylaxis, however, the immune system seemed tempered in the presence of music – with lower production of cytokines and histamines and thereby less mortality.[49] Remarkably, this effect of music also manifests itself in survival after transplantation. Enhanced production of anti-inflammatory cytokines and regulatory T-cells restrained the immune-system in the presence of music and thereby significantly lengthened the survival times of transplants.[20] Comparable effects of music on immunological and neurochemical functions have also been reported in humans.[8,69,70] This promising result should be further investigated.

Physiological effects induced by music are commonly explained by attenuation of autonomic function by stress reduction. Stress affects the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system in humans and animals alike. Stress reduction causes the sympathetic activity to shift to more parasympathetic activity, resulting in lower heart rate and blood pressure. The blood pressure-reducing effect of music has extensively been described in humans,[7,64] and it may hold for rodents as well. Corticosterone, the rodent's equivalent of human cortisol, is involved in regulating stress-responses and is an important biomarker for stress. Music interventions were associated with reduced corticosterone levels in several animal models.[16,26] Comparable effects of music on cortisol have been reported in humans.[71,72] In addition, the blood pressure reduction might be induced by autonomic regulation via sympathetic suppression by histaminergic receptors,[57] or on calcium level regulation via the calmodulin system.[15,39] An increase of calcium ions enhances dopamine synthesis, and increased dopamine levels in turn may inhibit sympathetic activity via specific D2 receptors and thus reduce blood pressure.[15,16,73] Increased calcium influx in the brain might be due to excitatory impulses, also represented by enhanced synaptic transmission.[39] Synaptic transmission can result in improved learning and memory functions, and boosts the formation of neural networks during brain development.[39,74,75]

Working mechanisms of music

The specific mechanisms by which music exerts its effects are unknown. It seems that at least the auditory pathway must be intact, as effects of music were not seen after lesions of the eardrum,[20] cochlea, auditory cortex, and suprachiasmatic nucleus.[57] As for the type of music, most of the studies in this review used classical music, with a preference for music composed by Mozart. This may be described to what is known as the Mozart-effect,[44] which implies an enhanced effect on spatial memory by listening to music composed by Mozart. As the findings of replication studies are inconsistent[76-78] a firm conclusion on the Mozart-effect cannot be drawn. Most of the 12 studies investigating other types of music, including folk music such as Korean Buk music[49] or Gong tone music[52] found statistically significant results as well, suggesting there is more to music than just the classical component. Different physiological effects were observed when playing different musical pieces, even when the music was in the same genre[56] or from roughly the same classical style.[58] More complex classical music seemed of more value to spatial memory than minimalistic classical music did.[44] One study compared tonal classical music of Mozart with the avant-garde classical music of Ligeti, the latter characterized by micro tonality and dissonant harmonies and can be subjectively described as unsettling.[56] Both pieces yielded opposite effects, suggesting that musical factors like tone, harmony or melody are all important in exerting effects. Effects of specific intervals, rhythm and melodies can also be seen in another study in which rats' spatial performance was negatively affected with reversed versions of the music, while original versions positively affected performance compared to controls.[17] In this study rhythm appeared to be a crucial element.[17] In other studies, rhythm also appeared to be important to achieve positive effects. Cultural music involving Gong tone or Buk instruments, both characterized by strong rhythmic patterns, induced positive effects on immunology.[49,52] These specific components of music triggering pathophysiological mechanisms warrant further investigation.

While low-frequency music altered or even abolished effects of music in rodents, higher frequency notes resulted in better responses.[20,53] Hearing abilities of rodents differ from those of humans, varying from 500 Hz to 64 kHz in rats and 2 kHz to 80 kHz in mice to 20 Hz to 20 kHz in humans,[79,80] which could explain improvement of results with higher frequency notes. No significant differences on neurologic outcomes were found between classical or rave music after methamphetamine injection,[34] however, music was played loudly and this might have been so stressful that it suppressed any effects. In addition, impaired immune function was seen after exposure to loud rock music,[51] again suggesting that music volume might affect any outcomes.

Limitations

The outcome of this systematic review faces several limitations. The sample sizes of the included studies were generally small. Additionally, we found a substantial unclear risk of bias (see Supplementary Material II) with the SYRCLE risk of bias tool.[23] Music interventions were heterogeneous and sometimes sparsely described. Furthermore, studies were performed in different populations and also with various types of control situations. Not every study considered the day-night cycle of rodents. When interpreting the results of this review, one should be aware of these limitations.

Conclusions

This systematic review finds music interventions to improve outcomes of brain structure and neuro-chemistry, behavior, immunology and physiology in rodents. These results support application of music as intervention in many healthcare areas. Future studies in both rodents and humans could look more into matters of musical complexity, rhythm and pitch as well as the frequency with which music interventions are offered.

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Supplementary material

Supplementary Material I. Data Sheet I search strategy.

Embase.com	1037	1016
Medline (ovidSP)	547	91
Web-of-science	807	473
Scopus	1007	220
Cochrane	19	1
PsycINFO (ovidSP)	962	646
Cinahl	88	43
Google scholar	200	127
Total	**4667**	**2617**

Embase.com
(music/de OR 'music therapy'/de OR (music OR musical OR musicotherap*):ab,ti) AND ([animals]/lim OR (animal* OR rat OR rats OR mouse OR mice OR murine):ab,ti)
Medline (ovidSP)
(music/ OR "music therapy"/ OR (music OR musical OR musicotherap*).ab,ti.) AND ((exp animals/ NOT humans/) OR (animal* OR rat OR rats OR mouse OR mice OR murine).ab,ti.)
PsycINFO (ovidSP)
(music/ OR "music therapy"/ OR (music OR musical OR musicotherap*).ab,ti.) AND ((exp animals/ NOT humans/) OR (animal* OR rat OR rats OR mouse OR mice OR murine).ab,ti.)
Cochrane
((music OR musical OR musicotherap*):ab,ti) AND ((animal* OR rat OR rats OR mouse OR mice OR murine):ab,ti)
Web-of-science
TS=(((music OR musical OR musicotherap*)) AND ((animal* OR rat OR rats OR mouse OR mice OR murine)))
Scopus
TITLE-ABS-KEY(((music OR musical OR musicotherap*)) AND ((animal* OR rat OR rats OR mouse OR mice OR murine))) AND doctype(ar)
Cinahl
(MH music OR MH "music therapy" OR (music OR musical OR musicotherap*)) AND ((MH animals+ NOT MH humans+) OR (animal* OR rat OR rats OR mouse OR mice OR murine))
Google scholar
Music|musical animal|animals|rat|rats|mouse|mice|murine

Supplementary Material II. SYRCLE Risk of Bias Table.

Author, year	Selection bias: Baseline Characteristics	Selection bias: sequence generation and allocation concealment	Performance bias: Random Housing	Performance bias: blinding of caregivers and/or investigators	Detection bias: outcome assessment	Attrition bias: incomplete outcome data	Reporting bias; selective outcome reporting	Other: other possible sources of bias.
Gao 2016	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Jiang 2016	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Lee 2016	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Xing 2016 (1)	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Xing 2016 (2)	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Xing 2016 (3)	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Cruz 2015	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Kim 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Kirste 2015	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Sheikhi 2015	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Escribano 2014	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
de Camargo2013	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Kim 2013	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Zhang 2013	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Marzban 2012	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Tasset 2012	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Uchiyama 2012	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Akiyama 2011	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
da Cruz 2015	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Amagdei 2010	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear
Li 2010	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear
Lu 2010	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Meng 2009	Low	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear
Nakamura 2009	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Xu 2009	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Erken 2008	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Feduccia 2008	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unlcear
Lemmer 2008	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Angelucci 2007 (1)	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Angelucci 2007 (2)	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Chikahisa 2007	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Author, year	Selection bias: Baseline Characteristics	Selection bias: sequence generation and allocation concealment	Performance bias: Random Housing	Performance bias: blinding of caregivers and/or investigators	Detection bias: outcome assessment	Attrition bias: incomplete outcome data	Reporting bias; selective outcome reporting	Other: other possible sources of bias.
Nakamura 2007	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Xu 2007	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Chikahisa 2006	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Kim 2006	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Kim 2004	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Sutoo 2004	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Morton 2001	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Nunez 2001	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Rauscher 1998	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear	Unclear
McCarthy 1992	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bueno 1998	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Supplementary Material III: Data Sheet 2 explanatory box behavioral tests.

T-Maze: Measures natural tendency of animal to enter an alternate arm if they know they previously visited the other arm (spatial memory). Animal is centrally placed in T-maze with one open arm which can be explored, the other arm is closed. Subsequently the animal is replaced in the start area, but now both arms are open. During training days, animals are given 5 or 10 trials. During test day, number of alterations and response latency are recorded.

Cross-Maze: A cross-maze consists of a center platform that extends four arms in a cross-formation and an arm leading to a start box (closed after starting). Each arm is equipped with two water nozzles (real and dummy) with four different marks. During learning tests, only one arm provided water, and when a rodent drank a water from the drinkable nozzle, the drinkable nozzle moved to the next arm in clockwise order. In testing days, trial ended when rodents drank water for two rounds (two times per arm) or after 10 minutes. Total running time in the maze and total number of errors (entering an arm without drinkable nozzle) were recorded.

Morris Water Maze: Pool with opaque water and a hidden platform below surface in a target quadrant. During training days, rats learned to find and climb the platform (spatial memory). During test day, the platform was removed and rats explored the pool for 60s. Total time spent in target quadrant was measured.

Elevated Plus Maze: Rodents are placed in center of an apparatus consisting of two opposing open arms and enclosed arms. Behavior is monitored for 5 minutes. Number of entries and time spent in open arms is recorded (anxiety).

Radial Arm Maze: Apparatus consists of a central octagonal plate and eight radiating arms. End of the arms contained small water basin. Rodents were allowed to explore for water and drink for 5 minutes. At test day, time spent for seeking and drinking water at the end of arms was counted, and test ended after rodent found water in all eight arms or when 5 minutes passed. Re-entering in a previously visited arm was an error, number of correct choices before error was also counted (spatial memory).

Marble Burying: Animal is placed in a cage with 5cm deep wood chip bedding with equally divided marbles on it. Number of marbles buried in a period of time is measured (stress behavior).

Light Dark Transition: Chamber with equally divided light compartment and dark compartment (separated by wall with opening). Rodent placed in dark compartment, and latency to go out into the light side for the first time was recorded as well as amount of time spent in each compartment for period of time (anxiety).

Open Field: Registration of locomotor behavior of rodents in an open top box for certain time period. The total distance and time spent in the central and peripheral area are recorded, as well as time spent immobile (anxiety).

Passive Avoidance task: On training day, rodent is placed in a light compartment, allowing to explore for time period. After certain time, a door is raised and rodent is allowed to explore the dark compartment. When dark compartment is entered with four paws (latency-time), door is closed and rodents receive a foot-shock. Retest session was a single trial without foot-shock, total time until animal entered other compartment was measured.

Conditioned Place Preference: Apparatus consists of two compartments (black and white) separated by removable wall. After 5 minutes habituation, duration of time spent in each compartment was registered over time period.

Step Down Avoidance Task: Evaluation of short memory. Rodents rest on a platform for 2 minutes. When stepping down the platform, a foot-shock is given for 2 seconds. 2 days after training session latency in step-down-avoidance-task was determined as time interval between the moment when rats first stepped down and when they placed all four paws on the ground.

Auditory Signal Detection Task: rodents are required to respond to sound stimuli by licking the water spout. Number of correct licks, missed licks and false licks is recorded. Each correct lick was rewarded with water. Correct licking rate is calculated.

Sound Duration Discrimination Task: Subsequently presentation of two sounds of different duration. Licking the spout during presentation of one of two sounds was rewarded with water, while licking in response to the other sound was not rewarded.

2

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Chapter 3

Meta-analysis evaluating music interventions for anxiety and pain in surgery

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Abstract

Background: This study aimed to evaluate anxiety and pain following perioperative music interventions compared with control conditions in adult patients.

Methods: Eleven electronically databases were searched for full-text publications of RCTs investigating the effect of music interventions on anxiety and pain during invasive surgery published between 1 January 1980 and 20 October 2016. Results and data were double-screened and extracted independently. Random-effects meta-analysis was used to calculate effect sizes as standardized mean differences (MDs). Heterogeneity was investigated in subgroup analyses and metaregression analyses. The review was registered in the PROSPERO database as CRD42016024921.

Results: Ninety-two RCTs (7385 patients) were included in the systematic review, of which 81 were included in the meta-analysis. Music interventions significantly decreased anxiety (MD –0.69, 95 per cent c.i. –0.88 to –0.50; $P < 0.001$) and pain (MD –0.50, –0.66 to –0.34; $P < 0.001$) compared with controls, equivalent to a decrease of 21 mm for anxiety and 10 mm for pain on a 100-mm visual analogue scale. Changes in outcome corrected for baseline were even larger: MD –1.41 (–1.89 to –0.94; $P < 0.001$) for anxiety and –0.54 (–0.93 to –0.15; $P = 0.006$) for pain. Music interventions provided during general anaesthesia significantly decreased pain compared with that in controls (MD –0.41, –0.64 to –0.18; $P < 0.001$). Metaregression analysis found no significant association between the effect of music interventions and age, sex, choice and timing of music, and type of anaesthesia. Risk of bias in the studies was moderate to high.

Conclusion: Music interventions significantly reduce anxiety and pain in adult surgical patients.

Introduction

Worldwide, an estimated 266–360 million surgical procedures are undertaken annually according to the WHO[1]. Surgical patients often suffer from preoperative anxiety and postoperative pain; recent data suggest that 75 per cent of patients facing surgery are anxious, despite anxiety-decreasing measures[2,3]. Preoperative anxiety can increase the level of postoperative pain[4] and, despite interventions to reduce postoperative pain, approximately 40–65 per cent of patients experience moderate to severe pain after surgery[5,6].

As the use of analgesics has inherent side-effects[6], music interventions have been suggested as a way to reduce perioperative anxiety[7,8] and postoperative pain[6,9]. Despite a large number of studies, perioperative music interventions are still not used widely. Two recently published meta-analyses[9,10] on the effect of music interventions in different hospital procedures, and of different forms of perioperative art therapy, reported small to moderate beneficial effects on anxiety and pain in surgical, but also in non-surgical, patients. Research on music interventions in healthcare often identifies heterogeneity in study populations and lack of negative studies possibly owing to publication bias. These factors may be the reason why perioperative music interventions are not often applied in clinical practice.

The purpose of the present study therefore was to perform a systematic review and meta-analysis of all RCTs evaluating the effects of music interventions on patients' anxiety and pain before, during and after exclusively invasive surgical procedures.

Methods

This systematic review and meta-analysis was conducted according to the PRISMA statement[11]. The review was registered in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO/) as record number CRD42016024921.

Search strategy

A dedicated biomedical information specialist helped define the search strategy. The electronic databases Embase, MEDLINE, OvidSP, Web of Science, Scopus, PsycINFO, OvidSP, CINAHL, Cochrane Central Register of Controlled Trials, PubMed publisher and Google Scholar were searched for publications on the effect of music interventions before, during and after surgery published between 1 January 1980 and 20 October 2016 (*Appendix S1*, supporting information).

3

Study selection

Titles and abstracts of articles identified by the search, and full texts of those deemed potentially eligible, were double-screened for relevance by four investigators independently. Inclusion criteria for the systematic review were: full-text article of an RCT; investigating effects of music interventions on anxiety and/or pain; mean age of participants at least 18 years; written in English; invasive surgical procedures, either open or laparoscopic, such as abdominal surgery or total knee surgery; use of general anaesthesia, regional anaesthesia or both; use of any recorded or live music intervention having melody, harmony and rhythm; intervention offered by a researcher or a music therapist; and intervention performed in a hospital or outpatient clinic. Studies involving non-invasive procedures such as endoscopy were excluded, as were those using quasi- or pseudo-randomization. Nature sounds were considered only when they were used in addition to music. If populations overlapped between studies, only the most recent or most complete study was included. Studies were included in the meta-analysis only if they included measures of dispersion of a particular outcome. A fifth investigator was consulted in the event of disagreement about inclusion of an article.

Data extraction

Data were extracted and checked by three authors independently. The following study characteristics were recorded: author, year of publication, journal, number of patients, sex ratio, mean age, inclusion period, mean follow-up, ethical approval, outcome scale used, type of surgery, type of anaesthesia, timing of the music intervention (before, during or after surgery), recorded *versus* live music intervention and description of intervention, and type of control group. Primary outcomes were mean anxiety scores and mean pain scores (including measures of dispersion) in the intervention and control groups measured at baseline and at the end of the study or within 7 days after operation. When available, outcome data on change from baseline, including measures of dispersion for both intervention and control groups, were also extracted. If a study used multiple time points, only the first and final time points were considered (at most 7 days after surgery).

Statistical analysis

Data were analysed using Review Manager version 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark). Outcome measures were pooled using the inverse-variance method in a random-effects model. Standardized mean differences (MDs) were calculated with Hedges' adjusted *g* using pooled weighted standard deviations. Effect sizes were summarized with 95 per cent confidence intervals. In five studies only an i.q.r. or range was provided; the i.q.r. was divided by 1.35[12] and the range by 4 to produce approximations of the standard deviation. Data were summarized and presented visually in forest plots. Funnel plots were constructed to investigate publication bias. Heterogeneity among included studies was analysed with both the Cochran Q statistic and the I^2 index. Risk of bias among studies was assessed by three reviewers using the Cochrane Collaboration risk-of-bias assessment tool[13]. Two-sided statistical significance was inferred at $P < 0.050$.

A metaregression analysis was conducted in Stata® release 14 (StataCorp, College Station, Texas, USA) to investigate possible associations between study characteristics and the effect of music. The following subgroups were chosen *a priori* for subgroup analyses: timing of intervention (before, during or after surgery); type of anaesthesia (general or regional); type of music intervention (chosen by investigator, chosen by patient from a list provided, or patient's own music). During data collection, other variables that could potentially influence the intervention effect were added: single (only 1 intervention during the course of the study) or multiple (several music interventions during the course of the study) music interventions; sex; and age. Multivariable metaregression analyses were carried out first with all variables, and subsequently based on the results of the subgroup analyses and univariable metaregression analyses, including only variables that were either statistically significant or had a β-coefficient larger than the corresponding standard error.

Back transformations were calculated in Microsoft Excel® (Microsoft Corporation, Redmond, Washington, USA) by multiplying the MD of both State–Trait Anxiety Inventory (STAI)[14] and visual analogue scale (VAS) scores for anxiety and VAS scores for pain with the typical among-person standard deviation, which was derived from pooling baseline standard deviations of control arms from studies that reported these.

Results

The literature search resulted in the inclusion of 92 RCTs[8,15–105] in the systematic review (7385 patients). Eighty-one of these were included in the meta-analysis (*Fig. 1*). Details of study characteristics are presented in *Table S1* (supporting information).

The studies investigated music interventions in many types of surgery and in different patient populations, with a mean(s.d.) age of 51.7(10.4) years and predominance of women (57 per cent). Most studies evaluating anxiety outcomes used the STAI (55 per cent) and/or a VAS (43 per cent); the studies evaluating pain outcomes used a VAS (79 per cent) and/or a numerical rating scale (21 per cent). In the majority of studies (67 per cent on anxiety, 64 per cent on pain) the effects of single interventions were investigated. Music interventions were offered before operation (anxiety: 17, 26 per cent; pain: 3, 5 per cent), during surgery (anxiety: 13, 20 per cent; pain: 13, 22 per cent), after operation (anxiety: 13, 20 per cent; pain: 21, 36 per cent), at multiple times (anxiety: 22, 33 per cent; pain: 21, 36 per cent) or not specified (anxiety: 1, 2 per cent). Four studies (4 per cent) investigated anxiety and/or pain-reducing effects of live music therapy provided by a music therapist, whereas all other studies used recorded music interventions. Control arms of studies provided standard medical care without (28, 30 per cent) or with (11, 12 per cent) a resting period, reported no music (13, 14 per cent), reported no intervention (17, 18 per cent), used a device with sham sounds (8, 9 per cent), provided headphones without music (6, 7 per cent) or with noise-blocking features (2, 2 per cent), used midazolam (1, 1 per cent) or had an unclear description (5, 5 per cent). Eleven RCTs[15–25] (12 per cent) did not report on quantitative data and could not therefore be included in the quantitative analyses (*Table S1*, supporting information).

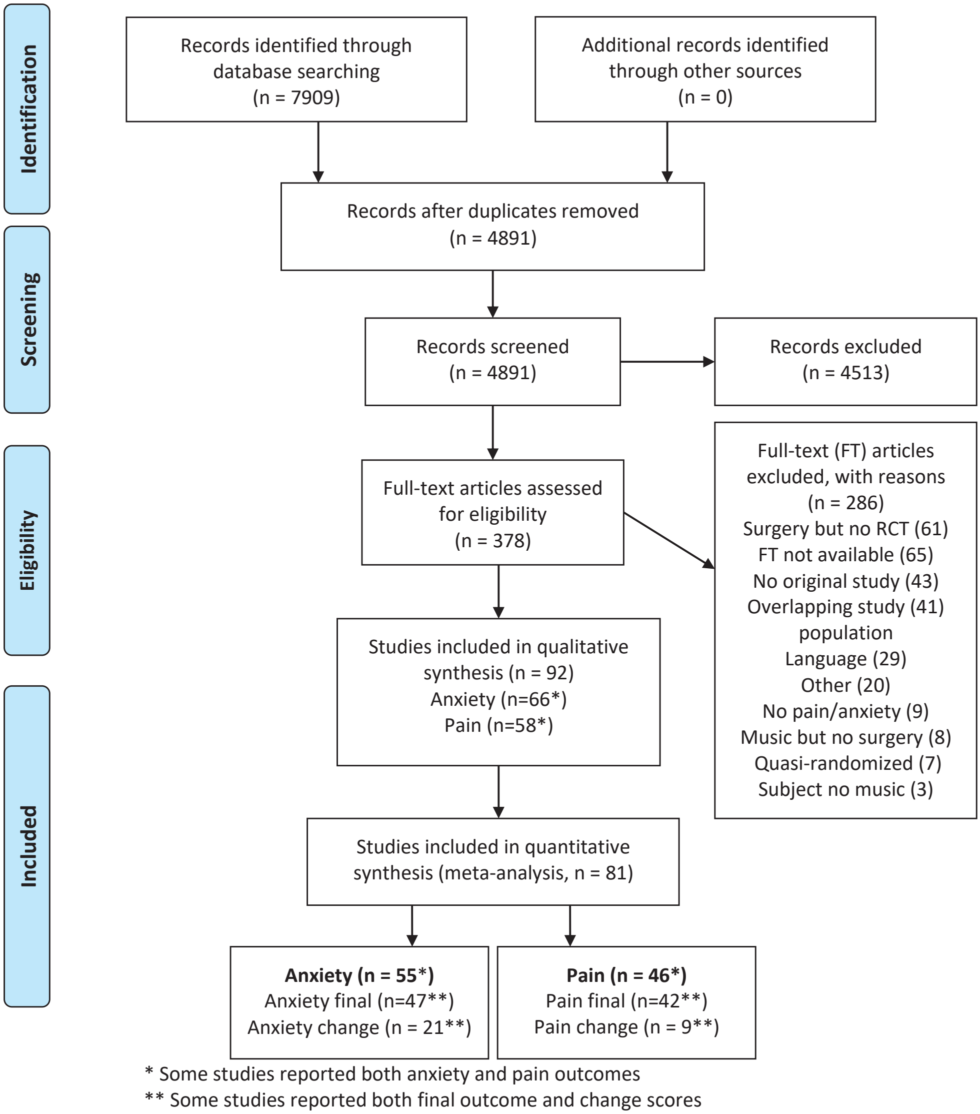

Figure 1. Flow chart showing selection of studies for review.

Risk-of-bias assessment

The included studies had a moderate to high risk of bias (*Fig. S1*, supporting information). As blinding of patients to music interventions during surgery is only feasible under general anaesthesia, the assessment was limited to blinding of personnel involved in patient care. All included studies reported the use of randomization, but studies that did not report specific methods of sequence generation or allocation concealment were assessed as having an unclear risk of selection bias. Few studies reported on attrition bias (43, 47 per cent), blinding of data collectors (33, 36 per cent), reporting bias (16, 17 per cent) and other bias (4, 4 per cent); in most studies, therefore, a majority of bias regarding these variables was unclear. Inspection of funnel plots for the presence of publication bias revealed a tendency towards asymmetry in the funnel plot for anxiety, but not in that for pain (*Figs S2* and *S3*, supporting information).

Effect of music interventions on anxiety and pain

Pooling data on the different outcome measures of anxiety from the intervention and control groups resulted in a moderate to large statistically significant MD of –0.69 (95 per cent c.i. –0.88 to –0.50; $P < 0.001$) (*Table 1* and *Fig. 2*; *Fig. S4*, supporting information). Pooling of the data on mean change in anxiety scores between postoperative outcomes and preoperative baseline measurements from the 21 studies that reported this revealed a large effect of music interventions in reducing anxiety, with a MD of –1.41 (–1.89 to –0.94; $P < 0.001$).

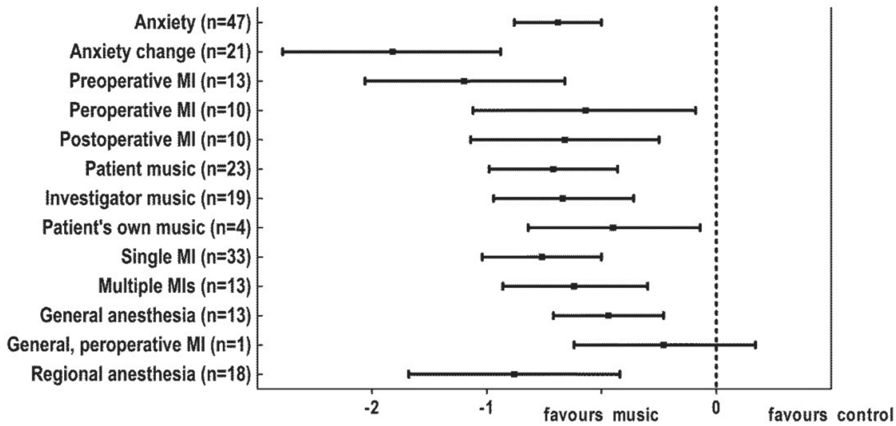

Figure 2. Summary forest plot for anxiety. Mean differences between music intervention and control groups are shown with 95 per cent confidence intervals. The number of studies in each subgroup analysis is indicated.

Pooling of the different outcome measures of pain resulted in a statistically significant MD of –0.50 (–0.66 to –0.34; $P < 0.001$), indicating a moderate effect of music interventions in reducing pain. Pooling of the data on mean change between postoperative outcomes and preoperative baseline measurements in pain scores (9 studies) yielded a MD of −0.54 (−0.93 to −0.15; $P = 0.006$) (*Table 1* and *Fig. 3*; *Fig. S4*, supporting information).

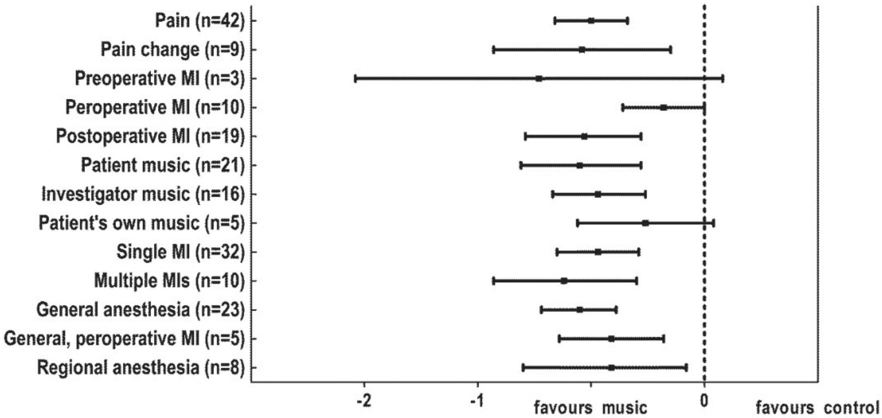

Figure 3. Summary forest plot for pain. Mean differences between music intervention and control groups are shown with 95 per cent confidence intervals. The number of studies in each subgroup analysis is indicated.

To facilitate clinical interpretation, effect sizes from the main analyses were back-transformed, demonstrating that music interventions led to a mean 6.3-point decrease on the 20–80-scale of the STAI and a mean 21-mm decrease on a 100-mm VAS for anxiety, and to a mean 10-mm decrease on a 100-mm VAS for pain.

Subgroup analyses

Subgroup meta-analyses showed that music interventions before, during and after surgery all led to a reduction in anxiety, with the largest effect seen when offered before surgery (*Table 1* and *Fig. 2*). Postoperative interventions had the largest effect in decreasing pain (*Table 1* and *Fig. 3*). Pooled analysis of the five studies[75,81,84,88,105] that investigated the effects of music interventions solely during general anaesthesia showed a statistically significant decrease in pain. Only one study[81] investigated the effect of music interventions during general anaesthesia on anxiety, and demonstrated no significant difference between the music and control groups. Fourteen studies[28,33,37,47,51,53,55,58,61,66,77,80,93,96] investigating music interventions during regional anaesthesia showed a large statistically significant anxiety-reducing effect. A moderate statistically significant pain-reducing effect was found for the eight[47,51,58,60,61,66,77,96] studies that investigated music interventions during regional anaesthesia. Pain reduction was enhanced by offering multiple interventions rather than a single music intervention[29,32,34,35,38,46,52,76,77,101]. An opposite trend was seen for anxiety, where a single intervention had a larger effect[8,27, 28,30,36,37,39,40,42,45,47,49,51,55,58,61,63,66,67,70,72–74,78,80,81,86,87,94–97,100,102]. The largest beneficial effect on both anxiety and pain was seen when patients selected music from a list provided. The smallest benefit was found when patients had freely chosen the music themselves[39,58,60,89,92,93,95].

Studies that had at least three items with low risk of bias were also analysed separately, resulting in a smaller but statistically significant MD of –0.61 (95 per cent c.i. –0.94 to –0.29; P <0.001) for anxiety and of –0.34 (–0.55 to –0.13; P = 0.002) for pain (*Figs S5* and *S6*, supporting information).

Metaregression

Overall, heterogeneity was high among studies (*Table 1*). Results of univariable and multivariable metaregression analysis are shown in *Tables S2* and *S3* (supporting information) respectively. These results were consistent with those of the subgroup meta-analyses. A statistically significant association between preoperative music interventions and pain was found in the data-driven multivariable regression analysis of this outcome. None of the other explanatory variables were significant, and no evidence was found for an association between any of the other variables and anxiety or pain.

Table 1. Results of meta-analyses for the outcome anxiety (55 studies) and pain (46). Values in parentheses are 95 per cent confidence intervals. *Some studies reported on the primary outcome and change in score. †Studies included in analysis used either preoperative, perioperative or postoperative interventions, not multiple. ‡Studies included in analysis used either general or regional anaesthesia, not both.

	No. of studies	Mean difference*	P	I^2 (%)
Anxiety				
Final anxiety score	47	–0.69 (–0.88, –0.50)	< 0.001	87
Change in anxiety score*	21	–1.41 (–1.89, –0.94)	< 0.001	95
Subgroup analyses				
Selection of music				
Chosen by patient from list provided	23	–0.71 (–0.99, –0.43)	< 0.001	88
Chosen by investigator	19	–0.67 (–0.97, –0.36)	< 0.001	87
Patient's own	4	–0.45 (–0.82, –0.07)	0.020	75
Timing†				
Preoperative	13	–1.10 (–1.53, –0.66)	< 0.001	89
Perioperative	10	–0.57 (–1.06, –0.09)	0.020	92
Postoperative	10	–0.66 (–1.07, –0.25)	0.002	87
No. of interventions				
Single	33	–0.76 (–1.02, –0.50)	< 0.001	91
Multiple	13	–0.51 (–0.64, –0.38)	< 0.001	0
Type of anaesthesia‡				
General	13	–0.47 (–0.71, –0.23)	< 0.001	69
General, only perioperative music	1	–0.23 (–0.62, 0.17)	–	
Regional	14	–0.88 (–1.34, –0.42)	< 0.001	92

	No. of studies	Mean difference*	*P*	I^2 (%)
Pain				
Final pain score	42	−0.50 (−0.66, −0.34)	< 0.001	78
Change in pain score*	9	−0.54 (−0.93, −0.15)	0.006	84
Subgroup analyses				
Selection of music				
Chosen by patient from list provided	21	−0.55 (−0.81, −0.28)	< 0.001	84
Chosen by investigator	16	−0.47 (−0.67, −0.26)	< 0.001	65
Patient's own	5	−0.26 (−0.56, 0.04)	0.090	61
Timing†				
Preoperative	3	−0.73 (−1.54, 0.08)	0.080	84
Perioperative	10	−0.18 (−0.36, 0.00)	0.050	44
Postoperative	19	−0.53 (−0.79, −0.28)	< 0.001	82
No. of interventions				
Single	32	−0.47 (−0.65, −0.29)	< 0.001	80
Multiple	10	−0.62 (−0.93, −0.30)	< 0.001	72
Type of anaesthesia‡				
General	23	−0.55 (−0.72, −0.39)	< 0.001	55
General, only perioperative music	5	−0.41 (−0.64, −0.18)	< 0.001	9
Regional	8	−0.41 (−0.80, −0.03)	0.040	84

Discussion

This meta-analysis found a statistically significant decrease in both anxiety and pain in adults receiving music interventions before, during or after surgery. The effect on anxiety seemed largest when the music intervention was offered before operation; however, music interventions offered during and after surgery also significantly reduced anxiety. Postoperative music interventions were most likely to reduce pain; a significant pain-reducing effect of preoperative music was also seen in the data-driven multivariable regression analysis. As preoperative anxiety is associated with postoperative pain[4], pain reduction noted after preoperative music interventions might be the result of decreased anxiety. In the present meta-analysis, the mean changes in anxiety and pain from baseline values showed even larger anxiety- and pain-reducing effects of music than did the direct comparison of postintervention outcomes. Previous meta-analyses that investigated music interventions also included other interventions[10], or other procedures that did not involve surgery[9]. Moreover, they included fewer RCTs. The results presented here underline and reinforce the findings of other studies[7,9,10,106]. The more specific inclusion criteria in the present meta-analysis, which investigated music interventions alone in exclusively surgical populations, emphasize the effect of the intervention, and make it more applicable in practice. The analysis of mean changes in scores between intervention and control situations, with outcome scores corrected for baseline values, reveals the true effect of the intervention more than previous studies have shown, and should encourage its implementation in surgery.

An important finding is that many different music interventions each have positive effects. Although most of the music interventions used in the studies were bound by restrictions, such as slow, soft, relaxing music (*Table S1*, supporting information), the effect does not seem to be related to one specific type of music. Moreover, it has been suggested that individual music preference is important to the effect of a music intervention[54]. Effect sizes in the present study were slightly higher when patients chose music from a list provided. The small number of studies that investigated freely chosen music compared with music selected by the investigator and preselected music makes it hard to draw definite conclusions about the importance of individual preferences. Besides individual music preference, specific features of the music intervention such as rhythm and harmony, and the use of specific instruments like string instruments, also seem important features in anxiety and pain reduction[107]. A placebo effect cannot be ruled out as the studies relied on self-reporting. It could be argued that a placebo effect is effective anyway[108], in this instance reducing anxiety and pain. However, the subgroup analysis of perioperative music interventions during general anaesthesia did show a statistically significant pain-reducing effect. Factors such as distraction strategies and interference from personnel and observers do not play a role when patients are under general anaesthesia[75,81,84], nor do the psychological effects of listening to music. These considerations militate against a mere placebo effect.

Overall, risk of bias in the included studies was moderate to high. Many studies did not adequately address methodological considerations (randomization techniques and power) and risk of bias, and were therefore scored as having an unclear risk. In randomized trials of non-pharmacological treatments, it may be difficult to blind the relevant parties and to exclude the influence of the provider's expertise[109]. Although the nature of music interventions makes it hard to perform double-blinded studies, suitable randomization and reporting following the CONSORT checklist for non-pharmacological trials[110] could help minimize the risk of bias in future trials. No clear association was found for any explanatory variable in either subgroup analyses or univariable meta-regression analyses. A statistically significant association was found between preoperative music interventions and pain in the data-driven multivariable regression analysis. However, the absence of this effect in the subgroup meta-analysis, the small number studies investigating the effect of preoperative music interventions on pain, and the possible issue of multiple testing make the reproducibility of this result questionable.

This study has strengths and limitations. A dedicated biomedical information specialist was consulted to identify all publications on this subject in the scientific literature. Bias was limited by excluding studies that generated randomization sequences inadequately. The present review is, however, limited by the overall high level of heterogeneity. Even though the search was limited to surgical patients, there is a wide variety of surgical procedures in the study population, with diverse methods of anaesthesia. These issues in part explain the large degree of heterogeneity. Moreover, the diverse control conditions also create variety in study populations. Publications might have been missed as a result of the language restriction (*Fig. 1*). The funnel plot for anxiety raises the possibility of publication bias. Previous publications of mainly favourable results might affect the conclusion of this review.

This review provides evidence for the implementation of music interventions before, during and after surgery. Preoperative anxiety and postoperative pain are clinically relevant issues that may determine morbidity, duration of hospital stay and even mortality[2]. Alleviating these factors may improve clinical outcomes and quality of life, may also lead to earlier discharge from hospital, and thus may help to reduce healthcare costs[111]. Pain relief after surgery continues to be an important medical challenge[112] and it has been shown that a minimum 12 (95 per cent c.i. 9 to 15)-mm reduction in VAS pain score signifies clinical relevance[113]. Based on this, at least some of the patients in the music intervention groups included in this meta-analysis experienced a clinically relevant reduction in pain. Defining minimally important differences to determine clinically relevant effects is challenging[114]. No clear minimally important differences for anxiety have been defined; however, minimally important differences for depression have previously been inferred at a MD of 0.50, and an MD of 0.24 has also been reported[114]. The pooled MD of –0.69 for anxiety reported in the present analysis therefore appears clinically relevant.

Some of the included studies have also investigated other parameters to evaluate the efficacy of music interventions. Music has, for instance, been shown to reduce the use of analgesics after surgery[24,35,39,60,76,82], and was more effective in reducing preoperative anxiety than orally administered midazolam[8]. More foot movement and a reduction in the rate of delirium was found following music interventions after hip and knee surgery in elderly patients[69]. Furthermore, duration of hospital stay after mastectomy was shorter for patients receiving music interventions compared with controls[102].

Acknowledgements

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Appendices

Appendix S1. Literature search.

Embase

(music/de OR 'music therapy'/de OR (music OR musical OR musicotherap*):ab,ti) AND (surgery/exp OR 'obstetric operation'/exp OR 'postoperative complication'/exp OR 'anesthesiological procedure'/exp OR 'perioperative nursing'/de OR 'postanesthesia nursing'/de OR 'operating room'/de OR 'recovery room'/de OR 'operating room personnel'/de OR (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*):ab,ti OR surgery:lnk)

Medline OvidSP

(music/ OR "music therapy"/ OR (music OR musical OR musicotherap*).ab,ti.) AND (exp "Surgical Procedures, Operative"/ OR exp "postoperative complications"/ OR "Anesthesiology"/ OR "perioperative nursing"/ OR "Operating Rooms"/ OR "recovery room"/ OR (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*).ab,ti. OR surgery.xs.)

Cochrane central

((music OR musical OR musicotherap*):ab,ti) AND ((surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*):ab,ti)

Web-of-science

TS=(((music OR musical OR musicotherap*)) NEAR/10 ((surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operation* OR operative* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*)))

Scopus

TITLE-ABS-KEY((music OR musical OR musicotherap*) W/10 (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operation* OR operative* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*))

PsycINFO OvidSP

(music/ OR "music therapy"/ OR (music OR musical OR musicotherap*).ab,ti.) AND (exp "Surgery"/ OR "Surgical Patients"/ OR exp "Postsurgical Complications"/OR exp "Surgical Complications"/ OR "Anesthesiology"/ OR (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*).ab,ti.)

Cinahl

(MH music+ OR MH "music therapy+" OR (music OR musical OR musicotherap*)) AND (MH "Surgery, Operative+" OR MH "postoperative complications+" OR MH "Anesthesiology+" OR MH "perioperative nursing+" OR MH "Operating Rooms+" OR MH "Post Anesthesia Care Units+" OR (surger* OR surgic* OR peroperat* OR perioperat* OR preoperat* OR postoperat* OR operati* OR interoperat* OR intraoperat* OR anesthe* OR anaesthe* OR perianesthe* OR peranesthe* OR perianaesthe* OR peranaesthe* OR preanasthe* OR preanaesthe* OR postanasthe* OR postanaesthe*))

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music surgery|operative|operation|perioperative|preoperative|postoperative|intraoperative|"operating theater"|"recovery Room"|anesthesia|anesthesiological|anaesthesia|preanesthetic|postanesthetic

Table S1. Study characteristics.
[a.] Study included in systematic review, not in meta-analysis. Abbreviations: n=number, I/C=intervention/control, R/L=recorded/live (intervention), (GA)-VAS=(global anxiety)- visual analogue scale, VRS=verbal rating scale, NRS=numeric rating scale, (C)- STAI=(Chinese)- state trait anxiety inventory, SAI=state anxiety inventory, DOS=Descriptive Ordinal Scale, HADS= Hospital Anxiety and Depression Scale, CABG=coronary artery bypass graft, CS=caesarian section, TKA=total knee arthroplasty, Tx=transplantation, AAMT= American Association of Music Therapy.

	Year	n patients (I/C)	n Male (%)	Mean age (SD) or range	Days follow-up	Pain scale	Anxiety scale	Surgery
Alam	2016	105 (54/51)	62 (59.5)	63,3 (.)	1	VAS	STAI short version	cutaneous carcinoma face surgery
Cigerci	2016	68 (34/34)	52 (76)	61,6 (10,7)	7	VAS	STAI	CABG
Finlay[a]	2016	98 (72/17)	40 (41)	68,1 (8,0)	4	VAS	.	TKA
Kipnis	2016	159 (82/77)	72 (45)	51,5 (14,0)	1	.	STAI	elective
Kongsawatvorakul	2016	73 (36/37)	0 (0)	42,9 (10.8)	1	VAS	STAI	large loop excision
McClurkin	2016	86 (41/45)	34 (40)	54,0 (.)	1	.	STAI	ambulatory
Tellez	2016	50 (25/25)	0 (0)	51,0 (9,1)	1	VAS	VAS	breast biopsy
Wiwatwongwana	2016	91 (44/47)	42 (46)	68,0 (9,0)	1	.	STAI	cataract
Chen	2015	30 (15/15)	10 (33)	68,0 (9,0)	1	VAS	.	TKA
Hansen	2015	49 (25/24)	9 (18.5)	48,5 (14,6)	11	NRS	STAI	abdominal and urinary track surgery, gynecologic surgery
Heidari	2015	60 (30/30)	33 (55)	58,6 (11,6)	1	.	VAS	CABG
Hudson	2015	160 (84/76)	36 (22.5)	54,4 (12,6)	1	NRS	STAI	varicose veins
Liu	2015	98 (47/51)	65 (66)	53,2 (15,8)	3	VAS	STAI	thoracic
Palmer	2015	127 (65/62)	0 (0)	59,0 (16,0)	1	.	GA-VAS	ambulatory breast
Wang[a]	2015	60 (30/30)	39 (65)	53,8 (11,2)	2	VAS	Zung SAS	lung cancer
Yates	2015	22 (11/11)	.	57,5 (12,0)	1	.	VRS	oncologic
Zhou	2015	170 (85/85)	85 (50)	47.0 (9,5)	discharge	.	SAI	radical mastectomy
Bae	2014	80 (40/40)	42 (52.5)	39,2 (1,8)	1	.	STAI, VAS	orthopedic

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Anesthesia	Timing	Music	N; minutes	R/L	Control
regional	per	standard soothing and nature sounds	1; 30	R	head phone no music
.	pre post	Turkish classical or Turkish folk	pre: 90, post: daily 30	R	standard procedure
regional	post	standard non lyrical classical, jazz, popular, folk, ethnic	daily (3 days); 15	R	noise-cancelling headphones
general	pre	standard new age or classical	1 ; 30	R	no music
regional	per	standard slow-rhythm classical	1 ; .	R	standard care
.	pre	non-lyrical, instrument jazz, classic, religious, nature sounds	1 ; 30	R	standard care
.	pre	standard new age music	1; 17	R	standard care in waiting room
regional	pre per	standard relaxing musical melodies, tones, rhythms and nature sounds	1 ; 40 (10 pre)	R	earphones no music
general	pre post	standard soothing piano and Chinese violin via broadcast	1; 120	R	nothing
.	pre post	standard non-lyrical pieces; native American flute, Bollywood Buddha Indian, shakuhachi bamboo flute	multiple ; .	R	no complementary therapy
.	.	standard light music with nature sounds	1 ; 30	R	30 min bed rest
regional	per	selection classical, easy listening, pop or online library	1 ; .	R	treatment as usual
general	post	standard soft, 60-80 BPM	3 ; 30	R	nothing
general	pre per	selection of R or L played music by therapist	1; 5	R	noise blocking earmuffs
general	pre post	standard relaxing personal non-lyrical new age and imagination music	5 ; 15-60	R with MT	no intervention
.	.	live music therapy	1; .	L	.
general	post	Chinese relaxation, classical folk, religious songs recommended by AAMT	2 ; 30	L	routine care
regional	per	selection CD classical, pop, religious, Korean pop, relaxation	1 ; 80	R	no treatment

	Year	n patients (I/C)	n Male (%)	Mean age (SD) or range	Days follow-up	Pain scale	Anxiety scale	Surgery
Ilkkaya	2014	50 (25/25)	42 (84)	32,2 (10,7)	1	.	VAS, STAI	surgical, urological, orthopedic
Mirbagher Ajorpaz	2014	60 (30/30)	29 (48)	.	1	VAS	.	open heart
Wang	2014	40 (20/20)	21 (53)	68,8 (3,0)	.	VAS	Zung SAS	gynecologic or lower limb
Graversen	2013	75 (40/35)	20 (26.5)	47,2 (6,3)	8	VAS	.	laparoscopic cholecystectomy
Jimenez-Jimenez	2013	40 (20/20)	12 (30)	43,9 (9,0)	1	.	STAI, VAS	elective varicose vein
Vachiramon	2013	100 (50/50)	67 (67)	64,0 (13,8)	.	.	STAI, VAS	Moh's
Zengin	2013	100 (50/50)	52 (52)	50,0 (15,0)	1	VAS	STAI	catheter placement
Guerrero	2012	101 (54/47)	0 (0)	25.1 (6,8)	1	VAS	STAI	first trimester surgical abortion
Jafari	2012	60 (30/30)	26 (43.4)	57,8 (10,7)	1	NRS	.	CABG/ valve repair
Johnson	2012	84 (43/41)	0 (0)	38,8 (2,2)	1	.	Rapid Assessment Anxiety Tool 0-10	gynecologic
Li	2012	60 (30/30)	0 (0)	.	1	VAS	.	CS
Ni	2012	172 (86/86)	60 (35)	40,9 (11,8)	1	.	STAI	neuro-surgery, gynecologic, general, urologic, plastic, cardio-vascular
Ottaviani	2012	62 (31/31)	45 (72)	68.8 (12.6)	1	VAS	VAS	knee joint lavage
Vaajoki	2012	167 (83/84)	84 (50)	63,0 (12,0)	3	VAS	.	major abdominal
Wu[a]	2012	26 (13/13)	0 (0)	25,1 (.)	1	.	VRS	surgical abortion
Binns- Turner	2011	30 (15/15)	0 (0)	56,6 (7,0)	1	VAS	SAI	mastectomy breast cancer
Cutshall	2011	100 (49/51)	77 (77)	62,8 (12,9)	3	VAS	VAS	CABG/ valve-repair
Ghetti	2011	18 (9/9)	11 (59)	50,1 (10.3)	1	NRS	.	organ Tx

Anesthesia	Timing	Music	N; minutes	R/L	Control
regional, sedation	pre per post	musical pieces (folk music)	.	R	ambient noise
general	post	sedative non-lyrical, 60-80BPM music, no strong rhythm/ percussion	1; 30	R	no disturbance
regional	pre	soft music	1; 30	R	relax no music
general	pre per post	standard music pillow with soft music (designed to reduce stress)	1 ; 57	R	pillow without music
regional	per	Henry Gorecki Symphony3	1 ; .	R	standard care
regional	pre per	self-chosen genre, song, artist radio	1 ; 15-60	R	standard care no music
regional	per	standard slow instrument Turkish classical	1 ; .	R	unclear
regional	per	Spanish (44%), hip-hop (23%), pop(11%), rock rap classical jazz easy listening reggae (22%)	1 ; .	R	routine pain control without headphone
general	post	cultural relaxation music pieces	1; 30	R	.
.	pre per post	soft country classical/ new age, inspiration	1; 112	R	routine care
regional	pre	Chinese classical	1 ; 30	R	nothing
general	pre	soothing Chinese / Taiwanese pop	1; 20	R	nothing
regional	pre per	lyric music	1; 15-30	R	.
general	post	self-chosen pop/ classical Finland music	3 ; 30	R	no intervention
regional	per	different genres	1 ; .	R	nothing
general	pre per post	classical, easy listening, inspiration, new age	1 ; > 90	R	standard care
general	post	summer, autumn, bird, night song	6 ; 20	R	20 rest
.	post	active engagemen selection preferred genre (spiritual/ religious, 1930-1940, musical, country, popular, rock, R&B)	1 ; 30-40	L	standard care

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	Year	n patients (I/C)	n Male (%)	Mean age (SD) or range	Days follow-up	Pain scale	Anxiety scale	Surgery
Kim	2011	219 (106/113)	122 (55.7)	.	1	VAS 0-5	Carah's Dental Anxiety Scale	surgical third molar extraction
Lee	2011	101 (48/53)	85 (84)	47,9 (15.9)	1	.	VAS	general, orthopedic, gynecologic, urologic, neuro-surgery, other
Li	2011	120 (60/60)	0 (0)	45,0 (9,4)	14	VAS	.	breast cancer
Allred	2010	56 (28/28)	25 (45)	63,9 (9,5)	1	VAS	VAS	TKA
Dabu-Bondoc	2010	40 (20/20)	.	41,0 (11,6)	2	VAS	.	laparoscopic, breast, orthopedic, plastic
Easter[a]	2010	213 (111/102)	69 (32.5)	53,5 (14.1)	1	DOS 0-10	.	eye, oral, neurologic, general gastro-enterologic, gynecologic orthopedic, urologic
Good	2010	198 (95/103)	63 (32)	48,7 (12,1)	3	VAS	.	major abdominal
Sen	2010	70 (35/35)	0 (0)	30,2 (3,9)	1	VAS	.	CS
Stein	2010	36 (17/19)	28 (77)	65,0 (11,0)	7	.	HADS	CABG
Bringman	2009	327 (177/150)	134 (41)	49,9 (13,6)	1	.	STAI	mixed
Nilsson	2009	58 (28/30)	.	66,6 (10,0)	1	NRS	NRS	CABG/ valve
Sen[a]	2009	60 (30/30)	60 (100)	22,5 (3,1)	1	VAS	.	urological
Ebneshahidi	2008	77 (38/39)	0 (0)	25,2 (4,37)	1	VAS	VAS	CS
Hook	2008	102 (51/51)	0 (0)	40,3 (.)	8	VAS	VAS	moderate-major elective
Kang[a]	2008	40 (20/20)	4 (10)	68,5 (7,2)	1	VAS	VAS	TKA
Simcock	2008	30 (15/15)	18 (60)	67.3 (9,1)	1	VAS	.	TKA
Szmuk	2008	40 (20/20)	20 (50)	52,0 (16,0)	1	VAS	.	laparoscopic
Walworth[a]	2008	27 (14/13)	12 (44)	46,5 (.)	1	VAS	VAS	brain

Anesthesia	Timing	Music	N; minutes	R/L	Control
regional	per	self-chosen classical, pop, folk, hymns, Korean style country, own favorites	1; 25	R	no music
75% general, 25% regional	pre	standard folk or pop	1; 10 (broad cast)	R	standard care
.	post	light music, classical Chinese folk, popular world, Chinese relaxation or recommended by AAMT	twice daily ; 30	R	nothing
both	post	easy listening	1; 20	R	quiet rest period
general	pre per	tape	2; pre 30, peroperative	R	blank cassette tape
both	post	country, easy listening, gospel, rock	1 ; .	R	No CD/ headset
.	post	back ground music (synthesizer, harp, piano, orchestra, slow jazz, inspiration)	multiple; 30	R	standard care, quietly lying
general	post	self- chosen not specified	1; 60	R	no music
general	pre	standard relaxing	1; 7	R	standard care
both	pre	standard mix	1; 42	R	midazolam
general	post	standard new age	1; 30	R	nothing
general	per	self-chosen	1; .	R	earphones no music
general	post	self-brought favorite tape	1 ; 30	R	headphone no music
general	pre post	Western, Malay or Chinese	8 ; 30	R	standard care
regional, sedation	per	folk, popular or classical	1 ; 98	R	ambient OR noise
general	per	selection not specified	1; .	R	headphone with white noise
general	per	selection of different styles	1; .	R	headphone no music
.	pre post	self-chosen live music, singing, playing or listening. Verbal counselingsongwriting progressive muscle relaxation, guided imagery	multiple; 30	L	routine hospital care

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	Year	n patients (I/C)	n Male (%)	Mean age (SD) or range	Days follow-up	Pain scale	Anxiety scale	Surgery
Reza	2007	100 (50/50)	0 (0)	26,0 (5,2)	1	VAS	VAS	CS
McCaffrey	2006	124 (62/62)	43 (35)	75,7 (6,1)	3	VAS	.	hip/knee
Sendelbach	2006	86 (50/36)	60 (70)	63,0 (13,5)	3	NRS	STAI	cardiac
Twiss	2006	60 (30/30)	20 (33)	73,9 (3,1)	4	.	STAI	cardio-vascular
Chang	2005	64 (32/32)	0 (0)	31,3 (4,4)	1	.	VAS	CS
Cooke	2005	120 (60/60)	60 (50)	54,5 (18,7)	1	.	STAI	ambulatory orthopedic, cystoscopy, biopsy
Masuda	2005	44 (22/22)	18 (41)	69,0 (6,0)	4	VAS	.	orthopedic
Nilsson	2005	50 (25/25)	48 (96)	56,5 (14,4)	1	NRS	NRS	open hernia repair
Padnamabhan	2005	69 (34/35)	35 (50)	.	1	.	STAI	ambulatory
Pongraweewan	2005	44 (22/22)	25 (57)	43,9 (20,8)	2	.	VAS	orthopedic
Ikonomidou	2004	55 (29/26)	0 (0)	34,0 (5,8)	1	VAS	VAS	gynecologic laparoscopy
Voss	2004	40 (19/21)	26 (64)	63,0 (13,0)	1	VAS	VAS	open heart
Bally	2003	113 (58/55)	64 (57)	59 (11)	1	VAS	STAI	coronary intervention
Laurion	2003	56 (28/28)	0 (0)	34,5 (7.4)	discharge	VRS	.	gynecologic
Nilsson	2003	100 (51/49)	69 (69)	54,0 (13,4)	1	NRS	.	varicose vein and inguinal hernia
Nilsson	2003	125 (62/63)	63 (50)	52,5 (13,7)	1	VAS	STAI	varicose vein and inguinal hernia
Bellan[a]	2002	144 (./.)	.	26-93	.	VAS	VAS	cataract surgery
Wang	2002	93 (48/45)	56 (60)	42,5 (11,0)	1	.	STAI	elective surgery
Yung	2002	20 (10/10)	.	68,0 (8,0)	1	.	C-STAI	trans urethral resection of prostate
Lepage	2001	50 (25/25)	31 (62)	38,4 (10,8)	1	.	STAI	non-oncologic

Anesthesia	Timing	Music	N; minutes	R/L	Control
general	per	Spanish guitar music	1; .	R	blank CD with headphones
.	post	CD musical preference, lullabies when awakening	4 days; 60	R	standard care
general	post	relaxing music (jazz, easy listening, pop)	twice daily; 20	R	quiet rest period
general	per post	selection from relaxing and CDs	1; .	R	standard
regional	per	western classical, new age or Chinese religion	1 ; 88	R	routine care
.	pre	classical, jazz, country and western, new age, easy-listening, other	1 ; 30	R	no headphone, routine care
both	post	western classical, gagak, noh, enka	1; 20	R	nothing
general	per post	new age synthesizer	multiple; peroperative and 60 post	R	sham cd
.	pre	track without binaural beat	1; 30	R	allowed to watch tv or read
regional	per	standard, not specified	1; .	R	no adjunct techniques
general	pre post	standard peaceful pan flute	2;30	R	blank compact disk
general	post	sedative non-lyrical music, synthesizer, harp, piano, orchestra, slow jazz, flute	1; 30	R	.
regional, sedation	pre, per, post	selfselected classical, soft rock, relaxation, country, other.	1; .	R	standard care
general	pre	standard piano	.	R	standard care
general	per (1) post (1)	soft, slow, flowing, rhythmic instrumental new-age synthesizer	multiple; peroperative 43 postoperative 60	R	blank CD
general	post	soft, relaxing, calm classical	1; 117	R	blank tape
.	pre per	relaxing (classical, country, jazz, soft rock)	1 or 2 ; .	R	routine background noise
.	pre	self-brought favorite CD from home	1; 30	R	routine care
.	pre	three slow rhythm pieces	1; .	R	nothing
regional	pre per post	pop, classical, jazz, new age	3 ; 120	R	nothing

	Year	n patients (I/C)	n Male (%)	Mean age (SD) or range	Days follow-up	Pain scale	Anxiety scale	Surgery
Nilsson	2001	58 (30/28)	0 (0)	50,5 (8,2)	2	VAS	.	hysterectomy
Good	1999	227 (118/109)	39 (17)	45.4 (11,0)	3	VAS	VAS	gynecologic gastro-intestinal, exploratory, urinary
Szeto	1999	9 (6/3)	.	58,0 (17,0)	1	.	STAI	surgical patients
Good	1998	38 (16/22)	3 (8)	40,6 (6,8)	3	VAS	.	major gynecologic or surgical abdominal
Koch	1998	43 (21/22)	27 (62)	53,5 (13.6)	1	VAS	STAI	lithropsy renal calculi
Taylor	1998	40 (20/20)	2 (4)	39,0 (7,9)	1	VRS	.	abdominal hysterectomy
Cruise	1997	62 (32/30)	20 (32.5)	69,6 (2,4)	1	.	STAI, VAS	cataract
Heiser[a]	1997	19	12 (62)	38,0 (9,0)	1	VAS	VAS	elective lumbar micro discectomy
Zimmerman	1996	64 (32/32)	44 (68)	67,0 (9,9)	3	VRS	,	CABG
Barnason	1995	67 (33/34)	46 (68)	67,0 (9,9)	4	.	STAI, NRS	CABG
Gaberson	1995	31 (16/15)	13 (41)	49,5 (18,3)	1	.	VAS	elective surgical procedures
Good	1995	42 (21/21)	11 (25)	46,0 (12,5)	3	Line 0-10 with 3 anchors	STAI, Distress of Pain Scale	abdominal
Winter	1994	50 (31/19)	0 (0)	37,0 (8,0)	1	.	STAI	elective gynecologic procedures
Heitz[a]	1992	40 (20/20)	3 (7)	49,0 (4,2)	2	VAS	.	mastectomy, thyroidectomy, parathyroidectomy
Gaberson[a]	1991	10 (5/5)	4 (40)	23-76	1	.	VAS	cataract, breast cyst, plastic eyelid, hand, veins, inguinal hernia
Steelman	1990	43 (21/22)	.	23-76	1	.	STAI	orthopedic
Kaempf	1989	33	.	.	1	.	STAI	arthroscopic orthopedic
Mullooly	1988	28 (14/14)	0 (0)	47,0 (5,0)	3	VAS	VAS 0-5	elective abdominal hysterectomy

Anesthesia	Timing	Music	N; minutes	R/L	Control
general	per	relaxing music with wave sounds	.	R	operating room sounds
.	post	soothing music: synthesizer, harp, piano, orchestral, slow jazz	2; 15	R	quietly lying in bed
.	pre	Chinese/ western slow rhythmical	1 ; 20	R	no music
general	post	western music: harp, synthesizer, orchestral piano, jazz	2 ; 15	R	resting in bed
regional	per	self-brought CD or suitable alternative from hospital	1 ; .	R	no headphone, ambient OR noise
general	post	self-brought	.	R	headphoneonly
regional, sedation	per	relaxing classical and soothing nature sounds	1 ; .	R	operating room noise
general	per post	country or instrument classic	1; 90	R	no music
general	post	soothing, relaxing country western instrument, fresh	2 ; 30	R	undisturbed bed rest
.	post	soothing instrument(country)	multiple; 30	R	undisturbed scheduled rest 30
.	pre	slow, quiet, instrument	1 ; 20	R	no auditory distraction
.	post	sedative music: synthesizer, harp, piano, orchestral, slow jazz	multiple; 156	R	routine care
.	pre	classical, country, jazz, popular, show music	1 ; 50	R	no cassette player
general	post	calm classical, stimulative classical, or popular calm quality	1; 93	R	no headphone
.	pre	slow, quiet, instrument	1 ; 20	R	no intervention
regional	per	classical, new age, instrument, easy listening/ popular, country	1 ; .	R	routine care, verbal distraction
.	pre	classical, tape 3 MusicRx Dr Bonny	1 ; 20	R	no music
.	post	easy listening instrumentmusic	2 ; 10	R	no intervention

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Table S2. Results of univariable meta-regression analysis.

Univariable factor	SMD intercept	95% C-I	P- value intercept	coefficient of variable	SE coefficient	P-value coefficient
Anxiety main analysis	**-.709**	**-0.94; -0.40**	**0.000**	-	-	-
Average age	-0.801	-1.61; 0.00	0.053	.004	.008	0.640
Proportion male	-0.650	-1.06; -0.20	0.002	-.181	.432	0.675
Choice patient selection	-0.694	-1.03; -0.30	0.000	-.031	.240	0.897
Choice investigator	-0.684	-0.99; -0.30	0.000	-.063	.244	0.796
Choice own	-0.735	-0.98; -0.40	0.000	.278	.416	0.503
Timing preoperative	-0.556	-0.89; -.020	0.001	-.307	.241	0.203
Timing peroperative	-0.804	-1.12; -0.40	0.000	.218	.244	0.372
Timing postoperative	-0.823	-1.14; -0.50	0.000	.276	.246	0.263
Timing multiple	-0.770	-1.05; -0.40	0.000	.217	.269	0.421
General anesthesia	-0.876	-1.33; -0.40	0.000	.381	.334	0.254
Pain main analysis	**-.502**	**-0.66; -0.34**	**0.000**	-	-	-
Average age	-0.122	-0.79; 0.55	0.722	-.007	.006	0.260
Proportion male	-0.521	-0.78; -0.26	0.000	.024	.314	0.940
Choice patient selection	-0.464	-0.69; -.024	0.000	-.077	.165	0.640
Choice investigator	-0.487	-0.69; -0.28	0.000	-.039	.171	0.819
Choice own	-0.534	-0.71; -0.36	0.000	.258	.245	0.294
Timing preoperative	-0.439	-0.63; -0.25	0.000	-.211	.178	0.236
Timing peroperative	-0.566	-0.78; -0.36	0.000	.156	.166	0.347
Timing postoperative	-0.423	-0.67; -0.17	0.001	-.134	.167	0.420
Timing multiple	-0.467	-0.65; -0.28	0.000	-.149	.195	0.444
General anesthesia	-0.395	-0.71; -0.08	0.014	-.165	.189	0.381

Abbreviations: SMD=standardized mean difference; C-I= confidence-interval.

Table S3. Results of data driven multivariable meta-regression analysis.

Multivariable factors	SMD intercept	95% C-I	P-value intercept	coefficient of variable	SE coefficient	P-value coefficient
Anxiety	**-.805**	**-2.14; 0.53**	**0.238**			
Choice patient selection				-.615	.585	0.293
Choice investigator				-.378	.576	0.512
Timing preoperative				-.231	.380	0.543
Timing peroperative				.500	.452	0.269
Timing postoperative				-.066	.527	0.900
General anesthesia				.693	.517	0.180
Pain	**-.209**	**-0.75; 0.33**	**0.447**			
Choice patient selection				-.185	.238	0.436
Choice investigator				-.101	.251	0.688
Timing preoperative				-.407	.190	0.032
Timing peroperative				.075	.214	0.726
Timing postoperative				-.047	.253	0.852
General anesthesia				-.110	.238	0.642

Abbreviations: SMD=standardized mean difference; C-I= confidence-interval.

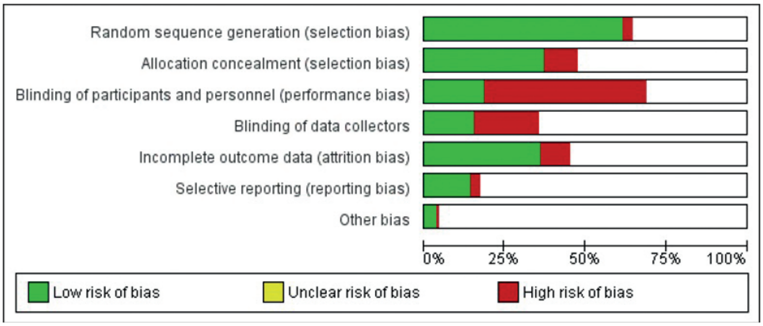


Figure S1. Summary Risk of Bias.

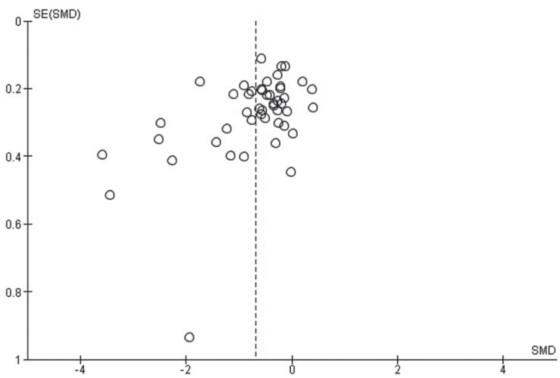


Figure S2. Funnel plot anxiety.

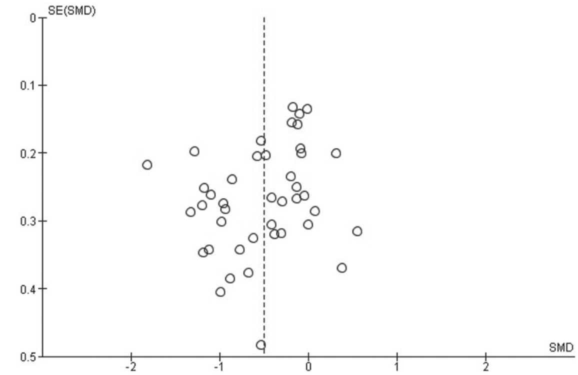


Figure S3. Funnel plot pain.

	Music			Control				Std. Mean Difference		Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**Year**	**IV, Random, 95% CI**
4.1.1 Main Anxiety										
Mullooly 1988	0.43	0.65	14	1.14	0.86	14	0.7%	-0.90 [-1.69, -0.12]	1988	
Winter 1994	41.5	1.8	31	44.3	2.8	19	0.8%	-1.24 [-1.86, -0.61]	1994	
Gaberson 1995	2.98	2.91	16	3.92	2.89	15	0.8%	-0.32 [-1.03, 0.39]	1995	
Good 1995	40	12.72	21	41.67	10.42	21	0.8%	-0.14 [-0.75, 0.46]	1995	
Barnason 1995	31.8	11.4	33	34.7	16	34	0.9%	-0.21 [-0.69, 0.27]	1995	
Cruise 1997	24.1	1	32	23.7	1	30	0.9%	0.39 [-0.11, 0.90]	1997	
Szeto 1999	33.33	6.38	6	46.33	4.73	3	0.3%	-1.94 [-3.77, -0.11]	1999	
Good 1999	2.3	2.4	118	2.8	2.5	109	0.9%	-0.20 [-0.46, 0.06]	1999	
Wang 2002	34.19	5.13	48	39.6	7.92	45	0.9%	-0.81 [-1.23, -0.39]	2002	
Yung 2002	37.6	7.41	10	37.7	7.27	10	0.7%	-0.01 [-0.89, 0.86]	2002	
Bally 2003	31.5	9.7	56	33.6	9.6	51	0.9%	-0.22 [-0.60, 0.16]	2003	
Nilsson 2003	30.7	6.9	62	29.3	6.8	63	0.9%	0.20 [-0.15, 0.55]	2003	
Voss 2004	1.3	0.9	19	4.8	3.2	21	0.8%	-1.43 [-2.13, -0.73]	2004	
Ikonomidou 2004	1.38	1.56	29	2.66	2.68	26	0.8%	-0.58 [-1.12, -0.04]	2004	
Cooke 2005	28.5	4.26	60	32.7	5.03	60	0.9%	-0.90 [-1.27, -0.52]	2005	
Nilsson 2005	0.3	0.9	25	1.1	2	25	0.8%	-0.51 [-1.07, 0.06]	2005	
Chang 2005	0.98	1.9	32	1.76	2.6	32	0.9%	-0.34 [-0.83, 0.16]	2005	
Pongraweewan 2005	0.409	1.182	22	0.909	2.389	22	0.8%	-0.26 [-0.85, 0.33]	2005	
Padmanabhan 2005	28	2.5	34	36.6	2.25	35	0.7%	-3.58 [-4.35, -2.80]	2005	
Twiss 2006	36.83	9.53	30	42.9	11.53	30	0.9%	-0.57 [-1.08, -0.05]	2006	
Reza 2007	0.1	0.707	50	0.38	1.589	50	0.9%	-0.23 [-0.62, 0.17]	2007	
Ebneshahidi 2008	1.1	1.4	38	1.3	1.2	39	0.9%	-0.15 [-0.60, 0.30]	2008	
Bringman 2009	30	7	177	34	7	150	1.0%	-0.57 [-0.79, -0.35]	2009	
Nilsson 2009	0.7	1.5	28	1.2	2	30	0.9%	-0.28 [-0.80, 0.24]	2009	
Stein 2010	7.24	4.96	17	7.11	5.03	19	0.8%	0.03 [-0.63, 0.68]	2010	
Allred 2010	2.79	2.08	28	3.03	2.87	28	0.8%	-0.09 [-0.62, 0.43]	2010	
Kim 2011	13.12	3.24	106	13.51	3.11	113	0.9%	-0.12 [-0.39, 0.14]	2011	
Lee 2011	5	2.7	48	6.2	1.2	53	0.9%	-0.58 [-0.98, -0.18]	2011	
Binns-Turner 2011	30.7	12.3	15	49.7	18.9	15	0.7%	-1.16 [-1.94, -0.38]	2011	
Ottaviani 2012	4.03	3.11	31	5.82	2.63	31	0.9%	-0.61 [-1.12, -0.10]	2012	
Li 2012	43.63	3.26	30	50.63	2.13	30	0.8%	-2.51 [-3.20, -1.82]	2012	
Johnson 2012	1.16	2.2	43	2.15	2.5	41	0.9%	-0.42 [-0.85, 0.02]	2012	
Guerrero 2012	48.5	9.7	54	44.5	11.1	47	0.9%	0.38 [-0.01, 0.78]	2012	
Vachiramon 2013	28.8	7.3	50	35.3	9.7	50	0.9%	-0.75 [-1.16, -0.35]	2013	
Jimenez-Jimenez 2013	1.31	0.3	20	2.36	0.3	20	0.6%	-3.43 [-4.44, -2.42]	2013	
Zengin 2013	38.74	8.94	50	43.26	6.92	50	0.9%	-0.56 [-0.96, -0.16]	2013	
Bae 2014	2.3	1.2	40	5.3	1.2	40	0.8%	-2.48 [-3.06, -1.89]	2014	
Ikkaya 2014	28	6.2	25	32.2	4.6	25	0.8%	-0.76 [-1.33, -0.18]	2014	
Wang 2014	42.55	4.76	20	50.75	1.68	20	0.7%	-2.25 [-3.06, -1.44]	2014	
Liu 2015	35.53	5.08	47	41.43	5.49	51	0.9%	-1.11 [-1.53, -0.68]	2015	
Zhou 2015	34.01	4.66	85	43.35	6	85	0.9%	-1.73 [-2.08, -1.38]	2015	
Hudson 2015	38.6	10.31	84	41.29	9.72	76	0.9%	-0.27 [-0.58, 0.04]	2015	
Palmer 2015	3.8	3.25	68	5.7	4.69	61	0.9%	-0.47 [-0.82, -0.12]	2015	
Heidari 2015	0.53	0.57	30	1.07	0.69	30	0.8%	-0.84 [-1.37, -0.31]	2015	
Kongsawatvorakul 2016	38.7	9.62	36	41.3	9.98	37	0.9%	-0.26 [-0.72, 0.20]	2016	
McClurkin 2016	30	9.12	41	34.2	8.76	45	0.9%	-0.47 [-0.90, -0.04]	2016	
Cigerci 2016	39	6.6	34	41.4	7.2	34	0.9%	-0.34 [-0.82, 0.14]	2016	
Subtotal (95% CI)			**1993**			**1935**	**39.3%**	**-0.69 [-0.88, -0.50]**		

Heterogeneity: Tau² = 0.35; Chi² = 350.22, df = 46 (P < 0.00001); I² = 87%
Test for overall effect: Z = 7.23 (P < 0.00001)

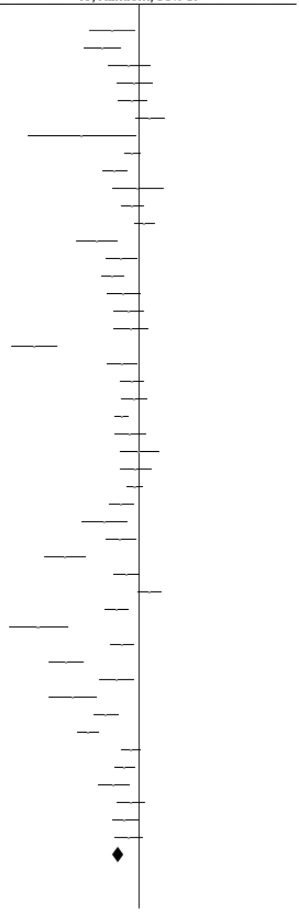


Figure S4. Summary forest plots meta-analyses anxiety and meta-analyses pain.

4.1.2 Main Pain									
Mullooly 1988	2.957	2.656	14	5.336	1.969	14	0.7%	-0.99 [-1.78, -0.20]	1988
Good 1995	6.58	2.26	21	5.23	2.52	21	0.8%	0.55 [-0.06, 1.17]	1995
Zimmerman 1996	0.68	1.3	32	0.88	1.8	32	0.9%	-0.13 [-0.62, 0.36]	1996
Good 1998	1.44	1.56	16	3.29	2.78	22	0.8%	-0.77 [-1.44, -0.10]	1998
Taylor 1998	5.83	1.63	20	6.48	1.7	20	0.8%	-0.38 [-1.01, 0.24]	1998
Koch 1998	3	2	21	3	2	22	0.8%	0.00 [-0.60, 0.60]	1998
Good 1999	2.5	2.3	118	2.9	2.3	109	0.9%	-0.17 [-0.43, 0.09]	1999
Nilsson 2001	1.6	0.9	30	2	1	28	0.9%	-0.42 [-0.94, 0.11]	2001
Nilsson 2003	2.1	1.4	62	2.9	1.6	63	0.9%	-0.53 [-0.89, -0.17]	2003
Laurion 2003	1.1	1.1	28	2.4	1.6	28	0.8%	-0.93 [-1.49, -0.38]	2003
Nilsson 2003-2	1.8	1.1	51	2.6	1.6	49	0.9%	-0.58 [-0.98, -0.18]	2003
Bally 2003	0.4	1	56	0.5	1.2	51	0.9%	-0.09 [-0.47, 0.29]	2003
Voss 2004	1.9	1.3	19	4.5	2.7	21	0.8%	-1.18 [-1.86, -0.51]	2004
Ikonomidou 2004	1.99	1.39	29	2.47	1.81	26	0.8%	-0.30 [-0.83, 0.24]	2004
Masuda 2005	2.2	2.2	22	3.1	2.1	22	0.8%	-0.41 [-1.01, 0.19]	2005
Nilsson 2005	2.1	1.5	25	3.8	1.9	25	0.8%	-0.98 [-1.57, -0.39]	2005
McCaffrey 2006	4.63	2.02	62	7.4	2.26	62	0.9%	-1.28 [-1.67, -0.90]	2006
Reza 2007	7.06	2.551	50	7.26	2.754	50	0.9%	-0.07 [-0.47, 0.32]	2007
Simcock 2008	2.41	1.67	15	4.03	2.89	15	0.7%	-0.67 [-1.41, 0.07]	2008
Szmuk 2008	3.3	2.7	20	5	2.7	20	0.8%	-0.62 [-1.25, 0.02]	2008
Ebneshahidi 2008	2.7	2.1	38	4.6	2.3	39	0.9%	-0.85 [-1.32, -0.39]	2008
Nilsson 2009	1.6	1.5	28	1.7	2.5	30	0.9%	-0.05 [-0.56, 0.47]	2009
Allred 2010	4.12	2.58	28	4.51	3.12	28	0.8%	-0.13 [-0.66, 0.39]	2010
Dabu-Bondoc 2010	4.5	3.3	20	5.4	2.5	20	0.8%	-0.30 [-0.93, 0.32]	2010
Good 2010	2.25	2.14	95	2.47	2.26	103	0.9%	-0.10 [-0.38, 0.18]	2010
Li 2011	0.09	0.29	60	0.76	0.43	60	0.9%	-1.82 [-2.24, -1.39]	2011
Binns-Turner 2011	4.15	3.02	15	6.49	2.09	15	0.7%	-0.88 [-1.63, -0.12]	2011
Kim 2011	2.15	1.25	106	2.16	1.19	113	0.9%	-0.01 [-0.27, 0.26]	2011
Ghetti 2011	2.17	1.58	9	3.56	3.16	9	0.6%	-0.53 [-1.47, 0.41]	2011
Jafari 2012	2.4	2.2	30	4.9	2.9	30	0.8%	-0.96 [-1.49, -0.42]	2012
Guerrero 2012	6.84	2.33	54	6.09	2.47	47	0.9%	0.31 [-0.08, 0.70]	2012
Ottaviani 2012	2.66	1.62	31	5.12	2.37	31	0.8%	-1.20 [-1.74, -0.65]	2012
Li 2012	3.27	1.01	30	4.87	1.36	30	0.8%	-1.32 [-1.88, -0.76]	2012
Vaajoki 2012	1	1.6	83	1.3	1.7	84	0.9%	-0.18 [-0.48, 0.12]	2012
Zengin 2013	3.14	1.06	50	3.86	1.84	50	0.9%	-0.48 [-0.87, -0.08]	2013
Graversen 2013	0	0.93	40	1	0.74	35	0.9%	-1.17 [-1.66, -0.68]	2013
Wang 2014	3.5	1.05	20	4.85	1.31	20	0.8%	-1.11 [-1.79, -0.44]	2014
Hudson 2015	3.94	2.01	84	4.17	1.8	76	0.9%	-0.12 [-0.43, 0.19]	2015
Chen 2015	4	1.31	15	3.53	1.06	15	0.8%	0.38 [-0.34, 1.11]	2015
Hansen 2015	2.9	2.07	25	2.74	2.38	24	0.8%	0.07 [-0.49, 0.63]	2015
Cigerci 2016	0.4	1.5	34	2.9	2.8	34	0.9%	-1.10 [-1.61, -0.59]	2016
Kongsawatvorakul 2016	2.55	4.12	36	3.33	3.9	37	0.9%	-0.19 [-0.65, 0.27]	2016
Subtotal (95% CI)			**1642**			**1630**	**35.5%**	**-0.50 [-0.66, -0.34]**	
Heterogeneity: Tau² = 0.20; Chi² = 190.47, df = 41 (P < 0.00001); I² = 78%									
Test for overall effect: Z = 6.23 (P < 0.00001)									
4.1.3 Change Anxiety									
Steelman 1990	-7.805	11.202	21	-7.545	10.145	22	0.8%	-0.02 [-0.62, 0.57]	1990
Bally 2003	-9.1	12.1	56	-7	10.8	51	0.9%	-0.18 [-0.56, 0.20]	2003
Voss 2004	-5	2.3	19	5	2.3	21	0.5%	-4.26 [-5.42, -3.10]	2004
Padmanabhan 2005	-11.1	2.5	34	-3.8	2.5	35	0.8%	-2.89 [-3.57, -2.20]	2005
Hook 2008	-2.67	1.23	51	-0.43	1.04	51	0.9%	-1.95 [-2.43, -1.48]	2008
Binns-Turner 2011	-10.8	7.7	15	7.8	11.6	15	0.7%	-1.84 [-2.71, -0.97]	2011
Bauer 2011	-0.5	1.1	49	-0.1	1.6	51	0.9%	-0.29 [-0.68, 0.11]	2011
Li 2012	-7.2	2.09	30	-0.03	3.5	30	0.8%	-2.46 [-3.14, -1.77]	2012
Ni 2012	-5.83	0.75	86	-1.72	0.65	86	0.8%	-5.83 [-6.52, -5.14]	2012
Johnson 2012	-2.58	2.5	43	-1.83	2.5	41	0.9%	-0.30 [-0.73, 0.13]	2012
Guerrero 2012	3.5	10.8	54	1.2	9	47	0.9%	0.23 [-0.16, 0.62]	2012
Vachiramon 2013	-9.9	7.4	50	-3.4	2.6	50	0.9%	-1.16 [-1.59, -0.74]	2013
Bae 2014	-3.72	1.4	40	-1.12	1.2	40	0.8%	-1.97 [-2.51, -1.44]	2014
Wang 2014	-6.65	4.65	20	0.9	3.34	20	0.7%	-1.83 [-2.58, -1.08]	2014
Palmer 2015	-2.68	2.93	68	0	2.27	61	0.9%	-1.01 [-1.38, -0.64]	2015
Kipnis 2016	-6.6	14.7	82	1.6	11.9	77	0.9%	-0.61 [-0.93, -0.29]	2016
McClurkin 2016	-9.2	8.44	41	-1.5	6.93	45	0.9%	-0.99 [-1.44, -0.54]	2016
Kongsawatvorakul 2016	-15.9	17.2	36	-10.2	19.6	37	0.9%	-0.31 [-0.77, 0.16]	2016
Wiwatwongwana 2016	-7	4.8	44	-2.9	4.4	47	0.9%	-0.88 [-1.32, -0.45]	2016
Alam 2016	-9.94	0.33	54	-9.63	0.38	51	0.9%	-0.87 [-1.27, -0.47]	2016
Tellez 2016	-4.6	2.7	20	-0.61	3.2	18	0.8%	-1.33 [-2.04, -0.62]	2016
Subtotal (95% CI)			**913**			**896**	**17.5%**	**-1.41 [-1.89, -0.94]**	
Heterogeneity: Tau² = 1.16; Chi² = 405.72, df = 20 (P < 0.00001); I² = 95%									
Test for overall effect: Z = 5.80 (P < 0.00001)									

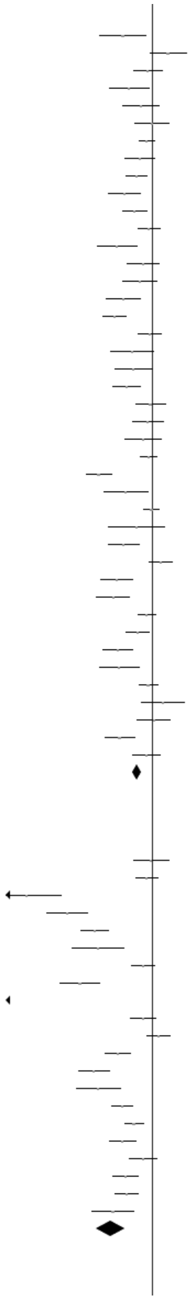


Figure S4 (Continued). Summary forest plots meta-analyses anxiety and meta-analyses pain.

3

4.1.4 Change Pain									
Bally 2003	0.3	0.9	56	0.2	0.6	51	0.9%	0.13 [-0.25, 0.51]	2003
Voss 2004	-2.8	2.2	19	-0.1	2.3	21	0.8%	-1.17 [-1.85, -0.50]	2004
Hook 2008	-0.37	1.22	51	0.02	0.58	51	0.9%	-0.41 [-0.80, -0.01]	2008
Bauer 2011	-0.7	1.8	49	1.4	10.9	51	0.9%	-0.26 [-0.66, 0.13]	2011
Binns-Turner 2011	2.97	1.98	15	5.07	1.92	15	0.7%	-1.05 [-1.82, -0.28]	2011
Li 2011	-4.39	0.5807	60	-3.72	0.5807	60	0.9%	-1.15 [-1.53, -0.76]	2011
Guerrero 2012	5.1	2.76	54	3.93	3.01	47	0.9%	0.40 [0.01, 0.80]	2012
Alam 2016	-0.41	0.23	54	-0.23	0.22	51	0.9%	-0.79 [-1.19, -0.40]	2016
Tellez 2016	-0.65	3.2	20	2.2	3.1	18	0.8%	-0.88 [-1.56, -0.21]	2016
Subtotal (95% CI)			**378**			**365**	**7.7%**	**-0.54 [-0.93, -0.15]**	
Heterogeneity: Tau² = 0.29; Chi² = 51.34, df = 8 (P < 0.00001); I² = 84%									
Test for overall effect: Z = 2.73 (P = 0.006)									
Total (95% CI)			**4926**			**4826**	**100.0%**	**-0.73 [-0.86, -0.61]**	
Heterogeneity: Tau² = 0.44; Chi² = 1078.83, df = 118 (P < 0.00001); I² = 89%									
Test for overall effect: Z = 11.12 (P < 0.00001)									
Test for subgroup differences: Chi² = 13.49, df = 3 (P = 0.004), I² = 77.8%									

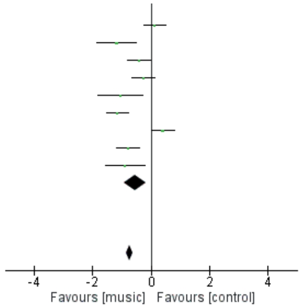
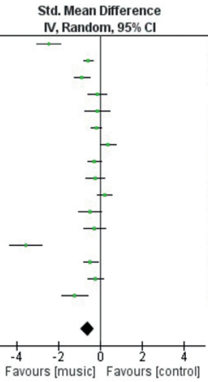


Figure S4 (Continued). Summary forest plots meta-analyses anxiety and meta-analyses pain.

	Music			Control				Std. Mean Difference	Risk of Bias						
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**A**	**B**	**C**	**D**	**E**	**F**	**G**
Bae 2014	2.3	1.2	40	5.3	1.2	40	5.8%	-2.48 [-3.06, -1.89]	−	+		−	+	+	+
Bringman 2009	30	7	177	34	7	150	6.9%	-0.57 [-0.79, -0.35]	+	+	−		+		
Cooke 2005	28.5	4.26	60	32.7	5.03	60	6.5%	-0.90 [-1.27, -0.52]	+	+	+	−	+	+	+
Ebneshahidi 2008	1.1	1.4	38	1.3	1.2	39	6.3%	-0.15 [-0.60, 0.30]		+	+	+	−	+	
Good 1995	40	12.72	21	41.67	10.42	21	5.7%	-0.14 [-0.75, 0.46]	+	+		−	+		
Good 1999	2.3	2.4	118	2.8	2.5	109	6.8%	-0.20 [-0.46, 0.06]	+	+	+	−			
Guerrero 2012	48.5	9.7	54	44.5	11.1	47	6.5%	0.38 [-0.01, 0.78]	+	+	−	−		+	
Hudson 2015	38.6	10.31	84	41.29	9.72	76	6.7%	-0.27 [-0.58, 0.04]	+		−		+	+	+
Kongsawatvorakul 2016	38.7	9.62	36	41.3	9.98	37	6.3%	-0.26 [-0.72, 0.20]	+	+	−		+		
Nilsson 2003	30.7	6.9	62	29.3	6.8	63	6.6%	0.20 [-0.15, 0.55]	+		+		+		
Nilsson 2005	0.3	0.9	25	1.1	2	25	5.9%	-0.51 [-1.07, 0.06]	+		+		+		
Nilsson 2009	0.7	1.5	28	1.2	2	30	6.1%	-0.28 [-0.80, 0.24]	+	+	−	+	+		
Padmanabhan 2005	28	2.5	34	36.6	2.25	35	5.1%	-3.58 [-4.35, -2.80]	+	+	+	+			
Palmer 2015	3.8	3.25	68	5.7	4.69	61	6.6%	-0.47 [-0.82, -0.12]	+	+	+				−
Reza 2007	0.1	0.707	50	0.38	1.589	50	6.5%	-0.23 [-0.62, 0.17]	+		+	+			
Winter 1994	41.5	1.8	31	44.3	2.8	19	5.7%	-1.24 [-1.86, -0.61]	+				+	+	
Total (95% CI)			**926**			**862**	**100.0%**	**-0.61 [-0.94, -0.29]**							
Heterogeneity: Tau² = 0.39; Chi² = 160.62, df = 15 (P < 0.00001); I² = 91%															
Test for overall effect: Z = 3.69 (P = 0.0002)															

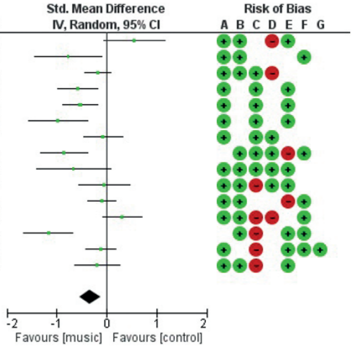


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of data collectors
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S5. Subgroup analysis of anxiety based on studies with Low Risk of Bias, that is those scoring at least three items with Low Risk of Bias.

Study or Subgroup	Music Mean	Music SD	Music Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Good 1995	6.58	2.26	21	5.23	2.52	21	5.3%	0.55 [-0.06, 1.17]	1995
Good 1998	1.44	1.56	16	3.29	2.78	22	4.9%	-0.77 [-1.44, -0.10]	1998
Good 1999	2.5	2.3	118	2.9	2.3	109	8.5%	-0.17 [-0.43, 0.09]	1999
Nilsson 2003-2	1.8	1.1	51	2.6	1.6	49	7.2%	-0.58 [-0.98, -0.18]	2003
Nilsson 2003	2.1	1.4	62	2.9	1.6	63	7.6%	-0.53 [-0.89, -0.17]	2003
Nilsson 2005	2.1	1.5	25	3.8	1.9	25	5.5%	-0.98 [-1.57, -0.39]	2005
Reza 2007	7.06	2.551	50	7.26	2.754	50	7.3%	-0.07 [-0.47, 0.32]	2007
Ebneshahidi 2008	2.7	2.1	38	4.6	2.3	39	6.6%	-0.85 [-1.32, -0.39]	2008
Simcock 2008	2.41	1.67	15	4.03	2.89	15	4.4%	-0.67 [-1.41, 0.07]	2008
Nilsson 2009	1.6	1.5	28	1.7	2.5	30	6.1%	-0.05 [-0.56, 0.47]	2009
Good 2010	2.25	2.14	95	2.47	2.26	103	8.3%	-0.10 [-0.38, 0.18]	2010
Guerrero 2012	6.84	2.33	54	6.09	2.47	47	7.3%	0.31 [-0.08, 0.70]	2012
Graversen 2013	0	0.93	40	1	0.74	35	6.3%	-1.17 [-1.66, -0.68]	2013
Hudson 2015	3.94	2.01	84	4.17	1.8	76	8.0%	-0.12 [-0.43, 0.19]	2015
Kongsawatvorakul 2016	2.55	4.12	36	3.33	3.9	37	6.6%	-0.19 [-0.65, 0.27]	2016
Total (95% CI)			**733**			**721**	**100.0%**	**-0.34 [-0.55, -0.13]**	

Heterogeneity: Tau² = 0.12; Chi² = 51.71, df = 14 (P < 0.00001); I² = 73%
Test for overall effect: Z = 3.13 (P = 0.002)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of data collectors
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure S6. Subgroup analysis of pain based on studies with Low Risk of Bias, that is those scoring at least three items with Low Risk of Bias.

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3

Chapter 4

Systematic review and meta-analysis of music interventions in hypertension treatment: a quest for answers

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Abstract

Background: Adverse effects, treatment resistance and high costs associated with pharmacological treatment of hypertension have led to growing interest in non-pharmacological complementary therapies such as music interventions. This meta-analysis aims to provide an overview of reported evidence on the efficacy of music interventions in the treatment of hypertension.

Methods: A systematic literature search was conducted for publications on the effect of music interventions on blood pressure in adult hypertensive subjects published between January 1990-June 2014. Randomized controlled trials with a follow-up duration ≥28 days were included. Blood pressure measures were pooled using inverse variance weighting.

Results: Of the 1689 abstracts reviewed, 10 randomized controlled trials were included. Random-effects pooling of the music intervention groups showed a trend toward a decrease in mean systolic blood pressure (SBP) from 144 mmHg(95%CI:137-152) to 134 mmHg(95%CI:124-144), and in mean diastolic blood pressure (DBP) from 84 mmHg(95%CI:78-89) to 78 mmHg(95%CI:73-84). Fixed-effect analysis of a subgroup of 3 trials with valid control groups showed a significant decrease in pooled mean SBP and DBP in both intervention and control groups. A comparison between music intervention groups and control groups was not possible due to unavailable measures of dispersion.

Conclusions: This systematic review and meta-analysis revealed a trend towards a decrease in blood pressure in hypertensive patients who received music interventions, but failed to establish a cause-effect relationship between music interventions and blood pressure reduction. Considering the potential value of this safe, low-cost intervention, well-designed, high quality and sufficiently powered randomized studies assessing the efficacy of music interventions in the treatment of hypertension are warranted.

Introduction

Hypertension has been documented as a major risk factor for cardiovascular morbidity and mortality.[1,2] Prevalence of hypertension in developed countries is estimated at 37% and is projected to increase to 42% by 2025.[3] When life-style adjustment approaches fail in reducing blood pressure, the main treatment modality in hypertension is pharmacological treatment. Conventional pharmacological treatment is associated with high costs and various adverse effects particularly in cases of combination therapy and treatment resistant hypertension.[4] This has led to a growing interest in non-pharmacological complementary therapies, such as music interventions, in the treatment of hypertension.

Music interventions have been found to affect clinical outcomes in various situations, including short-term effects on blood pressure during medical procedures such as surgery to long-term effects in the treatment of sleep disorders or depression.[5-8] A recent meta-analysis of studies conducted in diverse clinical settings demonstrated that music interventions lead to a significant reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart-rate in various disease states.[9] Another review found that listening to music may have a beneficial effect on anxiety, SBP, heart-rate, respiratory rate, quality of sleep and pain in patients with coronary heart disease.[10]

Music interventions can be administered in different ways. They can be either live or recorded and administered either with or without the involvement of a music therapist. Moreover, the music intervention can be chosen by the patient, by a music therapist or by a healthcare practitioner – the latter especially in the case of research. There are various definitions of music-based interventions, such as ‘music therapy’, ‘receptive music’ and ‘music medicine’. According to the definition of the American Music Therapy Association, music therapy is the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program. [11] The therapeutic relationship is an important aspect in this definition. The term ‘receptive music’ is meant as a broader explanation of music-based interventions and encompasses several techniques in which the client is a recipient of the music experience.[12] It may also be part of a therapeutic relationship. Another definition is music medicine and can either refer to selected and often specially composed music which is thought to have an effect itself [13] or can be defined as passive listening to prerecorded music provided by medical personal other than a music therapist. [14]

Several studies have been performed to examine the possible effects of music on hypertension. These studies are usually small in sample-size and an overview of reported outcomes is lacking. To investigate the potential anti-hypertensive effect of music interventions, we conducted a systematic review and meta-analysis of prospective randomized controlled trials that assessed the effect of music interventions on blood pressure in hypertensive patients.

In this article, we describe the effects of several types of music interventions in patients with hypertension. Overall, we will use the broader term music interventions. However when we specifically differentiate the interventions, we will refer to music therapy when a specific intervention includes the involvement of a music therapist in a therapeutic relationship. Music interventions without this therapeutic relationship will be referred to as recorded music interventions.

Methods

This systematic review was conducted according to the PRISMA guidelines.[15] The study was approved by the institutional review board (MEC 2014-384) and informed consent was waived. On June 6th, 2014 Embase, PubMed, Medline, Cochrane Central, Web of Science and Google Scholar were searched for publications on the effect of music on blood pressure in adult hypertensive patients (see Additional file 1). Results were screened manually on relevance by two independent investigators (AYRK, JRGE). Studies on the effect of music interventions on blood pressure in hypertensive patients with mean age ≥18 years were considered for inclusion. Studies conducted in humans, published after 1/1/1990, written in English, German, French, Dutch, or Spanish and with a follow-up of at least 28 days were included. Studies were excluded if the full text was not available. Cohorts that received any additional treatment other than music and/or standard medical therapy were also excluded. Cohorts with a medical history of hypertension, with or without medical treatment, or a mean SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg at baseline were included.[1] Music interventions had to be administered multiple times during the trial period. There were no limitations on the type of music administered, nor on the timing of each intervention.

Methods of analysis and inclusion criteria were specified and documented in advance. Only the most recent or most complete study was included if there was an overlap in study populations. In case of disagreement on the inclusion of a paper, an agreement was negotiated.

Data Extraction & Statistical Analyses

Microsoft Office Excel 2011 (Microsoft Corp., Redmond, WA, USA) was used for data extraction and statistical analyses. The following patient and study characteristics were recorded: age, sex, systolic and diastolic blood pressure at baseline, history of hypertension, use of antihypertensive medication, comorbidities, details of music intervention and length of follow-up. Primary outcome measures were reduction in SBP and DBP and mean

SBP and DBP at last follow-up. Secondary outcome measures were effects of music on anxiety and quality of life.

Weighted pooling was conducted on the patient characteristics. Mean SBP and DBP at baseline and at final follow up and mean reduction in SBP and DBP were pooled using inverse variance weighting in a random-effects model. When the number of studies was not sufficiently large to reliably estimate the tau-squared statistic (<4 studies), a fixed-effect model was used as well.[16] Studies that did not provide any measure of dispersion for the mean of a particular variable were excluded from the meta-analysis of that variable. Heterogeneity among the included studies was analyzed with both the Cochran Q statistic and the I2 index. Risk of bias among studies was assessed using the Cochrane Collaboration risk of bias assessment tool.[17] Funnel plots were used to investigate publication bias. Statistical significance was inferred at a p-value <0.05.

Results

The literature search resulted in 1689 publications. Ten of these studies, encompassing a total of 296 patients, met all of the described criteria and were included in the systematic review (Figure 1).[2,18-26] All of these were randomized controlled trials published in English. Table 1 provides an overview of the included studies and baseline patient characteristics.

Nine studies evaluated the effects of recorded music interventions whereas one study evaluated the effects of music therapy.[19] There was a large variation in follow-up duration and in the type, timing and duration of music intervention sessions among the included studies. Seven of the 10 included studies compared music interventions to various other interventions and, thus, did not allow for comparative analysis. Mean age of the patients in the music intervention arms was 65.2±7.3 years and 42% were male. A medical history of hypertension was reported in 92% of the patients and 78% used anti- hypertensive drugs.

Only three studies reported prevalence of comorbidities, such as respiratory disease or diabetes mellitus, which varied from 26% to 100% in their cohorts.[18,20,23] Overall, there was a moderate to high risk of bias among the included studies (see Additional file 2).[17] Due to the small variation in sample size of the included studies, analysis of publication bias was inconclusive (see Additional file 3).

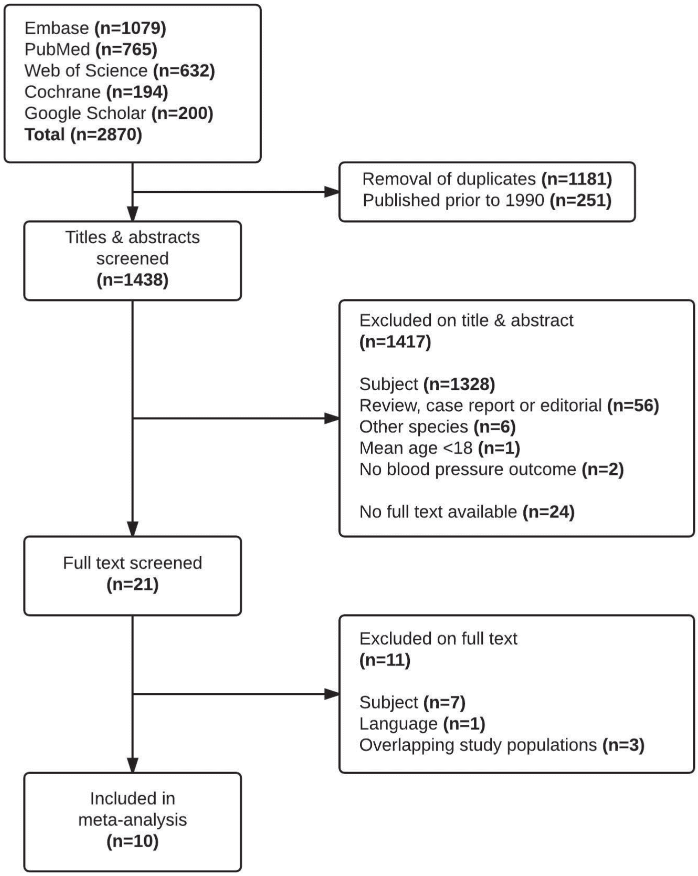

Figure 1. Flowchart of literature search and study selection.

Music interventions and blood pressure

Table 2 shows blood pressure data of the music intervention arms of all ten included studies, pooled in a random-effects model. In the pooled analysis of mean SBP and DBP at baseline and last follow-up, music interventions were associated with a decrease in SBP from 144 mmHg to 134 mmHg, as well as a decrease in DBP from 84 mmHg to 78 mmHg. Pooling of the mean *reduction* in blood pressure in each study also showed a reduction in both systolic and diastolic blood pressure after music interventions, though due to unavailable measures of dispersion, five of the studies were excluded from this analysis. Strong evidence of heterogeneity was observed among all outcome measures.

Table 1. Overview of publications, all RCTs. *=Study with Resting period/No intervention as control group. **=This study used music therapy whereas the others used recorded music interventions. RCT=randomized controlled trial; M=music arm; C=control arm; HT=hypertension.

First author	Year	Study arm	N	Age (years)	M %	History of HT %	Anti-HT drugs %	Follow-up (days)	Timing of intervention	Description
Bekiroglu[18] *	2013	M	30	75.5 (7.1)	57	100	90	28	1x/day	Turkish Classical
		C	30	78.2 (6.1)	57	100	90			Resting Period
Modesti [2]	2010	M	26	58.0 (-)	62	100	77	180	1x/day	Classical, Celtic, Indian
		C	29	58.0 (-)	55	100	73			Music Guided Slow-Breathing (Buteyko-Pranayama)
Zanini [19] *	2009	M	23	66.5 (9.1)	30	100	100	84	1x/week	Recreation, Improvisation, Composition, Listening of music **
		C	22	67.2 (9.6)	55	100	100			No Intervention (Standard Medical Therapy)
Chan [20] *	2009	M	23	>60	44	61	-	28	1x/day-1x/week	Western-, Chinese-, Asian Classical, Western Jazz
		C	24	>60	46	67	-			Resting Period
Tang [25]	2009	M	22	85.0 (5.0)	18	59	32	84	3x/week	Mozart
		C	19	86.0 (6.0)	11	68	42			Audio Relaxation Program Training (Revitalizer II)
Altena [24]	2009	M	15	59.0 (11.7)	53	100	100	63	Preferably daily	Slow Music
		C	15	60.0 (11.0)	47	100	100			Resperate® (Device Guided Breathing Exercises)
Pandic [22]	2008	M	22	66.5 (8.3)	18	100	77	112	3x/week	Relaxing Music
		C	31	70.4 (8.7)	32	100	77			Resperate® (Device Guided Breathing Exercises)
Logtenberg[23]	2007	M	15	59.0 (11.7)	67	100	100	56	1x/day	Various Kinds of Music
		C	15	62.7 (6.0)	20	100	100			Resperate® (Device Guided Breathing Exercises)
Schein[21]	2001	M	29	56.5 (8.0)	39	100	76	56	1x/day	Quiet Synthesized Music with Non-Identifiable Rhythm
		C	32	57.8 (9.4)	56	100	91			Breathe with Interactive Music (BIM) Device
Grossman [26]	2001	M	15	50.0 (4.0)	67	100	53	56	1x/day	Quiet Synthesized Music with Non-Identifiable Rhythm
		C	18	52.0 (12.0)	72	100	56			Breathe with Interactive Music (BIM) Device

Table 2. Pooled outcome measures of music intervention arms of included studies.

First author	SBP baseline (mmHg)	SBP end (mmHg)	DBP baseline (mmHg)	DBP end (mmHg)	Mean SBP reduction (mmHg)	Mean DBP reduction (mmHg)
Bekiroglu[18]	128.2 (6.7)	115.2 (5.3)	77.5*(-)	70.0*(-)	13.0*(-)	7.5*(-)
Modesti [2]	131.0 (13.0)	129.7*(-)	79.0 (9.1)	77.6*(-)	1.3 (7.0)	1.4 (5.4)
Zanini [19]	149.7 (6.4)	133.8 (13.4)	89.1 (9.1)	80.1 (10.6)	15.9*(-)	9.0*(-)
Chan [20]	143.8 (23.8)	130.1 (28.1)	73.1 (11.5)	67.7 (14.0)	17.3*(-)	5.4*(-)
Tang [25]	145.0 (19.0)	139.0 (17.0)	74.0 (10.0)	71.0 (10.0)	6.0*(-)	3.0*(-)
Altena [24]	133.9 (15.7)	131.0 (11.5)	78.4 (11.1)	75.0 (13.2)	2.9 (6.1)	3.4 (9.2)
Pandic [22]	151.8 (15.7)	135.1 (10.6)	82.7 (9.8)	78.7 (7.7)	16.0*(-)	4.1*(-)
Logtenberg [23]	150.4 (8.2)	138.2 (10.3)	87.0 (8.3)	81.5 (8.3)	12.2 (9.4)	5.5 (7.5)
Schein [21]	154.7 (8.5)	143.4*(-)	93.4 (7.1)	87.8*(-)	11.3 (12.8)	5.6 (6.2)
Grossman [26]	155.0 (11.0)	152.1 (12.1)	94.0 (6.0)	92.5 (9.1)	2.9 (12.1)	1.5 (9.1)
R-E model	**144.4**	**134.3**	**83.6**	**78.2**	**6.0**	**3.5**
(95% CI)	**(136.7-152.1)**	**(124.0-144.5)**	**(78.2-88.9)**	**(72.6-83.8)**	**(1.5-10.4)**	**(1.4-5.7)**
Heterogeneity	*X^2 P<0.001*	*X^2 P<0.001*	*X^2 P<0.001*	*X^2 P<0.001*	*X^2 P<0.001*	*X^2P=0.061*
	I^2=97%	*I^2=97%*	*I^2=95%*	*I^2=91%*	*I^2=84%*	*I^2=56%*

Data expressed as ″mean (SD)", "mean (95%CI)" or proportions. * Excluded from analysis due to unavailable measures of dispersion. R-E model=random-effects model; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Music interventions versus standard care

Three of the ten included studies compared music interventions to a control group that received either standard medical therapy or a resting period.[18-20] Mean age of the patients in the control groups was 73.6±7.8 years and 53% were male. A medical history of hypertension was reported in 89% of the patients. When comparing pooled mean SBP/DBP at baseline with pooled mean SBP/DBP at the end of the trial period in a random-effects model, a trend towards a decrease was found in pooled mean SBP and DBP in treatment as well as control groups, while fixed-effect analysis showed a significant decrease in both groups (Table 3). None of these 3 trials made a formal comparison of the observed reduction in blood pressure between the treatment and control groups. Although the magnitude of this reduction appeared to be greater in the experimental groups when represented graphically (Figures 2a and 2b), due to unavailable measures of dispersion a formal comparison of the mean *reduction* in SBP and DBP between the music interventions- and control group was not possible in this subgroup analysis.

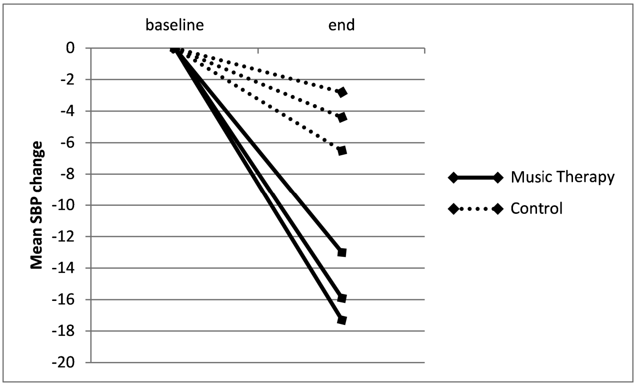

Figure 2a. Mean change in systolic blood pressure in different study-arms in the three comparative studies. SBP= systolic blood pressure.

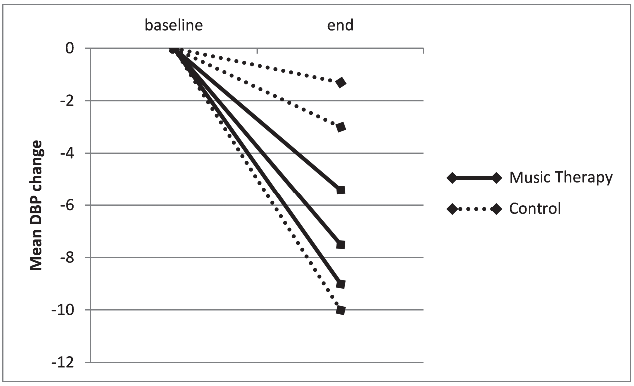

Figure 2b. Mean change in diastolic blood pressure in different study-arms in the three comparative studies. DBP= diastolic blood pressure.

Anxiety and quality of life

Five studies evaluated the effects of the music intervention on quality of life and anxiety.[2,18,19,23,24] One study found significant improvements in quality of life.[19] This finding was not supported by the other studies. Due to the large variety of questionnaires used in these studies, pooling of these results was not possible.

Table 3. Pooled outcome measures of the studies with both intervention and control arms.

		SBP baseline (mmHg)	SBP end (mmHg)	DBP baseline (mmHg)	DBP end (mmHg)
Intervention	Bekiroglu[18]	128.2 (6.7)	115.2 (5.3)	77.5*(-)	70.0*(-)
	Zanini [19]	149.7 (6.4)	133.8 (13.4)	89.1 (9.1)	80.1 (10.6)
	Chan[20]	143.8 (23.8)	130.1 (28.1)	73.1 (11.5)	67.7 (14.0)
Heterogeneity		*X^2 P<0.001 I^2=99%*	*X^2 P<0.001 I^2=96%*	*X^2 P<0.001 I^2=96%*	*X^2 P<0.001 I^2=91%*
R-E model		**140.4**	**126.0**	**81.2**	**74.1**
(95% CI)		**(123.7-157.2)**	**(111.5-140.5)**	**(65.5-96.9)**	**(61.9-86.2)**
F-E model		**138.2**	**117.5**	**82.9**	**75.6**
(95% CI)		**(136.5-140.0)**	**(115.7-119.2)**	**(80.0-85.9)**	**(72.1-79.0)**
Control	Bekiroglu[18]	121.2 (5.9)	114.7 (6.0)	80.0*(-)	70.0*(-)
	Zanini [19]	145.4 (5.6)	141.0 (19.8)	86.9 (11.3)	83.9 (12.4)
	Chan[20]	143.7 (22.1)	140.9 (26.4)	72.7 (12.8)	71.4 (13.6)
Heterogeneity		*X^2 P<0.001 I^2=99%*	*X^2 P<0.001 I^2=96%*	*X^2 P<0.001 I^2=94%*	*X^2 P=0.001 I^2=91%*
R-E model		**136.6**	**131.8**	**79.8**	**77.7**
(95% CI)		**(117.6-155.6)**	**(110.9-152.7)**	**(65.9-93.8)**	**(65.4-89.9)**
F-E model		**132.5**	**117.3**	**80.4**	**78.0**
(95% CI)		**(130.9-134.0)**	**(115.2-119.3)**	**(76.9-83.9)**	**(74.2-81.7)**

Data expressed as "mean (SD)", "mean (95%CI)" or proportions. * Excluded from analysis due to unavailable measures of dispersion. R-E model=random-effects model; F-E model=fixed-effect model; SBP=systolic blood pressure; DBP=diastolic blood pressure.

Discussion

This systematic review and meta-analysis of ten randomized controlled trials evaluating the effect of music interventions in the treatment of hypertension found a decrease in pooled mean SBP and DBP after application of music interventions, however this decrease did not reach statistical significance. In the subgroup of three studies with a standard medical therapy or resting control group, random-effects analysis revealed a trend towards a blood pressure decrease in both the intervention and the control groups, while fixed-effect analysis showed a significant decrease in both groups.[18-20]

Unfortunately, a valid comparison between the music intervention- and control group did not prove possible, and a cause-effect relationship between music interventions and hypertension remains to be determined.

Research has shown that relatively small decreases, as low as 5 mmHg reduction in systolic blood pressure, would result in 7% reduction in all-cause mortality, 9% reduction in coronary heart disease related mortality and 14% reduction in stroke-related mortality.[1,27] These numbers illustrate the substantial benefit of even small decreases in blood pressure, and if indeed in future studies music interventions prove to be effective, it would provide a valuable low cost therapeutic measure.

The mechanism by which music modulates blood pressure remains unclear. Studies on device-guided breathing hypothesize that reduction in blood pressure is achieved by modulating autonomous cardiovascular regulation by slowing down the breathing frequency.[2,21-25] As a result, baroreflex sensitivity is lowered, parasympathetic tonus increases and sympathetic tonus decreases, resulting in a decrease in blood pressure. Music listening might elicit the same relaxation response, resulting in a decrease in blood pressure. Another possible mechanism of action is that music interventions lead to increased brain dopamine levels via a calmodulin-dependent system. This increase in dopamine levels inhibits sympathetic activity via dopamine-2 receptors which in turn reduces blood pressure.[28]

Furthermore, music may direct one's attention to a more pleasant emotional state, thereby triggering feelings associated with physical and mental relaxation.[29] It might also give rise to positive emotions which are connected with the activation of the limbic system, thereby releasing endorphins affecting physiological systems.[30] Moreover, a recent review on magnitude of blood pressure reduction in the placebo arms of hypertension trials found a significant pooled blood pressure reduction of 6 mmHg after placebo intervention.[31] This non-trivial placebo effect should be taken into account when offering these patients any treatment.

The random-effects subgroup analysis of the three trials with comparable control groups showed a trend towards a decrease in blood pressure in both the intervention- and control groups.[18-20] Although a random-effects model may be most appropriate in this case in light of the substantial heterogeneity among these studies, the small number of studies makes quantitative estimation of the between-study variance in this subgroup very unreliable. We therefore chose to apply a fixed-effect model to this subgroup as well, which revealed a significant decrease in blood pressure in both intervention- and control groups. However, this fixed-effect analysis does not take the considerable heterogeneity that we observed into account. Thus, in the case of this subgroup, the inherent limitations of both methods renders these analyses inconclusive and the results should be interpreted with caution.

The observed blood pressure decrease in the control groups of this subgroup analysis may be explained in part by the fact that in two of these studies the patients were prescribed a resting period as control, possibly eliciting autonomic responses similar to those described above.[18,20] When visually assessing the mean *reduction* in SBP and DBP in each of these studies, the magnitude of this reduction appeared to be greater in the experimental groups, however a formal comparison of pooled mean *reduction* of blood pressure between the music and control group was not possible due to missing measures of dispersion concerning this reduction. As a result, a cause-effect relationship could not be established and the only conclusion to be drawn from our meta-analysis, is that we observed a significant decrease in blood pressure in hypertensive patients who underwent music interventions, but also in control patients. These observations could simply be the result of regression toward the mean.

Prevalence of co-morbidities, such as respiratory disease or diabetes mellitus, varied from 26% to 100% in the three studies that reported it.[18,20,23] Data on association of co-morbidities and response to music interventions were not available from these studies. The presence of comorbidities, but also etiology of hypertension, treatment resistance and possible seasonal effects could potentially influence the effect of an intervention.[31,32] These aspects should be taken into account when evaluating the effect of the intervention.

Anxiety, Depression and Quality of Life

Zanini et al. was the only study that found an association between music interventions and quality of life, which might be explained by the use of music therapy in their study in contrast to recorded music interventions in the other studies.[19] Although recorded music interventions were found to be as effective as music therapy in reducing periprocedural pain and anxiety in children undergoing medical procedures,[33] it is likely that the effect of music interventions in other settings may indeed be influenced by the method of administration. In some disease states, for instance in psychological or psychiatric disorders or rehabilitation, the involvement of a credentialed music therapy professional may provide better results than listening to music without a music therapist. Furthermore, the difference in effectiveness of music therapy compared with recorded music interventions may depend not only on the disease state, but also on which outcome is studied. Improvement of quality of life might be an outcome where dedicated involvement of a therapist providing personalized care may yield greater improvement than solely listening to music. Pain relief on the other hand, may be more strongly regulated by mechanisms triggered by both music therapy and recorded music interventions, such as redirecting someone's attention or activation of the limbic system and the subsequent release of endorphins. Pain relief, in contrast to improvement of quality of life, may therefore be less dependent on involvement of a music therapist. Furthermore, the variation in results concerning quality of life among the included studies might also be explained by the shorter duration of some studies and the difference in study populations.

As for anxiety, Bekiroglu et al. found no significant effects of music interventions.[18] As they suggest, this may be explained by the lack of high anxiety levels at baseline in their patient population, as most likely may be the case in the hypertensive patient population at large. Music interventions might be more effective in decreasing anxiety when patients face a more challenging condition causing extensive anxiety, such as patients suffering from myocardial infarction or facing surgery.[6,10,34,35]

Music intervention variability

A major complicating factor in our analysis of music interventions was the large variation in the type of music administered and the frequency and duration of interventions in the included studies(Table 1). Although the majority of interventions included classical, relaxing or slow music, no clear recommendations exist on how music interventions should be administered in the treatment of high blood pressure. A systematic review on music interventions in anxiety and pain relief in clinical practice provide some insights on which music may be most beneficial.[36] The authors recommend patient-preferred slow and flowing music, approximately 60 to 80 beats per minute, with a minimum duration of 30 minutes in length. Research in hypertensive animal models found music containing high-frequency sounds to stimulate dopamine synthesis leading to blood pressure reduction.[37] Moreover, music interventions may be greatly enhanced by preference and familiarity of the patients. Anxiety- and pain reducing effects appear to be greatest when people are given a choice of music to listen to or listen to their own favorite music and other research suggests patient-preferred music, as opposed to prescribed music, to be a critical factor in the effectiveness of music interventions.[5,10,35,38] The observed large variation in the types of music used, the applications of music interventions, and the outcomes studied, illustrate the complexity of the topic, and pose a major challenge for future studies.

Limitations

As with any meta-analysis, the general limitations inherent to meta-analyses should be taken into account.[39] Since the number of patients included in each study is very small and no formal comparison of the treatment effect between the music intervention- and control group was possible, no hard conclusions can be drawn concerning the effect of music interventions on hypertension. As described above, the inherent limitations of both fixed- and random-effects models in the case of a very small, heterogeneous sample of studies rendered our subgroup analysis inconclusive. There was significant heterogeneity in the reported outcomes, which is most likely the result of the large methodological variation among the included studies with regard to patient characteristics, the type of music administered, the duration of each intervention and the follow-up time.

Randomization was mentioned in all trials, though specific information on trial conduct, such as allocation concealment and blinding, was reported poorly and therefore quality assessment of the included studies was limited (see Additional file 2). This, as well as incomplete outcome data, gave rise to a moderate to high risk of bias in the included studies. Publication bias may have affected the outcomes, as some abstracts were unavailable as full-text articles (Figure 1).

Perspectives

Our results show that current studies on the effect of music interventions on lowering blood pressure in hypertensive patients do not provide evidence on a possible cause-effect relationship. Since music interventions may be of beneficial value in hypertensive patients, presenting a potential adjuvant to standard pharmacological treatment, there is a need for further high quality research on the subject. Music interventions could not only be of value in case of multidrug therapy or treatment resistant hypertension, but might also be offered as a durable treatment modality in developing countries. However, well-designed high-quality, sufficiently powered randomized controlled trials are first required to establish a cause-effect relationship between music interventions and blood pressure reduction in hypertensive patients.

This research, ideally in the form of large, well-reported randomized controlled trials following the CONSORT statement for nonpharmacological trials with clearly-defined interventions and controls and adequate statistical analyses, could explore the ability of music interventions in lowering blood pressure in a large population, examine the permanence of the reduction in blood pressure and elucidate which patients could benefit most.[40] The influence of different forms of music intervention, with regard to factors such as genre and patient-preference, should be investigated. In addition both music therapy and recorded music interventions could be analyzed to obtain more knowledge on the manner of administration of music interventions in the treatment of hypertension. Finally, evaluation of factors that may play a role in the sensitivity to corrections of elevated blood pressure, such as baroreflex sensitivity, can be explored.

Conclusion

This systematic review and meta-analysis found a trend towards a decrease in blood pressure in hypertensive patients who received music interventions. Unfortunately, this decrease does not provide proof for a cause-effect relationship, as a formal comparison with the control group is lacking. Therefore the most important conclusion of this study is that the quest for answers is still ongoing. Considering the potential value of this safe, low-cost intervention, there is an urgent need for well-designed, high quality, sufficiently powered randomized studies that assess the efficacy of music interventions in lowering blood pressure.

Acknowledgements

We would like to thank Wichor Bramer, biomedical information specialist, for his expertise with the literature search. We would like to thank Nanno Kleefstra for providing measures of dispersion for the outcome measure in his trial.

Appendices

Appedix 1. Literature Search.

Embase.com 1079

(music/de OR 'acoustic stress'/de OR 'music therapy'/de OR singing/de OR musician/de OR 'auditory stimulation'/de OR 'MP3 player'/de OR 'tape recorder'/de OR 'compact disk'/de OR (music* OR melod* OR song* OR ((audi* OR acoustic* OR sound*) NEAR/6 (stimul* OR stress)) OR mp3 OR earphone* OR headphone* OR ((ear OR head) NEXT/1 phone*) OR 'compact disk' OR ((cd OR cassette) NEXT/1 player*) OR speaker*):ab,ti) AND ('abnormal blood pressure'/de OR 'elevated blood pressure'/exp OR 'blood pressure measurement'/exp OR 'blood pressure meter'/exp OR 'blood pressure'/exp OR (hypertens* OR ((blood OR arter* OR diastol* OR systol*) NEAR/3 pressure) OR sphygmomanomet*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (ovidSP) 751

(music/ OR "music therapy"/ OR singing/ OR "Acoustic Stimulation"/ OR "MP3-player"/ OR "Tape Recording"/ OR Radio/ OR "Compact Disks"/ OR (music* OR melod* OR song* OR ((audi* OR acoustic* OR sound*) ADJ6 (stimul* OR stress)) OR mp3 OR earphone* OR headphone* OR ((ear OR head) ADJ phone*) OR "compact disk" OR ((cd OR cassette) ADJ player*) OR speaker*).ab,ti.) AND (exp "Hypertension"/ OR "Blood Pressure Determination"/ OR exp "blood pressure"/ OR (hypertens* OR ((blood OR arter* OR diastol* OR systol*) ADJ3 pressure) OR sphygmomanomet*).ab,ti.) NOT (exp animals/ NOT humans/)

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((music* OR melod* OR song* OR ((audi* OR acoustic* OR sound*) NEAR/6 (stimul* OR stress)) OR mp3 OR earphone* OR headphone* OR ((ear OR head) NEXT/1 phone*) OR 'compact disk' OR ((cd OR cassette) NEXT/1 player*) OR speaker*):ab,ti) AND ((hypertens* OR ((blood OR arter* OR diastol* OR systol*) NEAR/3 pressure) OR sphygmomanomet*):ab,ti)

Web-of-science 632

TS=(((music* OR melod* OR song* OR ((audi* OR acoustic* OR sound*) NEAR/6 (stimul* OR stress)) OR mp3 OR earphone* OR headphone* OR ((ear OR head) NEAR/1 phone*) OR "compact disk" OR ((cd OR cassette) NEAR/1 player*) OR speaker*)) AND ((hypertens* OR ((blood OR arter* OR diastol* OR systol*) NEAR/3 pressure) OR sphygmomanomet*)))

PubMed publisher 14

((music*[tiab] OR melod*[tiab] OR song*[tiab] OR ((audi*[tiab] OR acoustic*[tiab] OR sound*[tiab]) AND (stimul*[tiab] OR stress)) OR mp3[tiab] OR earphone*[tiab] OR headphone*[tiab] OR ear phone*[tiab] OR head phone*[tiab] OR compact disk*[tiab] OR cd player*[tiab] OR cassette player*[tiab] OR speaker*[tiab])) AND (((blood[tiab] OR arter*[tiab] OR diastol*[tiab] OR systol*[tiab]) AND pressure[tiab]) OR sphygmomanomet*[tiab])) AND publisher[sb]

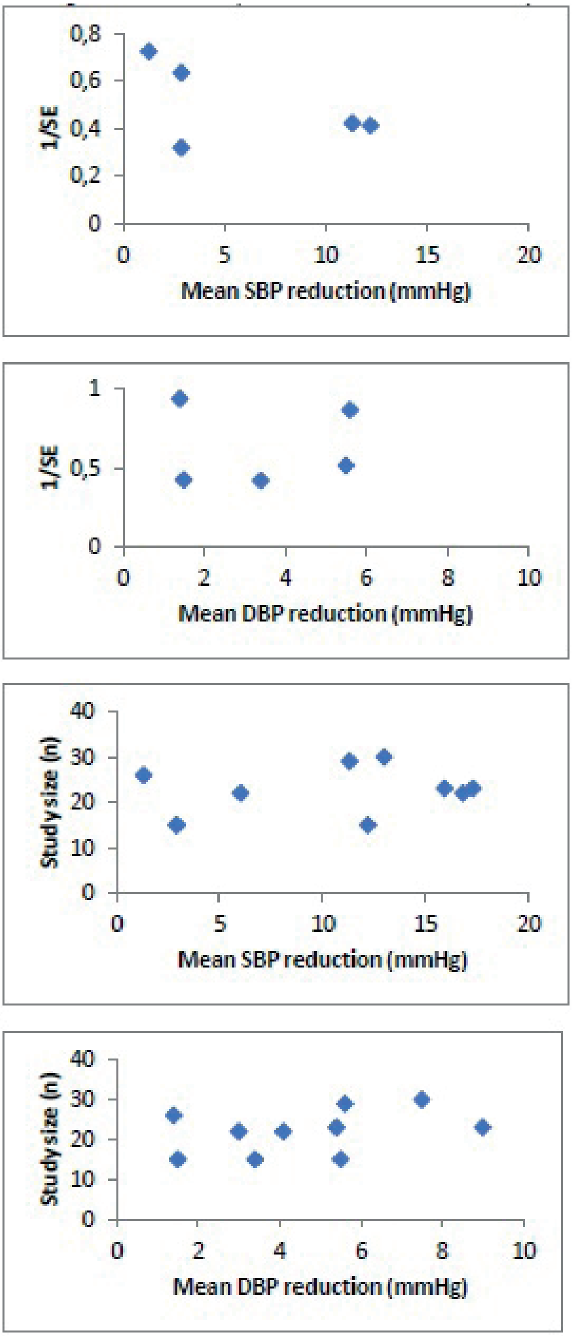
Google scholar

Music|singing|musician|"auditory stimulation "blood pressure"|hypertension

Appendix 2. Risk of Bias Assessment.

	Sequence generation	Allocation sequence concealment	Blinding of participants*	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessment	Incomplete outcome data	Other potential sources of bias
Bekiroglu (2013)	Adequate	Unclear	Inadequate	Unclear	Inadequate	Adequate	No missing data	-
Modesti (2010)	Unclear	Unclear	Inadequate	Adequate	Unclear	Adequate	2 missing data	-
Zanini (2009)	Adequate	Unclear	Inadequate	Unclear	Unclear	Adequate	1 missing data	-
Chan (2009)	Adequate	Adequate	Inadequate	Inadequate	Inadequate	Adequate	3 missing data, imputation of mean	Funding by School of Nursing of Hong Kong Polytechnic University (A-PH29)
Tang (2009)	Adequate	Unclear	Inadequate	Unclear	Unclear	Adequate	2 missing data	Funding John J. Locke Jr. Charitable Trust, Perpetuity
Altena (2009)	Adequate	Adequate	Inadequate	Unclear	Unclear	Adequate	No missing data, ITT analysis	Financial support Medical Research Foundation Zwolle
Pandic (2008)	Adequate	Adequate	Inadequate	Unclear	Unclear	Unclear	1 missing data	Grant Health & Medical Care Committee Göteborg & Bohuslän
Logtenberg (2007)	Adequate	Unclear	Inadequate	Unclear	Unclear	Adequate	No missing data, ITT analysis	Financial support Medical Research Foundation and Langerhans Foundation
Schein (2001)	Adequate	Unclear	Inadequate	Adequate	Adequate	Adequate	4 missing data	Sponsored by InterCure Ltd, Chief Scientist is last author
Grossman (2001)	Unclear	Inadequate	Inadequate	Adequate	Adequate	Adequate	1 patient changed study-arm	Sponsored by InterCure Ltd, Chief Scientist is last author

* Blinding of participants was judged as inadequate in all studies as participants cannot be blinded for music- interventions. ITT=Intention To Treat.



Appendix 3. Funnel plots. Funnel plots of mean reduction in blood pressure against each study's precision or size. Because of missing measures of dispersion in 5 out of 10 studies, plotting was also performed against study size.

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PART II

Anxiety, pain, and music in pediatric surgery

Chapter 5

Music interventions in pediatric surgery (the MUSIC study): a randomized clinical trial

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Abstract

Background: Perioperative music interventions have been shown to reduce anxiety and pain in adults. This inexpensive, easily applicable intervention could be of benefit to children as well. Our objective was to determine the effects of music interventions on distress, anxiety, and postoperative pain in infants having surgery.

Methods: The MUSIC study was designed as a parallel single-blind randomized controlled trial with an a-priori formulated hypothesis. Data were collected between August 2015 and October 2016 in a single tertiary care children's hospital. There was a 24 hours follow-up with blind primary outcome assessment. A random sample of 432 eligible 0-3 years old infants admitted for orchidopexy, hypospadias, or inguinal hernia repair receiving general anesthesia and caudal block were asked for participation. Subjects were assigned to a preoperative music intervention (PM), or pre- and intraoperative music intervention (PIM), or no music intervention (control) via random allocation using a computer-generated list with use of opaque envelopes. The main outcome measure was the postoperative level of distress assessed with the COMFORT-B scale; furthermore preoperative level of distress; preoperative anxiety; and physiologic measurements such as heart rate and blood pressure were measured. The trial was registered at Dutch Trial Register, number NTR5402, www.trialregister.nl.

Results: 195 infants with median age 6.9 months (IQR 3.3-11.1) were randomized, 178 of whom were included in the primary analysis. A non-significant difference in COMFORT-B scale scores between the PIM-group and control group at 4 hours after surgery was found (mean difference -1.22 (95%CI -2.60; 0.17); p=0.085). Additional analysis showed weak non-significant evidence for an interaction effect between music exposure and COMFORT-B score at baseline; p=0.027 with a Bonferroni-adjusted significance level of 0.025. General linear modeling showed a statistically significantly reduced heart rate after the preoperative music intervention in the holding area in the combined PM- and PIM-group compared to the control group; p=0.003. The differences in heart rate between the three study arms at all time points were not statistically significant; p=0.069.

Conclusions: Music interventions do not seem to benefit all young infants having surgery. The potential benefits of music interventions in the preoperative period and in more distressed children warrant further exploration.

Introduction

Perioperative anxiety and pain are frequent in the pediatric population. Up to 75% of children scheduled to undergo surgery experience fear and anxiety during the preoperative period.[1,2] Preoperative anxiety is a significant predictor for the level of postoperative pain[3] and almost 80% of all patients undergoing surgery experience postoperative pain.[4] Postoperative pain management still remains an important issue in pediatric surgery[5] and as both preoperative anxiety and postoperative pain may impair recovery from surgery, interest is growing in finding ways that may help reduce these symptoms, such as perioperative music.

Music interventions can reduce anxiety and pain perioperatively [6,7] and have shown their benefit to children in various health care procedures.[8,9] A meta-analysis evaluating effects of music interventions in pediatric surgery found significantly reduced pain, anxiety and distress in children.[10] Due to methodological issues such as unclear reporting on risk of bias or power calculation, the need for a rigorous trial investigating benefits of music in pediatric surgery was mentioned, however.[10]

Preoperative as well as postoperative music interventions have been shown to reduce postoperative anxiety and pain in adults, but intraoperative music interventions during general anesthesia have also been shown to reduce anxiety and pain.[7,11,12]

We hypothesized that intraoperative music interventions might amplify the anxiety- and pain-reducing effects of preoperative music interventions, and aimed to examine whether preoperative and intraoperative music interventions could decrease distress, anxiety and postoperative pain in young children having different types of common elective surgical procedures.

Methods

This study was a parallel, single-blind, randomized controlled trial. This study was approved by the University´s Institutional Review Board (IRB#2015-264) and written informed consent was obtained from all parents or legal representatives of subjects participating in the trial. The trial was registered prior to patient enrollment at www.trialregister.nl (NTR5402, principal investigator: prof. R.M.H. Wijnen, date of registration: 27 August 2015). Participants were recruited between September 2015 and October 2016 in the Erasmus Medical Center – Sophia Children's Hospital, Rotterdam, the Netherlands. The study was reported following the CONSORT guidelines for randomized trials of non-pharmacological treatment.[13]

Participants

Eligible for participation were infants aged 0-3 years, American Society of Anesthesiologists (ASA) physical status 1 or 2, admitted for orchidopexy, hypospadias, or inguinal hernia repair receiving general anesthesia and caudal block, and with parents' good knowledge of Dutch or English language. Hearing impairment, emergency surgery, premedication with midazolam, impaired communication with parents or missing informed consent applied as exclusion criteria.

Intervention

Subjects were allocated to either a preoperative music intervention (PM-group), pre- and intra-operative music intervention (PIM-group); or no music intervention (control). The music intervention consisted of 15.08 minutes of music repeatedly played. The music (Supplemental material 1) was based on recommendations from literature,[14] such as slow, flowing rhythm, approximately 60-80 beats per minute and played by string instruments; and was reviewed by qualified music therapists. Music was played with a volume of approximately 45 decibel (limited to 60 decibel) via the Sony MDR-ZX550BN headphone (©2014 Sony Corporation, Tokyo, Japan). The medical technical department approved safety of headphones. Following use, the headphone was cleaned and disinfected with chlorine and alcohol. If the headphones were not tolerated, music was played via Bose Soundlink Mini Bluetooth speaker II (©2014 Bose Corporation, Framingham, USA).

Outcomes

The primary outcome was behavioral change assessed with the COMFORT-B scale (Supplemental material 2), an observational scale ranging from 6 (no distress or pain) to 30 (extreme distress or pain) and validated to assess distress and postoperative pain in children aged 0-3 years.[15-17] Secondary outcomes were change in Numeric Rating Scale (NRS) score for observed pain, level of preoperative anxiety at the holding area and at induction of anesthesia assessed with the modified Yale Preoperative Anxiety Scale – Short Form (m-YPAS-SF) (Supplemental material 3),[18,19] physiologic parameters, incidence of emesis, use of anesthetics and analgesics. For day-care patients, telephonic evaluation of postoperative pain 24 hours postoperatively was done with the ten-item Parental Postoperative Pain Measure – Short Form (PPPM-SF).[20] Salivary cortisol was collected before, during and after surgery, but after collection of 30 samples, only two provided enough saliva for analysis and the collection was stopped.

Procedure

The investigator (RK) explained the study procedure to the parents at the preoperative consultation or via telephone. At the day of surgery, baseline characteristics and measurements were taken at the ward. The investigator (RK) and a research assistant accompanied the child and one parent to the holding area and operating room (OR). A preoperative music intervention was played to subjects in PM- and PIM-groups, starting at departure from the ward, continuously played at the holding area, and stopped upon arrival in the OR preparation room. Before entering the OR, the music playing device was removed. Subjects in the control group were also accompanied but did not receive a music device. The parent left the OR after induction of anesthesia. After application of caudal block, all patients received headphones, but only the PIM-group was exposed to music during surgery. Just before awakening from anesthesia, the headphones were removed.

Anesthetic treatment

A standard anesthesia protocol was applied. EMLA cream® was applied at the intravenous line insertion site. Anesthesia was induced with propofol IV (2-4 mg/kg), or by inhalation of sevoflurane in a mixture of oxygen and air. Fentanyl IV (1 µg/kg) was administered. A laryngeal mask was placed. A caudal block was given with ropivacaine 0.2%, 1.5 ml/kg. Anesthesia was maintained with sevoflurane (0.6-1.0 MAC) in a mixture of oxygen and air. Fentanyl IV (1 µg/kg) was administered when heart rate (HR) or blood pressure (BP) increased with ≥ 20% compared to induction of anesthesia. At the end of surgery, acetaminophen IV 20 mg/kg, and in children > 6 months additionally diclofenac IV 1 mg/kg, was administered. Analgesia in the first 24 hours postoperative hours consisted of a weight-based dose of acetaminophen and, in children > 6 months, a weight-based dose of diclofenac. A numeric rating scale (NRS) score > 4 on the PACU indicated administration of morphine 0.1 IV mg/kg.

Surgical treatment

Surgical treatment was inguinal hernia repair, undescended testis surgery, or hypospadias correction. Inguinal hernia repair was performed standardly with a unilateral or bilateral open inguinal approach. Undescended testis surgery was done with orchidopexy via an open inguinal approach if the testis was palpable; and with a laparoscopic or open inguinal approach followed by either orchidopexy, orchiectomy of the testicular remnant, or a Fowler-Stephens I procedure if the testis was non-palpable. Hypospadias was corrected using the tubularized incised plate urethroplasty (TIP) technique.

Randomization

A computer generated, blocked randomization list with equal allocation ratio was generated by our statistician. Patients were enrolled by one researcher (RK). After obtained written informed consent, participants were subsequently allocated by the use of opaque envelopes to either the PM-group, the PIM-group or the control group. Usually the primary researcher (RK) assisted by a research assistant attended the subjects and managed the interventions. Two-minute video-recordings of subjects (made with iPad mini 2 (© Apple Inc. Cupertino, USA)) before or after interventions allowed blind primary outcome assessment afterwards by trained observers. Primary outcome assessors, surgeons, anesthesiologists and operating room (OR) staff were blinded to the study group allocation.

COMFORT-B outcome assessment

Two outcome assessors were trained to reliably apply the COMFORT-B scale by video footage. Inter-rater agreement was calculated with the linearly weighted Cohen's kappa (a score above 0.65 was considered acceptable) on ten assessments following training, and revealed a Cohen's kappa coefficient of 0.77 and 0.84 for each assessor versus the trainer. Two and four months after training sessions, inter-rater reliability between outcome assessors was repeatedly calculated over 10 video assessments and revealed Cohen's kappa coefficients of 0.72 and 0.82, respectively.

Sample size

Sample-size calculation was based on an analysis of covariance (ANCOVA) model with adjustment for the baseline COMFORT-B score and trial arm. For previous COMFORT-B scores collected in the Erasmus MC – Sophia Children's Hospital (97,802 observations) the mean (SD) score was 12.8 (3.7), and the within-subject correlation of the measurements was approximately 0.25. We estimated a 2-point difference on the COMFORT-B scale to be a clinically relevant effect from the music intervention, which yields a moderate effect size of 0.54. To obtain a power of 80% using a two-sided Bonferroni-adjusted significance level of 0.025 to correct for multiple comparisons, each study arm required 61 subjects. To account for possible drop-outs, the total sample size was chosen to be 195 subjects.

Statistical analysis

Data were collected on a case record form, transferred to and double checked in the OpenClinica open source software, version 3.8 (© OpenClinica LLC and collaborators, Waltham, MA, USA, www.OpenClinica.com). Data were analyzed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Normally distributed variables are summarized using means and standard deviations; continuous variables that were not normally distributed are summarized using medians and interquartile ranges (IQRs), and categorical variables are summarized using percentages. Kolmogorov-Smirnoff testing was used to assess normality of outcomes. Data were compared between treatment groups using chi-square or Fisher exact tests for categorical variables, and Kruskal-Wallis or Mann-Whitney U tests for continuous variables. NRS scores had a skewed distribution and were coded as 0 (no pain) vs ≥ 1 (minor to severe pain) before analyzing differences between groups. Outcomes were assessed at six different time points: T1 ward preoperative (COMFORT-B, physiological variables, baseline values); T2 holding area (COMFORT-B, physiological variables, m-YPAS-SF); T3 during surgery (physiological variables, m-YPAS-SF (at induction)); T4 30 minutes postoperative at PACU (COMFORT-B, physiological variables); T5 ward 4 hours postoperative (COMFORT-B, physiological variables); T6 ward 24 hours postoperative (COMFORT-B, physiological variables).

Primary outcome analysis of the COMFORT-B score was done with analysis of covariance (ANCOVA), using baseline score and study arm as predictors. Multivariable analysis was performed to adjust the ANCOVA model for the possible confounders age, preoperative fasting time, diagnosis, and method of administration (headphone versus speaker) at T1, T2, T4, T5, and T6. In an additional analysis only at T5, the interaction term of study arm and baseline COMFORT-B score was added to the ANCOVA model, to examine whether the effects of the intervention varied between infants who were more or less distressed at baseline. For the analysis of preoperative anxiety with the continuous variable m-YPAS-SF, both music intervention groups were combined as they had the same preoperative intervention.

General linear models were used to evaluate the effect of music intervention(s) over time on physiologic outcomes HR, systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and oxygen saturation (SpO2). A general linear model is a linear regression model for repeated measurements in which a covariance matrix of the errors of different observations of the same patient is used to describe the within-subject correlations. Study arm and time point were used as independent variables (T1: ward preoperative (HR, SBP, DBP, MAP), T2: holding area (HR), T3: mean during surgery (HR, SBP, DBP, MAP, SpO_2), T4: Post anesthesia care unit (PACU) 30 minutes postoperative (HR, SpO_2), T5: ward 4 hours postoperative (HR, SBP, DBP, MAP). During surgery, physiologic variables were measured every 5 minutes and the mean results were included as a time point in the model. An unstructured error covariance matrix was used in the general linear model. An additional analysis was performed for HR at the time points ward and holding with both music intervention groups combined as they had the same preoperative intervention.

The analyses were based on a modified intention-to-treat principle, as patients were analyzed according to the randomized study arm, with the exception that patients who did not receive surgery (for instance due to local skin infection or general illness) or caudal anesthesia (due to failure of the anesthetic procedure) were excluded. Patients with missing data for the COMFORT-B score at baseline or follow-up were excluded from the ANCOVA models, but data were used in other analyses (such as analyses of physiological parameters). The statistical tests were two-sided with a significance level of 0.05, a Bonferroni correction (adjusted significance level of 0.025) was applied to adjust for multiple comparisons in the primary outcome analysis.

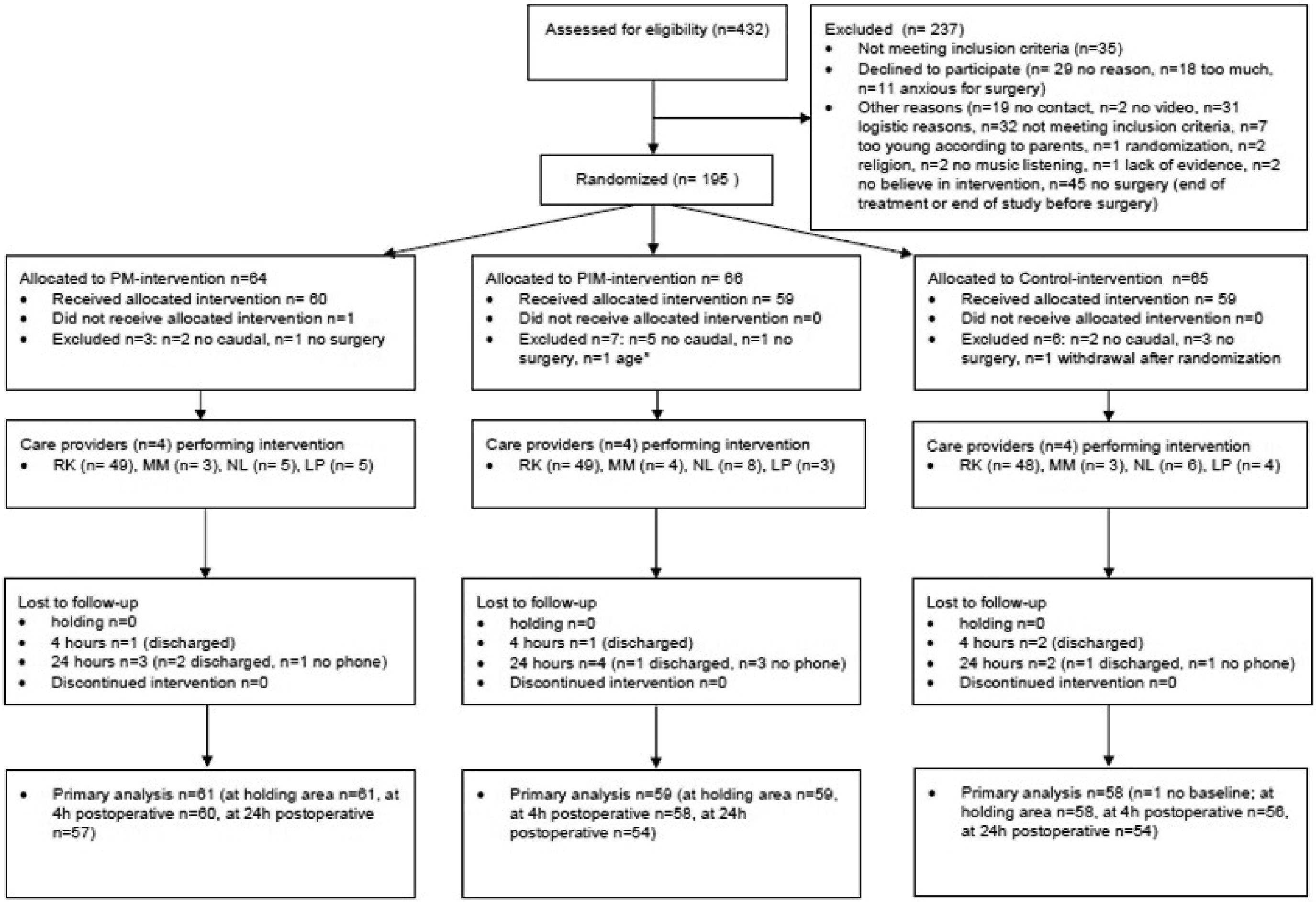

Figure 1. Flowchart. PIM= pre- and intraoperative music, PM= preoperative music, Control= no music. *Surgery of one patient was postponed due to fever, but patient was 4 years of age at second time.

Results

One hundred ninety-five infants participated in the trial. Seventeen of those were excluded, leaving 178 infants for primary outcome analysis (see Figure 1 flowchart). The median age was 6.9 months (IQR 3.3-11.1), and 92% were boys (see Table 1 baseline characteristics divided by study group). The time between randomization and initiation of the intervention was approximately one hour, and follow-up was 24 hours.

Effect of music interventions on COMFORT-B scores

Figure 2 presents the raw mean COMFORT-B difference scores between baseline and follow-up for the three groups. The music intervention seemed to induce a greater decrease in COMFORT-B scores from baseline in both music interventions groups compared to the control group, but no significant difference was found between all study-groups at 4 hours postoperatively; p=0.219, nor between the PIM-group and control group; p=0.085. COMFORT-B scale scores as well as change scores at follow-up, together with the mean differences between study-groups, are shown in Table 2. Additional analysis of an interaction between study arm and baseline score of 174 subjects showed weak evidence for a greater reduction in COMFORT-B scores at 4 hours postoperative following music intervention(s) (compared to controls) in patients with higher baseline COMFORT-B scores; however, the interaction was not statistically significant with p=0.027 and p=0.078 for the PIM-group and the PM-group, respectively. Results from the multivariable analysis showed that a longer total duration of preoperative fasting statistically significantly increased COMFORT-B scores 4 hours postoperatively; p=0.026.

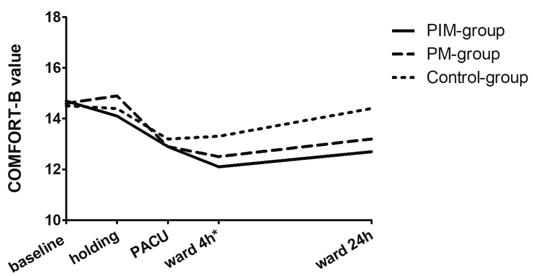

Figure 2. Mean COMFORT-B values for each study group from baseline to follow-up. *No statistically significant differences were found between study groups in the primary analysis at any time point, but additional analysis showed weak non-significant evidence for the association between higher COMFORT-B scores at baseline and greater reductions in COMFORT-B scores at four hours after surgery between the PIM-group and the Control group; p=0.027. PIM=pre- and intraoperative music, PM=preoperative music, Control=no music, PACU=post anesthesia care unit.

Effect of music interventions on secondary outcomes

We found no statistically significant differences between the three study groups in NRS pain scores, preoperative anxiety, PPPM-SF scores (see Table 3) or in the use of drugs (see Supplemental Material 4). We found no statistically significant differences in occurrence of emesis between the three study groups (n=1/57 in PIM, n=3/60 in PM; n=2/53 in control); p=0.621.

Table 1. Baseline characteristics of the study groups. PIM=pre- and intraoperative music, PM=preoperative music, Control=no music, MI=music intervention, r=right, l=left, b=bilateral, FS-I= Fowler Stephens- I procedure. [a]Of one subject, COMFORT-B baseline score was missing, leaving 178 subjects for primary analysis. [b]Subjects in all study groups received headphones during surgery, however only subjects allocated to the PIM-group received an MI during surgery.

	Total n=179[a]	PIM n=59	PM n=61	Control n=59
Sex m/f *n (%)*	164/15 (92/8)	56/3 (95/5)	52/9 (85/15)	56/3 (95/5)
Age in months *median (IQR)*	6.9 (3.3-11.1)	6.9 (3.4-11.8)	6.6 (3.2-10.6)	7.3 (3.3-10.9)
Diagnosis				
Inguinal hernia *n (%)*	102 (57)	33 (56)	37 (61)	32 (54)
r/l/b	54/35/13	19/11/3	18/13/6	17/11/4
Undescended testis *n (%)*	41 (23)	16 (27)	10 (16)	15 (25)
Orchidopexy r/l/b	15/15/4	6/5/1	2/4/2	7/6/1
Open FS-I	3	3	-	-
Orchiectomy	4	1	2	1
Hypospadias *n (%)*	36(20)	10 (17)	14 (23)	12 (20)
Weight kilogram *median (IQR)*	7.7 (5.4-10.0)	7.6 (5.3-10.0)	7.0 (5.2-9.9)	8.0 (5.8-10.0)
Comfort-score *n (%)*	178 (99)	59 (100)	61 (100)	58 (98)
Baseline *mean (SD)*	14.6 (2.4)	14.7 (2.7)	14.6 (2.6)	14.5 (1.8)
NRS baseline *median (IQR)*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Intervention by				
Headphone *n (%)*	95 (80)	47 (80)	48 (79)	-
Speaker *n (%)*	24 (20)	12 (20)	12 (20)	-
No MI *n(%)*	60 (34)	-	1 (2)	59 (33)
Induction				
Intravenously	39 (22)	9 (15)	12 (20)	18 (30)
Inhalation	140 (78)	50 (85)	49 (80)	41 (70)
Duration (minutes)				
Preoperative MI *mean (SD)*	15.8 (6.4)	15.9 (5.7)	15.8 (7.0)	-
Intra-operative MI[b] *mean (SD)*	47.2 (29.5)	45.5 (23.6)	-	-
Anesthesia *mean (SD)*	70.0 (31.1)	66.9 (24.9)	72.5 (37.2)	70.3 (30.2)
Surgery *mean (SD)*	39.5 (26.7)	37.4 (21.6)	41.5 (31.3)	39.5 (26.5)
Preoperative fasting h:mm				
median (IQR)	8:17(6:44-11:18)	8:05 (6:38-12:38)	8:39 (6:58-9:58)	8:17 (6:46-11:42)
Glucose-drink Y/N n (%)	93/80 (54/46)	30/26 (54/46)	31/29 (52/46)	32/25 (56/44)

Table 2. Mean COMFORT-B scores and difference between means following ANCOVA analysis at the different time points in the study with correction for baseline value. PIM=pre- and intraoperative music, PM=preoperative music, control=no music, PO=postoperative, m=minutes, h=hours.[a]Change from baseline. [b]Subjects at home (n=111) were scored with Parental Postoperative Pain Measurement-Short Form; not with COMFORT-B score.

Time	Study group	n	COMFORT-B scores		Difference between means (95% CI)		p-value
			Mean (SD)	*Change[a]*			
Ward							
Baseline	PIM	59	14.7 (2.7)	.	.	.	.
	PM	61	14.6 (2.6)	.	.	.	.
	Control	58	14.5 (1.8)	.	.	.	.
Holding							
	PIM	59	14.1 (2.6)	-0.5 (3.8)	**PIM-PM**	-0.77 (-1.81; 0.28)	0.148
	PM	61	14.9 (3.2)	0.3 (4.3)	**PM-Control**	0.49 (-0.56; 1.53)	0.360
	Control	58	14.4 (2.9)	-0.1 (3.0)	**PIM-Control**	-0.28 (-1.34; 0.78)	0.600
PACU							
30 m PO	PIM	59	12.9 (4.0)	-1.8 (4.6)	**PIM-PM**	0.04 (-1.49; 1.57)	0.959
	PM	61	12.9 (4.4)	-1.8 (5.1)	**PM-Control**	-0.36 (-1.90; 1.24)	0.647
	Control	58	13.2 (4.4)	-1.3 (4.4)	**PIM-Control**	-0.32 (-1.87; 1.24)	0.687
Ward							
4 h PO	PIM	58	12.1 (4.0)	-2.6 (4.9)	**PIM-PM**	-0.44 (-1.81; 0.92)	0.522
	PM	60	12.5 (3.6)	-2.0 (4.2)	**PM-Control**	-0.77 (-2.15; 0.61)	0.271
	Control	56	13.3 (3.7)	-1.2 (3.5)	**PIM-Control**	-1.22 (-2.60; 0.17)	0.085
Ward							
24 h PO[b]	PIM	23	12.7 (3.7)	-1.2 (5.0)	**PIM-PM**	-0.52 (-1.55; 2.59)	0.615
	PM	18	13.2 (3.7)	-1.1 (5.8)	**PM-Control**	-0.97 (-3.4; 1.41)	0.417
	Control	14	14.4 (1.2)	1.5 (2.4)	**PIM-Control**	-1.49 (-3.74; 0.76)	0.190

Table 3. Overview of observed behavioral secondary outcomes. Music interventions did not lead to any significant differences in secondary outcome between study groups at follow up. PIM=pre- and intraoperative music. PM=preoperative music, Control=no music, MUSIC*=music groups (PIM and PM) combined. NRS=Numeric Rating Scale recoded in 0 versus ≥1, PO=postoperative, PPPM-SF=Parental Postoperative Pain Measurement-Short Form.

	n total	PIM	PM	control	p-value
NRS					
baseline 0 *n subjects*	178	49	50	53	0.287
≥1 *n subjects*		10	11	5	
holding 0 *n subjects*	179	53	45	49	0.070
≥1 *n subjects*		6	16	10	
30 PO 0 *n subjects*	179	44	41	43	0.644
≥1 *n subjects*		15	20	16	
4H PO 0 *n subjects*	174	48	48	45	0.870
≥1 *n subjects*		10	11	12	
24H PO 0 *n subjects*	54	21	13	11	0.395
≥1 *n subjects*		2	4	3	
PPPM-SF					
24 hours PO *median (IQR)*	111	1 (0-2)	1 (0-3)	2(0-4)	0.180
Yale Preoperative Anxiety		**MUSIC***		**control**	**p-value**
holding (scale 23-100)	109 / 54	29 (23-35)		29 (23-42)	0.605
induction (scale 23-100)	109 / 55	60 (35-83)		60 (38-90)	0.811
change	107 / 54	28.5 (24.5)		28.1 (30.2)	0.923

Effect of music on physiologic parameters

Table 4 shows the results of general linear modeling on physiologic variables over time. Variables were measured at several time points (see Methods). The analyses showed a significant effect of time (p=0.002) and a non-significant result for the combined main effect of study group and its interaction with time on heart rate (p=0.069). The latter effect indicates whether there was any difference between study groups over all time points. This effect of study group over all time points was not significant for the outcomes SBP, DBP, MAP and saturation. When the general linear model analysis was repeated for only the time points ward and holding, with the PIM and PM groups combined, the combined effect of study group was significant (p=0.003) for heart rate, indicating a reduced heart rate after preoperative music intervention.

Table 4. General linear model analysis of physiologic variables at several time points. Different outcomes were measured at different time points (see the Methods section for an overview). Data presented as mean (95%CI). P-values reflect the combined main effect of study arm and its interaction with time. PIM= pre- and intraoperative music, PM=preoperative music, Control= no music, HR= heart rate, SBP= systolic blood pressure, DBP=diastolic blood pressure.

Time		HR	SBP	DBP	MAP	SpO_2
	p-value	*0.069*	*0.270*	*0.264*	*0.452*	*0.611*
Ward	PIM	130 (125; 136)	87 (80; 94)	54 (49; 60)	65 (60; 71)	-
Baseline	PM	128 (123; 134)	92 (85; 99)	59 (54; 64)	70 (65; 76)	-
	Control	129 (123; 134)	97 (91; 103)	53 (48; 57)	68 (63; 73)	-
Holding	PIM	127 (128; 132)	-	-	-	-
	PM	127 (121; 132)	-	-	-	-
	Control	134 (129; 139)	-	-	-	-
Surgery	PIM	126 (122; 130)	77 (74; 81)	35 (33; 37)	53 (51; 56)	99.2 (98.9; 99.5)
Mean	PM	125 (121; 128)	80 (77; 83)	37 (35; 39)	55 (53; 58)	99.0 (98.7; 99.3)
	Control	126 (122; 130)	82 (78; 85)	37 (35; 39)	56 (54; 59)	99.0 (98.7; 99.3)
PACU	PIM	127 (122; 133)	-	-	-	98.0 (97.5; 98.5)
30min PO	PM	129 (123; 134)	-	-	-	98.0 (97.5; 98.5)
	Control	132 (126; 137)	-	-	-	97.7 (97.2; 98.2)
Ward	PIM	126 (122; 131)	96 (89; 102)	52 (46; 58)	67 (61; 72)	-
4h PO	PM	128 (123; 133)	94 (87; 101)	52 (46; 59)	66 (61; 72)	-
	Control	132 (127; 136)	98 (91; 105)	56 (49; 63)	71 (65; 77)	-

Discussion

This randomized controlled trial investigating music exposure before and during pediatric surgery did not demonstrate lower distress in all children < 4 years of age. Additional analysis correcting for the interaction between study arm and baseline score showed weak evidence for an interaction effect between music exposure and distress scores at baseline, suggesting that children with higher distress scores at baseline may benefit more from music than those with lower distress scores. We found a statistically significant reduction in heart rate following music interventions in the preoperative period compared to controls.

Promising results from earlier studies suggest that music interventions could be valuable in health care; the more so because side-effects have not been reported and the intervention is inexpensive. Several meta-analyses investigating effects of music interventions on anxiety and pain in adult populations undergoing diverse types of minor and major surgery and other procedures have all shown worthwhile results.[6,7,21,22] Promising results have also been reported for children undergoing surgery.[9,23-26] Prior studies investigated effects of music interventions [9,23,24,26] or music entrainment[25] (entrainment describes the phenomenon that different amounts of energy transferred between moving bodies are eliminated, until both bodies move synchronically,[27] for instance with foot tapping). Studies were performed in mostly school-aged children in diverse types of surgery, ranging from major cardiac surgery to arthroscopy. We propose several reasons why our results do not meet the results from previous studies.

First, our subjects were young. Above-mentioned studies were all performed in older children, and one study also reported more evident improvement on pain perception in older children in its population.[23] On the contrary, studies in premature infants suggest benefits from music interventions.[28,29] Previous studies in premature infants have mostly been performed under calm conditions with infants receiving music interventions in the incubator.[28] Subjects in our study received a music intervention in a busy perioperative environment. While music might help older children and adults to create a personal environment, it might contribute to an abundance of stimuli to young infants.

Second, the timing and choice of music might have played a role. Most studies in children used postoperative music interventions.[9,23-26] We chose to provide preoperative music interventions to decrease both preoperative anxiety and postoperative pain in infants, as previous studies demonstrated anxiety and pain reduction from preoperative music interventions.[30-32] This timing however might have affected the intervention's effect. Additionally the preoperative music intervention sometimes lasted short (Table 1). Previous research used durations between 20 and 45 minutes [9,23,24,26] and longer exposure might result in larger effects. We applied investigators' selected music, as previous studies did.[23,24,26] The importance of personal preference to a music intervention was previously highlighted in adults however,[6,33] and this may also hold for children.

Third, we found a significant influence of longer fasting time before surgery on COMFORT-B scores after surgery and our patients might have been hungry. This hunger might negate any positive effects of music interventions. Shortening of fasting time above all would reduce signs of distress prior to and after surgery.[34]

Finally, young infants are unable to self-report pain and distress and therefore we have to rely on observations by others. On the one hand, this prevents the risk of performance bias. On the other hand, observations are in no way the gold standard for pain assessment and introduce unreliability with the risk of underestimating the treatment effect.

The specific biology underlying a music intervention's effect is not yet fully understood. The distraction theory argues that music can shift one's focus on something pleasant.[14]

Hearing music might evoke pleasant memories, thereby providing relaxation. Note that this is less likely to hold for young infants as they lack memories. Another explanation suggests that music decreases the activity of the sympathetic nervous system. Music can reduce levels of cortisol.[35,36] It may also decrease physiological parameters such as heart rate,[6] as we found in our study. Future studies could use blood samples to determine levels of cortisol, or analyze heart rate variability as an assessment of the sympathetic and parasympathetic balance,[37] and of immediate postoperative pain.[38,39]

Strengths and limitations

The main strengths of our study are the single-blind outcome assessment and that it was sufficiently powered. A double-blind study would have been the best way to minimize bias, but this is not feasible with this type of intervention unless completely performed under general anesthesia. Infants underwent common types of elective surgery, but not major surgical procedures such as abdominal surgery, which are presumed to be more painful and distressing. One could imagine that the potential effect of an anxiety- and pain-reducing intervention might be larger in the presence of higher anxiety or pain levels in major surgical procedures. The study was performed in a single tertiary care center which limits the generalizability of the results, as does the mainly male patient population. Furthermore, in general, the OR environment during induction may differ between procedures. Even though a calm and quiet environment during the standardized induction of anesthesia was aimed for in all subjects, there may have been differences.

Implications and recommendations

This is the first large RCT in infants evaluating the effects of music interventions on perioperative distress. Music interventions reduced distress in children who were more distressed at baseline, but not in all children. No adverse effects have been reported from music interventions in healthcare to our knowledge. Music has proven to benefit adult surgical patients, and implementation strategies have been suggested for perioperative music in routine practice.[40] Future research could explore the potential benefits of music in older children undergoing major surgical procedures, and furthermore explore the interrelationships between age, music taste and music's effects, and possible benefits of postoperative versus pre-and intraoperative interventions in children.

Conclusion

Music interventions do not seem to benefit all young infants having surgery. Music interventions have proven their value to reduce distress and pain in adult surgery, and to some extent in pediatric surgery. The potential benefits of music interventions in the preoperative period and in more distressed children deserve further exploration.

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Appendices

Appendix 1. Description of music intervention. All patients in PM groups and PIM groups received the same music.

Composer		Song
1.	Johannes Brahms	Lullaby Op 49 No 4
2.	Forrest Gump	Theme Song (fragment)
3.	W A Mozart	Lullaby K 350
4.	Ludovico Einaudi	Una Mattina
5.	J Pachelbel	Canon in D Major

Appendix 2 COMFORT- Behavior scale

https://www.comfortassessment.nl/ © Copyright English version: Monique van Dijk, Erwin Ista

Alertness
1. deeply asleep (eyes closed, no response to changes in the environment)
2. lightly asleep (eyes mostly closed, occasional responses)
3. drowsy (child closes his/her eyes frequently, less responsive to the environment)
4. awake and alert (child responsive to the environment)
5. awake and hyper-alert (exaggerated responses to environmental stimuli)

Calmness/ Agitation
1. calm (child appears serene and tranquil)
2. slightly anxious (child shows slight anxiety)
3. anxious (child appears agitated but remains in control)
4. very anxious (child appears very agitated, just able to control)
5. panicky (severe distress with loss of control)

Respiratory response (only in mechanically ventilated children)
1. no spontaneous respiration
2. spontaneous and ventilator respiration
3. restlessness or resistance to ventilator
4. actively breathes against ventilator or coughs regularly
5. fights ventilator

Crying (only in spontaneously breathing children)
1. quiet breathing, no crying sounds
2. occasional sobbing or moaning
3. whining (monotonous sound)
4. crying
5. screaming or shrieking

Physical movement
1. no movement
2. occasional, (three or fewer) slight movements
3. frequent, (more than three) slight movements
4. vigorous movements limited to extremities
5. vigorous movements including torso and head

Muscle tone
1. muscles totally relaxed; no muscle tone
2. reduced muscle tone; less resistance than normal
3. normal muscle tone
4. increased muscle tone and flexion of fingers and toes
5. extreme muscle rigidity and flexion of fingers and toes

Facial tension
1. facial muscles totally relaxed
2. normal facial tone
3. tension evident in some facial muscles (not sustained)
4. tension evident throughout facial muscles (sustained)
5. facial muscles contorted and grimacing

Total score: …

Numeric Rating Scale pain: … estimate of pain (0 = no pain to 10 = worst possible pain)

Appendix 3 The modified Yale Preoperative Anxiety Scale (mYPAS-SF)

A. Activity
1 = Looking around, curious, playing with toys, reading (or other age-appropriate behavior); moves around holding area/treatment room to get toys or go to parent; may move toward OR equipment
2 = Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality
3 = Moving from toy to parent in unfocused manner, nonactivity-derived movements; frenetic/frenzied movement or play; squirming, moving on table, may push mask away or clinging to parent
4 = Actively trying to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or will not separate from parent, desperate clinging

B. Vocalizations
1 = Reading (nonvocalizing appropriate to activity), asking questions, making comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond
2 = Responding to adults but whispers, "baby talk," only head nodding
3 = Quiet, no sounds or responses to adults
4 = Whimpering, moaning, groaning, silently crying
5 = Crying or may be screaming "no"
6 = Crying, screaming loudly, sustained (audible through mask)

C. Emotional expressivity
1 = Manifestly happy, smiling, or concentrating on play
2 = Neutral, no visible expression on face
3 = Worried (sad) to frightened, sad, worried, or tearful eyes
4 = Distressed, crying, extreme upset, may have wide eyes

D. State of apparent arousal
1 = Alert, looks around occasionally, notices/watches what anesthesiologist does with him/her (could be relaxed)
2 = Withdrawn, child sitting still and quiet, may be sucking on thumb or face turned into adult
3 = Vigilant, looking quickly all around, may startle to sounds, eyes wide, body tense
4 = Panicked whimpering, may be crying or pushing others away, turns away

Scoring: Divide each item rating by the highest possible rating (i.e., 6 for the "vocalizations" item and 4 for all other items), add all of the produced values, divide by 4, and multiply by 100.

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Appendix 4 Overview of drug use. [a]Incidental use of Sufentanil (n=14), Remifentanil (n=1) or Alfentanil (n=1) instead of fentanyl. [b]Incidental use of Marcaine (n=14).

Medication	*n total*	*PIM*	*PM*	*Control*	*P-value*
EMLA *median n of patches (IQR)*	172	2 (2-2)	2(2-2)	2(2-2)	0.472
Propofol *mean (SD)*	13/21/24	27.5 (17.2)	28.1 (16.3)	39.9 (30.6)	0.168
Fentanyl[a] *mean (SD)*	39/40/34	10.8 (8.3)	12.5 (10.9)	12.1 (8.3)	0.675
Acetaminophen *mean (SD)*					
perioperative	57/57/57	161.6 (70.8)	152.3 (64.3)	162.0(66.3)	0.682
total 24 H PO	53/58/57	362.0 (233.9)	396.5 (220.6)	430.6(234.4)	0.297
Diclofenac *mean (SD)*					
perioperative	30/30/32	10.5 (3.1)	9.8 (2.9)	10.4 (2.8)	0.622
total 24 H PO	20/22/27	22.5 (10.2)	21.3 (9.6)	24.3 (17.0)	0.725
Ibuprofen *total 24 H PO median (IQR)*	5/10/9	120 (73-153)	103 (93-139)	100(73-135)	0.836
Piritramide PO rescue medication *n (%)*	15/179	6/53 (11)	5/56 (9)	4/55 (7)	0.800
Ropivacaine[b] *mean (SD)*	53/57/56	8.8 (4.0)	8.6 (3.8)	8.8 (3.4)	0.949
Ephedrine/ Phenylephrine *n y/n (%)*	179	5/54 (9)	2/59 (3)	1/58 (2)	0.175
Anti-emetics perioperative *n y/n (%)*	179	15/44 (25/75)	9/52 (15/85)	11/48(19/81)	0.330
Dexamethasone	179	9/50 (15/85)	9/52 (15/85)	8/51 (14/86)	0.965
Granisetron *perioperative*	179	15/44 (25/75)	5/56 (8/92)	11/48(19/81)	0.042
Granisetron *postoperative*	171	3/49 (6/94)	1/57 (2/98)	2/53 (4/96)	0.527

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Chapter 6

What are the validity and reliability of the modified Yale Preoperative Anxiety Scale-Short Form in children less than 2 years-old?

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Abstract

Background: Accurate measurement of preoperative anxiety is important for pediatric surgical patients' care as well as for monitoring anxiety-reducing interventions. The modified Yale Preoperative Anxiety Scale – short form is well validated for this purpose in children aged 2 years and above, but not in younger children. We aimed to validate the Dutch version of the modified Yale Preoperative Anxiety Scale – short form for measuring preoperative anxiety in infants less than 2 years-old.

Methods: Two investigators independently assessed infants' anxiety at the holding area and during induction of anesthesia with the modified Yale Preoperative Anxiety Scale – short form and the COMFORT-Behavior scale – live and from video observations. Construct validity and responsiveness of both scales were tested with Pearson correlation coefficient. Internal consistency of the modified Yale Preoperative Anxiety Scale – short form was assessed using Cronbach's α, and interrater reliability and intra-rater reliability were tested using the intraclass correlation coefficient and Cohen's linearly weighted kappa. Hypotheses for sufficient interrater reliability (r > 0.60) and validity (r >0.65) had been formulated a priori in line with the COSMIN guidelines.

Results: Behavior of 129 infants (89.1% male) with a median age of 6.5 months (range 0.9-16.5 months) was observed. The correlations between the modified Yale Preoperative Anxiety Scale – short form and COMFORT-Behavioral scale were strong at the holding area and at induction of anesthesia, as were the correlation of change scores between the holding area and induction. Internal consistency of the modified Yale Preoperative Anxiety Scale – short form was excellent at both the holding area and at induction of anesthesia. Interrater reliability was good-to-excellent on scale level and moderate-to-good on item level.

Conclusion: These findings support the validity and reliability of the Dutch version of the modified Yale Preoperative Anxiety Scale – short form for infants <2 years of age.

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Introduction

Preoperative anxiety and distress can affect children before, during and after surgery,[1] and lead to negative behavioral changes even six months after discharge.[2] Children, also young children, who are anxious during induction of anesthesia are more prone to develop postoperative negative behavioral changes, such as nightmares, separation anxiety, and aggression toward authority.[3] While older children tend to be more anxious about the anesthetic and surgical processes, younger children may suffer from separation anxiety from parents [4] or from preoperative fasting (as children are too young to explain).

Evidence is increasing on the impact of early-life anxiety and distress. Early-life stress can negatively affect the sympathetic nervous systems and hypothalamic-pituitary-adrenal axis (effects arising before the age of 18 months) and might alter the stress system development.[5] Infants may be highly vulnerable to preoperative anxiety due to their age-related cognitive immaturity.[6] They can show suspicious behavior in relation to unfamiliar adults from 7 months of age,[7] and thus reflect a subjective sense of unease. Anxiety is a subjective sense of unease, dread or foreboding. Anxiety and pain behaviors can often not be distinguished, especially in infants, and distress is often the combination of both.[8]

To improve perioperative care and to monitor anxiety-reducing interventions, the Yale Preoperative Anxiety Scale (YPAS) has been developed for children aged 2 years and above.[4] This scale has been modified [6] and shortened in the past years,[9] and remains the 'gold standard' to evaluate preoperative anxiety in children. Nevertheless, many common procedures in children are performed at the infantile age or even at neonatal age, such as pyloromyotomy and pediatric inguinal hernia repair.[10] Thus, the accurate measurement of preoperative anxiety in our youngest patient population is important as well.

Aim and hypotheses

The use of validated health care instruments simplifies measuring the effect of interventions and the interpretation thereof. We aimed to test validity and reliability of the modified Yale Preoperative Anxiety Scale- Short Form (mYPAS-SF) for measuring preoperative anxiety in less than 2 years-old infants.

A priori hypothesis was formulated considering the expected relation between the mYPAS-SF and the COMFORT-B. We hypothesized a moderate positive correlation of at least $r > 0.60$ between the mYPAS-SF and the COMFORT-B at the holding area, and of $r > 0.65$ at induction of anesthesia. Furthermore, we expected a responsiveness (the correlation of the change values between the holding area and induction of anesthesia) of at least $r > 0.70$.

Methods

The guidelines of the Consensus-based Standards for the Selection of health Measurement INstruments (COSMIN) were applied in this clinimetric study (www.cosmin.nl; accessed last on November 30, 2017).[11] The data were collected within the framework of a large prospective perioperative trial and the study protocol was approved by the local Medical Ethical Committee (MEC 2015-264) at Erasmus University Medical Center, The Netherlands. The study has been performed according to the Declaration of Helsinki. Written informed consent was sought from the children's parents or legal representatives.

Participants

The study sample of the prospective perioperative trial consisted of 0-3-year-old infants admitted to the Erasmus MC- Sophia Children's Hospital in Rotterdam, the Netherlands, in the period September 2015-October 2016. Subjects had elective surgery for inguinal hernia, undescended testicles or hypospadias, performed under general anesthesia with caudal block. Eligible for participation were infants 0-2 years old. Subjects for whom informed consent from parents or legal representatives was missing were excluded from the analysis.

Instruments

mYPAS-SF. The mYPAS-SF is an observational checklist [9] with four response categories, each consisting of four to six distinct behavioral descriptions (Supplementary Data S1). Four categories of behavior are assessed: activity, vocalizations, emotional expressivity, and state of apparent arousal. Partial weights are used to calculate a total score ranging from 23 (low anxiety) to 100 (high anxiety). Previous research has shown good to excellent inter- and intra-observer reliability and validity.[6,12] Previously translated Dutch versions of the m-YPAS-SF were used in this study.[13]

COMFORT-B scale. The COMFORT scale was originally designed to assess ventilated children's distress.[14] It has been shortened since, and the resulting observational COMFORT-B scale has shown good validity and reliability to score distress and postoperative pain in 0-3 year old infants.[15-17] It consists of the six items alertness, calmness, muscle tone, movement, facial tension and crying (in spontaneous breathing children) or respiratory response (in ventilated children). Each item has five response categories, and the total score is calculated from counting the scores on individual items, ranging from 6 (calm) to 30 (distressed) (Supplementary Data S2).

Procedure

Parents of candidate subjects were invited to participate at preoperative consultation. At the day of surgery, the child's baseline characteristics and vital signs were recorded at the ward. The child was then accompanied by one parent and one investigator (observer 1) during transfer to the holding area and operation room (OR). The total duration of the transfer was approximately 15 minutes. At arrival in the holding area, observer 1 assessed live behavior with the use of the mYPAS-SF, while making 2-minute video recordings. These recordings were afterwards assessed by observer 2 for mYPAS-SF as well as COMFORT-B. Video recordings were made again in the OR during 2 minutes before induction of anesthesia (from presentation of mask to induction in case of inhalation induction, or from just before infusion of anesthetic to induction in case of intravenous induction). Live behavior was assessed at the same time. For all video recordings, a computer-generated randomized list determined the order in which the videos were assessed (holding area first, or induction of anesthesia first) as well as whether first the COMFORT-B scale or first the mYPAS-SF would be applied.

Training for outcome assessment

An experienced colleague trained the outcome assessor for both COMFORT-B assessment and mYPAS-SF assessment, first from video footage and thereafter by live observations of infants at the ward and OR. The training was completed with ten live assessments by both the experienced colleague and the assessor simultaneously. Inter-observer agreement was calculated with linear weighted Cohen's kappa; a $\kappa \geq 0.65$ was considered sufficient to reliably perform outcome assessment. The kappa for the results of ten paired assessments for the COMFORT-B scale was 0.77, and that for the mYPAS-SF was 0.82, both reflecting sufficient inter-rater reliability.

Anesthetic treatment

Induction and maintenance of anesthesia was standardized. At the ward, EMLA cream® was applied at potential sites of injection (usually both hands). After arrival in the OR, the anesthetist decided on either intravenous or inhalational induction of anesthesia. Anesthesia was induced intravenously with propofol IV (2-4mg/kg), or by inhalation of sevoflurane in a mixture of oxygen and air. After induction of anesthesia, a laryngeal mask was placed, and a caudal block with ropivacaine 0.2% was given. Anesthesia was maintained with sevoflurane (0.6-1.0 MAC) in a mixture of oxygen and air.

Statistical analysis

All data but linearly weighted Cohen's kappa were analyzed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Linear weighted Cohen's kappa was calculated at the Vassarstats website, www.vassarstats.net; assessed at October 16, 2017. Normally distributed variables are summarized using means and standard deviations; continuous variables that were not normally distributed are summarized using the median and the interquartile ranges (IQRs); and categorical variables are summarized using percentages. Comparisons were made in distress and anxiety scores between infants <1 year of age, and infants ≥1 year of age using Mann-Whitney U Tests for not normally distributed values.

Construct validity reflects the degree to which the scores of a measurement instrument are consistent to relational scores with other instruments.[18,19] Responsiveness reflects the ability of an instrument to detect change over time, and reflects the validity of change in multiple scores.[18,19] The correlation between mYPAS-SF and COMFORT-B scores reflected the level of construct validity. The correlation between the change scores of the two scales (difference between holding and induction assessment) represented level of responsiveness. Results were compared to the a priori formulated hypotheses (see aim and hypotheses).

Reliability reflects the extent to which scores of patients who have not changed, are the same for repeated measurements under several conditions.[19] First, internal consistency – reflecting the degree of interrelatedness among items – of the mYPAS-SF was calculated using Cronbach's α and the result was interpreted as follows: <0.50 unacceptable; 0.51-0.6 acceptable; 0.61-0.7 questionable; 0.71-0.8 moderate; 0.81- 0.90 good; >0.91 excellent. Next, regarding the reliability of the mYPAS-SF we calculated the inter-rater reliability and intra-rater reliability. The inter-rater reliability on scale-level was calculated with the intra-class correlation coefficient (ICC) using a two-way random model, based on absolute agreement in single measures. The measure of reliability was interpreted as follows: ICC <0.50 poor reliability; 0.50-0.75 moderate reliability; 0.76-0.90 good reliability; 0-91-1.00 excellent reliability.[20] The inter-rater reliability on item-level was then tested with linear weighted Cohen's kappa over simultaneously observed video-recordings. Lastly, the intra-rater reliability for one observer was calculated from the results of the same videos assessed twice at a two-month interval. Strength of agreement on item level was interpreted as follows: <0.20, poor agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, good agreement; and 0.81-1.00 very good agreement.

Cut off scores were used to identify the anxious versus non-anxious patient at both the holding area and at induction of anesthesia. A cut off value of 17 on the COMFORT-B was found in previous research.[16] Receiving-Operating-Characteristic curves were used to determine cut off values on the mYPAS-SF, with a cut off value of ≥ 17 on the COMFORT-B scale interpreted as anxious (value 1) and values below 17 as non-anxious (value 0). The mYPAS-SF value with the optimal combination of sensitivity and specificity was selected as cut off score for preoperative anxiety. Two-sided statistical significance was defined as $p < 0.05$.

Results

Behavior of 129 patients was assessed (see Figure 1 flowchart and Table 1 patient characteristics). Video footage was missing for four subjects at the holding area (in two cases due to technical problems and in two cases due to lack of video registration) and for two subjects during induction of anesthesia (in one case due to technical problems and in one case due to lack of video registration)). There was a male predominance (89.1%) and the median age was 6.5 months (IQR 3.3 – 9.9 months). Mean values of mYPAS-SF scores as well as from COMFORT-B scores at the holding area and induction of anesthesia, as well as the mean change scores are represented in table 2. A statistically significant difference in anxiety- and distress scores was found between infants < 1 year of age and infants > 1 year of age at the induction of anesthesia and at the change in scores between the holding area and induction of anesthesia.

Table 1. Patient characteristics (n=129).

	Total
Sex n(%)	
Male	115 (89.1)
Female	14 (10.9)
Age in months median(range)	6.5 (0.9-16.5)
Type of surgery n(%)	
Inguinal hernia (m/f)	59/14 (46/11)
Undescended testis	25 (19)
Hypospadias	31 (24)
Type of induction n(%)	
Inhalation	110 (85)
Intravenous	19 (15)
Parental presence at induction n(%)	129 (100)

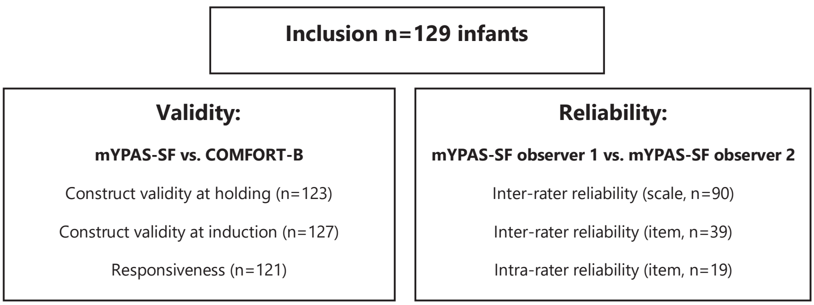

Figure 1. Flowchart on validity and reliability assessment.

Table 2. Median values (IQR) of video-assessed modified Yale Preoperative Anxiety Scale-Short Form scores together with cut-off values. Cut off values indicate the non-anxious versus anxious patient. A statistically significant difference was found in scores between infants <1 year and ≥1 year. *P- value indicates the statistical difference in mYPAS-SF scores between <1 year and ≥1 year of age.

	n	mYPAS-SF median (IQR)	COMFORT-B median (IQR)	p-value*	Cut off (sensitivity/ pecificity)
Holding area	123	23 (23-40)	14 (14-15)		37 (0.91/0.86)
<1 year of age	105	23 (23-40)	14 (14-15)	0.657	
≥1 year of age	18	26 (23-41)	14 (14-14)		
Induction of anesthesia	127	73 (46-94)	18 (15-22)		57 (0.92/0.95)
<1 year of age	108	67 (44-90)	17 (15-22)	0.001	
≥1 year of age	19	90 (79-94)	23 (19-24)		
Change	121	37 (9-60)	4 (2-8)		
<1 year of age	104	34 (6-56)	4 (2-8)	0.008	
≥1 year of age	17	56 (38-69)	8 (4-10)		

Construct validity and responsiveness

Validity was tested over n=123 video observations at the holding area and n=127 video observations at induction of anesthesia. The correlations between mYPAS-SF and COMFORT-B were strong both at the holding area; r = 0.72 (95% confidence interval (CI) 0.62 - 0.81); p<0.001, and at induction of anesthesia; r = 0.92 (0.89 - 0.94); p<0.001. Responsiveness was tested over n=121 video observations, a strong correlation of r = 0.82 (0.74 - 0.88); p<0.001 was found for the change scores of the mYPAS-SF and COMFORT-B between the holding area and at induction of anesthesia (see Figure 2).

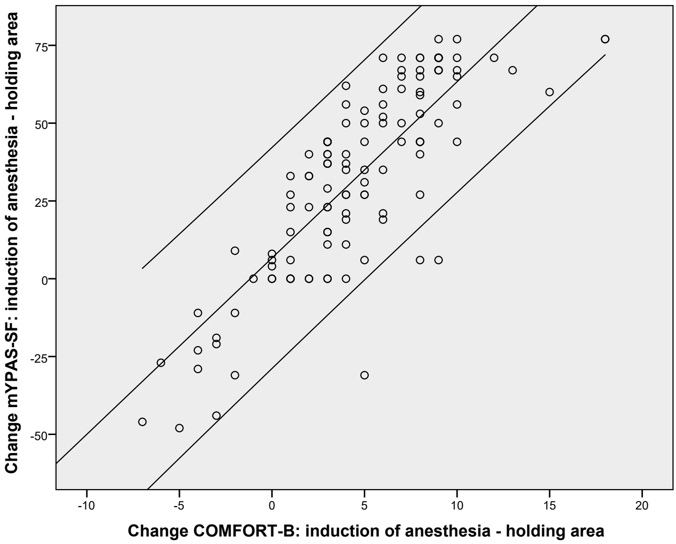

Figure 2. The correlation of the change values of the modified Yale Preoperative Anxiety Scale - short form and the COMFORT-Behavioral scale with its 95% confidence interval.

Reliability

Internal consistency was excellent for mYPAS-SF (Cronbach's alpha 0.93 at the holding area and 0.93 at induction of anesthesia) and moderate-to-good for COMFORT-B (Cronbach's alpha 0.79 at the holding area and 0.87 at induction of anesthesia). Inter-rater reliability on scale levels was tested over n=90 observations and showed moderate reliability at the holding area (ICC (95% CI) =0.57(0.42-0.70) and good reliability at the induction of anesthesia (ICC=0.81(0.71-0.87)), see Figure 2. Reliability on item-level showed moderate to good agreement on inter-rater reliability over n=39 videos and good to excellent agreement on intra-rater reliability over n=19 videos (see Table 3).

Table 3. Reliability on item-level for the modified Yale Preoperative Anxiety Scale-Short Form. κ=linear weighted Cohen's kappa .

Reliability	Item	κ (95% CI)
Inter-rater	Activity	0.41 (0.20 – 0.62)
	Vocalization	0.68 (0.52 – 0.85)
	Emotion	0.60 (0.41 – 0.79)
	Apparent arousal	0.60 (0.40 – 0.80)
Intra-rater	Activity	0.85 (0.67 – 1)
	Vocalization	0.95 (0.89 – 1)
	Emotion	0.88 (0.75 – 1)
	Apparent arousal	0.93 (0.82 – 1)

Cut off scores

Separate cut off scores were defined for results obtained in the holding area and at induction of anesthesia. A clinical cut off score of 37 at the holding area presented with excellent sensitivity (0.91) and good specificity (0.89); a clinical cut off score of 57 at induction of anesthesia presented with good sensitivity (0.92) and excellent specificity (0.95) (Table 2).

Discussion

Our results confirm our hypotheses that the mYPAS-SF has sufficient validity and reliability to support the use of this scale for evaluating preoperative anxiety for children less than 2 years-old. The original m-YPAS[6] has proven its validity for over 20 years. It has been translated into other languages and tested with good results[12,21-23] in many different populations. As the mYPAS-SF remains the mostly used scale for assessing preoperative anxiety in children aged 2 years and above, a logical step was to validate this scale in the younger population.

One could argue whether the term distress would be more appropriate to describe feelings of preoperative anxiety in infants. The concepts of psychological and behavioral distress have been defined to encompass all behaviors of negative affect and responses to aversive internal and external stimuli, associated with pain, anxiety and fear.[14] As written in the introduction, distress is often used to indicate a combination of anxiety and pain.[8] As the preoperative situation is mostly not associated with pain, the term anxiety seems suitable for the use in infants as well.

Our results show good reliability at induction of anesthesia, and moderate to good reliability at the holding area. Previous validation studies have reported lower inter-rater reliability at the holding area as well.[4,12,23] The decreased reliability can in part be explained by the low variance in scores, as 75% of the infants had low scores on both the m-YPAS-SF and the COMFORT-B scale at the holding area.

Several other possible reasons spring to mind. Behaviors at the holding area were sometimes difficult to assess because very young infants do not display behaviors such as talking, or were asleep (n=13, 10.6%). As a next step to make the mYPAS-SF more suitable for infants, selected items could be deleted and new items added to more specifically cover behavioral aspects for this age-group.

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The difference in anxiety levels between infants <1 and ≥1 year of age also gives room for thought. Developmental age affects how children express their anxiety. Young children are less likely to experience separation anxiety than older children, and therefore may be more easily comforted by healthcare providers.[24] Even though all infants in our sample were accompanied by one parent during induction of anesthesia, still, the older infants in the sample experienced high levels of anxiety. The high percentages of anxious infants at the holding (25%) and at induction of anesthesia (65%), and the higher levels of anxiety in the older study population, indicate the need for development of anxiety-reducing interventions in the OR.

An additional aspect contributing to high levels of distress and anxiety in infants could be mandatory preoperative fasting. This cannot be explained to very young infants and their feelings of hunger could contribute to discomfort and consequently higher scores on the mYPAS-SF. Currently more attention is being paid to postoperative consequences of preoperative fasting and possibilities to shorten the fasting time.[25]

Clinical relevance

The use of validated health care instruments is important to accurately measure the effect of interventions. Over 200 000 inpatient operative procedures have been done in children in the United States in 2009.[10] Many common procedures in children are performed at the infantile age or even at neonatal age, such as pyloromyotomy, pediatric inguinal hernia repair, and gastroschisis or omphalocele correction (together almost 20 000 procedures in 2009).[10] In addition, there is a rapidly increase in the number of outpatient procedures, including those in infants. It therefore seems important to have a valid instrument to measure preoperative anxiety in regular infant patient care and to evaluate the effects of anxiety reducing interventions. With the validation of the mYPAS-SF for children aged 0-2 years, this is now possible.

Strengths and limitations

Strengths of the study are the large sample size and specific age range. Furthermore, we addressed construct validity and responsiveness as well as various types of reliability (internal consistency, inter-rater reliability and intra-rater reliability). Responsiveness had not been tested before. Video assessment was randomized to prevent structurally moderation of scores as a consequence of repeated observation. Some limitations need to be addressed. First, COMFORT-B assessment by two observers, video and live, would have strengthened our validity results. Second, a COMFORT-B cut off score for pain was used to identify a cut off score for anxiety. Although anxiety and pain show interrelation in terms of distress, they are not interchangeable and this limits the interpretation of the results. Third, the patient population was predominantly male. The low number of girls prevented valid evaluation of gender differences in assessment of anxiety. Although this does not interfere with the validity and reliability assessment of the mYPAS-SF, the generalizability of our results to both boys and girls is limited.

Conclusion

The findings of this study support the validity and reliability of the mYPAS-SF to assess levels of preoperative anxiety in children less than 2 years old. These results support the use of this scale in clinical circumstances, and in evaluating preoperative anxiety-reducing interventions.

Acknowledgements

We are thankful to Ko Hagoort, MA for critically reviewing the manuscript. J.M. Berghmans, MD is thanked for providing Dutch translations of the modified Yale Preoperative Anxiety Scale.

Appendices

Appendix 1 The mYPAS-SF[9]

A. Activity
1 = Looking around, curious, playing with toys, reading (or other age-appropriate behavior); moves around holding area/treatment room to get toys or go to parent; may move toward OR equipment
2 = Not exploring or playing, may look down, may fidget with hands or suck thumb (blanket); may sit close to parent while waiting, or play has a definite manic quality
3 = Moving from toy to parent in unfocused manner, nonactivity-derived movements; frenetic/frenzied movement or play; squirming, moving on table, may push mask away or clinging to parent
4 = Actively trying to get away, pushes with feet and arms, may move whole body; in waiting room, running around unfocused, not looking at toys or will not separate from parent, desperate clinging

B. Vocalizations
1 = Reading (nonvocalizing appropriate to activity), asking questions, making comments, babbling, laughing, readily answers questions but may be generally quiet; child too young to talk in social situations or too engrossed in play to respond
2 = Responding to adults but whispers, "baby talk," only head nodding
3 = Quiet, no sounds or responses to adults
4 = Whimpering, moaning, groaning, silently crying
5 = Crying or may be screaming "no"
6 = Crying, screaming loudly, sustained (audible through mask)

C. Emotional expressivity
1 = Manifestly happy, smiling, or concentrating on play
2 = Neutral, no visible expression on face
3 = Worried (sad) to frightened, sad, worried, or tearful eyes
4 = Distressed, crying, extreme upset, may have wide eyes

D. State of apparent arousal
1 = Alert, looks around occasionally, notices/watches what anesthesiologist does with him/her (could be relaxed)
2 = Withdrawn, child sitting still and quiet, may be sucking on thumb or face turned into adult
3 = Vigilant, looking quickly all around, may startle to sounds, eyes wide, body tense
4 = Panicked whimpering, may be crying or pushing others away, turns away

Scoring: Divide each item rating by the highest possible rating (i.e., 6 for the "vocalizations" item and 4 for all other items), add all of the produced values, divide by 4, and multiply by 100.

Appendix 2. COMFORT- Behavior scale

https://www.comfortassessment.nl/

Alertness
1. deeply asleep (eyes closed, no response to changes in the environment)
2. lightly asleep (eyes mostly closed, occasional responses)
3. drowsy (child closes his/her eyes frequently, less responsive to the environment)

4. awake and alert (child responsive to the environment)
5. awake and hyper-alert (exaggerated responses to environmental stimuli)

Calmness/ Agitation
1. calm (child appears serene and tranquil)
2. slightly anxious (child shows slight anxiety)
3. anxious (child appears agitated but remains in control)
4. very anxious (child appears very agitated, just able to control)
5. panicky (severe distress with loss of control)

Respiratory response (only in mechanically ventilated children)
1. no spontaneous respiration
2. spontaneous and ventilator respiration
3. restlessness or resistance to ventilator
4. actively breathes against ventilator or coughs regularly
5. fights ventilator

Crying (only in spontaneously breathing children)
1. quiet breathing, no crying sounds
2. occasional sobbing or moaning
3. whining (monotonous sound)
4. crying
5. screaming or shrieking

Physical movement
1. no movement
2. occasional, (three or fewer) slight movements
3. frequent, (more than three) slight movements
4. vigorous movements limited to extremities
5. vigorous movements including torso and head

Muscle tone
1. muscles totally relaxed; no muscle tone
2. reduced muscle tone; less resistance than normal
3. normal muscle tone
4. increased muscle tone and flexion of fingers and toes
5. extreme muscle rigidity and flexion of fingers and toes

Facial tension
1. facial muscles totally relaxed
2. normal facial tone
3. tension evident in some facial muscles (not sustained)
4. tension evident throughout facial muscles (sustained)
5. facial muscles contorted and grimacing

Total score: …

Numeric Rating Scale pain: … estimate of pain (0 = no pain to 10 = worst possible pain)

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Chapter 7

What is the level of parental anxiety in pediatric surgery and how is it related to preoperative distress in children?

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Abstract

Aim: Preoperative distress in children is associated with difficult induction of anesthesia and negative responses after surgery. Parents experience anxiety as well when their child is about to undergo an operation. Mutual anxiety between children and their parents has been reported. We aimed to identify the levels of preoperative parental anxiety, investigate possible predictive factors and evaluate mutual anxiety between parent and child.

Methods: Eligible were infants and toddlers scheduled to undergo common elective surgeries and their parents. The Spielberger State Trait Anxiety Inventory (STAI) was used to test parental predisposition for anxiety (10-item trait form) and preoperative, situational anxiety (6-item state form), and the Amsterdam Preoperative Anxiety and Information Scale (APAIS) to test preoperative anxiety. Children's distress was assessed with the COMFORT-Behavior scale. Multivariable linear regression analysis was performed with parental anxiety at the operating room (STAI-state) as outcome variable.

Results: 188 children (median age 6.9 months; 90% boys) and their accompanying parent participated. Thirty percent (n=56) of parents were classified as anxious according to the STAI-state at induction of anesthesia. Multivariable regression analysis revealed the following predisposing factors for preoperative parental anxiety: a predisposition for anxiety ($B=0.263$; $p<0.001$), more distress in the child ($B=0.168$; $p=0.04$), and younger age of the child ($B=0.059$; $p=0.02$). Mothers were more anxious than fathers ($B=1.608$; $p=0.002$).

Conclusions: In our hospital, over one third of parents accompanying their children to surgery is anxious at induction. The association between increased parental anxiety and higher distress levels in their children could affect the perioperative procedure and postoperative outcome.

Introduction

Induction of anesthesia is considered one of the most anxious events for parents and the child that undergoes surgery.[1] Preoperative anxiety is associated with problematic induction of anesthesia, higher probability of emergence delirium, more postoperative pain. In the long term, the child may suffer from, post-traumatic stress disorder, eating disorder or sleeping disturbance up to six months after discharge .[2-4]

Parents may also experience anxiety and distress when their child is scheduled for operation. Parental anxiety is partially affected by intrinsic psychological factors such as coping style, locus of control or predisposition for anxiety, [5,6] as well as extrinsic factors such as the child's age – i.e., more anxiety when the child is younger.[7,8]

Mutual interaction can occur between the child's preoperative distress and that of the parent.[9] In contrast to wide belief, parental presence during anesthesia induction does not reduce the child's preoperative anxiety.[10,11] Moreover, children from anxious parents may be at greater risk of developing postoperative pain.[5]

Aim

We aimed to measure the levels of preoperative parental anxiety of infants and toddlers undergoing surgery. We hypothesized that intrinsic (predisposition for anxiety) and extrinsic (child's age, child's distress and medical history) factors affected parental preoperative anxiety. Insight into these potentially predicting factors could help to develop a tailor-made approach to guide parent and child in the best possible way.

Methods

Data were collected in a large tertiary university children's hospital in The Netherlands in the period September 2015-October 2016, as part of a large randomized controlled trial study evaluating pre- and intraoperative music interventions in infants to reduce distress.[12] The study protocol was approved by the local Medical Ethical Committee (MEC 2015-264) at Erasmus Medical Center, The Netherlands. Written informed consent was obtained from legal representatives of all children.

Participants

Infants aged 0-3 years scheduled to be operated on inguinal hernia, undescended testicles or hypospadias, and their parents were eligible for participation. Excluded were infants with hearing impairments and those for whom informed consent was missing.

Outcomes

Parental preoperative anxiety was evaluated with two validated questionnaires. The Spielberger State Trait Inventory (STAI)[13] is a widely used questionnaire with good validity and reliability to assess levels of anxiety in adults..[14] The original STAI has been translated into Dutch, shortened and validated resulting in a 10-item STAI-trait form (STAI-T-10) which measures a predisposition for anxiety [14] and a 6-item STAI-state form (STAI-S-6) which measures situational anxiety.[15] For trait anxiety scores ≥ 23 on the STAI-T-10 implies a high level of predisposed anxiety.[14] For state anxiety mean score plus one SD on the parental STAI-S-6 at the outpatient clinic was used to determine a high level of anxiety, according to previous research, resulting in a cut-off score of ≥ 15.[16]

Furthermore, the Amsterdam Preoperative Anxiety and Information Scale (APAIS) evaluates preoperative anxiety and need for information in the direct preoperative period in adult patients,[17] and in parents of pediatric surgical patients alike.[18] The questionnaire contains six items each with five response categories. Two items evaluate anesthetic-related anxiety, two items evaluate surgery-related anxiety and two items evaluate the need for information about the anesthetic and the surgical procedure. Level of anxiety is derived from the sum score of the four different anxiety items. A previously determined cut-off score of ≥ 13 on the APAIS was used to determine a high level of preoperative anxiety.[17]

The level of distress in children was evaluated with the COMFORT-Behavior (COMFORT-B) scale. This scale has good validity and reliability to score distress (and postoperative pain) in 0-3 years old infants.[12,19] The total score ranges from 6 to 30 (Appendix 1). Children were filmed for two minutes using an iPad mini 2 (© Apple Inc. Cupertino, USA), to allow for blind assessment of COMFORT-B scores afterwards. Furthermore, heart rates of parents and children were measured at the ward and in the preparation room of the OR.

Study procedure

Parents were invited to participate in the perioperative music intervention study at the preoperative consultation at the outpatient clinic, or by telephone. After providing consent, parents received the STAI-T-10 questionnaire at home which they returned completed in the hospital at the day of surgery. One parent was allowed to accompany their child in the operating room (OR) during induction of anesthesia and the scores from the attending parent were used in the study. At the day of surgery, the APAIS questionnaire was completed by the parent approximately 60 minutes before surgery. Video recordings of the child were made for COMFORT-B assessment; and parental and infant heart rate were measured.

During transfer from the ward to the holding area and OR, the parent and the child were accompanied by an investigator. Children in the intervention groups received a music intervention by headphones during transfer. In the OR preparation room, the parent completed the STAI-S-6, 2-minute video recordings were again made for COMFORT-B assessment and heart rates of both parent and child were measured. Thereafter, parent and child entered the OR.

Anesthetic regimen

Approximately 60 minutes before induction of anesthesia, EMLA cream® was administered on both hands. Anesthesia was induced either intravenously with propofol IV (2-4 mg/kg), or by inhalation of sevoflurane in a mixture of oxygen and air according to the assessment of the anesthesiologist.

Data collection

The following characteristics were retrieved concerning the infants: age, sex, medical history, surgical history, type of surgery, type of induction (inhalation or intravenous), duration between entrance holding area and induction of anesthesia and presence or absence of music intervention. The COMFORT-B scores of children were assessed afterwards from the two-minute video recordings by two trained assessors with sufficient interrater reliability tested before the start of the study (linearly weighted Cohen's kappa of at least 0.72).[12]

Statistical analysis

Normally distributed variables were summarized using means and standard deviations, continuous variables that were not normally distributed were summarized using medians and interquartile ranges (IQRs), and categorical variables were summarized using percentages. Change scores were calculated between parental STAI-S score at home and the score at the OR, change in parental heart rate between the ward and at the OR, and changes in children's heart rate and COMFORT-B score between the ward and at the OR. Based on the predefined cut-off scores, the numbers of anxious parents in the ward (based on the APAIS) and just before induction of anesthesia (based on STAI-state) were calculated.

Multivariable linear regression analysis was used to investigate the association between the dependent variable parental STAI state anxiety (STAI-S-6), which was measured immediately prior to induction at the OR and the following independent variables: 1. STAI trait anxiety (STAI-T-10); 2. parental gender; 3. child's medical history (yes; yes including previous surgery; yes including prematurity); 4. type of surgery (inguinal hernia; undescended testis; hypospadias); 5. child's COMFORT-B score in the OR; 6. child's age; and 7. preoperative intervention in the RCT. Pearson product moment correlation coefficients were calculated to assess linear associations between parental STAI-S-6 and APAIS, and parental STAI-S-6 and parental heart rate in the OR. Subjects with missing data were excluded from analyses (complete case analysis). Statistical significance was set at $p < 0.05$ (two-sided). All data were analyzed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp).

Results

Data from a total of 188 pairs of children and their accompanying parent were analyzed. The accompanying parent to the OR was the mother in 68% of cases (n=128). Ninety percent of infants were male and the median age of the total group was 6.9 months (IQR 3.3-11.3 months). Patient characteristics are presented in table 1.

Table 1. Characteristics of children (N=188). h=hours m=minutes. *Eighteen children were girls, all having surgery for inguinal hernia. **Time from ward to theater was only registered for 125 subjects as this was registered in the preoperative intervention study arms. ***Infants were offered sucrose two hours prior to surgery.

Variable	N (%)
sex	
boy*	170 (90.4)
age in months *median (IQR)*	6.9 (3.3-11.3)
medical history	
yes	76 (40.4)
yes, including previous surgery	9 (4.8)
yes, including prematurity	51 (27.1)
type of surgery	
inguinal hernia	110 (58.5)
undescended testis	42 (22.3)
hypospadias	36 (19.2)
type of induction	
inhalation	149 (79.2)
intravenously	39 (20.8)
Time ward-theater** mean (SD) n=125	25m (8m)
Time sober median (IQR) n=180	7h47m (6h20m – 10h42m)
Sucrose*** y/n	100 (53.2)

Anxiety and distress scores

Parental anxiety scores are presented in table 2. At the ward, 68 parents (37%) were anxious according to the cut-off scores of the APAIS, and at the OR, just before induction of anesthesia, 56 (30%) of parents were anxious according to the cut-off scores of the STAI-S-6. There were significant correlations between score on APAIS and scores on STAI-S-6 (n=178; r = 0.698; 95% CI 0.62 to 0.77) (see Figure 1). Sixteen parents (8.5%)

were identified with a predisposition for anxiety according to the STAI-T-10 cut-off. Their mean STAI-S-6 at the OR was statistically significantly higher compared to the mean of the parents without a predisposition for anxiety, respectively 15.3 (SD 3.1) and 12.7 (SD 3.3); p=0.004. There was no statistically significant difference in general level of anxiety between parents (STAI-T-10 mothers 16.7 (SD 4.4) compared to fathers 16.0 (SD 4.5); p=0.351), however mothers were more anxious than fathers at the OR (STAI-S-6 mothers 13.5 (3.3) compared to fathers 11.7 (3.1); p=0.001). STAI-S-6 scores and parental heart rate at the OR were positively associated (n=175, r = 0.337; 95% CI 0.20 to 0.46).

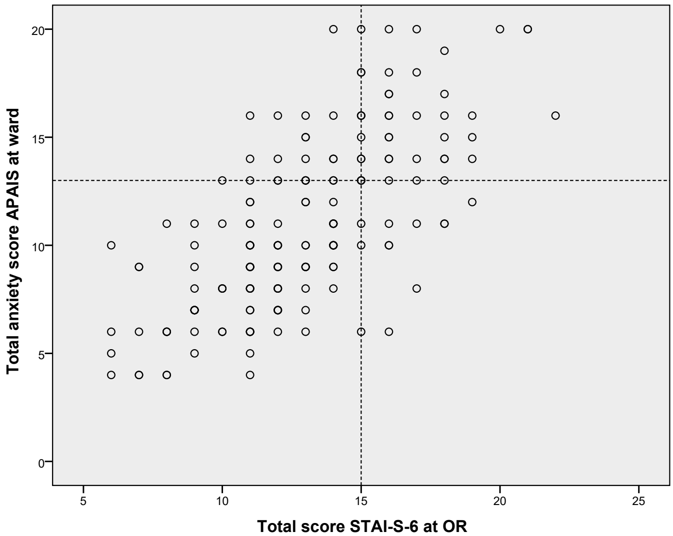

Figure 1. **Scatterplot showing parental scores on Amsterdam Preoperative Anxiety Scale (APAIS) at the ward and Spielberger State and Trait Anxiety Inventory – State short form (STAI-S-6) at the OR.** The horizontal and vertical dashed lines indicate cut-off scores for high anxiety on the APAIS as well as STAI-S-6.

Variables affecting parental anxiety

Multivariable linear regression analysis with STAI-S-6 scores as outcome variable (table 3) showed that mothers were generally more anxious than fathers at induction of anesthesia (B=1.608; p=0.002), as well as parents with a predisposition of anxiety (STAI-T-10) (B=0.263; p<0.001). Also, parents of younger and more distressed children and with a younger child having surgery had higher STAI-S-6 scores, respectively (B=-0.059; p=0.020) and (B=0.168; p=0.040). Parental anxiety tended to be less when the child underwent inguinal hernia repair compared to surgery for hypospadias or undescended testis (B= -1.173; p=0.059). The independent variables together predicted 26.5% of the variance in parental preoperative anxiety. Medical history in children, or previous surgery, and the preoperative music intervention that was tested in the RCT, were not statistically significantly associated with parental anxiety.[12]

Table 2. Anxiety and distress scores as well as heart rate of parents and children. STAI-S-6=Spielberger State Trait Anxiety Inventory state short form, STAI-T-10= Spielberger State Trait Anxiety Inventory trait short form, OR=operation room, COMFORT-B= COMFORT-Behavioral assessment.

	Parent total *n (%)*	**Mother** *mean SD*		**Father** *mean SD*			**Child** *mean (SD)*	
Baseline			*n*		*n*			*n*
STAI-T-10	167 (89)	16.7 (4.4)	116	16.0 (4.5)	51			
Ward								
APAIS		17.9 (5.5)		16.2 (4.5)				
Anxiety	185 (98)	11.5 (4.1)	126	10.0 (3.6)	59			
Information		6.5 (2.2)		6.2 (2.0)				
Heart rate	183 (97)	78.8 (12.0)	125	74.0 (14.4)	58	Heart rate	129 (20.0)	173
						COMFORT-B	14.5 (2.4)	187
OR								
STAI-S-6	179 (95)	13.6 (3.2)	123	11.7 (3.0)	56			
Heart rate	180 (96)	90 (14)	122	82 (17)	58	Heart rate	130 (19)	159
						COMFORT-B	14.4 (2.9)	188

Table 3. Results of multivariable linear regression analysis with outcome STAI-S-6 from parent at OR (n=166). STAI-S-6=Spielberger State Trait Anxiety Inventory state short form, STAI-T-10= Spielberger State Trait Anxiety Inventory trait short form, CI= confidence interval, COMFORT-B= COMFORT-behavior assessment. *There was a distinction made between medical history involving previous surgery (indicated as yes surgery) and medical history without previous surgery (indicated as yes).

	Coefficient	**95% CI**	**p-value**
STAI-T-10 parent	0.263	0.159; 0.367	**<0.001**
Parent attending			
Father	*Reference*		
Mother	1.608	0.620;2.597	**0.002**
Medical history*			
No	*Reference*		
Yes	0.099	-0.919; 1.117	0.848
Yes surgery	-0.246	-2.402; 1.911	0.822
Type of surgery			
Hypospadias	*Reference*		
Inguinal hernia	-1.173	-2.389; 0.043	0.059
Undescended testis	-0.285	-1.713;1.143	0.694
Age in months child	-0.059	-0.109; -0.009	**0.020**
COMFORT-B score child OR	0.168	0.008; 0.328	**0.040**
Study-arm (MUSIC trial[13])	-0.225	-0.791;0.341	0.434

Discussion

In our study over 30% of parents accompanying their child to the OR for minor surgery were anxious according to both the APAIS and the STAI state questionnaires. Parents with a predisposition for anxiety were more anxious at the OR compared to parents with a lower general level of anxiety, as were mothers compared to fathers, and parents of distressed and younger children.

The origin of parental anxiety within this context is multifactorial by nature. For one, certain personality traits predispose for anxiety,[5,6] as confirmed in our study where higher STAI state scores were correlated to higher STAI trait scores.

The association between higher levels of parental anxiety and higher distress scores in children was as we hypothesized beforehand. Previous studies have also shown associations between parental anxiety and child anxiety, such as correlations between maternal heart rate variability or maternal salivary cortisol levels and pediatric distress at induction.[9,20] Moreover, associations between parental preoperative anxiety and children's postoperative pain have been found.[5]

Parental presence or absence at induction of anesthesia is not common everywhere. Previously, a review found no difference in children's anxiety with or without parental presence at induction of anesthesia.[11] For some parents (and children) it might be better that the parents do not accompany the child into the induction area. Future research could focus on anxiety predisposition and the level of preoperative anxiety in parents and their children. For instance, high scores on the STAI-trait might predict which parent would need special attention. In this regard it would also be helpful to explain parents that their presence is not mandatory.

We found less preoperative anxiety in parents when children were having surgeries for inguinal hernia. A study in dermatological surgery found that parents were more anxious when their child underwent major surgery opposed to minor .[8] It is assumable that parental anxiety increases when more complex surgeries are performed, such as surgery for esophageal atresia instead of inguinal hernia. Parents whose child undergoes major surgery might benefit from more support. Another factor that might affect anxiety levels of parents is whether or not a child has a medical history. For instance, in our study, the children that underwent inguinal hernia repair were often born prematurely and already faced many medical investigations. We did not find any evidence for the relation between previous surgery and level of parental anxiety in our data. A possible explanation could be that these parents are more experienced with hospital life and consequently do not experience heightened anxiety before the current surgery.

Over the past two decades increasing attention has been developed to decrease preoperative anxiety, in children as well as in their parents, in order to contribute to the perioperative care process and decrease the burden of surgery in children and their parents as well. Examples of such strategies are providing more extensive information on what to expect in the preoperative consultation, or newer methods of preoperative counseling, for instance via preoperative OR visits.[21,22] Anxiety can perhaps partially be reduced by decreasing waiting time immediately preoperatively, and by offering anxiety-decreasing interventions to both parent and child, such as video-distraction,[23] or the use of music interventions.[24] Measurement of predisposition for anxiety could help in offering tailor-made accompaniment for parents who either score high on anxiety-questionnaires or ask for additional accompaniment themselves, by, for example, specialized nurses.

Strengths and limitations

Strengths of the study are the large sample size, the use of several validated questionnaires to investigate anxiety in parents, the video recordings allowing for blind outcome assessment of children's distress on the COMFORT-B and the distinction between maternal and paternal parental anxiety. Limitations of this study include the mainly male patient population. Parents reported their own anxiety and this might have resulted in socially desirable answers. Future trials might use salivary cortisol samples or heart rate variability when assessing parental anxiety. We have only investigated associations, and not causality, between parent's and child's anxiety, and cannot make conclusions on causes of anxiety.

Conclusion

In our hospital, over one third of parents accompanying their children to minor and common surgery for inguinal hernia, orchidopexy or hypospadias can be defined as anxious. There is an association between increased anxiety and higher distress levels in children. Anxious parents and children must be identified to offer tailor-made treatment for each parent and child undergoing surgery.

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PART III

General Discussion

Chapter 8

General Discussion

Increasing attention is being paid to make care affordable, with a larger focus on personalized interventions and treatment. This thesis has focused on the working mechanisms and applicability of music interventions in healthcare. The use of music interventions in healthcare has rapidly gained interest for its wide applicability, ease of use and lack of side effects. We aimed to investigate the effectiveness of music interventions to alter specific conditions such as anxiety and pain. Part I of this thesis provides a literature overview of physiological effects associated with music interventions in rodents and humans, as well as its effects on perioperative anxiety and pain. Part II focused on the applicability of music interventions in pediatric perioperative care in a large randomized controlled trial, as well as on infants' and parents' anxiety while facing the child's surgery. Anxiety is often studied in relation to music and we validated an existing, well-known instrument for preoperative anxiety measurement for the use in our youngest patient population. Application of this instrument allows for more accurate measurement of anxiety and implementing anxiety-reducing interventions.

Accumulating knowledge on the working mechanisms of music

As written in *chapter 1*, music induces effects which are in part expressed by responses from the autonomic nervous system that turns from a more sympathetic state to a more parasympathetic state. These responses are also found in *chapter 2*: music interventions were associated with decrease in heart rate, blood pressure and cortisol in rodents. Apart from responses related to the shift in autonomic nervous systems, rodents also showed enhanced expression of neuropeptides in the limbic system (as described in *Chapter 1*) after music exposure.[1-3] This response to music, also in rodents, stipulates the activation of the basal brain circuits by sound and music. In rodent studies, animals were exposed to music and test-situations before an actual exam took place. Even though these periods were mostly short, it might have been that rodents learned expectations regarding the music (acoustic stimulus) during test-phase, and experienced reward after fulfillment of their expectations during exam.

Evidence is accumulating that music during general anesthesia decreases pain and other negative behaviors after surgery.[4-6] This suggests that during general anesthesia, auditory impulses might reach the brain stem and evoke responses. Previously, many contrary results have been published regarding transmission of auditory impulses during general anesthesia.[5,7-9] It would be interesting to see if there is a relation between the depth of anesthesia, for instance via bispectral index monitoring, EEG, or via f-MRI, to the transmission of auditory impulses such as music during general anesthesia. The evidence on this relation is still lacking. Functional MRI would be the most interesting, however is not possible during surgery. Perhaps this might be done with volunteers, or in experimental research.

Music, anxiety and pain in adults

New treatments in healthcare are nowadays introduced via the evidence-based-medicine principle. This principle is important in Western medicine. The highest level of evidence is provided by a systematic review and meta-analysis of randomized controlled trials investigating a specific intervention.

In *chapter 3* we searched for all available evidence in scientific literature and found that perioperative music interventions decrease anxiety and pain around surgery in adult patients. Earlier performed meta-analyses investigated the effects of music on anxiety and pain in a wider range of procedures, not only surgical procedures but non-invasive procedures as well.[10,11] Significant decreases in anxiety and pain were found in both meta-analyses, with in addition significant beneficial effects on heart rate, blood pressure, use of analgesics and patient satisfaction. To make results more applicable in clinical practice, we narrowed our inclusion criteria to only surgical procedures and chose to only measure anxiety and pain. Our results from *chapter 3*, together with the results from previous studies, provide the highest level of evidence for music interventions in reducing perioperative anxiety and pain. Our literature search has extended until October 2016. Since then, several new studies have been published evaluating music interventions on anxiety and pain perioperatively, all showing favorable effects from music in adults.[5,12-19] All these publications on this subject,[11,20-22] support the conclusions from our meta-analysis that perioperative music interventions reduce anxiety and pain in adults. This should be enough to now focus on implementing music interventions in perioperative healthcare practice in adults.

Implementation

Implementation science focuses on the systematic uptake of research findings and other evidence based practices into routine practice.[23] Any change in healthcare practices requires to understand the barriers and facilitators that respectively hinder and help this process.[24] Implementation strategies should be based on the identified barriers and facilitators. Carter and colleagues implemented perioperative music interventions in several veterans affairs hospitals, using the Consolidated Framework for Implementation Research (CFIR).[22] This framework evaluates five domains in the implementation of new treatments, including the essential component of treatment (music in this specific situation), evaluation of outer setting (availability of the intervention and economic strategy), evaluation of inner setting (willingness to commit and capability to change a process, for instance by health care personnel), individuals involved (willingness of patients to change) and the implementation phase itself (equipment to deliver the intervention, protocol for integration in routine workflow with responsible staff and the actual use of intervention in routine practice).[22] Carter and colleagues have found a modest readiness to implement music interventions among care providers, and a good acceptability to receive music interventions in patients, especially those predisposed to opioid overuse. Perhaps these patients were more open for non-pharmacological therapies to alleviate their pain. Care providers' reluctance to implement music interventions might be due to little knowledge of the anxiety- and pain-reducing effects and neurophysiological mechanisms of music. Carter et al. recommend performing more implementation studies as there is need for improvement on the translation generated knowledge from research to healthcare practice.[22] Now it is time to perform these studies in a wide range of Dutch hospitals. The Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) guidelines can be applied when designing an implementation study. It describes a framework for the reporting of healthcare-improving knowledge.[25]

It seems worthwhile to implement music interventions in perioperative adult treatment. There should be a clear protocol on the introduction and maintenance of the perioperative music intervention, such as in Figure 1. This protocol should stipulate when and by whom music interventions are offered to patients during the entire perioperative process, from preoperative consultation to the postoperative stay in the PACU (or even the ward). Readiness for change and capability should be evaluated in perioperative personnel, starting with stakeholders such as surgeons, anesthetists, and management. Nurses could have an important role implementing the music interventions although the current shortages in nursing staff warrants efficiency. Extensive education on the working mechanisms and effect of music interventions is an important step. Equipment needed for implementation should be easily available, and staff should continuously be reminded of the intervention until automatization is established.

Music

For the intervention itself, recorded music interventions should be used, delivered via a digital music player and headphones. There is still debate on the best type of music intervention. Rhythm seems to be an important component of music to induce certain effects, whereas pitch seems to be of less importance, a result that was also found in *chapter 2*.[26] String instruments are recommended.[27] The importance of a listener's music preference to a music intervention's effect is discussed. Some studies report lessening of anxiety and pain and improved relaxation with exposure to self-chosen music (compared to investigator selected music).[28-30] This finding was confirmed in the meta-analyses of Vetter et al,[11] who found lesser anxiety, pain and use of analgesics when patients listened to self-selected music. Investigator selected music was only more effective in reducing systolic blood pressure. Our meta-analysis (*chapter 3)* did not show a difference in the level of anxiety and pain reduction between patient-selected music from a pre-selected list, over investigator-selected music, or over self-brought music from home. As only four studies used music that was brought from home by patients this analysis might have lacked power. A previous study found both preferred (self-chosen) music (listening to recorded music) and self-composed music (by entrainment with music therapist) to decrease pain, but found different pain pathways to be affected.[31] Listening to preferred music would have reduced pain by means of distraction, while entrainment would have reduced pain by actively controlling the pain. A systematic review in neuro-imaging studies to different brain areas affected in familiar and non-familiar music found increased motor pattern of activation by familiar music, that was thought to reflect audio-motor synchronization by rhythm and anticipation on melody and harmony in songs.[32] In conclusion, the effect of music thus seems to be a result of specific components of the music, whereby familiarity with, as well as expectations to the music seem additive to its neurobiological effect.

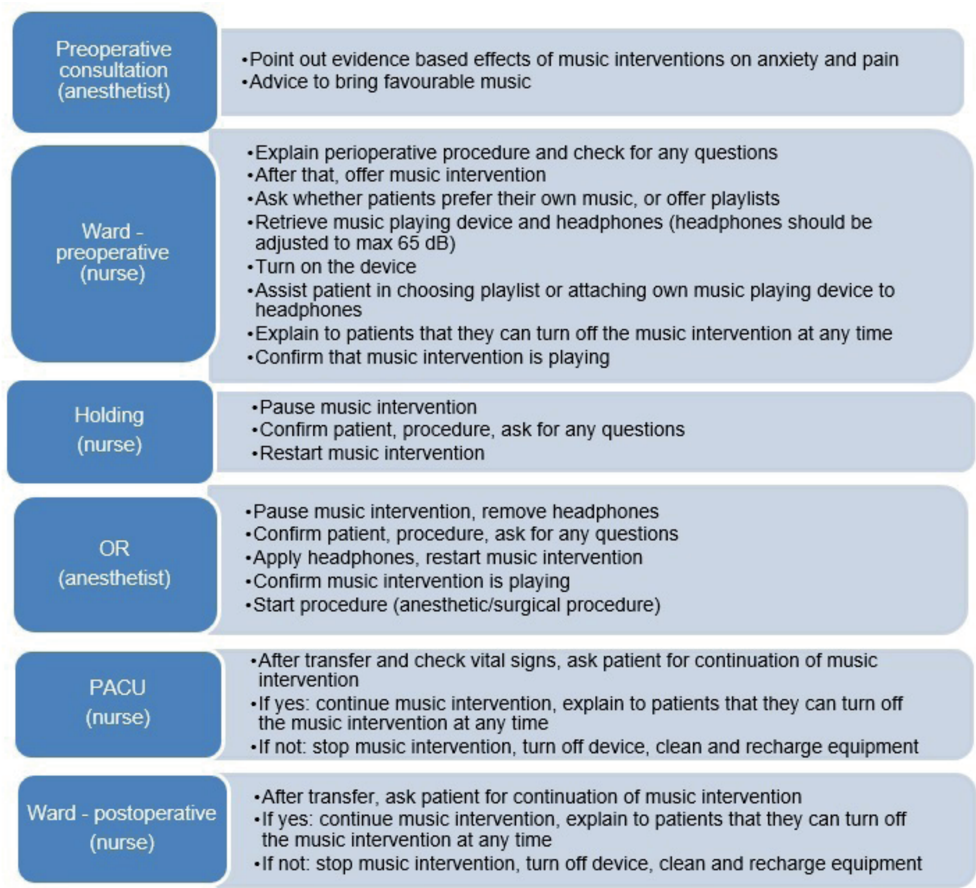

Figure 1. Protocol for perioperative music interventions. OR=operating room, PACU=post anesthesia care unit.

Patients could be advised to bring familiar, self-selected music with a rhythm around 60-80 BPM. Furthermore several music lists can be created by volunteers or hospital staff in consultation with a music therapist, from which patients can choose.

Procedure

The music intervention should be offered before, during, and after surgery. I would recommend to provide headphones to all patients due to sanitation (especially in the operating room) and infection prevention. Headphones volume should be limited to 65dB to prevent hearing damage. Over-ear phones have better noise-canceling properties than on-ear or in-ear headphones do (therefore less volume is required to hear the music), and are less close to the eardrum (what limits damage).[33] Although headphones with a cord can more easily be adjusted to self-brought music devices, wireless headphones are advisable as there are already many different devices with cords in the head- and neck area during surgery and postoperatively. All materials that are offered by the hospital should be checked by the technical department before use. There should be sanitation protocols, i.e. cleaning of headphones with chlorohexidine after each use in accordance with regulations of the local infection prevention department, or provision of disposable headphone covers as in airplanes. Equipment to deliver music has to be purchased and music lists have to be compiled, especially for patients who do not bring their own music.

Financial

Attention should be paid to music rights that may apply for playing music in hospitals (at this moment regulated by BUMA/STEMRA in the Netherlands), as well as for copyrights (not applicable when patients play their own music from their own device). Together with health care insurance companies we should look for opportunities to finance music interventions in standard healthcare.

Music, anxiety, and distress in pediatrics

Part I of this thesis has focused on the evidence for music interventions in experimental research as well as evidence from randomized controlled studies in adults regarding physiology, and anxiety and pain perioperatively. In the perioperative healthcare practice in adults, we are now ready to focus on implementation. The evidence from adult studies however does not yet hold for perioperative music interventions in children. The studies in Part II dealt with perioperative anxiety and pain in young children, and the potential of music to alleviate these symptoms. Anxiety can be understood as a subjective sense of unease, dread or foreboding. In young children, it may be hard to distinguish between anxiety and pain behaviors, and the term distress is often used to describe the combination of both.[34,35] Distress encompasses all behaviors of negative affect and responses to aversive internal and external stimuli, associated with pain, anxiety and fear,[36] but also hunger, loneliness and unfamiliar environments. Facing surgery, children can be anxious or distressed directly related to the surgical procedure, but also due to the unfamiliar hospital environment, and separation.[37] We have studied distress (encompassing sense of unease, anxiety and pain) in children pre-operatively as well as postoperatively with the COMFORT-Behavior assessment. Regarding the behaviors experienced prior to surgery, we chose to use the term anxiety as distress encompasses both anxiety and pain, but usually there was not yet pain prior to surgery, in accordance with the terminology in adults.

In contrast to the promising results in adult patients, we cannot yet state that music interventions help decrease all children's anxiety and pain. Pre- and intraoperative music interventions seemed to decrease young children's preoperative heart rate and postoperative distress, but we found no decrease in behavioral anxiety or pain after exposure to a music intervention in a large randomized controlled trial we performed in children 0-3 years old (median age 6.9 months) (*chapter 5*). Other studies in children, both premature infants,[38,39] young infants[40] and older children,[41] show conflicting results as well.

Perhaps the conflicting results can be explained by the stage of cognitive development, which might affect a child's responses to music.[42] As the brain is extensively developing in the first years of life (and thereafter to a lesser extent), it is possible that music interventions are not yet received in the way adults receive them. We do know that children are able to hear sounds from five months pregnancy, and that prenatal music exposure can provoke physiological responses.[43-45] We also know that preterm born babies can be affected by music. But perhaps to very young children, music interventions in the perioperative setting might lead to an abundance of stimuli and therefore result in different responses. As described in *chapter 5*, music interventions in children have often been investigated postoperatively, and not preoperatively like we did. In adults, preoperative anxiety can affect postoperative pain[46] and, in this regard, we have found preoperative music interventions to affect both preoperative anxiety and postoperative pain.[4] These findings were confirmed in children (5-12 years old).[47,48] However, in infants it is much more difficult to know the causes of distress than in verbal children, which complicates designing appropriate interventions.

For instance, another finding in *chapter 5* was the children's increased discomfort probably caused by prolonged preoperative fasting. In recent years more attention is being paid to postoperative consequences of preoperative fasting, and shortening of the fasting time.[49] Liberally fluid intake until 30 minutes preoperatively does not affect residual gastric volume,[50] and shorter preoperative fasting avoids potential negative outcomes such as dehydration, ketoacidosis, reduced arterial blood pressure, and patient discomfort. Until recently, guidelines suggested a pediatric preoperative fasting time of 2 hours for clear fluids.[50] These guidelines were however often exceeded. In our trial, many children had their last meal the evening before surgery, sometimes increasing the preoperative fasting time to over 12 hours, for instance because parents did not want to wake their babies early to give the final feeding.[51] This might have undone positive effects from music interventions. It is essential therefore that parents are counseled about preoperative feeding. New protocols for preoperative fasting are being developed. The new guideline in our institution is now, March 2019, intake of clear fluids until surgery.

Chapter 6 reports on a clinimetric study in which validity and reliability of the modified Yale preoperative anxiety scale – short version (m-YPAS-SF) was tested in young children. This scale is widely used to measure preoperative anxiety in children aged 2 years and above, but not in younger ones.[52] We found good construct validity, and also good reliability of this scale. The high number of anxious children in this study underlines the urgent need for anxiety- and distress reducing measures perioperatively. Over 50 percent of our population was defined as anxious at time of inducing anesthesia (Table 2 in *Chapter 6*). Other studies also report on the high prevalence of preoperative anxiety in children.[53] As we know that preoperative distress and anxiety can negatively affect postoperative pain, and emergence delirium when awaking from anesthesia[47,48] and even result in long term consequences such as nightmares and separation anxiety,[48,54] this is an issue that clearly needs to be addressed. We investigated the anxiety- and distress decreasing effect of music preoperatively, but did not find protective effects (*chapter 5*). This might have been due to the lack of a gold standard assessment for anxiety and pain in infants or the timing or duration of the intervention or too many stimuli in the environment. We should focus on investigating different preoperative anxiety decreasing interventions for infants and their parents.

The protective effects of parental presence during induction are being debated. In our hospital it is common practice that one parent accompanies the child into the operating room until after induction. It is thought that parents have a calming effect on their child. Previous studies, however, have also reported on increased child anxiety with increased sympathetic nerve activity in mothers,[55,56] and parental fear has been shown to intensify children's preoperative anxiety.[57] Therefore parental presence might not always be helpful. The study presented in *Chapter 7* shows a high number of anxious parents just before induction of anesthesia in their child. To many parents the anesthetic and surgical process is frightening and it could be questioned whether all these parents should be exposed to the distressing event of their child's induction. Parents should be more involved in the perioperative process, starting with counseling on the different findings in earlier research. They should decide themselves whether they want to stay with their child during induction. This approach fits well with the patient- and family centered care approach which is advocated in our hospital and many other hospitals as well. Furthermore, the possible sedative effect of the music intervention on parents, when played via speakers, was interesting. As we know that music interventions can decrease adult anxiety preoperatively, this might be a welcome intervention to parents facing surgeries in their children as well.

The challenges of randomized controlled trials in non-pharmacologic interventions

Nowadays, new treatments are introduced after properly conducted randomized controlled trials. To improve the quality of research reports, the Consolidated Standards of Reporting Trials (CONSORT) statement was introduced in 1996.[58] In randomized trials of non-pharmacological treatments it may be difficult to blind the relevant parties and to exclude the influence of the provider's expertise.[59] Thus a checklist for non-pharmacological trials was developed to help minimize the risk of bias in future trials.[60] This checklist helps encountering possible issues when starting up a trial, and we strictly followed it when designing the MUSIC study (*chapter 5*). For instance, we managed to perform single blinded outcome assessments using video recordings of patients which were assessed later without the assessors knowing the group assignment. However, the strict regulations also might intervene with the study of a non-pharmacological intervention.

To illustrate this, the research protocol should accurately describe the timing of the intervention. We had stipulated that music should standardly be played during the transfer from ward to OR, the duration of which widely differed, however, resulting in very short, or sometimes very long interventions, perhaps too short or too long for some children to exert a positive effect. However, this simulates the reality where the operating room processes may face delays or accelerations. Additionally, to ensure blinding of the outcome assessors, the music intervention had to be stopped - and the headphones removed - before making the video recording for post-intervention measurement. This itself sometimes changed the behavior of the infants. Standardization of the research process is necessary to limit bias, but might affect an intervention effect when outcomes are based on behavioral observations.

Other outcomes affected by music in pediatrics and adults

Apart from perioperative anxiety and pain, many other outcomes are studied in relation to music interventions. Even though we did not study other outcomes, it is worth mentioning them as they emphasize the value of integrating music interventions in healthcare. Live and recorded music interventions have been found to exert positive effects on sleep quality, heart rate and feeding in neonates.[38] Still, many different outcome variables have been studied, and duration and type of intervention varied.[38,61,62] This heterogeneity in interventions, populations and outcomes makes it hard to draw definite conclusions on the best way to apply music interventions in neonates. It would be helpful to focus on few, measurable and objective outcomes, to contribute to the highest level of evidence according to the pyramid of evidence to allow for formation of guidelines and protocols.

An increasing number of studies in adults indicate that music interventions may have an analgesic-sparing effect perioperatively.[4,63-67] This is promising as it might help limiting negative side-effects of analgesics and deserves further evaluation. A systematic review in older patients (>60 years) found less occurrence of delirium and acute confusion (measured with Neelon and Champagne Acute Confusion Scale) in adults who received music interventions after hip surgery in the three studies that tested it.[68] In March 2019, The Music as Medicine research group started data collection in a multicenter randomized controlled trial (M-CHOPIN) aiming to include >500 patients undergoing hip surgery and investigating the effect of perioperative music interventions on delirium, use of analgesics, length of hospital stay, and independence in activity (using Katz-ADL-6).

Apart from perioperative music interventions, more attention should be given to the positive effects of music interventions offered to adults and children admitted to an intensive care unit.[69] As addressed recently, the potential of music interventions affecting delirium, physiological signs of anxiety, quality of life and perhaps care costs in the Intensive Care unit should be further explored.[70] Considering the positive outcomes on neuroplasticity and neurogenesis in the brain, music interventions in the intensive care unit and other hospital wards could maybe improve recovery after acquired brain injury. Accumulating evidence with f-MRI studies suggest that music listening results in increased functional connectivity and enhanced brain activation in neurologic rehabilitation patients by increase of blood flow through damaged brain areas[71] as well as increased functionality in cortex and cerebellum in patients with Alzheimer disease.[72] Even though reviewing only experimental research in rodents, the promising results from *chapter 2* on neurogenesis and neuroplasticity encourage further exploration of music on neurologic functioning.

Lastly, newer methods to investigate activation of the autonomic nervous system such as heart rate variability that measures sympathovagal balance, and galvanic skin response, are being introduced in music in medicine research allowing for even more objective outcome assessment.[73] Moreover, music's effects on inflammatory markers and the immune system are extensively being studied,[74,75] also encompassing more objective outcome measures. Altogether, these studies contribute to the increasing body of knowledge on the value of music interventions in healthcare.

Future directions

Research in music interventions is gaining interest, seeing that in 2019 several dozens of music intervention or music therapy studies are being conducted worldwide according to the trial registry clinicaltrials.gov. We have found level-1-evidence for the perioperative use of music to decrease anxiety and pain in adults. There is every reason, therefore, to implement this intervention in daily healthcare practice – the more so because thus far no negative side-effects have been reported.[76]

Even though the focus should be on the implementation of perioperative music, different features that might enhance the effect deserve further investigation. An interesting aspect is the tempo of the music. The rationale for the use of music with tempo of 60-80 BPM is that it would entrain with the heartbeat.[30] Music played at a higher tempo would activate the sympathetic nervous system, increase the heart rate, and thus be less suitable in the perioperative process. The question is often whether rock music has the same positive effects as for instance classical music when a patient favors rock music. For now, rock music is often associated with a tempo above 60-80BPM, what would increase physiological parameters and thus would activate the sympathetic nervous system. A recent study in cats having surgery with general anesthesia showed increased heart rate and blood pressure with exposure to rock music, and not to pop music or classical music.[77] Whether this could be attributed to the tempo is unknown.

Furthermore, musicology sciences could help in discovering identical features in the music interventions that have been researched thus far. Musicology allows the analysis of different music features such as structure, construction, rhythm, timbre, and melody. The results of this analysis might as well help identifying the best type of music intervention, that is, if there is one.

Notably with reference to *chapter 5*, we cannot state that music interventions are per se beneficial to young children. As positive effects have been reported in older children receiving postoperative music interventions,[78-82] we should inventory for which pediatric patient groups we have gained enough evidence, and for which additional research is needed. Currently, the IMPECT-study is performed in Sophia Children's Hospital investigating the effect of music interventions on anxiety, pain, use of medication and quality of life in adolescents with the age of 12-24 years old. If results are promising, the next step can be an implementation study in these older pediatric patients. As we furthermore concluded that anxiety- and pain measurement is challenging in infants and toddlers, newer methods to measure activity of the autonomic nervous system, such as heart rate variability or sympathovagal balance, need to be adopted in pediatric music research.[73] Also parents should be more involved in reporting their child's distress. Older children are able to self-report pain and distress, which facilitates assessment and evaluation.

Lastly, we could examine the effect of perioperative music interventions on parents' anxiety. In our trial, some children resisted wearing headphones. We then played music via loudspeakers and the relaxing effect on parents and healthcare practitioners was a serendipitous finding. Therefore, playing relaxing music via a loudspeaker could be considered, in analogy with the beneficial effects of music played in the emergence room waiting or the dentist' waiting.[83-86]

Conclusions

From the results of the studies in this thesis, we conclude that music interventions induce neuro-physiological responses in rodents, that are comparable to the effects also found in humans. Music interventions prior to, during and after surgery reduce perioperative anxiety and pain in adults, these effects are not restricted to one specific type of music. In young infants undergoing minor surgery these effects have not been confirmed. Music interventions indeed may alleviate heightened anxiety and distress of infants and toddlers before surgery. Anxiety and distress in these patient groups can be assessed with the short form of the modified Yale preoperative anxiety scale. Many parents are anxious when their child is having surgery, especially at time of induction of anesthesia.

For the future we propose performing implementation studies to introduce music interventions in daily surgical practice.

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Chapter 9

Summary / Samenvatting

Summary

The studies described in this thesis aimed to investigate the working mechanism of music interventions and the applicability of such interventions in healthcare practice, especially for relieving perioperative anxiety and pain.

Chapter 1 introduces 'music in medicine', the need for developing new treatments via the evidence-based-medicine route, and points out the importance of validated instruments to accurately measure results of interventions. A music intervention is the use of music with the intention to alter a specific condition, such as anxiety and pain.

The first part (chapters 2-4) provides literature overviews of music intervention outcomes in experimental and human studies.

Basic (animal) research might help elucidate the physiological and pathophysiological mechanisms of music interventions and thus aid understanding the biological working mechanisms of music. We therefore performed a systematic review of 42 experimental research studies in rodents. Various outcomes relating to brain structure and neurochemistry; behavior; immunology; and physiology were analyzed. Overall, music interventions were associated with many statistically significant improvements in neurochemistry and neurogenesis, spatial memory and anxiety-related behaviors, immune responses and physiology.

Then, we performed a systematic review and meta-analysis on the anxiety- and pain-relieving properties of perioperative music interventions in humans. With 92 randomized controlled trials, of which 81 were included in the meta-analysis, it is the largest of its kind to date. All trials evaluated the effect of music interventions before, during and/or after many types of invasive surgical procedures. The meta-analysis showed statistically significant lower levels of both anxiety and pain in patients who received a perioperative music intervention compared to control patients who did not receive a music intervention. Music interventions provided during general anaesthesia also resulted in statistically significantly less pain compared to controls.

Lastly, another systematic review and meta-analysis concerned evidence on the efficacy of music interventions in hypertension treatment. There is growing interest in the value of non-pharmacological therapies such as music interventions to lower blood pressure. Ten randomized controlled trials were included in the review and meta-analysis. A trend towards a lowering of blood pressure was shown in hypertensive patients who received music interventions, but a cause-effect relationship between music interventions and blood pressure reduction could not be established.

From *part I* of this thesis, we conclude that music interventions exert effects via a biological mechanism, as rodents are affected by music as well. The majority of experimental studies

in rodents used classical music, but as other types of music exerted positive effects as well the effect is not restricted to one type of music. The findings from the meta-analysis considering perioperative music interventions provide the highest level of evidence to support the implementation of music as anxiolytic and analgesic intervention in adults having invasive surgery – and this should be the next step. Considering the potential value of music interventions in the treatment of hypertension, well-designed, high-quality and sufficiently-powered randomized studies should be performed.

The second part (chapters 5-7) describes prospective clinical studies on music interventions in the Pediatric Surgical department at the Erasmus Medical Center- Sophia Children's Hospital in Rotterdam, the Netherlands.
First, a large parallel, single-blind, randomized controlled trial (the MUSIC study; Music Under Surgery In Children) is described on the effects of music interventions on distress, anxiety, and postoperative pain in infants undergoing surgery. One hundred ninety-five infants (median age 6.9 months) took part in this research. The surgical procedures consisted of orchidopexy, hypospadias, or inguinal hernia repair. A music intervention was applied either before surgery or both before and during surgery; or not at all (the control group). The main outcome measure was the postoperative level of distress assessed with the COMFORT-B scale; furthermore, the preoperative levels of distress were measured, as well as heart rate, blood pressure, and level of oxygen in the blood. We discovered that music interventions do not seem to benefit all young infants undergoing surgery, but mostly those who displayed above-normal distress before surgery. Additionally, we found that children who had received music interventions before surgery had a lower heart rate when arriving in the operating room.

Previous research has also investigated effects of music interventions on preoperative anxiety. This, however, not yet possible in infants less than 2 years old, simply because a validated preoperative anxiety questionnaire for this population was not yet available. So, we set out to validate the Dutch version of the modified Yale Preoperative Anxiety Scale-Short Form (mYPAS-SF) for measuring preoperative anxiety in infants younger than 2 years. We assessed the behaviors of 129 infants (89.1% male) with a median age of 6.5 months scheduled for surgery using this Dutch version as well as the COMFORT-B scale, at the holding area and at induction of anesthesia. Strong correlations were found between the scores on both instruments, implying good validity of the mYPAS-SF to measure preoperative anxiety in children less than 2 years old.

The final study reported is a study on preoperative anxiety in children and their parents. It has been suggested that parent-child pairs can experience mutual preoperative anxiety, which could adversely affect each other. Parents of 188 children answered validated anxiety questionnaires, and we assessed the children's behavior using validated behavior assessment. The results showed that over one-third of parents experienced considerable preoperative anxiety at their children's surgery – and generally mothers experienced higher levels of anxiety than fathers did. Anxiety levels of parents were associated with a higher general level of anxiety, preoperatively more distressed children, and a younger children's age at time of surgery.

From *part II* of this thesis, we conclude that music interventions could be valuable for infants in the preoperative period, and especially for more distressed children. Furthermore, preoperative anxiety in infants less than 2 years old can from now on be measured with the mYPAS-SF. This scale makes it possible to validly and reliably measure and interpret anxiety-reducing-interventions in this young population. Considering the high proportion of parents experiencing preoperative anxiety, there should be more focus on identification of anxious parents and children to offer tailor-made treatment for each parent and child undergoing surgery.

The *General Discussion* is dedicated to the most important study findings and their clinical implications; and recommendations are made for new research and patient care.

Samenvatting

De studies in dit proefschrift gaan voornamelijk over het werkingsmechanisme van muziekinterventies en het nut van muziek voor patiënten. Een muziek interventie wordt gezien als het gebruik van muziek met het doel een specifieke conditie te beïnvloeden. In dit proefschrift is dan ook gekeken of muziek kan zorgen voor minder angst en pijn rondom operatieve procedures.

De *Algemene Introductie* gaat in op muziekinterventies in de gezondheidszorg, de noodzaak van wetenschappelijk-onderbouwd bewijsmateriaal, en het gebruik van gevalideerde meetinstrumenten om het resultaat van interventies te meten.

Het eerste deel (hoofdstuk 2-4) betreft literatuuronderzoek over muziekinterventies bij dieren en mensen.
Experimenteel onderzoek bij ratten en muizen kan meer inzicht geven in de manier waarop een interventie een lichaam, of een ziekteproces, beïnvloedt. We hebben een systematisch review uitgevoerd van 42 onderzoeken naar muziekinterventies bij ratten en muizen gericht op de mogelijke effecten op de hersenfunctie, het gedrag, en immunologische en fysiologische aspecten. Globaal gezien waren muziekinterventies geassocieerd met verbeteringen op bijvoorbeeld de ontwikkeling en het herstel van de hersenen, geheugen, angst-gerelateerd gedrag, het afweersysteem en hartslag en bloeddruk. De meeste onderzoekers hadden klassieke muziek laten horen, maar andere types muziek hadden ook een positief effect.

Vervolgens hebben we een systematische review en meta-analyse uitgevoerd naar de angst- en pijn-verminderende eigenschappen van muziekinterventies rondom operaties. Met 92 gerandomiseerd gecontroleerde onderzoeken, en een meta-analyse toegepast op 81 daarvan, is dit tot nu toe de grootste in zijn soort. Deze onderzoeken gingen over het effect van muziekinterventies op angst en pijn bij volwassenen vóór, tijdens, en/of na een invasieve ingreep. Uit onze analyse bleken lagere angst- en pijnscores bij patiënten die een muziekinterventie kregen, in vergelijking met patiënten die geen muziekinterventie kregen (de controlegroep). Patiënten die een muziekinterventie kregen tijdens algehele narcose, ervaarden ook minder pijn na een operatie in vergelijking met de controlegroep.

Ten derde hebben we een systematische review en meta-analyse uitgevoerd naar wetenschappelijk bewijs voor het effect van muziekinterventies bij behandeling van hypertensie. Er komt steeds meer belangstelling voor het gebruik van niet-farmacologische methoden om bloeddruk te verlagen, zoals muziekinterventies. Tien gerandomiseerd gecontroleerde onderzoeken werden geïncludeerd in de meta-analyse. Bij patiënten met hoge bloeddruk die een muziekinterventie aangeboden kregen bleek een trend naar een daling van de bloeddruk, maar een causaal verband kon niet worden aangetoond.

Uit *Deel I* van dit proefschrift concluderen we dat aan muziek een biologisch werkingsmechanisme ten grondslag ligt, dat niet gebonden is aan één soort muziek. Verder is er overtuigend wetenschappelijk bewijs dat het zin heeft muziekinterventies rondom operaties bij volwassen te implementeren, en dit moet dan ook de vervolgstap zijn. De waarde van muziekinterventies voor het verlagen van hoge bloeddruk zal dit verder moeten worden onderzocht in strikt opgezet en uitgevoerd gerandomiseerd gecontroleerd onderzoek met een voldoende aantal proefpersonen.

Het tweede gedeelte (hoofdstuk 5-7) beschrijft prospectieve klinische studies op de afdeling Kinderchirurgie van het Erasmus MC-Sophia Kinderziekenhuis in Rotterdam, Nederland.
Het begint met de beschrijving van een geblindeerde, gerandomiseerd gecontroleerde studie ((de MUSIC studie, Music Under Surgery In Children (muziek rondom operaties bij kinderen)) naar de effecten van muziekinterventies op onrust, stress, angst en postoperatieve pijn bij 195 zuigelingen en peuters die een operatie ondergingen. De operatie betrof een liesbreuk, een niet-ingedaalde testis of hypospadie en een muziekinterventie werd aangeboden of voorafgaande aan de operatie, of voor én tijdens de operatie, of helemaal niet (de controlegroep). De belangrijkste uitkomstmaat was de mate van comfort na de operatie (gemeten met de COMFORT-gedragsschaal). Verder werd ook gekeken naar comfort vóór de operatie, en hartslag en bloeddruk. De muziekinterventies bleken niet bij álle kinderen te zorgen voor meer comfort, maar waren wel nuttig voor de kinderen die meer onrustig waren vóór de operatie. Ook zagen we dat kinderen die een muziekinterventie kregen vóór de operatie een lagere hartslag hadden voor de operatie dan de kinderen in de controlegroep.

Omdat de meest gebruikte schaal voor het meten van preoperatieve angst nog niet gevalideerd was bij kinderen onder de twee jaar, hadden wij voor ogen om de Nederlandse versie van de ‘modified Yale Preoperative Anxiety Scale-Short Form’ (mYPAS-SF) te valideren. We hebben het gedrag van 129 kinderen (89.1% jongens) met een mediane leeftijd van 6.5 maanden beoordeeld met de deze versie en met de COMFORT-gedragsschaal (die is gevalideerd voor het meten van discomfort bij jonge kinderen), zowel op de holding als tijdens inductie van anesthesie. We vonden een sterke correlatie tussen de scores van deze meetinstrumenten, die wijst op een goede validiteit van de geteste schaal.

Als laatste wordt een studie besproken naar preoperatieve angst bij ouders van jonge patiënten, en bij deze kinderen zelf. Uit eerder onderzoek is namelijk gebleken dat de kinderen wat dit betreft beïnvloed kunnen worden door de ouders, en omgekeerd. De ouders van 188 kinderen die werden geopereerd hebben verschillende gevalideerde vragenlijsten beantwoord naar angst – en specifiek angst in relatie tot de operatie. Het gedrag van de kinderen werd geobserveerd met de COMFORT-gedragsschaal. Meer dan een derde van de ouders bleek aanzienlijke angst te ervaren voordat hun kind een operatie zou ondergaan – en de moeders meer dan de vaders. Het angstniveau bij ouders was geassocieerd met een algemeen hogere aanleg voor angst, meer onrustige kinderen bij aanvang van de operatie, en jongere kinderen in de populatie.

Uit *Deel II* concluderen we dat het zin heeft de waarde van muziekinterventies in de preoperatieve periode en bij meer onrustige kinderen verder te onderzoeken. Voor het meten van preoperatieve angst óók bij kinderen jonger dan 2 jaar kan gebruik worden gemaakt van de mYPAS-SF. Gezien het hoge percentage ouders dat angst ervaart voordat hun kind wordt geopereerd, zou er meer focus moeten liggen op het aanwijzen en begeleiden van angstige ouders en kinderen.

Het laatste hoofdstuk, de *Algemene Discussie,* is gewijd aan een bespreking van de resultaten van de studies en de betekenis daarvan voor de klinische praktijk. Er worden aanbevelingen gedaan voor nieuw onderzoek en voor het implementeren van muziekinterventies in de patiëntenzorg.

Addendum

About the Author

List of Publications

List of Co-authors

PhD-Portfolio

Dankwoord

About the author

Anne Yvonne Rosalie Kühlmann was born on the 17th of September 1987 in Wageningen, The Netherlands. After primary school education at the Arnhemse Montessori school, she completed secondary school at the Stedelijk Gymnasium Apeldoorn in 2006. In the same year, she started her study Medicine at the university of Groningen (Rijksuniversiteit Groningen). During her medical training, she went to Cape Town, South Africa for an international traineeship in a pediatric orthopedic hospital. In the last year of medical training, she performed a research elective in Isala Zwolle where she was introduced to the concepts of Integrative Healthcare and healing environments, both concepts that fitted well to her education. Rosalie obtained her Medical Degree in 2014 and directly started her PhD training for the 'Music as Medicine' program at the Department of Pediatric Surgery of the Erasmus MC-Sophia Children's hospital, University Medical Center in Rotterdam, The Netherlands. Under supervision of prof. dr. R.M.H. Wijnen and prof. dr. M. van Dijk as promotors, and prof. dr. J. Jeekel as co-promotor, she learned more on the opportunities of music in healthcare. After two years of full-time research, she combined research with her work as a residence (ANIOS) at the Department of Pediatric Surgery at the Erasmus MC-Sophia Children's hospital, where her attraction to physiology, anesthesiology and trauma care was further developed. This was followed by a residency (ANIOS) at the Intensive Care department of het Westfriesgasthuis in Hoorn, The Netherlands. In 2019 she started her residency in Anesthesiology at the St. Antonius Hospital, Nieuwegein, the Netherlands, where she worked while finishing her thesis.

List of publications

This thesis

Kühlmann AYR, Etnel JRG, Roos-Hesselink JW, e.a. *Systematic Review and Meta-Analysis of Music Therapy in Hypertension Treatment: A Quest for Answers.* BMC Cardiovasc Disord. 2016 Apr 19;16(1):69.

Kühlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. *Meta-analysis evaluating music interventions for anxiety and pain in surgery.* Br J Surg 2018;105:773-83.

Kühlmann AYR, Lahdo N, Staals LM, van Dijk M. *The Modified Yale Preoperative Anxiety Scale-Short Form also shows promising validity and reliability in children less than 2 years-old.* Paediatr Anaesth. 2019 Feb;29(2):137-143. doi: 10.1111/pan.13536. Epub 2018 Dec 23.

Kühlmann AYR*, de Rooij A, Hunink MGM, De Zeeuw CI and Jeekel H (2018) *Music Affects Rodents: A Systematic Review of Experimental Research.* Front. Behav. Neurosci. 12:301. doi: 10.3389/fnbeh.2018.00301

Kühlmann AYR, van Dijk M, Staals LM, e.a.; *Music interventions for anxiety and pain in pediatric surgery: the MUSIC study, a randomized controlled trial.* Anesth Analg 2019 Jan 8. doi: 10.1213/ANE.0000000000003983. [Epub ahead of print]

Other publications

Kühlmann AYR, Jeekel J, Pierik EGJM. *Beter met Kunst?* Ned Tijdschr Geneeskd 2015;159(0):A9606.

Kühlmann AYR, Jeekel J. *Effecten van muziek op operatiepatiënten.* Ned Tijdschr Geneeskd 2016;160:A9841

Kühlmann AYR*,Massoud M*, van Dijk M, et al. *Does the Incidence of Postoperative Complications After Inguinal Hernia Repair Justify Hospital Admission in Prematurely and Term Born Infants?* Anesth Analg 2018. doi: 10.1213/ANE.0000000000003386

Kühlmann AYR, Kroese LF, Jeekel J. *Dubbelpublicatie: Muziek vermindert angst en pijn bij operaties: systematische review en meta-analyse.* Ned Tijdschr Geneeskd

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Copromotor:	Prof. dr. J. Jeekel

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Literature		
Research MB	08-2014	0.7 ECTS
Biostatisical Methods I: CC02	01-2015	5.7 ECTS
Good Clinical Practice (BROK)	01-2015	1.0 ECTS
CPO Course	04-2015	0.3 ECTS
Integrity in Science	05-2015	0.3 ECTS
NIHES ESP meta-analysis	08-2015	1.0 ECTS
Biomedical English Writing	02-2016	3.0 ECTS
Advanced Pediatric Life Support	02-2017	1.5 ECTS

Seminars:

ITON cursus Muziek en Brein	12-2014	0.4 ECTS
Imagination, Music & the Brain	01-2015	0.2 ECTS
Peer-to-Peer meeting Live Long Arts	05-2015	0.3 ECTS

Conferences:

Presentation at NVML congress	11-2014	1.0 ECTS
Presentation at V&VN congress	11-2014	0.5 ECTS
Invited speaker Integrity Course	06-2015	0.5 ECTS
TULIPS JOD	11-2015	0.3 ECTS
Presentation Ronde Tafel		
Integrative Healthcare Radboud MC	11-2015	0.3 ECTS
Sophia Research days	2014/2015/2016/2017	1.0 ECTS
Congress Beijing 2016	06-2016	1.0 ECTS
Poster		0.3 ECTS
Presentation De Doelen	01/02-2016	1.0 ECTS
Invited Speaker CPO course Erasmus MC	04-2017	0.3 ECTS
Oral Presentation Chirurgendagen	05-2017	1.0 ECTS

EUPSA Congress	05-2017	1.0 ECTS
Oral presentation EUPSA		1.0 ECTS
NVA Kinderanesthesiedagen	06-2017	0.3 ECTS
2x oral presentation NVA		2.0 ECTS
Presentation 'Nacht van de Wetenschap'	10-2017	0.5 ECTS
Presentation Jackson Reese Symposium	11-2017	1.0 ECTS
Presentation Studium Generale Groningen	11-2017	1.0 ECTS
EUPSA Congress	06-2018	0.3 ECTS
Oral presentation EUPSA		1.0 ECTS
Presentation Studium Generale Utrecht	10-2018	1.0 ECTS
EUPSA Congress	06-2019	0.3 ECTS
Oral presentation EUPSA		1.0 ECTS

Teaching Tasks:

Supervision hours with co-promotors	06-2014/11-2017	2.0 ECTS
Supervision students	04-2016	0.5 ECTS
Supervision of two Master Thesis	06-2016/11-2016	3.0 ECTS
Research meetings Kinderchirurgie	2016/2017	1.0 ECTS
		38.5 ECTS

Ad

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Beste professor Jeekel, beste Hans, veel dank voor de leerzame tijd als onderzoeker van de Muziek als Medicijn onderzoeksgroep. Vanaf het begin heeft u altijd het belang van gedegen onderzoek via evidence-based-medicine principes benadrukt, en uitgelegd dat deze basis nodig is om muziek daadwerkelijk te implementeren in de reguliere gezondheidszorg. Uw kennis heeft mij veel geleerd over wetenschappelijk onderzoek en de gezondheidszorg in het algemeen. Uw doorzettingsvermogen en passie zijn bewonderingswaardig en een voorbeeld voor iedereen.

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Rosalie Kühlmann, juli 2019

Appendix

Appendix

Muziek vermindert angst en pijn rond operaties*

Systematische review en meta-analyse

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*Dit onderzoek werd eerder gepubliceerd in The British Journal of Surgery (2018;105:773-83) met als titel 'Meta-analysis evaluating music interventions for anxiety and pain in surgery'. De oorspronkelijke publicatie telde naast de huidige auteurs ook de volgende medeauteurs: prof.dr. M.G.M. Hunink, prof.dr. M. van Dijk en drs. A. de Rooij.

Nederlands Tijdschrift van Geneeskunde 2018;162:D3186

Samenvatting

Doel

Onderzoeken wat de effecten zijn van muziek op angst en pijn rond operaties. Dit artikel is een bewerking van onze eerdere publicatie in *The British Journal of Surgery,* (2018;105:773-83).

Opzet

Systematische review en meta-analyse van gerandomiseerde, gecontroleerde onderzoeken (RCT's).

Methode

In 11 elektronische databases zochten wij naar RCT's waarin het effect van muziekinterventies op angst en pijn voor, tijdens en/of na operatie bij volwassenen was onderzocht. Artikelen gepubliceerd in de periode van 1 januari 1980 tot 20 oktober 2016 werden onafhankelijk tweevoudig doorzocht door 4 personen en de onderzoeksgegevens van relevante artikelen werden steeds door 2 personen onafhankelijk van elkaar geëxtraheerd. Effectgroottes werden berekend als gestandaardiseerd gemiddelde-verschil (SMD) met een 'random effect'-analyse. De mate van heterogeniteit van de RCT's onderzochten wij met subgroep-analyses en meta-regressieanalyses. De review werd geregistreerd in de PROSPERO-database onder nummer CRD42016024921.

Resultaten

In totaal namen wij 92 RCT's (7385 patiënten) op in onze systematische review, waarvan 81 ook in de meta-analyse. Bij patiënten die een muziekinterventie kregen zagen wij een statistisch significante afname van angst (SMD: -0,69; 95%-BI: -0,88- -0,50) en van pijn (SMD: -0,50; 95%-BI: -0,66- -0,34) ten opzichte van controlegroepen die geen interventie kregen. Na correctie voor beginwaarden was de afname nog groter, zowel van angst (SMD: -1,41; 95%-BI: -1,89- -0,94) als van pijn (SMD: -0,54; 95%-BI:-0,93- -0,15). Wij vonden ook een statisch significante vermindering van postoperatieve pijn bij patiënten die een muziekinterventie hadden gekregen tijdens een operatie onder algehele narcose, vergeleken met de controlegroep (SMD: -0,41; -0,64- -0,18). Het risico op bias werd geschat als gemiddeld tot hoog.

Conclusie

Muziekinterventies vóór, tijdens en/of na een operatie leiden tot minder angst en pijn bij volwassen patiënten.

Introductie

Mensen die een operatie moeten ondergaan ervaren vaak angst en pijn vóór en na de operatie. Angst voorafgaand aan een operatie kan leiden tot meer pijn na de operatie.[1] Ongeveer 40-65% van de patiënten ervaart na de operatie matige tot ernstige pijn, ondanks verschillende vormen van pijnstilling.[2]

Er is in toenemende mate aandacht voor muziekinterventies om eventuele angst en pijn van patiënten rond operaties te verminderen. Hoewel een positieve werking van muziek is aangetoond in een groot aantal onderzoeken, zijn muziekinterventies nog niet geïntegreerd in de dagelijkse patiëntenzorg. Dat deze interventies nog niet zijn ingevoerd komt mogelijk door gebrek aan bewijs voor de effectiviteit op het hoogste niveau (bewijsniveau 1), een gebrek dat is te verklaren door de vele variaties in studies, onderzoekspopulaties en interventies. Recentelijk werden bijvoorbeeld 2 meta-analyses van muziekinterventies gepubliceerd, waarvan de ene betrekking had op zowel chirurgische als niet-chirurgische patiëntenpopulaties,[3] en de andere op zowel muziekinterventies als andere interventies.[4]

Ons doel was om in een systematische review en meta-analyse de bevindingen naast elkaar zetten van alle gerandomiseerde, gecontroleerde onderzoeken naar het effect van perioperatieve muziekinterventies op angst en pijn die tot 20 oktober 2016 gepubliceerd waren. Dit artikel is een bewerking van onze eerdere publicatie in *The British Journal of Surgery*.[5]

Methode

Deze systematische review en meta-analyse werden uitgevoerd volgens het PRISMA-statement en geregistreerd in de PROSPERO-database (www.crd.york.ac.uk/PROSPERO) onder nummer CRD42016024921.[6] Wij doorzochten 11 elektronische databases op RCT's waarin het effect van muziekinterventies vóór, tijdens of na een operatie werd onderzocht en die in de periode van 1 januari 1980 tot 20 oktober 2016 gepubliceerd waren; de volledige zoekstrategie is te vinden in de oorspronkelijke publicatie.[5] De artikelen die wij vonden met onze zoekstrategie werden onafhankelijk tweevoudig doorzocht op titel en samenvatting door 4 personen. De artikelen die potentieel geschikt waren werden daarna gelezen om te bezien of ze in aanmerking kwamen voor inclusie.

Wij hanteerden de volgende inclusiecriteria: het moest gaan om Engelstalige, als volledige tekst beschikbare onderzoeksartikelen van RCT's over de effecten van muziekinterventies op angst of pijn bij patiënten van 18 jaar en ouder. Alle operaties moesten invasief zijn (open of laparoscopische procedure), onder algehele of regionale anesthesie. Zowel interventies met live muziek als die met opgenomen muziek waren acceptabel, zolang er maar sprake was van melodie, harmonie en ritme. Zowel onderzoekers als muziektherapeuten mochten de interventies geven en het onderzoek mocht zijn uitgevoerd in een ziekenhuis of een polikliniek.

Redenen voor exclusie waren niet-invasieve procedures zoals endoscopie, en onderzoeken waarbij pseudo- of quasi-randomisatietechnieken waren gebruikt. Natuurgeluiden werden alleen overwogen wanneer zij een aanvulling waren op een muziekinterventie.

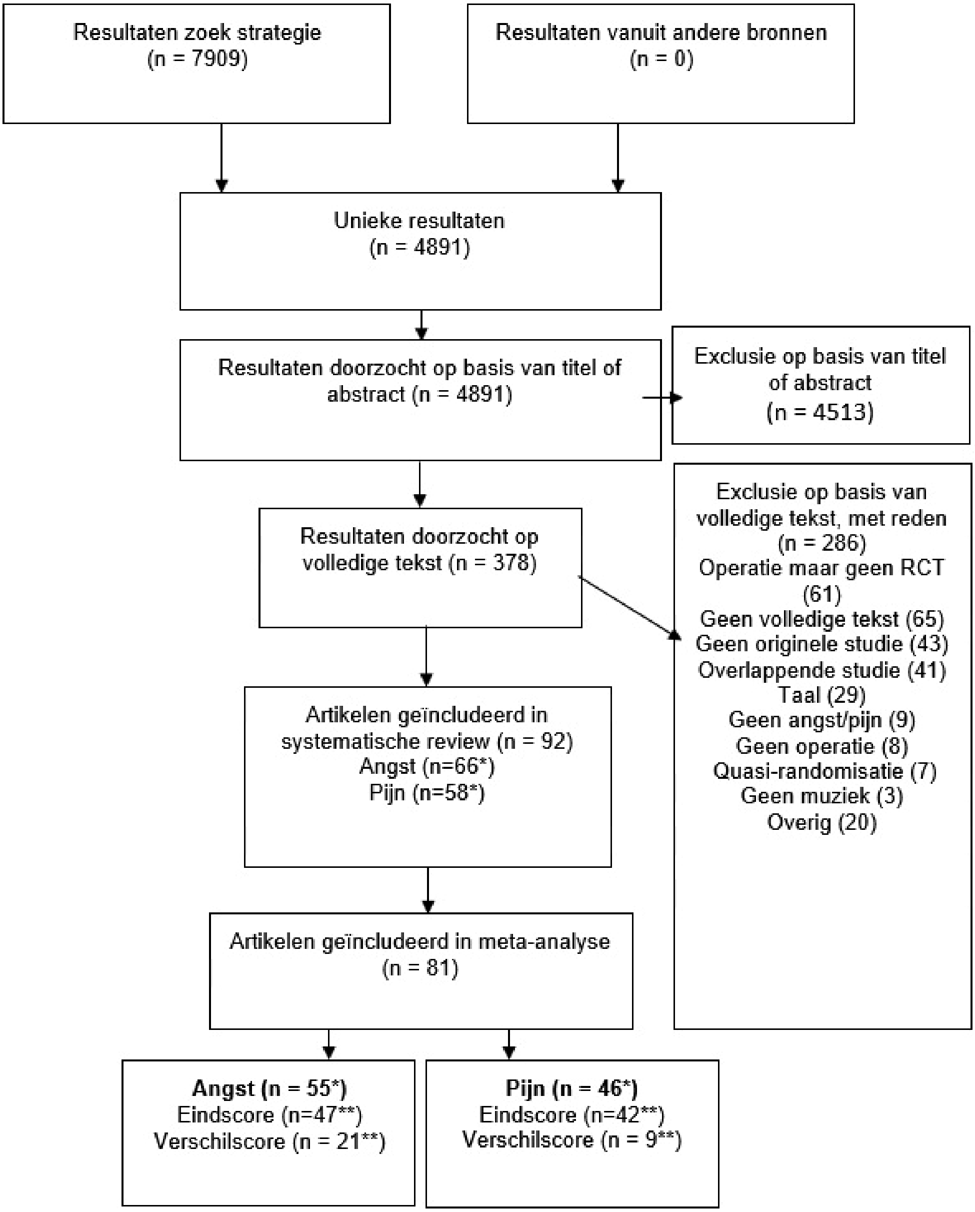
Voor de meta-analyse kwamen alleen artikelen in aanmerking waarin de spreiding van kwantitatieve uitkomstmaten werd vermeld. Drie auteurs deden onafhankelijk een dubbele data-extractie. De volgende gegevens werden onder andere geregistreerd: het aantal patiënten, de uitkomstschaal, het type operatie en anesthesie, de soort muziekinterventie en het moment van toediening (vóór, tijdens of na operatie). Primaire uitkomstmaten waren angst- en pijnscores (met spreidingsmaat) en, indien vermeld, ook de verschillen in de scores vóór en na de muziekinterventie (met spreidingsmaat).

Statistische analyse

Primaire statistische analyses werden uitgevoerd met Review Manager 5.3.5 (The Nordic Cochrane Center, Kopenhagen, Denemarken). Uitkomstmaten werden samengevoegd met de omgekeerde-variantie-methode in een 'random effect'-model. Gestandaardiseerde verschillen tussen gemiddelden ('standard mean differences', SMD's) werden berekend met behulp van Hedges' g met gepoolde gewogen standaarddeviaties, weergegeven met 95%-betrouwbaarheidsintervallen en geïnterpreteerd als volgt: ≥ 0,20: klein effect; ≥ 0,50 gemiddeld effect; ≥ 0,80 groot effect. Het risico op bias werd geanalyseerd met de 'Cochrane Collaboration risk of bias tool'. De mate van heterogeniteit van de onderzoeken werd onderzocht met subgroep-analyses. Meta-regressieanalyses naar mogelijke verbanden tussen de onderzoekseigenschappen en de effecten van muziek werden uitgevoerd in Stata versie 14 (StataCorp, College Station, Texas, VS). Tweezijdige statistische significantie werd gelijkgesteld aan $p < 0{,}05$. Ter verduidelijking van de klinische effecten werden de uitkomstmaten teruggerekend naar klinische angstscores ('State trait anxiety inventory' (STAI)) en pijnscores op een visueel-analoge schaal (VAS). Een uitgebreidere beschrijving van de onderzoeksmethodes is in het originele artikel te vinden.[5]

Resultaten

De figuur toont het stroomdiagram met de resultaten van de zoekstrategie. Uiteindelijk werden 92 RCT's met in totaal 7385 patiënten opgenomen in de systematische review, waarvan 81 in de meta-analyse. De basiskenmerken van deze RCT's staan in de online-appendix van ons oorspronkelijke artikel.[5] De gemiddelde leeftijd van de onderzoekspopulatie was 51,7 jaar (SD: 10,4); deze populatie bestond voor 57% uit vrouwen. 11 RCT's (12%) vermeldden geen spreidingsmaten en werden daarom niet meegenomen in de meta-analyse.



Figuur 1.

* Sommige artikelen rapporteerden zowel angst- als pijn uitkomstmaten
** Sommige artikelen rapporteerden zowel eind- als verschilscores

Risico op bias

Elk van de geïncludeerde onderzoeken had een gemiddeld tot hoog risico op bias. In veel publicaties ontbraken de gegevens om het risico op bias te schatten en daarom werd dit risico bij deze artikelen beoordeeld als 'onduidelijk'. Wij bekeken 'funnel plots' om het risico op publicatiebias te schatten. Een tendens naar asymmetrie, wat mogelijk wijst op publicatiebias, werd gevonden bij angst maar niet bij pijn (zie figuren S2 en S3 bij in de oorspronkelijke publicatie).

Muziekinterventies en angst

Het effect van muziek op angst is onderzocht in 47 van de RCT's (tabel 1). De vermindering van angst na een muziekinterventie was gemiddeld, vergeleken met de controlegroep (SMD: -0,69; 95%-BI: -0,88- -0,50). Wanneer gecorrigeerd werd voor de angstscore vóór operatie (de beginwaarde) was het verschil in afname van angst tussen de muziekinterventiegroep en de controlegroep groot (SMD: -1,41; 95%-BI: -1,89- -0,94). Teruggerekend van de SMD naar de oorspronkelijke schaal was de afname van angst in de muziekinterventiegroep 21 mm op een VAS van 100 mm, en 6,3 punten op de 20-80-punts-STAI.

Tabel 1. Resultaten van de meta-analyses van angst (n=55 onderzoeken) en pijn (n=46 onderzoeken).[1] Afkortingen: N= aantal onderzoeken, SMD= gestandaardiseerd gemiddeld verschil, B-I= betrouwbaarheidsinterval, I= inconsistentie. [a]Sommige onderzoeken rapporteerden zowel de eindwaarde, als de verschil-score. [b]Onderzoeken in deze sub-analyse gaven óf preoperatieve, óf intra-operatieve, óf postoperatieve interventies; onderzoeken met meerdere interventies zijn niet meegenomen. [c]Onderzoeken in deze sub-analyse gaven óf algehele narcose, óf regionale anesthesie, niet beiden.

Meta-analyse	Subgroep-analyse	N	SMD	95% B-I	P-waarde	I^2(%)
Angst		47	-0.69	-0.88; -0.50	<0.001	87
Angst verandering[a]		21	-1.41	-1.89; -0.94	<0.001	95
	Muziek selectie					
	Patiënt-keuze uit lijst	23	-0.71	-0.99; -0.43	<0.001	88
	Onderzoeker keuze	19	-0.67	-0.97; -0.36	<0.001	87
	Patiënt- eigen muziek	4	-0.45	-0.82; -0.07	0.020	75
	Moment van interventie[b]					
	Preoperatief	13	-1.10	-1.53; -0.66	<0.001	89
	Intra-operatief	10	-0.57	-1.06; -0.09	0.020	92
	Postoperatief	10	-0.66	-1.07; -0.25	0.002	87
	Aantal interventies					
	Eenmalig	34	-0.76	-1.02; -0.50	<0.001	91
	Meerdere	13	-0.51	-0.64; -0.38	<0.001	0
	Soort anesthesie[c]					
	Algehele narcose	13	-0.47	-0.71; -0.23	<0.001	69
	Algeheel met intra- operatieve interventie	1	-0.23	-0.62; 0.17	-	
	Regionaal	14	-0.88	-1.34; -0.42	<0.001	92

Ap

Meta-analyse	Subgroep-analyse	N	SMD	95% B-I	P-waarde	I^2(%)
Pijn		42	-0.50	-0.66; -0.34	<0.001	78
Pijn verandering[a]		9	-0.54	-0.93; -0.15	0.006	84
	Muziek selectie					
	Patiënt-keuze uit lijst	21	-0.55	-0.81; -0.28	<0.001	84
	Onderzoeker keuze	16	-0.47	-0.67; -0.26	<0.001	65
	Patiënt- eigen muziek	5	-0.26	-0.56; 0.04	0.090	61
	Moment van interventie[b]					
	Preoperatief	3	-0.73	-1.54; 0.08	0.080	84
	Intra-operatief	10	-0.18	-0.36; 0.00	0.050	44
	Postoperatief	19	-0.53	-0.79; -0.28	<0.001	82
	Aantal interventies					
	Eenmalig	32	-0.47	-0.65; -0.29	<0.001	80
	Meerdere	10	-0.62	-0.93; -0.30	<0.001	72
	Soort anesthesie[c]					
	Algehele narcose	23	-0.55	-0.72; -0.39	<0.001	55
	Algeheel met intra- operatieve interventie	5	-0.41	-0.64; -0.18	<0.001	9
	Regionaal	8	-0.41	-0.80; -0.03	0.040	84

Muziekinterventies en pijn

Het effect van muziek op pijn is onderzocht in 42 van de RCT's (zie tabel 1). De vermindering van pijn na een muziekinterventie was gemiddeld, vergeleken met de controlegroep (SMD: -0,50; 95%-BI: -0,66- -0,34). De effectgrootte voor afname van pijn ten opzichte van de beginwaarde was eveneens gemiddeld (SMD: -0,54; 95%-BI: -0,93- -0,15), vergeleken met de controlegroep. Terugrekenen naar de oorspronkelijke schaal gaf een afname van pijn van 10 mm op de VAS van 100 mm in de muziekinterventiegroep.

Subgroep-analyses

Resultaten van de subgroep-analyses zijn weergegeven in tabel 2. Alle interventies, ongeacht het moment van interventie (vóór, tijdens of na operatie), leidden tot vermindering van angst. De vermindering van pijn was statistisch significant bij een interventie na de operatie. De toepassing van meerdere interventies gaf een grotere afname van pijn dan een eenmalige interventie. Muziekinterventies tijdens een operatie onder algehele narcose waren gerelateerd aan een statistisch significante daling van pijn na de operatie. Bij muziekinterventies tijdens regionale anesthesie werd een grote vermindering van angst gezien en een gemiddelde vermindering van pijn. Het effect was het grootst wanneer de patiënt zelf de muziek kon uitkiezen uit een voorgeselecteerde lijst.

Meta-regressieanalyses

De studies vertoonden een grote mate van heterogeniteit (zie tabel 2). Met univariabele en multivariabele meta-regressieanalyses onderzochten wij variabelen die eventueel het effect van muziek op angst en pijn konden verklaren. Hierbij bleek geen rol weggelegd te zijn voor de variabelen leeftijd, geslacht, type anesthesie en keuze en timing van de muziekinterventie. Een statistisch significant verband werd wel gevonden voor preoperatieve muziekinterventies en afname van pijn.

Beschouwing

Uit deze meta-analyse blijkt dat zowel angst als pijn statistisch significant afnemen bij volwassenen die vóór, tijdens of na een operatie een muziekinterventie krijgen. De afname ten opzichte van de controlegroep is nog groter wanneer de uitkomsten worden gecorrigeerd voor de beginwaarden bij het onderzoek. Muziekinterventies vóór de operatie lijken het gunstigst te zijn als het gaat om angstvermindering, terwijl het effect op pijn het grootst lijkt te zijn bij muziekinterventies ná de operatie. Een preoperatieve muziekinterventie kan overigens ook een positieve invloed op postoperatieve pijn hebben, mogelijk door de samenhang van preoperatieve angst en postoperatieve pijn.[1]

Eerdere meta-analyses betrokken ook andere vormen van interventies,[4] keken alleen naar het effect op preoperatieve angst,[7] of includeerden ook niet-chirurgische procedures.[3,8] De kracht van onze meta-analyse is dat wij alleen onderzoeken naar muziekinterventies rondom chirurgische procedures hebben geïncludeerd, met als resultaat meer homogeniteit in de onderzoeken en een grotere nadruk op het effect van de interventie; deze meta-analyse geeft een bewijs van het hoogste niveau voor het effect van muziekinterventies op angst en pijn rond operaties.

Het soort muziek

Een belangrijke bevinding van deze meta-analyse is dat het effect van muziek niet aan één specifiek type muziek te danken is: veel verschillende soorten muziekinterventies, met verschillende instrumenten, leidden tot angst- en pijnvermindering (zie tabel S1 in de oorspronkelijke publicatie).[5] Wanneer de patiënt de muziek zelf mocht kiezen uit een voorgeselecteerde lijst leek de muziek een iets groter effect te hebben op de vermindering van angst en pijn; dit effect verschilde echter niet significant van het effect van de muziek die door de onderzoekers was uitgekozen, of van muziek die de patiënt zelf had meegenomen. Het zou interessant zijn meer onderzoek te doen naar het soort muziek en het belang van persoonlijke voorkeur. Ritmische en harmonische muziek, en het gebruik van snaarinstrumenten, lijken alle een gunstige invloed te hebben op perioperatieve angst en pijn.[9]

Placebo-effect?

Bij alle geïncludeerde onderzoeken werd gebruikgemaakt van zelfrapportage met gevalideerde meetinstrumenten. Bij deze methode wordt nog weleens de mogelijkheid van een placebo-effect geopperd. Een placebo-effect dat bestaat uit angst- en pijnvermindering kan overigens ook als een reëel effect worden gezien.[10] In de subgroep-analyse van muziekinterventies onder algehele narcose zagen wij echter ook vermindering van postoperatieve pijn. Onder algehele narcose kan nauwelijks sprake zijn van een placebo-effect,[11] en ook psychologische effecten van het luisteren naar muziek spelen dan geen rol. Deze overwegingen pleiten dan ook tegen een placebo-effect.

Risico op bias

Het risico op bias in de geanalyseerde onderzoeken werd geschat op gemiddeld tot hoog. Methodologische kenmerken, zoals steekproefberekening en randomisatietechnieken, waren vaak niet goed beschreven, met als gevolg dat er een hoger risico op selectiebias of 'attrition bias' was. Bij onderzoek naar niet-farmacologische interventies kan het lastig zijn om selectiebias te beperken met bijvoorbeeld adequate blindering van proefpersonen of beoordelaars van uitkomstmaten. Juist dan is het van belang om te zorgen voor adequate methodiek en te rapporteren volgens de CONSORT-checklist voor niet-farmacologisch onderzoek.[12]

We hebben ernaar gestreefd een zo compleet mogelijk overzicht te krijgen van relevante publicaties op dit gebied, onder andere door een biomedische informatiespecialist te betrekken bij het opstellen van de zoekstrategie. Onderzoeken waarbij de randomisatiemethode gebrekkig was of niet was vermeld, werden uitgesloten om het risico op bias te minimaliseren. Desondanks was er sprake van een grote heterogeniteit in de onderzoekspopulatie, de soorten operaties en de controlegroepen waarin het effect van muziek werd onderzocht (zie de supplementaire informatie bij de oorspronkelijke publicatie). Door alleen Engelstalige publicaties te includeren hebben wij misschien relevante onderzoeken over het hoofd gezien (zie de figuur). Als laatste beperking moet worden gemeld dat de funnel-plot vooral bij angst wees op publicatiebias, mogelijk door publicatie van met name positieve resultaten.

Conclusie

Perioperatieve angst en pijn belasten de patiënt en zijn klinisch relevante fenomenen die verband houden met morbiditeit, de duur van de ziekenhuisopname en zelfs mortaliteit.[13] Vermindering van angst en pijn heeft een weerslag op iemands kwaliteit van leven en kan leiden tot verbetering van de klinische situatie, mogelijk tot eerder ontslag uit het ziekenhuis en uiteindelijk tot minder zorgkosten.[14] Sommige onderzoeken die wij includeerden in onze analyse beschrijven ook andere relevante effecten van muziekinterventies, zoals minder gebruik van pijnstillers, minder delierepisodes, snellere postoperatieve mobilisatie, en ook een kortere opnameduur. Kortom, er lijkt alle reden te zijn om muziekinterventies in te zetten vóór, tijdens of na een operatie.

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